

## **CHAPTER 1. INTRODUCTION TO THESIS.**

### **1.1. Introduction.**

#### *1.1.1. Recent historical context and current utility.*

In 1996, the European Society of Cardiology and the North American Society of Pacing and Electrophysiology supported a Task Force which produced a now seminal paper: “Heart rate variability: standards of measurement, physiological interpretation and clinical use” (*Circulation*, 93, 1043–1065). In the thirteen years since, this paper has become *Circulation’s* third most cited (Cerutti *et al.*, 2006). Over the same period, the number of annual publications reporting heart rate variability (HRV) has risen to approximately 500, ranging in application from dinosaurs to religion (Taylor and Studinger, 2006). It appears that HRV has become a widely applied tool as a non-invasive index of autonomic nervous system (ANS) outflow. Arguable the most important application of HRV is in diagnosis and predicting outcomes in a number of disease states affecting the ANS. Indeed a role of HRV for the assessment of cardiac autonomic function in post-myocardial infarct (MI) patients has been well established (Task Force, 1996).

#### *1.1.2. Applications of heart rate variability within this thesis.*

The rise in HRV’s popularity stems not only from its appeal as a measure of cardiac autonomic modulation for clinicians and researchers but also from technological and computing advancements allowing for its ever speedier determination. Developments in wireless ECG telemetry combined with improved computer processing power and enhanced software capabilities enable easy and instantaneous determination of both simple and more complex measures of HRV. These capabilities can be viewed as either helpful or a hindrance; helpful because they have allowed for greater application and further understanding of this measure; a hindrance due to a loss in its simplicity and increased difficulty in standardisation of methodology.

As well as providing the context as to which HRV can be used; the Task Force report provides recommendations relating to the technical and experimental requirements for its determination. A recommendation for independent assessment of equipment to be carried out to ensure valid and reliable measures is also stressed.

In this thesis, all assessments of HRV were made in strict adherence to the conditions set out by the Task Force. Separate and independent validity and reliability assessments of novel devices used to record and analyse heart rate interval data were carried out in each of the study populations. The standards of these devices matched or exceeded those of the Task Force report. Throughout the present study, reliability was defined as the repeatability of repeat measures. Where measures demonstrated good repeatability, these were considered reliable.

In 2001, 4% of all United Kingdom (UK) deaths were due to heart failure and in 2008 an estimated 912,000 people were suffering from heart failure. Severe ANS dysfunction underlines the condition. Evidence of HRV in heart failure is less extensive when compared to that of MI, particularly for measures obtained from short electrocardiograph (ECG) recordings. In MI, decreased HRV is indicative of abnormalities in vagal and/or sympathetic nervous system function and is the most powerful ambulatory ECG predictor of cardiac mortality (Kleiger *et al.*, 1987). In heart failure, evidence points to a depressed HRV relating to increased mortality; particularly in chronic sufferers (Chattipakorn *et al.*, 2007).

Treatment for heart failure often consists of a specific pharmacological strategy aimed at reducing symptoms, hospitalisations, delaying disease progression and improving quality of life. In selected cases, heart failure can be treated by surgery, such as valve replacement, coronary artery bypass surgery or even transplantation. The later treatment occurs in those patients with the severest symptoms and was at one point the final option available. Developments in treatment for this patient group include mechanical support of the failing heart with a left ventricular assist device (LVAD). Whilst there are data concerning the effects of the former treatments on HRV (Goldsmith *et al.*, 1997), very little information is available concerning the HRV response to LVAD treatment.

Exercise plays an important role not only in the prevention of cardiovascular disease but also in its treatment. The standard treatment for MI is for patients to enrol onto an exercise programme. Exercise is not as yet a standard treatment in heart failure but its status has recently changed from one of avoidance to one of inclusion in the treatment of stable, less severe patients (Dickstein *et al.*, 2008). There are a small number of studies demonstrating a favourable HRV response to training in heart failure patients but the majority of these report 24 h measures and only utilise aerobic exercise (Coats *et al.*, 1992). There are no data as to the effects of different modes of exercise on short-term measures of HRV when prescribed in heart failure.

## **1.2. Aim.**

The aim of this thesis was to report changes in short-term measures of HRV in chronic heart failure patients following specific surgical and exercise interventions. Procedures and devices would first be assessed in healthy participants.

## **1.3. Outline.**

The majority of empirical work carried out in this thesis utilised a combination of novel wireless ECG and computer software systems for the first time in heart failure populations. In recognition of the Task Force recommendations, chapters two and three assess the reliability and agreement of data from these systems with criterion values. These analyses were first carried out in healthy participants before being repeated in a heart failure population, the outcomes of which are reported in chapter six. Chapter four assessed the association between the heart rate (HR) response to acute exercise and resting HRV in healthy participants and resulting data provided norms for comparison in heart failure patients. The Task Force report provides norm values for short-term measures of HRV but these data are currently obsolete. The body of literature available since the report provides a source for updating these norms and in chapter five data from relevant studies were reviewed and analysed. These data for the first time present a

reference to aid identification of abnormal HRV in diseased populations including patients with heart failure.

Chapters eight to 10 present empirical work carried out in heart failure patients. Differences in the impact of aerobic versus resistance only exercise training on selected physiological, functional and HRV measures obtained in mild-to-moderate heart failure patients are assessed in chapter eight. This is followed in chapter nine by assessments of the association between acute HR responses to exercise and measures of HRV and the impact of exercise training on these associations. Similar data had not been available prior to the completion of these studies.

Chapter 10 observes the degree of autonomic dysfunction in severe heart failure patients being assessed for transplantation and treated with LVADs. This chapter is purely observational and was deliberately performed in a current, real-life, clinical setting to demonstrate the practical utility of the employed HRV methodology. Data concerning differences in short-term HRV measurements between patients prior to, in-situ with and following LVAD treatment are unique and could aid understanding of the mechanisms underlying recovery in this critical patient population.

Chapter 11 summarises the findings of the thesis and proposes future directions.

#### **1.4. Thesis notes format.**

In the present thesis each chapter represents a discrete piece of work which is linked to the other chapters by a common theme (Figure 1-1). In a number of chapters (two, three, four; and eight and nine) a common methodology and population were used. The methodology sections of proceeding chapters are *italicised* to avoid the reader having to repeat read. References have been placed at the end of each chapter and conform to the format proposed by the American Psychological Association (APA).

## 1.5. References.

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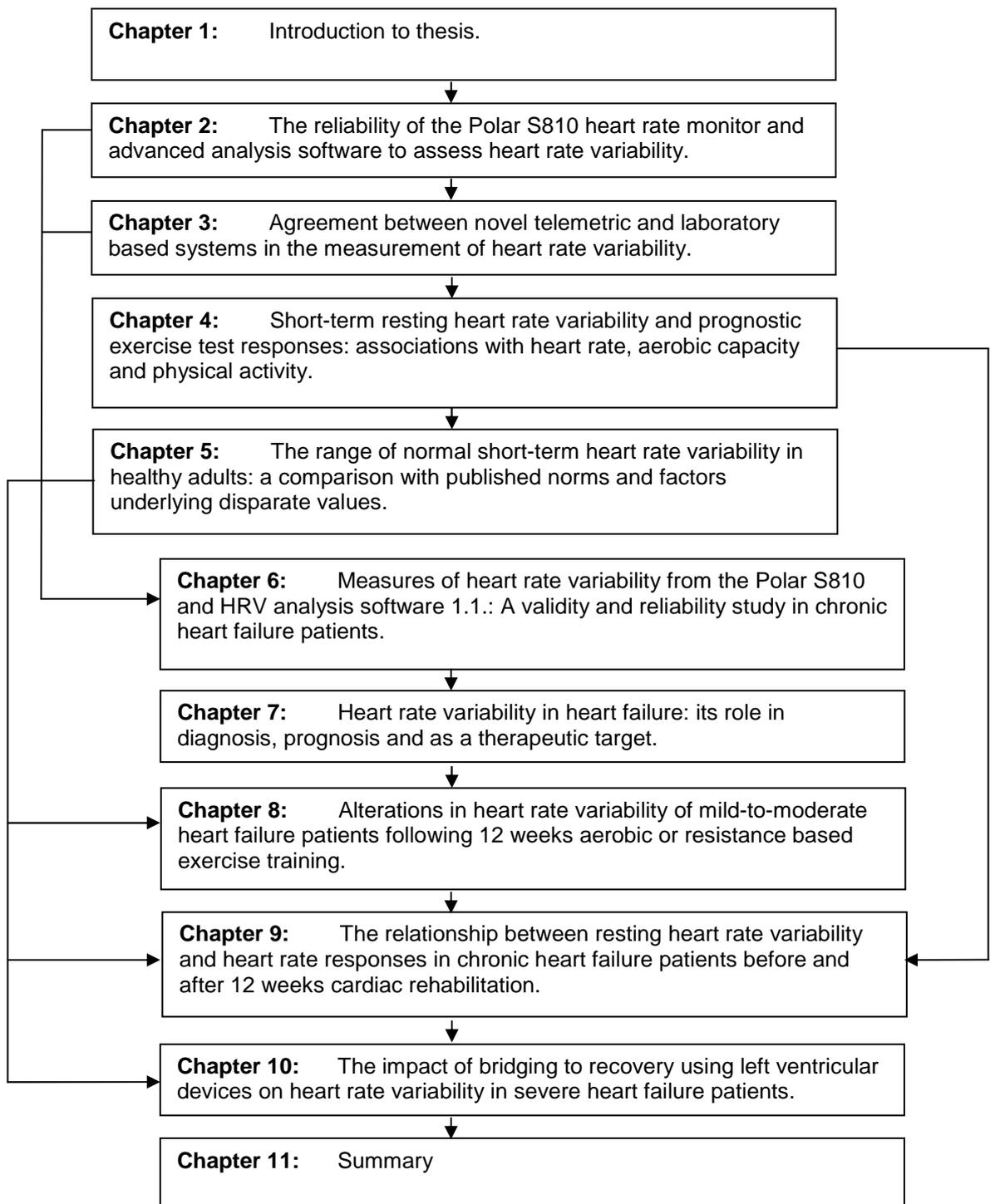


Figure 1-1. Outline graphic of thesis.

## **CHAPTER 2. THE RELIABILITY OF THE POLAR S810 HEART RATE MONITOR AND ADVANCED ANALYSIS SOFTWARE TO ASSESS HEART RATE VARIABILITY.**

### **Abstract.**

The aims of the present study were to assess the reliability of short-term HRV measures obtained from both the Polar S810 (S810) and advanced HRV analysis software 1.1 (HRV 1.1). The effect of altering parameter settings within the HRV 1.1 software was also assessed. Reliability in the present study is defined as the repeatability of repeated measures.

19 males and 14 females, median (range) age 34.0 (20-59) and 47.5 (25-63) respectively, performed a supine rest on three separate occasions during which RR intervals were recorded with the S810. The signal was corrected for artefacts before separate statistical and spectral analyses were undertaken by S810 specific and advanced HRV 1.1 software. To assess repeatability, intraclass correlation coefficient (ICC) and between- and within-subjects coefficient of variation (CV) were calculated. *Post-priori* repeated measures ANOVA (rm-ANOVA) was used to assess the effect of altering selected parameter settings in the advanced HRV analysis software on measures of HRV. Reliability was assessed in eight measures of HRV, three in the time domain and five in the frequency domain.

Both S810 and HRV 1.1 display acceptable to good reliability of short-term HRV and no setting in the HRV 1.1 was more reliable than the other when assessed by ICC. When assessed by CV, short-term HRV showed unacceptably large inter-individual variation for S810 and HRV 1.1 measures; intra-individual variation was equally unacceptable but was 50% lower in both systems. For both systems, time domain indices were more reliable than those of the frequency domain. Specifically altering the parameter settings within HRV 1.1 analysis software significantly altered both HRV index outcomes and reliability.

Studies using the advanced HRV analysis software 1.1 should indicate and give justification for chosen parameter settings and maintain these for repeated measures. Wide variation between individuals illustrates the variable nature of

short-term measures of HRV and highlights the need for establishing a range for so called 'normal' HRV.

This chapter, in truncated form has been published in *Medicine and Science in Sports and Exercise* (see appendix IV).

## **2.1. Introduction.**

Heart rate variability (HRV) is considered a valuable non-invasive marker of autonomic modulation (Akselrod *et al.*, 1981; Taskforce, 1996; Pagani *et al.*, 1997; Malik, 1998) and particularly cardiac vagal tone (Goldberger *et al.*, 2001; Malpas, 2002). In clinical situations, its importance lies in its use as an independent indicator of mortality and morbidity and of sudden cardiac death in patients with cardiovascular disease (Kleiger *et al.*, 1991; Tsuji *et al.*, 1996; La Rovere *et al.*, 2003).

The measurement of HRV is conducted by two distinct methodologies. Until recently, the majority of studies had utilised ambulatory ECG data from 24 h Holter recordings, which allows for determination of HRV in both time and frequency domains. For reasons of practicality, feasibility and a similar prognostic value to 24 h ambulatory records (Bigger *et al.*, 1993), an increasing number of studies have utilised HRV obtained from shorter (5 – 15 minutes) ECG recordings. Indices of HRV are obtained either by extraction from 24-hour Holter recordings (Bigger *et al.*, 1993) or from analysis of a single ECG recorded under stable, resting (Sandercock *et al.*, 2004, Reland *et al.*, 2005) and increasingly under cardiovascular stressful conditions (Carrasco *et al.*, 2003; Lee *et al.*, 2004; Reland *et al.*, 2005).

In an attempt to standardise the measurement of HRV, the European and North American Task Force introduced recommendations for RR and HRV determined by short- and long-term recordings (Task Force, 1996). When assessing short-term measures of HRV, an RR recording period of a minimum of 5-min is preferred. Equipment designed to analyse short-term HRV should incorporate both non-parametric (fast Fourier) and parametric (autoregressive) spectral

analyses. The report also suggests that frequency domain analysis be carried out in preference to time domain analysis in short (2 – 7-min) recording periods as their physiological interpretation may be easier than those of the time domain under such conditions.

According to Kautzner (1995, p.165); “HRV has substantial potential in physiological studies and investigations. However, spontaneous variation of HRV parameters in time may have deleterious effects on its value.” Kautzner also states the practical utility of the assessment of HRV is related to its reproducibility over time.

The significance of this statement is highlighted by the number of studies which have assessed the reproducibility/repeatability of HRV in both healthy (Sinnreich *et al.*, 1998; Marks and Lightfoot., 1999; Ziegler *et al.*, 1999; Lord *et al.*, 2001; Dionne *et al.*, 2002; Carrasco *et al.*, 2003; Sandercock *et al.*, 2004; Reland *et al.*, 2005) and clinical (Kamalesh *et al.*, 1995; Kautzner *et al.*, 1995; Pardo *et al.*, 1996; Lord *et al.*, 2001; Parati *et al.*, 2001) populations.

The general consensus from studies assessing the reproducibility/repeatability of HRV indices is that long-term (24 h) HRV is moderately reproducible while short-term HRV seems to have a lower stability or the degree of reproducibility may be manoeuvre-dependent (Pitzalis *et al.*, 1996; Sandercock *et al.*, 2005).

From the number of studies cited above it is clear that short-term HRV measurements are becoming more commonplace. In tandem with this increase in use of short-term HRV is an increase in the number of new technologies aimed at improving the efficiency and quality of short-term HRV analyses. It is beyond the remit of this chapter to review the numerous different RR measurement instruments and equipment currently available. Suffice to say there are many, each with varying specifications and measurement parameters. Moreover, reliability coefficients for equipment used to obtain RR data and subsequent HRV determination are often not reported in the literature (Reland *et al.*, 2005).

The Task Force also recommends that when employing commercial equipment in studies investigating physiological and clinical aspects of HRV, independent

tests of the equipment used should always be required. Such tests will help ensure both the reliability of HRV measures from short-term recordings and the quality of different HRV analysis equipment. Reliability in the present context refers to the reproducibility of the observed value when the measurement is repeated (also referred to as repeatability). Throughout this chapter references to reliability will be made in the context of these definitions.

In the light of these recommendations, several studies have been conducted to assess the reliability of HRV measurements obtained from a variety of instruments used to measure RR intervals. Sandercock *et al.* (2004) assessed the test-retest reliability of short-term (5-min) resting HRV measures obtained from three commercially available analysers (TF5 HRV analysis system, Cardio<sub>2</sub> CP stress system (CP) and CardioTens 24 h ambulatory ECG recorder (CT)) under three commonly used conditions – 1) lying supine, 2) standing and 3) lying supine with controlled breathing. Using coefficient of variation (CV), intraclass correlation coefficients (ICC) and limits of agreement (LoA), the authors reported large ranges for CVs (1-235%) and ICC ( $R = 0.16-0.99$ ), dependent on the measure of HRV assessed and the position in which the measurement was made. CVs in condition 1 (supine) were lower for the majority of HRV measures compared to conditions 2 (standing) and 3 (controlled breathing). It appears that RR intervals obtained in the supine position provide greater reproducibility of short-term HRV measures. However, the authors also reported an agreement between instruments in the size of CVs for HRV measures under the varying conditions, suggesting that some other factors (e.g. biological and experimental variation) were the major sources of variation between tests. These factors should be considered in future studies utilising measures of short-term resting HRV. The study of Sandercock *et al.* highlights the importance of reliability assessment of HRV measures, both across and within varying conditions and between and within different instrumentation. Sandercock *et al.* also illustrated a concern present in many reliability studies of HRV, the use of incorrect statistical procedures to assess repeatability.

In the majority of the studies highlighted above, measurement of HRV was made using a high quality electrocardiogram (ECG) with a sampling frequency above

250 Hz and an accurate algorithm to detect the QRS complex (as recommended by the Task Force). Moreover, RR intervals were recorded either from a fixed laboratory ECG analyser or from recently developed ambulatory ECG recorders or Holter monitors, permitting out of laboratory use. Both types of systems, however, require the use of complex and expensive hardware and software equipment, limiting the clinical and investigative use of HRV.

An alternative to the classic stationary or ambulatory ECG is the development of the wireless heart rate monitor (HRM). The Polar S810 HRM (S810) allows the detection of instantaneous RR recordings with a resolution of 1 ms. Accompanying Polar software allows for determination of HRV measures from RR interval data obtained by S810. Also newly available is the advanced HRV analysis software 1.1 (HRV 1.1) programme (Kuopio, Finland). Developed by Niskanen *et al.* (2004), this software allows for the determination of RR interval data obtained by the S810. The programme also offers greater flexibility in terms of the parameters used to calculate HRV; for example, a degree of manipulation is afforded to account for unwarranted low frequency baseline trend components sometimes present in RR interval data. The software also provides a substantive report detailing HRV measures in time, frequency and non-linear domains. Features such as these are not present with the S810.

The relatively new S810 and HRV 1.1 potentially afford the measurement of HRV in both clinical and physical training fields at a fraction of the cost of currently available systems. In accordance with the Taskforce recommendations, however, it is necessary to determine the reliability of these methods before their use on a regular basis.

While attempts to assess the validity of HRV indices using the S810 have been made (Kingsley *et al.*, 2005; Gamelin *et al.*, 2006), the repeatability of resting supine HRV obtained using S810 and utilising the appropriate statistical procedures is lacking. The effect of altering HRV 1.1 on the reliability of measures is also unknown.

The aim of the present investigation was to assess repeatability of short-term supine HRV measurements obtained from the Polar S810 HRM and subsequent

HRV derived by S810 and advanced HRV analysis software 1.1 programmes, utilising the appropriate statistical procedures.

## **2.2. Methods.**

### *2.2.1. Recruitment of Participants.*

Staff and students of a South East England University were recruited for this study in accordance with approval received by the university ethics committee. Volunteers responded to advertisements (e.g. group email to all university faculty members, advertisement poster) placed internally within the university. Contact details for the research team were made clear on all advertisements. Following an initial phone conversation, volunteers were sent an information pack containing:

1. An information sheet detailing what was required of the participant prior to and during each visit to the laboratory
2. A detailed informed consent form
3. A physical activity readiness questionnaire (PARQ), and
4. A physical activity rating questionnaire (PAR)

Participants were requested to read and complete the documents provided in the information pack prior to their initial visit to the laboratory. Any questions raised by participants were addressed at the initial visit. All participants were free from contraindications to exercise as indicated by the PARQ.

### *2.2.2. Participants.*

Thirty three volunteers, 19 males with a median age 34.0 (range 20 - 59) and 14 females with median age 47.5 (range 25 - 63), were included in the study. The mean  $\pm$ SD height and mass for all participants was  $1.73 \pm 0.11$  m and  $74.6 \pm 15.6$  kg. All participants were healthy, defined as being free from illness at the time of testing. None were known to be taking any medication or have any cardiovascular problems that may have influenced the procedures carried out. All procedures were approved by the Ethics Committee of the appropriate university faculty. Informed consent was provided by each participant prior to commencing the experimental procedures.

### 2.2.3. *Instrumentation and data acquisition.*

RR intervals and heart rate (HR) were recorded via a Polar S810 heart rate monitor (HRM) (Polar Electro OY, Kempele, Finland). The S810 was set to record beat-to-beat RR intervals with a sampling frequency of 1000 Hz providing an accuracy of 1ms for each RR period (Cottin *et al.*, 2004).

The S810 recorded continuously for a duration of 10 minutes. S810 recordings were transferred to a password protected PC via Polar specific software (Polar Precision Performance 4.03, Polar Electro OY, Kempele, Finland). Once downloaded, RR interval files are automatically stored in the Polar software programme. Reliability of S810 HRV was assessed from a 300s segment within the Polar software according to the manufacturer's guidelines. The same segment of RR interval data was exported as a .txt file to a separate folder for later reliability analysis using the HRV 1.1 software (Kuopio, Finland).

### 2.2.4. *Experimental design.*

Participants reported to the laboratory on three occasions. The mean period between the first and third experimental day was  $13 \pm 8$  days. Due to the observation that circadian rhythm can significantly influence HRV measures (Lord *et al.*, 2001; Singh *et al.*, 2003), attempts were made to ensure participants reported at similar times on each visit. In accordance with current data capture guidelines of RR interval data for HRV analysis, participants were asked to refrain from eating and smoking two hours prior to testing. Where testing took place in the morning, participants were instructed to eat a light breakfast at least two hours prior to testing. Participants were also asked to abstain from caffeine and alcohol containing foods and beverages on test days, and to avoid heavy physical exertion and alcohol consumption during the 48 hours preceding test days. Where participants failed to meet the protocol requirements an assessment was made on the potential impact of their behaviour on HRV measures and where necessary the test was rescheduled.

On each occasion (trial) participants underwent 10 minutes of RR interval recordings. The S810 chest strap (transmitter) was fitted in accordance with manufacturer's instructions. The S810 receiver (watch) was then placed on the

participant's wrist and heart rate (HR) checked by depressing the red start button on the S810 watch. Participants next lay on a bed with the head supported by a pillow in a quiet laboratory under thermoneutral conditions. Participants were asked to relax and the researcher monitored their HR visually for two or three minutes until it became stable. One 10-min S810 recording was then made by depressing the start button a second time. Following 10-min, the end of recording was marked by pressing the start button on the S810 for a third time and the recording was stopped approximately five seconds later using the stop button.

#### 2.2.5. *Raw cardiac data processing.*

The Polar software contains an automatic RR interval filtering and interpolation algorithm. Prior to extraction of any segments the entire time series was error corrected using a moderate filter power set at a minimum beat protection zone of six beats·min<sup>-1</sup>. The effects of this interpolation method on spectral measures of HRV obtained from stationary tachograms where <15% of beats are rejected are only minor (Jurca *et al.*, 2004). Huikuri *et al.* (1996) provide a comprehensive detail of the beat filtering and interpolation algorithms. Following abnormal interval removal, the S810 algorithm substitutes detected errors with interpolated intervals (usually two to four intervals) calculated from differences between previous and next accepted RR intervals. After filtering and correcting, 10-min RR interval time series (corresponding to each of the ECG recordings) were stored on the hard drive of a password protected computer for later HRV analysis using Polar S810 specific and advanced HRV analysis software respectively.

#### 2.2.6. *Heart rate variability analysis.*

S810. The second part of the data analysis process was the transformation of the RR interval data into time and frequency domain HRV. RR interval data were transformed into frequency and time domain data within the Polar software using its internal HRV analysis feature. The Polar software uses an auto-regressive model (order 21) in which to calculate frequency domain indices. In accordance with the recommendations in the Taskforce report, the resulting power spectrum was divided into the following default spectral bands: VLF (very low frequency;

0.0033-0.04 Hz), LF (low frequency; 0.04-0.15 Hz) and HF (high frequency: 0.15-0.40 Hz). Only LF, HF in raw and normalised units and LF:HF ratio were used for the reliability analysis. Due to the short (5-min) recording session, measures of total power (TP) and VLF were not used for comparison or reliability assessments. The Task Force report stated that TP and VLF may yield ambiguous values when obtained from such short recordings and should be avoided (Task Force, 1996). In addition, time domain analysis was also carried out to obtain rMSSD (root mean square of successive differences) and SDNN (the standard deviation of normal to normal (NN) intervals). Only these measures were extracted from the time domain analysis as recommended by the Task Force report.

HRV 1.1. The same segment of the RR interval time series (between 160s and 460s) was imported into the advanced HRV 1.1 software. The use of these time points was to ensure HRV was derived from stable RR intervals. The same segment was also used for comparisons of alternate settings within the HRV 1.1 software.

The findings of two validation studies using RR interval data collected using a heart rate monitor analogous to the S810 (Ruha *et al.*, 1997) and consequently analysed by the HRV 1.1 programme, have been published (Niskanen *et al.*, 2004).

#### 2.2.7. *Application of alternative settings in HRV 1.1.*

The HRV 1.1 software enables the user to alter specific parameters such as the detrending of RR series and the interpolation of RR series used to calculate HRV. The need to adjust such parameters is present when very low frequency trend components (VLF) require removal from the RR series (Niskanen *et al.*, 2004). Such trends were observed for a number of participants in the present study. The filtered RR data were therefore detrended using the smoothness priors approach (Gersh, 1991). This approach is the default method used by the software and behaves like a time varying finite impulse response high-pass filter, reducing noise and allowing for a mono-component signal in each band (Cottin *et al.*, 2004). Applying it to different occasions is easy as it has only one

adjustable parameter. This method of detrending removes the VLF component, power within the frequency bands of interest (LF and HF) remains largely unaffected (Niskanen *et al.*, 2004).

Several important *post-priori* observations from the analysis of HRV using the HRV 1.1 software were made. There is great subjectivity for the setting values of the parameters by which HRV values are determined. The software developers provide default values for a number of parameter settings but upon accessing the software some of these were not set (e.g. interpolation rate). Moreover, for some parameter settings that greatly affected the outcome of HRV values (e.g. the smoothing parameter  $\lambda$  (or alpha)), little guidance as to a suitable setting was provided by the software developers.

It was therefore deemed necessary to investigate this further by assessing the effect of altering parameter settings within the HRV 1.1 software on commonly used measures of HRV. In addition, it was hoped that some recommendations as to the appropriate parameter settings applicable to certain situations could be made.

The parameter settings with most ambiguity as to their appropriate value/setting were chosen as the parameters to which adjustments would be made. These were the detrending component, its corresponding regularisation parameter ( $\lambda$ ) and the interpolation rate.

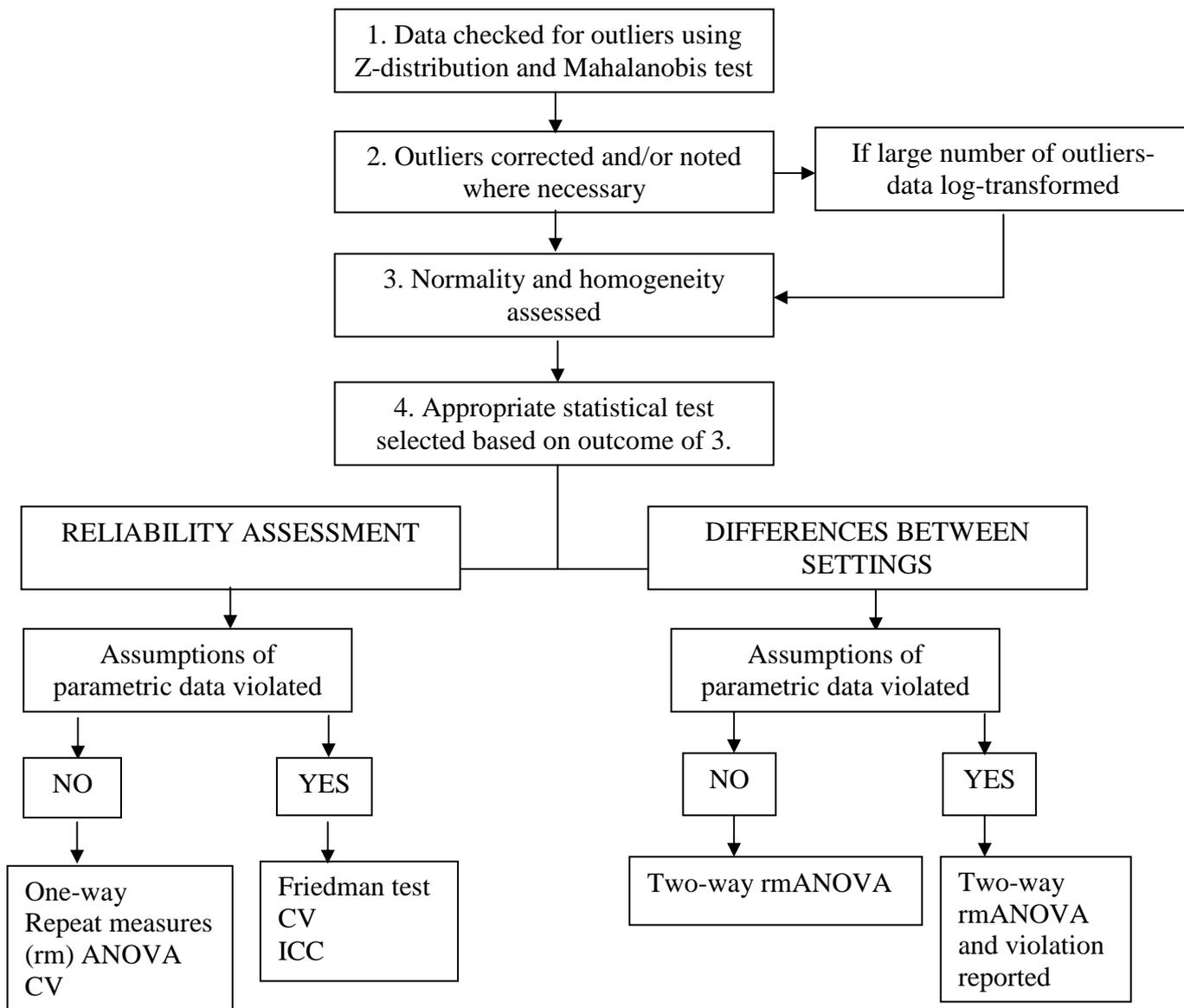
HRV values were grouped according to the adjusted setting for each parameter in the following manner:

1. Settings 1 (S1) – Detrend = smoothness priors; interpolation rate = 2 Hz;  $\lambda = 1000$ . (These were the actual default settings upon opening the advanced HRV analysis software and differed to those described by Niskanen *et al.*, 2004).
2. Settings 2 (S2) – Detrend = smoothness priors; interpolation rate = 4 Hz;  $\lambda = 500$ .
3. Settings 3 (S3) – Detrend = none; interpolation rate = 2 Hz.

The reliability of HRV values obtained when using these parameter settings was assessed. In addition, values for HRV were assessed for differences between the three settings.

#### 2.2.8. *Statistical Analysis.*

All statistical analysis was carried out using SPSS version 13.0 (SPSS inc. Chicago, Illinois, USA). Prior to statistical analysis, data were checked for univariate and multivariate outliers using standard Z-distribution cut-offs of  $\pm 3.29$  and Mahalanobis distance tests respectively. Where outliers were found, data were assessed and in the case of incorrect data entry were corrected. Re-assessment of outliers was then carried out on the corrected data set(s). Where outliers were still found present these were noted accordingly but not removed. Where data sets were found to contain large numbers of outliers logarithmic transformation (ln) was applied. The normality of data sets was then assessed using a Kolmogorov-Smirnov test. Homogeneity of variance was assessed by doubling the smallest variance within the data set. When this value exceeded the value for the largest variance in the data set, the assumption of homogeneity was violated. Where assumptions for parametric testing were not met, an appropriate non-parametric statistical test was used (e.g. Friedman test). Figure 2-1 illustrates the data screening procedure for reliability assessment and the comparison of different settings.



**Figure 2-1. Flow diagram to illustrate data screening procedure and selection of appropriate statistical tests for reliability and settings comparison assessments.**

To assess repeatability and for global comparison with previous data, intraclass correlation coefficients (ICCs) were calculated using the estimates of within and between subject variability obtained from a one-way random effects analysis of variance model. There is no universal standard for classifying intraclass correlation coefficients and tests of statistical significance of reproducibility measures have little practical utility (Morrow and Jackson, 1993). In the present study, reproducibility was considered poor if  $R < 0.40$ , acceptable if coefficients ranged from 0.41 to 0.60, good if coefficients ranged from 0.61 to 0.80, and excellent if  $R \geq 0.81$ . Others have adopted such criteria for assessing the

repeatability of short-term HRV (Marks and Lightfoot, 1999; Lee *et al.*, 2004; Reland *et al.*, 2005).

As a measure of absolute reliability the coefficient of variation (CV) was calculated. The CV was calculated for each individual and defined as the standard deviation between the three recording days divided by mean of the three days, and expressed as a percentage. The mean of all individual CVs were then calculated and presented in graphical format. Between subject CVs were also calculated to evaluate inter-individual variation. The use of CV in the present study was prompted not only by its use in previous studies (Sandercock *et al.*, 2004; Reland *et al.*, 2005) but also by the recommendation that ICC should not be used alone when assessing reliability due, in part, to its dependency on the heterogeneity of the sample population (Bland and Altman, 1990; Atkinson and Neville, 1998; Sandercock *et al.*, 2004). Hopkins (2000) suggests the use of CV to assess variation between repeat measures. The distinction of low, medium or high CV has been used by some researchers to quantify the meaning of values (Toyry *et al.*, 1995; Reland *et al.*, 2005). Accordingly, a CV of less than 10% was considered low, modest when between 10 and 20%, and high when above 20%.

To assess effects of parameter setting alterations, repeated measures ANOVA (rmANOVA) was used to identify significance of difference. Where a significant effect for group was observed, *post-hoc t*-tests were conducted with Bonferoni adjustment to identify where the differences lay. An alpha of  $P < 0.05$  was used to assess level of significance.

### 2.3. Results.

Data were gathered from 33 volunteers. Due to a technical failure with the S810, trial two data for one participant were not entered into the reliability analysis of the S810. A technical failure with the HRV 1.1 omitted trial three data for two participants, therefore reducing the number of data sets to 30.

For reliability analysis, data screening revealed a total of 24 and 13 outliers within HRV 1.1 and S810 data sets respectively. Reported outliers were corrected and/or noted where necessary. Often this simply consisted of correcting a value incorrectly entered into the database. No outliers were removed from the data sets as values were within those reported in the literature. Some data sets were skewed as a result of containing outliers and were subjected to log-transformation. Where this did not correct the data, non-parametric analysis was conducted accordingly.

For comparison of differences between settings, many data sets displayed large numbers of outliers subsequently distorting the normality of distribution. To avoid a large loss of data, data were log-transformed where necessary. This was apparent for the time domain variables SDNN and rMSSD and for frequency domain variables LFms<sup>2</sup>, HFms<sup>2</sup>, and HFnu.

#### 2.3.1. Reliability.

Presented in Tables 2-1 – 2-4 are the mean ( $\pm$ SD) HRV values from the HRV 1.1 software with settings one to three and S810 in each trial. The values of rMANOVA as a test of systematic bias and ICC for repeated HRV measures are also shown.

##### 2.3.1.1. Intraclass correlation coefficient (ICC).

HRV 1.1. In S1, two ICCs were greater than 0.81 (SDNN and LF) and values for all HRV indices ranged from 0.36 – 0.85. In S2 the ICC values ranged from 0.38 – 0.80 and in S3 from 0.39 – 0.80. Of note was the finding that a poor  $r$  value in one setting was mirrored by the other two settings. Likewise, a higher  $r$  value for

one setting was also accompanied by a high  $r$  value in the other two settings. For both time and frequency domains and in all three settings, none of the HRV parameters displayed systematic bias (rmANOVA,  $P > 0.05$ ).

S810. Eight ICCs were generated for each measure of HRV obtained using the S810 and polar software. ICC values ranged poor to good (0.42 – 0.79). The same HRV indices as those of the advanced HRV analysis software displayed low and higher  $r$  values respectively. Similarly, there was no systematic bias between trials ( $P > 0.05$ ).

#### 2.3.1.2. Coefficient of variation (CV).

Coefficients of variation for advanced HRV analysis software and S810 are presented together in Figures 2-2 to 2-5 but are described here separately.

HRV 1.1. The average trial between-subject CV for each parameter obtained with S1, S2 and S3 is displayed in Figure 2-2. In S1 (range 25 – 182%) and S2 (26 – 187%), between subject CVs were high ( $> 20\%$ ) for time and frequency domain indices except for mean RR and LFnu which displayed moderate CVs (range 13 – 18% for both S1 and S2). In S3, high CVs were reported for measures in both domains; however, the range was lower (22 – 108%) than that observed for S1 and S2. Mean RR and LFnu also displayed lower CVs with S3 (range 7 – 11%). CVs for LFms<sup>2</sup> with S1 (118%) and S2 (112%) were greater than S3 (48%). Similar examples were displayed for HFms<sup>2</sup> and LF:HF.

In order to facilitate comparisons of the reliability of HRV measurements from the three different settings and to previous published data, the overall between-subjects mean CV from each setting is displayed in Figure 2-3. On observation S3 demonstrated the lowest overall CV (38%), with CVs for S1 (76%) and S2 (75%) approximately 50% larger than S3.

Within-subject CVs from S1, S2 and S3 are shown in Figure 2-4. Similar patterns to those observed for between-subject CVs were witnessed; however, the range of values was much smaller. CVs ranged from 7 – 62% for S1 and S2

with S3 demonstrating the smallest range in CV (7 – 33%). One-way ANOVA revealed this difference to be significant ( $P < 0.001$ ).

Overall lower within-subject CVs (Figure 2-5) for HRV measures obtained using S3 demonstrates greater reliability of these settings. The highest overall CVs, and therefore the least reliable, were observed with S2.

S810. Between-subject CVs for indices of HRV obtained using S810 follow the same pattern as for those obtained by the HRV 1.1 with S1 and S2 (Figure 2-2). Excluding mean RR, CVs were again greater than 20% for all time and frequency indices and ranged from 23 – 215%. Mean RR had a CV ranging from 13 – 18%. As with S1 and S2 of the HRV 1.1 software, the largest mean CVs were observed for LF (119%) and HF (168%) in absolute units.

Within-subject CVs again follow a similar pattern to their corresponding between subject CVs. With the exception of rMSSD and LF, however, within subject CVs from S810 were slightly lower than the HRV 1.1 software with S1 and S2 but not S3, ranging from 7 – 57%. A within-subjects CV of less than 20% was shown only for mean RR and LFnu.

**Table 2-1. Mean ( $\pm$ SD) values and reliability of HRV measures obtained from the advanced HRV analysis software with Settings 1: smoothness priors detrend; interpolation rate = 2 Hz,  $\lambda = 1000$ .**

HRV Measure	Trial 1	Trial 2	Trial 3	ANOVA	ICC
mRR (ms)	989.3 $\pm$ 177.1	983.3 $\pm$ 176.3	994.6 $\pm$ 145.0	$P = 0.85$	0.80
SDNN (ms)	58.3 $\pm$ 37.6	54.8 $\pm$ 24.6	54.9 $\pm$ 26.3	$P = 0.83^*$	0.81
rMSSD (ms)	54.1 $\pm$ 46.8	51.0 $\pm$ 32.2	50.8 $\pm$ 30.0	$P = 0.34^*$	0.74
LF (ms <sup>2</sup> )	320 <sup>†</sup> (208 – 600)	276 <sup>†</sup> (237 – 617)	237 <sup>†</sup> (193 – 814)	$P = 0.35$	0.85
LFnu	61.9 $\pm$ 19.7	63.3 $\pm$ 15.9	64.6 $\pm$ 14.5	$P = 0.76$	0.50
HF (ms <sup>2</sup> )	213 <sup>†</sup> (101 – 337)	306 <sup>†</sup> (129 – 425)	165 <sup>†</sup> (72 – 384)	$P = 0.88^*$	0.37
HFnu	38.1 $\pm$ 19.7	36.7 $\pm$ 15.9	35.4 $\pm$ 14.5	$P = 0.75$	0.50
LF:HF	2.5 $\pm$ 2.2	2.3 $\pm$ 1.5	2.4 $\pm$ 1.7	$P = 0.75$	0.36

mRR, mean time (ms) between normal r-waves; SDNN, the standard deviation of normal to normal intervals; rMSSD, route mean square of the standard deviation of normal to normal interval differences; LF, low frequency spectral power; HF, high frequency spectral power; nu, normalised units; LF:HF, the ratio of low to high frequency spectral power; \* $P$ -value obtained from Freidman test.;<sup>†</sup>Values presented are median and (25<sup>th</sup> - 75<sup>th</sup>) quartile range.

**Table 2-2. Mean ( $\pm$ SD) values and reliability of HRV measures obtained from the advanced HRV analysis software with Settings 2: smoothness priors detrend; interpolation rate = 4 Hz,  $\lambda = 500$ .**

HRV Measure	Trial 1	Trial 2	Trial 3	ANOVA	ICC
mRR (ms)	989 $\pm$ 177	983 $\pm$ 176	995 $\pm$ 145	$P = 0.85$	0.80
SDNN (ms)	51.7 $\pm$ 33.1	48.1 $\pm$ 22.6	48.0 $\pm$ 24.2	$P = 0.98^*$	0.78
rMSSD (ms)	54.1 $\pm$ 45.9	51.2 $\pm$ 32.3	50.8 $\pm$ 30.1	$P = 0.34^*$	0.73
LF (ms <sup>2</sup> )	419 <sup>†</sup> (287 – 727)	330 <sup>†</sup> (311 – 939)	303 <sup>†</sup> (206 – 836)	$P = 0.30$	0.74
LFnu	60.2 $\pm$ 22.0	62.7 $\pm$ 16.4	61.1 $\pm$ 16.1	$P = 0.78$	0.50
HF (ms <sup>2</sup> )	317 <sup>†</sup> (131 – 472)	373 <sup>†</sup> (161 – 591)	302 <sup>†</sup> (101 – 721)	$P = 0.44^*$	0.42
HFnu	39.8 $\pm$ 21.9	37.4 $\pm$ 16.4	38.9 $\pm$ 16.1	$P = 0.78$	0.50
LF:HF	2.5 $\pm$ 2.2	2.4 $\pm$ 1.7	2.2 $\pm$ 1.8	$P = 0.55$	0.38

mRR, mean time (ms) between normal r-waves; SDNN, the standard deviation of normal to normal intervals; rMSSD, route mean square of the standard deviation of normal to normal interval differences; LF, low frequency spectral power; HF, high frequency spectral power; nu, normalised units; LF:HF, the ratio of low to high frequency spectral power; \* $P$ -value obtained from Freidman test.; <sup>†</sup>Values presented are median and (25<sup>th</sup> - 75<sup>th</sup>) quartile range.

**Table 2-3. Mean ( $\pm$ SD) values and reliability of HRV measures obtained from the advanced HRV analysis software with Settings 3: no detrend; interpolation rate = 2 Hz.**

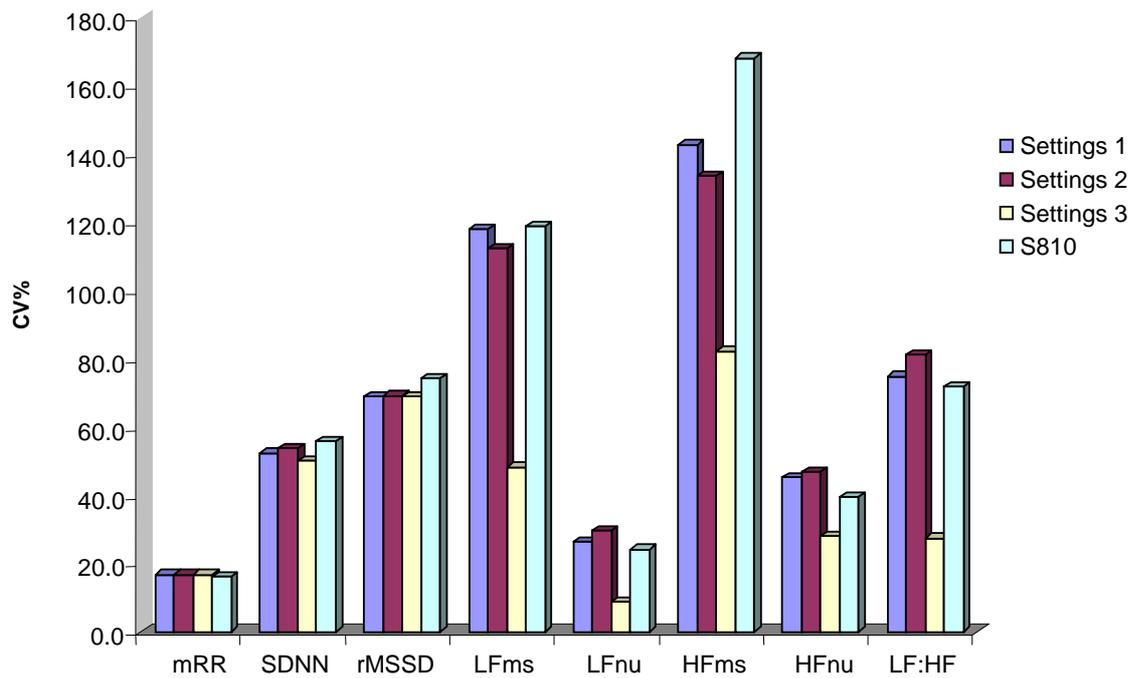
HRV Measure	Trial 1	Trial 2	Trial 3	ANOVA	ICC
mRR (ms)	989 $\pm$ 177	983 $\pm$ 176	995 $\pm$ 145	$P = 0.85$	0.80
SDNN (ms)	66.9 $\pm$ 40.1	67.2 $\pm$ 29.3	65.4 $\pm$ 30.8	$P = 0.93$	0.79
rMSSD (ms)	54.5 $\pm$ 46.1	51.6 $\pm$ 32.5	51.2 $\pm$ 30.3	$P = 0.29^*$	0.74
LF (ms <sup>2</sup> )	2812 $\pm$ 1243	2568 $\pm$ 1289	2835 $\pm$ 1424	$P = 0.15$	0.80
LFnu	75.7 $\pm$ 8.6	75. $\pm$ 5.5	76.8 $\pm$ 6.1	$P = 0.52$	0.47
HF (ms <sup>2</sup> )	692 <sup>†</sup> (464 – 1056)	894 $\pm$ 678	859 $\pm$ 538	$P = 0.65^*$	0.50
HFnu	24.3 $\pm$ 8.6	24.8 $\pm$ 5.5	23.3 $\pm$ 6.1	$P = 0.10^*$	0.47
LF:HF	3.5 $\pm$ 1.1	3.2 $\pm$ 0.8	3.5 $\pm$ 1.0	$P = 0.16$	0.39

mRR, mean time (ms) between normal r-waves; SDNN, the standard deviation of normal to normal intervals; rMSSD, route mean square of the standard deviation of normal to normal interval differences; LF, low frequency spectral power; HF, high frequency spectral power; nu, normalised units; LF:HF, the ratio of low to high frequency spectral power; \* $P$ -value obtained from Freidman test.; <sup>†</sup>Values presented are median and (25<sup>th</sup> - 75<sup>th</sup>) quartile range.

**Table 2-4. Mean ( $\pm$ SD) values and reliability of HRV measures obtained from the S810.**

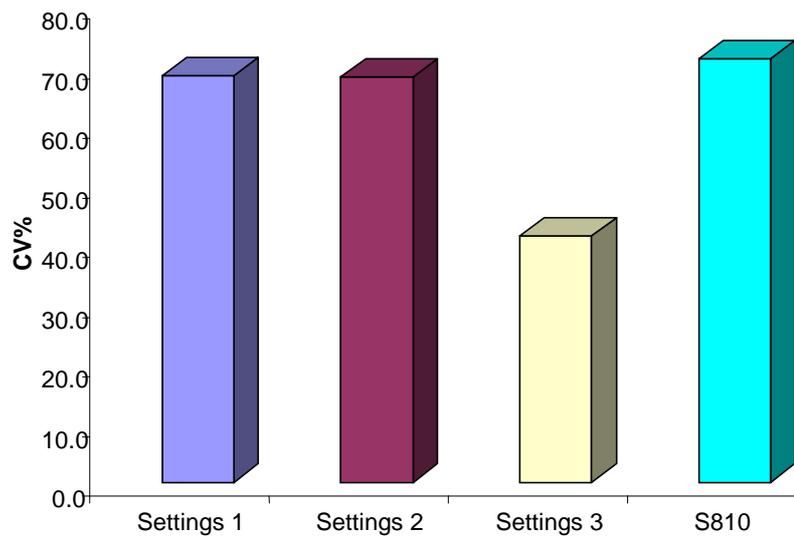
HRV Measure	Trial 1	Trial 2	Trial 3	ANOVA	ICC
mRR (ms)	988 $\pm$ 176	976 $\pm$ 168	1000 $\pm$ 134	$P = 0.18$	0.79
SDNN (ms)	70.0 $\pm$ 42.4	67.7 $\pm$ 37.2	65.1 $\pm$ 33.7	$P = 0.81$	0.78
rMSSD (ms)	55.8 $\pm$ 51.0	51.0 $\pm$ 33.9	54.4 $\pm$ 35.3	$P = 0.54^*$	0.67
LF (ms <sup>2</sup> )	1002 <sup>†</sup> (588 – 1852)	1218 <sup>†</sup> (528 – 1549)	1087 <sup>†</sup> (485 – 2236)	$P = 0.75^*$	0.75
LFnu	62.1 $\pm$ 15.2	62.6 $\pm$ 14.5	61.6 $\pm$ 15.2	$P = 0.85$	0.57
HF (ms <sup>2</sup> )	418 <sup>†</sup> (312 – 1004)	616 <sup>†</sup> (388 – 1208)	651 <sup>†</sup> (248 – 1316)	$P = 0.67^*$	0.42
HFnu	37.9 $\pm$ 15.2	37.4 $\pm$ 14.5	38.4 $\pm$ 15.2	$P = 0.85$	0.57
LF:HF	2.3 $\pm$ 1.9	2.2 $\pm$ 1.5	2.0 $\pm$ 1.3	$P = 0.46^*$	0.42

mRR, mean time (ms) between normal r-waves; SDNN, the standard deviation of normal to normal intervals; rMSSD, route mean square of the standard deviation of normal to normal interval differences; LF, low frequency spectral power; HF, high frequency spectral power; nu, normalised units; LF:HF, the ratio of low to high frequency spectral power; \* $P$ -value obtained from Freidman test.; <sup>†</sup>Values presented are median and (25<sup>th</sup> - 75<sup>th</sup>) quartile range.

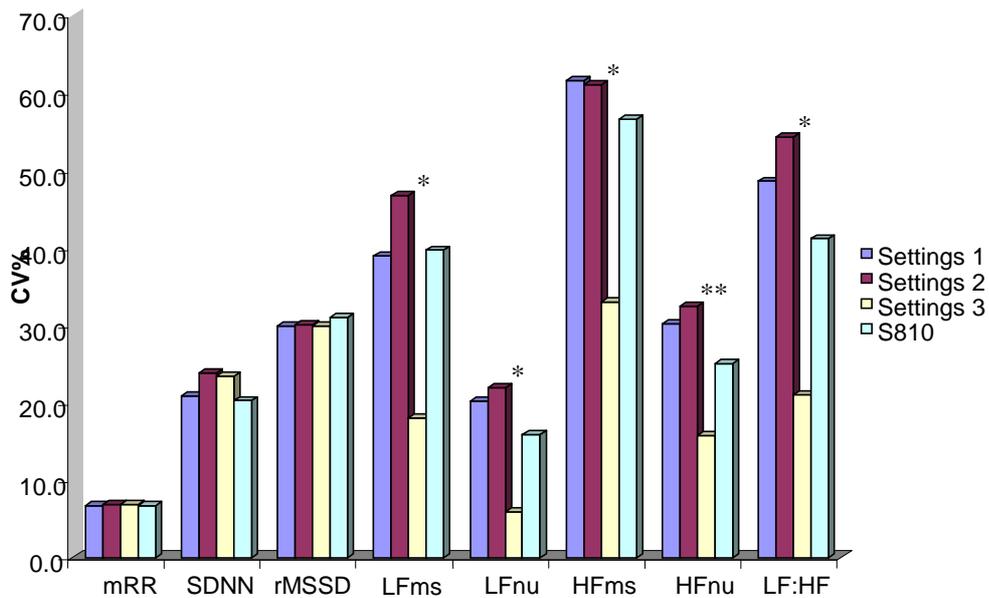


mRR, mean time (ms) between normal r-waves; SDNN, the standard deviation of normal to normal intervals; rMSSD, route mean square of the standard deviation of normal to normal interval differences; LF, low frequency spectral power; HF, high frequency spectral power; nu, normalised units; LF:HF, the ratio of low to high frequency spectral power.

**Figure 2-2. Between-subjects mean CV (%) for each HRV measure obtained from the advanced HRV analysis software S1, S2, S3 and S810.**

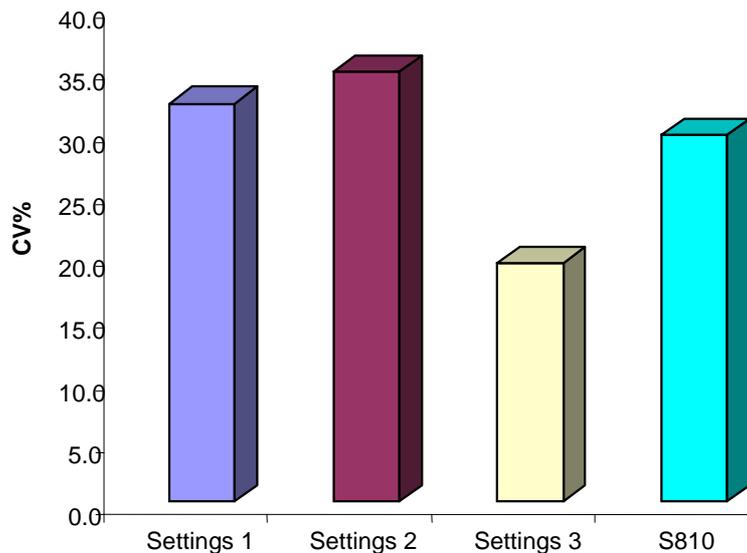


**Figure 2-3. Overall mean between-subjects CV (%) for all HRV measures as obtained from the advanced HRV analysis software S1, S2, S3 and S810.**



mRR, mean time (ms) between normal r-waves; SDNN, the standard deviation of normal to normal intervals; rMSSD, route mean square of the standard deviation of normal to normal interval differences; LF, low frequency spectral power; HF, high frequency spectral power; nu, normalised units; LF:HF, the ratio of low to high frequency spectral power; \*Indicates S3 is significantly ( $P < 0.001$ ) different from S1 and S2 as obtained by Kruskal-Wallis and *post-hoc* Mann-Whitney U tests; \*\*Indicates S3 is significantly ( $P < 0.001$ ) different from S1 and S2 as obtained by one-way ANOVA and *post-hoc* t-tests.

**Figure 2-4. Repeated trials (within-subjects) mean CV (%) for each HRV measure obtained from the advanced HRV analysis software S1, S2, S3 and S810.**



**Figure 2-5. Overall mean repeated trials (within-subjects) CV (%) for all HRV measures obtained from the advanced HRV analysis software S1, S2, S3 and S810.**

2.3.2. *Effects of altering advanced HRV analysis software parameter settings.*

Tables 2-5 and 2-6 display the outcomes of rmANOVA and where necessary *post-hoc* independent *t*-tests between settings 1, 2 and 3 for time domain and frequency domain HRV measures.

Alteration of the parameter settings did not affect the time domain variable mean RR as this variable is automatically computed from non-detrended selected RR interval signal (Tables 2-1 – 2-3), therefore this variable is not included in this analysis. For the time domain variable SDNN there was a significant difference ( $P < 0.05$ ) between the three settings. *Post-hoc* analysis revealed a significant difference between S2 and S3 ( $P < 0.05$ ). There was no difference between settings for rMSSD ( $P = 0.99$ ).

Altering the parameter settings had a significant effect on all measures of HRV in the frequency domain. RmANOVA displayed a significant difference ( $P < 0.001$ ) between settings for the HRV indices LF, LFnu, HF and HFnu. *Post-hoc t*-tests revealed a significant difference ( $P < 0.001$ ) between S1 and S3 and S2 and S3 for each of these measures. A significant difference between settings ( $P < 0.05$ ) was also found for the HRV measure LF:HF. *Post-hoc* analyses revealed a significant difference between S1 and S3 and similarly between S2 and S3 ( $P < 0.01$ ).

**Table 2-5. Mean ( $\pm$ SD) values of time domain HRV measures and assessment of differences (ANOVA) between values obtained from different parameter settings (S) in the HRV analysis software.**

HRV measure	Condition	S1	S2	S3	ANOVA <sup>†</sup>	Post-hoc <sup>††</sup>
SDNN (ms) ln	Trial 1	3.9 $\pm$ 0.5	3.8 $\pm$ 0.5	4.1 $\pm$ 0.5	<i>P</i> < 0.05	<i>P</i> < 0.05 S2 vs S3
	Trial 2	3.9 $\pm$ 0.4	3.8 $\pm$ 0.5	4.1 $\pm$ 0.4		
	Trial 3	3.9 $\pm$ 0.5	3.8 $\pm$ 0.5	4.1 $\pm$ 0.4		
rMSSD (ms) ln	Trial 1	3.7 $\pm$ 0.7	3.7 $\pm$ 0.7	3.8 $\pm$ 0.7	<i>P</i> = 0.99	N/A
	Trial 2	3.8 $\pm$ 0.6	3.8 $\pm$ 0.6	3.8 $\pm$ 0.6		
	Trial 3	3.8 $\pm$ 0.6	3.8 $\pm$ 0.6	3.8 $\pm$ 0.6		

SDNN, standard deviation of normal to normal intervals; rMSSD, route mean square of successive differences; ln, natural logarithm; <sup>†</sup>Reported *P* value is the outcome of between groups' (settings) two-way rmANOVA; <sup>††</sup>Reported *P* value is the outcome of *post-hoc t*-tests between each group

**Table 2-6. Mean ( $\pm$ SD) values of frequency domain HRV measures and assessment of differences (ANOVA) between values obtained from different parameter settings (S) in the HRV analysis software.**

HRV measure	Condition	S1	S2	S3	ANOVA <sup>†</sup>	Post-hoc <sup>††</sup>
LF (ms <sup>2</sup> ) ln	Trial 1	5.9 $\pm$ 1.1	6.1 $\pm$ 0.9	7.9 $\pm$ 0.4	<i>P</i> < 0.001	<i>P</i> < 0.001
	Trial 2	5.9 $\pm$ 0.9	6.2 $\pm$ 0.9	7.7 $\pm$ 0.4		S1 vs S3
	Trial 3	5.9 $\pm$ 1.0	6.1 $\pm$ 0.9	7.9 $\pm$ 0.4		S2 vs S3
LFnu	Trial 1	61.9 $\pm$ 19.7	60.2 $\pm$ 22.0	76.6 $\pm$ 6.9	<i>P</i> < 0.001	<i>P</i> < 0.001
	Trial 2	63.3 $\pm$ 15.9	62.7 $\pm$ 16.4	75.2 $\pm$ 5.5		S1 vs S3
	Trial 3	64.6 $\pm$ 14.5	61.1 $\pm$ 16.1	76.8 $\pm$ 6.1		S2 vs S3
HF (ms <sup>2</sup> ) ln	Trial 1	5.4 $\pm$ 1.3	5.7 $\pm$ 1.2	6.7 $\pm$ 0.7	<i>P</i> < 0.001	<i>P</i> < 0.001
	Trial 2	5.3 $\pm$ 1.2	5.6 $\pm$ 1.2	6.6 $\pm$ 0.6		S1 vs S3
	Trial 3	5.2 $\pm$ 1.2	5.5 $\pm$ 1.3	6.6 $\pm$ 0.7		S2 vs S3
HFnu ln	Trial 1	3.5 $\pm$ 0.5	3.5 $\pm$ 0.6	3.1 $\pm$ 0.3	<i>P</i> < 0.001	<i>P</i> < 0.001
	Trial 2	3.5 $\pm$ 0.4	3.5 $\pm$ 0.5	3.2 $\pm$ 0.2		S1 vs S3
	Trial 3	3.5 $\pm$ 0.4	3.6 $\pm$ 0.5	3.1 $\pm$ 0.2		S2 vs S3
LF:HF	Trial 1	2.5 $\pm$ 2.2	2.5 $\pm$ 2.2	3.5 $\pm$ 1.1	<i>P</i> < 0.05	<i>P</i> < 0.01
	Trial 2	2.3 $\pm$ 1.5	2.4 $\pm$ 1.7	3.2 $\pm$ 0.8		S1 vs S3
	Trial 3	2.4 $\pm$ 1.7	2.2 $\pm$ 1.8	3.5 $\pm$ 1.0		S2 vs S3

LF, low frequency spectral power; HF, high frequency spectral power; LF:HF, the ratio of low to high frequency spectral power; ln, natural logarithm; nu, normalised units; <sup>†</sup>Reported *P* value is the outcome of between groups' (settings) two-way rmANOVA; <sup>††</sup>Reported *P* value is the outcome of *post-hoc* t-tests between each group.

### 2.3.3. *Summary of findings.*

Due to the large number of comparisons and the nature of analyses undertaken it was deemed advantageous to produce a ‘checklist summary’ of findings from which the reader may extract information of particular interest as follows:

- 1) HRV 1.1 software and S810 display acceptable to good reliability of short-term HRV when assessed using ICC;
- 2) When assessed by CV, most measures showed unacceptably large inter-individual variation for both the HRV 1.1 software and S810;
- 3) Intra-individual variation was equally unacceptable although was approximately 50% lower in both systems;
- 4) For both systems time domain indices were more reliable than those of the frequency domain;
- 5) Specifically altering the parameter settings within the HRV 1.1 software significantly changed HRV outcomes and the reliability of measures was also significantly affected;
- 6) Reliability of short-term HRV obtained from the HRV 1.1 software and/or S810 compared favourably to that of previous literature;
- 7) The present findings confirm large variations in resting HRV values in healthy adults.

## **2.4. Discussion.**

The 1996 Task Force report stresses that the reliability of new methods to assess HRV should be routinely assessed. In this study, HRV index reliability was therefore evaluated when obtained via the relatively new Polar S810 and via the analysis software for advanced HRV analysis (Niskanen *et al.*, 2004). There are many complementary ways to assess the reliability of a measurement. One method, the intraclass correlation coefficient (ICC), a measure of intra-subject reliability, is often recommended (Atkinson and Nevill, 1998) and commonly used in HRV studies (Carrasco *et al.*, 2003; Lee *et al.*, 2004; Sandercock *et al.*, 2004; Reland *et al.*, 2005). Some, however, suggest it should not be conducted

alone, partly due to its dependency on the heterogeneity of the sample population (Bland and Altman, 1990; Atkinson and Neville, 1998). In keeping with previous literature (Sandercock *et al.*, 2004; Reland *et al.*, 2005) and as suggested (Hopkins, 2000), conventional coefficient of variation (CV) was also calculated. The CV quantifies the variations between two measurements and may be of use from a clinical standpoint.

Another criterion sometimes used for assessing repeatability of HRV parameters is the similarity of the mean of repeated measures (Kamalesh *et al.*, 1995). In the present study the results of the repeated-measures ANOVA used to assess this displayed no instances where parameters demonstrated significant differences, regardless of settings. However, the use of tests of mean difference to assess repeatability has previously been deemed incorrect (Bland and Altman, 1986; Lee *et al.*, 1989). The difference between means does not represent individual subject variation between repeated measures. Where means display no difference, this does not indicate that an individual's measurement will be similar on repeated occasions.

#### 2.4.1. *Reliability assessed by ICC.*

The main findings of the present study were that classical time domain HRV indices calculated by the S810 and the advanced HRV analysis software (regardless of settings), from short RR interval recordings at rest in the supine position, show good reliability. Moreover, acceptable reliability for frequency domain indices was shown.

##### 2.4.1.1. Reasons for varied ICC values.

ICC outcomes tend to suggest that the advanced HRV analysis software and S810 provide acceptable to good reliability for the majority of HRV indices and that time domain are more reliable than frequency domain measures. To explain the lower reliability of frequency indices one can look to the nature of ICC in relation to absolute and normalised values used in this domain. In their discussion on the use of ICC to assess agreement between two methods, Bland

and Altman (1990) highlight the important fact that ICC is dependent on the homogeneity between subjects (or inter-individual variability). When large inter-individual dispersions are present this can often inflate ICC values and vice-versa when small inter-individual dispersion presents. On closer examination of the present study findings, the ICC values for normalised frequency indices can be explained by this observation. For example, compared to LF in absolute units ( $\text{ms}^2$ ), LF in normalised units (LFnu) displays a low ICC value despite low dispersion across the three trials. However, a higher ICC value was confirmed for LF and could be associated with its higher inter-individual dispersion displayed in this variable (Bland and Altman, 1990). Similar findings to the ones presented here have been reported elsewhere (Carrasco *et al.*, 2003; Højgaard *et al.*, 2005). In addition, where differences between means are small and variation is large, the coefficient is improved. Large differences between means, regardless of the size of variation will produce lower coefficients. Closer inspection of the values for some frequency indices obtained from the advanced HRV analysis software and S810 illustrate this well. Between trial differences in HF, in particular between trials 1 – 2 and 1 – 3, are large. Although not statistically significant, the reliability of this index is affected by this difference.

#### 2.4.2. *Reliability assessed by CV.*

The findings for reliability when assessed using CV contrast to the findings when ICC was used to assess reliability. Inter-individual variation was found to be large, with wide variations observed between participants. The large range in between-subject CV highlights the variable nature of HRV even when obtained within a group of apparently healthy individuals displaying so called ‘normal’ HRV.

Although lower values and ranges than those for between-subjects CV was observed, within subject CVs, which represent the repeatability of measures, were also poor and unacceptable (i.e. > 10%) for most HRV indices assessed.

#### 2.4.2.1. Reason for varied CV values.

Variation in measures between participants and from test to retest can be explained, in part, by the findings of a similar study assessing reliability of short-term HRV (Sandercock *et al.*, 2004). In assessing the reliability of three different systems, similarities between instruments in the size of CVs across each HRV index and in various conditions lead the authors to conclude that biological and/or experimental variation were responsible for the observed test-retest variation in CVs. The present study also found similarities in the size of CVs for each HRV measure across each trial as reported by the S810 and the advanced HRV analysis software, lending support to the notion of biological variation within the participants was responsible for the variation of repeated measures CVs observed.

Despite contrasting values for ICC and variable and poor CVs reported in the present study, the data remain comparable with those reported in the literature.

#### *2.4.3. Previous data comparisons.*

In contrasting the present findings to those of previous studies, particular selection of those studies utilising similar participants (e.g. healthy adults) assessed under similar conditions (e.g. supine at rest with free breathing) was made. For a detailed review of the reliability of short-term HRV in various subject cohorts and under various conditions, readers are directed to a comprehensive and scholarly review by Sandercock *et al.* (2005). The overall consensus from the review conducted by Sandercock *et al.* was that when recorded under resting (supine) and controlled conditions, short-term HRV is a moderately reliable measurement.

The review by Sandercock *et al.* included studies published up to 2001. Since 2001, six peer reviewed studies assessing the reliability of short-term HRV indices in healthy adults have been published (Carrasco *et al.*, 2003; Gerritsen *et al.*, 2003; Lee *et al.*, 2004; Sandercock *et al.*, 2004; Højgaard *et al.*, 2005; and Reland *et al.*, 2005). Of these, three utilise both ICC and CV, two rely on CV and one relies solely on ICC to assess reliability.

In the most recent study using ICC and CV to assess the reliability of short-term HRV in post-menopausal women, Reland *et al.* (2005) reported “almost perfect” reliability for time domain and frequency domain indices of HRV when assessed using ICC. For time domain measures, correlation coefficients ranged from  $r$  0.84 – 0.91. For frequency domain, ICCs ranged from  $r$  0.73 – 0.88. These values show a similar trend for greater reliability of time versus frequency domain indices, however, values are somewhat higher than those of the present study, particularly for frequency domain measures. Contrasts for CV estimates are made difficult by the lack of clarity as to whether between- or within-subjects CV were determined by Reland *et al.* Assuming that within-subject CVs were used, Reland *et al.* report better reliability for all HRV indices, with CVs ranging from 4.2% to 6.4% (mean 5.1%) and 5.4% to 31% (mean 16.2%) for time and frequency domain indices respectively.

Values for LFnu, HFnu and LF:HF from S3 were similar between the two studies, however, these measures presented the poorest reliability in Reland *et al.* The authors rightly reported that these variables represent the ratio of at least two absolute HRV indices and thus variability of each absolute component further adds to variability of the ratio. The high CV for LF:HF observed in the present study can be attributed to the same factor. The lower CVs for LFnu and HFnu can also be explained by the dependence of these indices on variation of absolute values for LF and HF. Where a negative change in repeat measures of LF occurred, a corresponding negative change in HF also occurred; and vice versa when a positive change in LF occurred, this was generally accompanied by a positive change in HF. This ensured little change to the ratio of these variables and hence the lower variability of these measures across the three trials.

Interestingly the Reland *et al.* values discussed above were obtained from supine, free breathing conditions and were found to be more reliable than either supine controlled breathing (20 breaths·min<sup>-1</sup>) or standing; thus lending support to the use of these conditions in the present study.

In a thorough examination of the reliability of HRV from 5-minute RR intervals recorded supine at rest as in the present study, Sandercock *et al.* (2004) reported good to excellent reliability of HRV indices obtained from three different

instruments. Mean time and frequency domain ICCs ranging from  $r$  0.79 - 0.92 and  $r$  0.75 - 0.81 respectively across the three instruments indicated a similar finding for better reliability for time domain measures. Higher overall (combined time and frequency domain) ICCs for each instrument (mean ICC range:  $r$  0.77 – 0.85 from three instruments) compared to the advanced HRV analysis software (mean ICC range:  $r$  0.64 – 0.65) and S810 ( $r = 0.65$ ) used in the present study were also apparent. This suggests that the instruments assessed by Sandercock *et al.* (2004) afford more reliable measurement of HRV indices than that of S810 and/or advanced HRV analysis software, regardless of parameter settings.

Reasons for the differences in size of ICC coefficients between the present study and that of Sandercock *et al.* (2004) could be due to differences in the amount of variation between subjects within each study. However, Sandercock *et al.* (2004) do not present the data from which reliability of indices obtained supine were assessed making comparison of subject variation not possible.

When comparing CVs between the two studies, results on the reliability of both time and frequency domain HRV indices agree better. Sandercock *et al.* present almost identical values and patterns in CV for both time and frequency domain indices across all three instruments to those of the present study. Almost mirroring the present findings and regardless of instrument, mean RR, SDNN, LFn<sub>u</sub> and HF<sub>u</sub> displayed the best reliability (values not given - only presented in graphical format) with LF, HF and LF:HF showing poorest reliability. Overall mean values for CVs reported by Sandercock *et al.* were no lower than approximately 40% for any instrument. Comparing to findings from the present study, it would appear that the advanced HRV analysis software (32.1% and 34.6%, S1 and S2 respectively) and the S810 (29.5%) displayed marginally better overall reliability than those of instruments assessed by Sandercock *et al.* (2004). S3 (19.2%) however displayed much greater overall reliability compared to that of any instrument assessed by Sandercock *et al.* The improvement in reliability of HRV indices when assessed using S3 compared to S1 and S2 and reasons for this are discussed as a separate section (2.4.4) within this chapter.

The findings of the present study also show slightly lower reliability of HRV compared to those in a similarly recent study (Lee *et al.*, 2004). In this study, the

authors observed excellent reproducibility for mean RR and SDNN ( $r = 0.86$  and  $0.94$  respectively) measured supine at rest. Frequency domain measures displayed less reproducibility with coefficients ranging from  $r 0.62 - 0.87$ , again in agreement with the present and previous (Reland *et al.*, 2005) findings. In addition and similarly to the present study, when displayed in normalised units, HRV indices were less reliable compared to absolute values; a finding most likely due to the nature of the ICC as already discussed.

A major concern of the findings of Lee *et al.* was that all absolute HRV indices displayed systematic bias. The authors report excellent reproducibility without commenting on the finding that repeated measures were statistically different from each other. Therefore, one could carry out the same test assuming reliable measures of HRV would be obtained although these could be significantly different. Without correcting for this systematic bias between trials, either methodologically or statistically, the findings of Lee *et al.* should be viewed with caution.

This study also highlights the concern of sole reliance on ICC as an indication of reliability. Perhaps the use of an additional statistical analysis test such as CV would have helped to identify where large variations exist. Indeed, when calculated from data of Lee *et al.* the CV for the index LF was poor (32%).

Gerritsen *et al.* (2003) supports the consensus of moderate reliability demonstrated here for mean RR, SDNN, LF and HF in middle/elderly aged men and women (CVs ranging from 8% to 76%). There are, however, some concerns regarding the methodology employed by Gerritsen *et al.* Firstly, no indication as to the time between repeat measures was taken. Whilst it has been shown that short-term HRV is equally reliable when recorded sequentially (Freed *et al.* 1994) and with longer durations between recordings (e.g. 6 months, Sinnreich *et al.* 1998), it would be useful to be able to categorise the findings of Gerritsen *et al.* according to the duration between tests. Secondly, HRV was derived from RR intervals only 3-minutes in duration. No justification as to why the recommended standardised 5-minute period was given, although recordings of  $>2$  minutes should be sufficient to assess both HF and LF indices of HRV (Task Force, 1996).

Perhaps most importantly, Gerritsen *et al.* did not provide details of how incorrect beats were analysed and/or processed (e.g. manually or automatically). Furthermore, whilst authors informed that spectral analysis was carried out, details of the type of spectral method utilised (e.g. FFT or autoregressive modelling) was not given. The authors reported the combined mean outcomes for each index from both test sessions, failing to provide information on the magnitude and the statistical significance of differences between tests. Finally, it appears no attempt to ensure consistency in the time of day that HRV measures took place was made. To their credit the authors acknowledge the possible effects diurnal rhythm may have had on HRV as a result of this. In addition, the authors claim that the data may be of greater value due its representation of typical daily clinical testing as opposed to so called “clean” laboratory studies. The numerous methodological issues present in the study by Gerritsen *et al.* limit their reliability estimates and as a result only tenuous comparisons to the present and previous studies can be made.

One factor relating to not only the studies discussed above but to the majority of HRV reliability studies is that coefficients are calculated over two testing periods (test – retest protocol) compared to three as in the present study. Indeed, Sandercock *et al.* (2005) cite this as one of the potential factors contributing to differences between two previous similar studies (Marks and Lightfoot, 1999; Pitzalis *et al.*, 1996). Indeed, increasing the number of repeated measures can significantly alter the power of a study and the resultant outcomes of reliability coefficients (Vickers, 2003). In light of this, the following section reviews those recent studies assessing reliability of HRV from more than two repeat measures.

Carrasco *et al.* (2003) assessed the reproducibility HRV indices in 11 healthy adults on three separate occasions approximately one day apart. The authors found greater reliability for both time (mean ICC =  $r$  0.88) and frequency (mean ICC =  $r$  0.82) domain indices of HRV than the present study and coefficients were in agreement with studies utilising two repeat measures. Moreover, and similarly to the majority of literature, large coefficient of variations despite good ICC outcomes were also reported (CV range 50% to 160% for frequency domain indices only). These findings were observed in a small cohort of similarly aged

young adults, utilising autoregressive modelling for calculation of spectral indices.

The findings of Carrasco *et al.* do not differ from those of studies utilising only one retest, particularly those where retests took place after one week (Lee *et al.*, 2004; Sandercock *et al.*, 2004; Reland *et al.*, 2005), providing support to previous findings that short-term HRV indices are, on average, moderately reliable. Furthermore, there appears to be little effect of the type of spectral analysis conducted on the outcome of reliability measures and inter-individual variation appears to be similar regardless of age.

Some caution should be exercised with the findings of Carrasco *et al.* CV results are calculated from the pooled data of both repeated measures and those of five different manoeuvres (supine, supine with controlled breathing, standing, exercise and recovery) meaning they do not represent CV of solely HRV indices obtained in the supine position. In addition, logarithmic transformation was applied to all data prior to pooling and subsequent CV calculations. Logarithmic transformations of data represent a problem when assessing reliability because assessment is no longer independent of the unit in which the measurements are made. For example, whether RR intervals are measured in seconds or milliseconds should have no bearing on repeatability outcomes and, indeed, standard deviation and the mean will both differ by a factor of 1000 as will the CV. With logarithmic transformed data, however, standard deviation and mean values will differ, thus, rendering different CVs.

Pitzalis *et al.* (1996) demonstrated a range of ICC values similar to those in the present study. The authors reported coefficients ranging from  $r = 0.29 - 0.77$  which are more akin to the coefficients of the present study (range of  $r = 0.36 - 0.74$ ). As with the present study, coefficients were calculated over three repeated testing periods. However, the variation in duration between repeated trials was much greater than of the present study, with variations of 1 to 265 days. The fact that similar coefficients are reported may suggest that the number of repeat trials *per se* and not the duration between trials has a greater influence on the outcome of ICC and the measure of reliability of HRV measurements.

However, when reliability of HRV indices is assessed using three repeat measures, the available literature proves equivocal as to the effect this has on reliability coefficients compared to when reliability is assessed using only two repeat measures.

One common theme that runs throughout the findings for reliability of short-term HRV indices, both in the present study and those of previous studies, is the large amount of inter-individual (between-subject) variation, particularly for the frequency domain indices. This large variation makes difficult the determination of a 'normal' HRV profile.

Along with recommendations to standardise measurements, the Task Force (1996) also published so called 'normal' values for the commonly used indices of short-term HRV. The values and ranges for normal HRV presented by the Task Force paper were published over 10 years ago and based on only a handful of studies available at that time. Furthermore, adjustments for normal limits for age, sex and environment were not made due again to a lack of data. As a result, these values do not provide a solid foundation to base research and/or clinical findings.

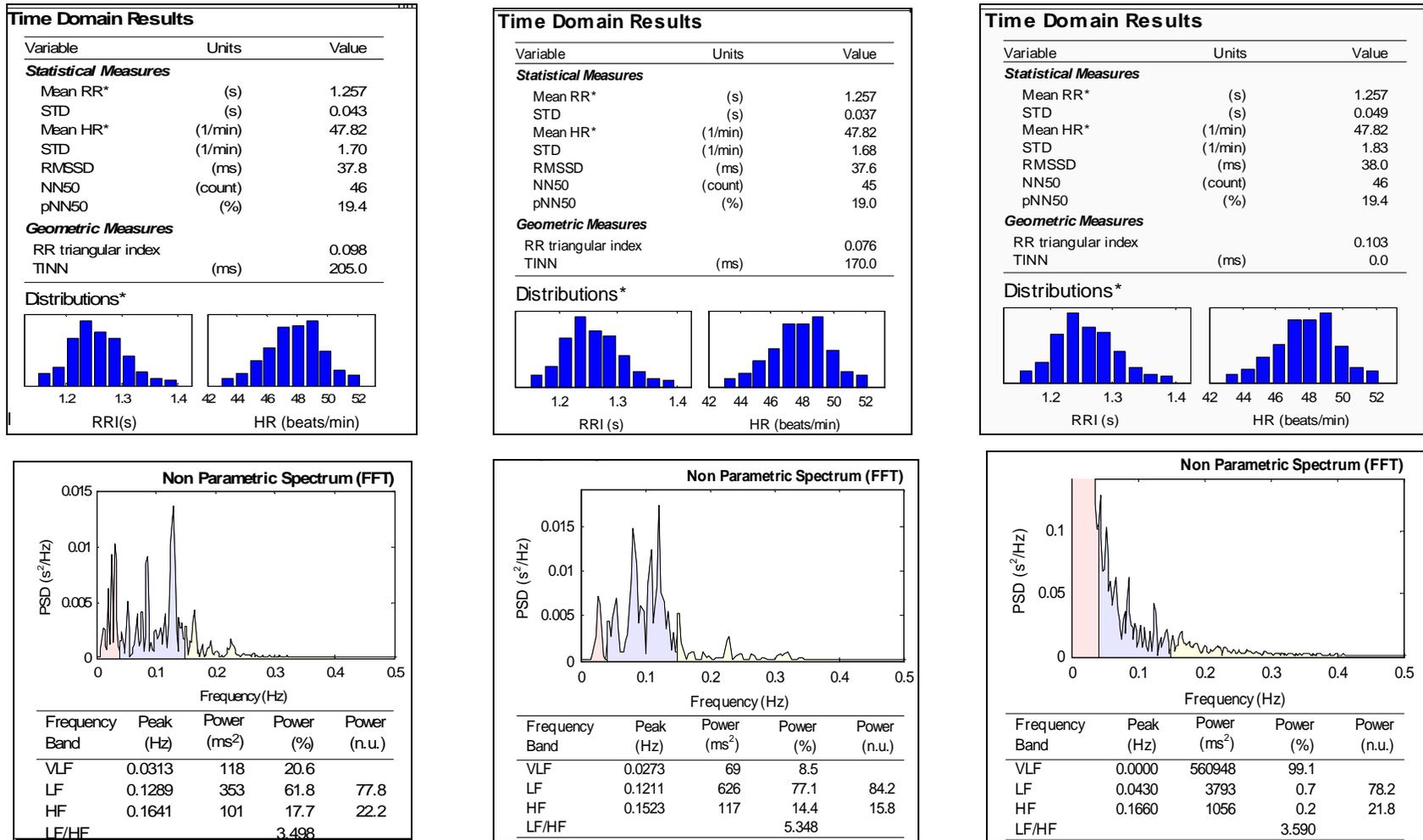
As a result of greater interest in the study and application of HRV, there are now available a significant number of studies assessing HRV in large cohorts of normal populations. Analysis of such studies, perhaps in the form of meta-analysis or weighted means analysis, could present more accurate and comprehensive values and ranges for commonly used short-term HRV indices. The identification of the range of normal values will be of significant benefit to those involved in the study and application of HRV, particularly when drawing comparisons between healthy and clinically based populations.

#### 2.4.4. *Comparison of heart rate variability with differing advanced HRV analysis software parameter settings.*

In order to assess the effect of altering the parameter settings of the advanced HRV analysis software on subsequent HRV index outcomes, differences between

HRV obtained from three different settings were analysed (S1, S2 and S3; see method section for detailed description of the different settings assessed). When the detrend option was deselected (S3 - see Table 2-5) there was a significant difference in SDNN and all frequency domain indices of HRV compared to when a smoothness priors detrend was applied (S1 and S2). Figure 2-6 provides a graphical illustration of the effect of altering parameter settings for one individual participant trial. The important point to illustrate is the substantial increase in the amount of power in the VLF band with S3 as a result of there being no detrend to account for this. These individual findings were observed for mean data (Figures 2-2 – 2-6). As a result of the removal of a detrend, the overall mean value for frequency domain indices increased. The increase in mean values was greater than that of the standard deviation, thus explaining the lower CV and hence the greater reliability.

Figure 2-6. Values for time domain (upper panels), power spectrum and frequency domain (lower panels) measures as presented in the HRV1.1. Values obtained using settings 1 (left panel), settings 2 (middle panel) and settings 3 (right panel) respectively.



VLF: very low frequency power, LF: low frequency power, HF: high frequency power: LF:HF: the ratio of LF power to HF power.

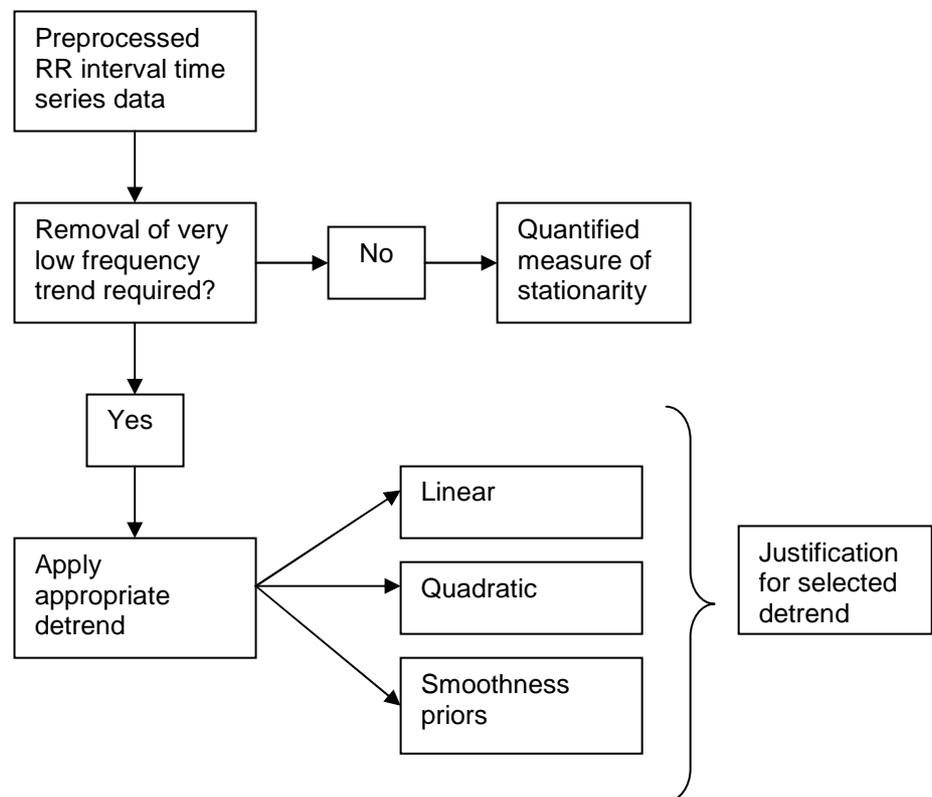
Clearly then, applying a smoothness priors detrend within the HRV 1.1 can alter HRV outcomes significantly, particularly those of the frequency domain. These findings do not support the developers claim that applying this detrend does not significantly affect higher frequency measures (Niskanen *et al.*, 2004).

The developers provide an example of application of the smoothness priors detrend that shows little or no effect on the LF and HF components whilst successfully removing the VLF component. However, details of the conditions (i.e. data types) pertaining to the use of one particular trend over another are not given making comparison to the present findings difficult. Differences between studies may have resulted from adoption of differing interpolation rates, alpha adjustment values or prior RR interval screening and illustrates a need for clarity in detailing the parameter settings used to derive HRV in order to facilitate comparisons between studies. The authors, to their credit, emphasize that when using a detrend method users should ensure detrending does not cause a loss of any useful information from the frequency components of interest (e.g. LF, HF or both).

The finding that altering parameters within the advanced HRV analysis software affects HRV outcomes is not surprising and is well documented in the original Niskanen *et al.* (2004) paper. The present study highlights the difficulty in selecting the appropriate parameter settings for the calculation of HRV and the importance of ensuring that supporting information on the use of the software is both accurate and sufficient. Also highlighted is the need for future studies utilising this and/or similar software to detail the nature of any detrending applied to RR interval data and provide justifications for the decision(s) made. Where this is not possible, the use of some other quantifiable index of stationarity within the RR interval time series should be provided. Examples of such quantification of stationarity are provided in the studies of Lee *et al.* (2004) and Carrasco *et al.* (2003). Figure 2-7 suggests a systematic approach to the analysis of short-term RR interval data that should be adopted by future studies using the advanced HRV analysis software to obtain HRV.

Finally, for studies using this software to derive and assess indices of HRV from more than one assessment, users should be aware that altering the parameter settings to account for anomalies in RR interval series data can significantly alter the outcome and, perhaps more importantly, the reliability of HRV outcomes.

With this in mind, however, and when utilising RR intervals recorded from the S810, the advanced HRV analysis software does provide moderate to good reliability of HRV indices when assessed over three repeat trials. These findings are in agreement with those of the majority of studies assessing short-term HRV using similar protocols.



**Figure 2-7. A suggested outline for selecting and presenting appropriate detrend and stationarity procedures to RR interval time series data.**

#### 2.4.5. Study limitations.

Components known to contribute to HRV are not all physical in nature but include emotional and psychological factors. Stress, sleep levels, mental activity and arousal state are all known to contribute to the overall level of HRV (Parati

and DiRienzo, 2003). Closer assessment of some of these variables may have provided additional explanation for large variations expressed in the present study.

Some environmental conditions that could not be strictly controlled within our laboratory may also have had some effect on resulting outcomes, particularly the variation between trials. For example, due to a technical failure with air circulation facilities, the ambient temperature differed for some individuals between trials. Thermoregulation processes are known to affect HRV, with particularly contribution to oscillations of HR below 0.003 Hz (Task Force, 1996; Strauss, 2003). Body temperature was not assessed in the present study, however the observed variation in HRV outcomes due to thermoregulation in participants affected by altered ambient temperature conditions cannot be ruled out. Moreover, although only an infrequent issue, it was not possible to control and/or maintain the noise level outside of the laboratory where testing took place. Noise conditions of each trial may therefore have differed slightly and this may have contributed to the observed variation.

These confounding environmental issues were recognised and all possible action was taken to limit their potential impact (e.g. fans were used to improve air circulation, rescheduling of tests if too warm/noisy).

There is some evidence that, in female participants, the phase of menstruation should be considered when assessing HRV outcomes (Yildirim *et al.*, 2002). This factor was not accounted for in the present study. However, in none of the studies involving female subjects was the phase of menstrual cycle accounted and this perhaps illustrates the difficulty in doing so, particularly in a clinical setting.

There is no standard that qualitatively defines the results of repeatability statistics; for example, no consensus exists about the meaning of  $r = 0.5$  for ICC. This gives rise to inconsistency in the interpretation of the clinical significance of any given ICC. Several interpretations are presented in the literature. For example, an ICC of at least 0.7 is referred to in one paper (Chaudhuri *et al.*, 2002) as desirable to demonstrate reasonable repeatability whereas for others an ICC of  $< 0.6$  is considered indicative of low repeatability (Piepoli *et al.*, 1996). Greater ambiguity exists where authors have attempted to sub classify the

meaning of values for ICC. For example, an ICC of  $r < 0.4$ ,  $r = 0.4 - 0.75$ , and  $r > 0.75$  is interpreted in one paper as indicative of poor, fair to good, and good to excellent repeatability respectively (Fleiss, 1986). Others have used further sub classifications of ICC values as follows: ICC  $> 0.20$  indicates poor; 0.21–0.40 fair; 0.41–0.60 moderate; 0.61–0.80 good; and 0.81–1.00 excellent repeatability respectively (Pinnington *et al.*, 2004).

The present study utilised the interpretation of ICC as described by Fleiss based on its use in previous studies similarly assessing the reliability of short-term HRV (Lee *et al.*, 2004; Reland *et al.*, 2005). However, awareness of the fact that these interpretations are open to criticism is important and hence its inclusion here.

## **2.5. Recommendations.**

The Task Force published recommendations for the collection of short-term RR interval time series data and subsequent HRV determination in an effort to standardise procedures and allow for easier comparisons amongst studies. It is recommended that studies try to adhere to these standards as differences in methodologies employed between studies make it difficult to compare and contrast findings.

Future studies assessing the reliability of HRV can provide statistical justification for the number of repeat trials selected (Vickers, 2003) and researchers would be encouraged to do so.

More specifically to the advanced HRV analysis software developed by Niskanen *et al.*; it is recommended that studies utilising the measurement of HRV obtained using the programme provide details and appropriate justifications of any trend removal methods employed. In addition, if the outcomes of HRV are to be assessed on more than one occasion (e.g. reliability or treatment studies), users should ensure the same parameter settings are maintained throughout.

Reliability of HRV has shown to differ in clinical, patient populations including sufferers of diabetes (Zieglar *et al.*, 1999), chronic heart failure (Ponikowski *et al.*, 1996) and heart transplant recipients (Lord *et al.*, 2001). Studies assessing the reliability of HRV derived using the advanced HRV analysis software and/or S810 in clinical populations are needed to validate their use in such populations.

## **2.6. Conclusions.**

Overall, the present study findings indicate that short-term HRV in healthy adults at rest and in the supine position, derived from RR intervals recorded using the Polar S810 and subsequently analysed by Polar and/or advanced HRV analysis software programmes show moderate to good reliability for most measures of HRV when assessed by ICC. Moreover, the present study found time domain indices of HRV to be more reliable than those of the frequency domain and this is in accordance with more recent studies assessing the reliability of short-term HRV under similar conditions. Reported coefficients for frequency domain indices were somewhat lower than those presented in the literature, possibly due to larger inter-subject variations observed in the present study. When assessed by CV the present study found inter-individual variation of HRV indices to be poor from both advanced HRV analysis software and S810 and this was in agreement with the available literature. By comparison, intra-individual variation between tests was more reliable and showed greater reliability than the majority of previous studies.

The reliability of HRV measurements from the advanced HRV analysis software are altered with different parameter settings. Studies should, therefore, indicate and justify parameter settings used.

Wide variation in the resting indices of HRV in healthy adult populations presented both in this and previous studies warrant the identification of the range of so called 'normal' HRV.

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### **CHAPTER 3. AGREEMENT BETWEEN NOVEL TELEMETRIC AND LABORATORY BASED SYSTEMS IN THE MEASUREMENT OF HEART RATE VARIABILITY.**

#### **Abstract.**

The use of the Polar S810 heart rate monitor (S810) to obtain HRV has been validated in only two studies. These studies actually assessed the ability of the S810 to record and process RR intervals. The validity of HRV values obtained by S810 software *per se* has yet to be assessed. The aim of the present study was to assess the agreement of short-term HRV measures obtained using the S810 and accompanying software with those from an established method (Cardioperfect (CP)).

Thirty three participants (19 males) (median age 36, range 20-63) underwent simultaneous, 5-min, supine RR interval recordings. Each RR interval time series was analysed using the software supplied with the recording equipment. Two comparisons were then made. First, a comparison of RR interval data recording and editing only was made. Second, comparisons were made for measures of HRV derived from edited RR interval data. Agreement between RR intervals and standard HRV measures were assessed using intraclass correlation coefficient and limits of agreement.

Agreement of HRV measures derived from RR intervals recorded and edited by the S810 and CP was not acceptable indicating that these methods should not be used interchangeably for the assessment of HRV. Agreement analyses for the number of RR intervals recorded and edited by the two system's software showed excellent intraclass correlation coefficients (ICC lower 95% confidence interval  $> 0.75$ ) and acceptably narrow limits of agreement (LoA). These data indicate that the number of RR intervals recorded by S810 can agree well with those recorded from a standard 12-lead ECG. This is true even after application of system specific data editing procedures. Commercial RR interval recorders may offer a simple, inexpensive alternative to full 12-lead ECG in the recording and editing of RR intervals for subsequent HRV analysis in healthy populations.

**This chapter, in truncated form has been published in the European Journal of Applied Physiology ( see appendix III).**

### **3.1. Introduction.**

Differences in the observed value and true value of a measure can be due to measurement error. Some understanding of measurement error is therefore important for those taking or using measurements. Suggested important aspects of measurement error include concurrent validity (Hopkins, 2000). Concurrent validity concerns agreement between the observed value and the true or criterion value of a measure. Throughout this chapter references to validity will be made in the context of this definition.

In chapter two, the reliability of short-term, resting supine heart rate variability (HRV) obtained by the Polar S810 heart rate monitor (S810) was assessed and revealed the S810 to show considerable promise for HRV studies, primarily due its ease-of-use and affordability. The study in chapter two was conducted due to a lack of data pertaining to the reliability of HRV obtained from S810. It was found the S810 displayed moderate to good reliability of HRV measures, and this was in agreement with other similar devices assessed in the literature (Sandercock *et al.*, 2004a). The importance of reliability to the validity of a measurement was discussed and the fact that a measure cannot be valid if it is not reliable, yet it can be reliable and not display validity was stressed. This has important implications for the findings observed in chapter two as although the S810 has been shown to display moderate to good, and in some cases excellent reliability, whether or not the values obtained are valid remains questionable.

In addition, as newer technologies and systems for the assessment of short-term HRV are introduced to the market, and in order to ensure comparability across laboratories making use of such methods, it is important to quantify the agreement between the systems being used. Indeed, independent assessment of new technologies is required to ensure validity of measures (Task Force, 1996).

With reference to the S810, it appears that only two studies exist specifically assessing the validity of RR interval data obtained from short-term recordings by the S810. Kingsley *et al.* (2005) compared RR intervals and heart rate obtained at rest and during exercise using the S810 in comparison to a non-ambulatory

(ECG) method and found good agreement between the two devices for resting and low activity conditions. The authors also reported similar findings for spectral HRV indices at rest.

In a more recent study and due to a lack of data as to the (in their own words) “accuracy” of S810 in the position, Gamelin *et al.* (2006) investigated the validity of the S810 to measure RR intervals in the supine position. The authors reported significant, but “meaningless” differences in RR interval time recorded by the S810 in comparison to a two-lead ECG method. They also found no differences in the values for HRV obtained from the two RR interval signals and concluded that the S810 is a valid tool for the measurement of RR interval and subsequent HRV.

There are, however, concerns over potentially misleading conclusions presented by both Kingsley *et al.* (2005) and Gamelin *et al.* (2006). These concerns pertain to the exact nature of the methodologies used by both studies and the resulting outcomes produced as a result.

Prior to discussing the concerns with Kingsley *et al.* and Gamelin *et al.* a brief description of the S810 HRV analysis system is required to provide background for the following argument. The S810 system at its most basic includes a chest belt (transmitter), a wrist watch receiver and software package. The wrist receiver displays and records heart rate and or RR intervals received from the chest strap. Data is stored in the watch and is then downloaded to PC via the software package (Polar Precision Software, Polar OY, Kempele, Finland). Within the software, data are viewed in the software window. In the case of RR intervals, two avenues for data evaluation are available at this point:

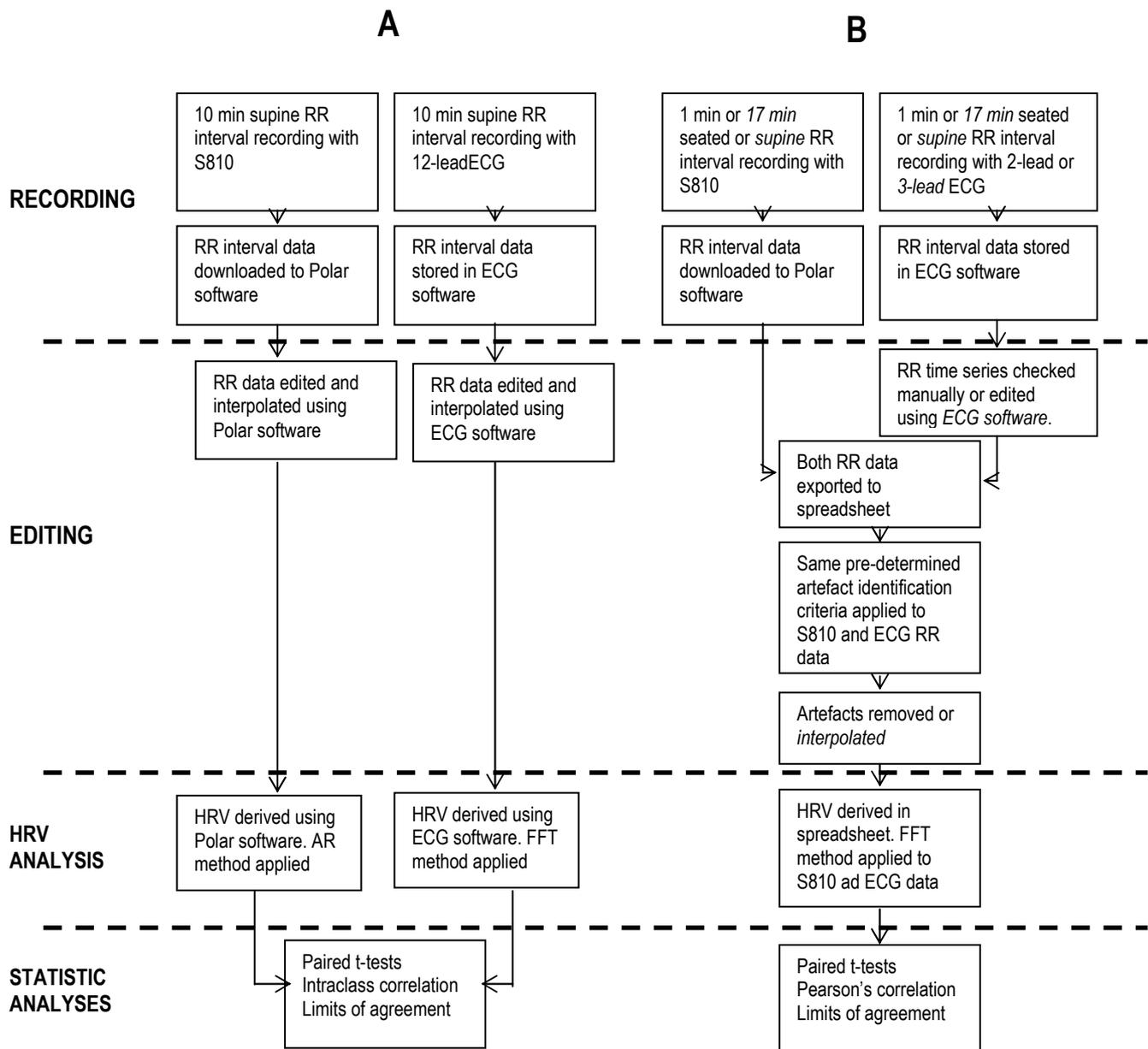
- 1) RR data can be exported from the software as an ASCII file and imported into a suitable, separate spreadsheet package for subsequent HRV analysis.
- 2) RR data viewed in the software window can be selected in its entirety or a segment of the RR time series (e.g. 5-min) can be selected and HRV values are obtained by the software.

The key differences between (1) and (2) above are that whereas in both cases RR data are downloaded to the same Polar software, in (1) the RR interval data (or a

segment thereof) are exported from the Polar software to a separate spreadsheet and analysed for artefact and/or corrected using pre-determined criteria (i.e. a difference of >200ms between adjacent RR intervals is considered artefact). HRV is then obtained using either fast Fourier transformation (FFT) or autoregressive (AR) techniques. In (2), however, data are corrected for noise using the filter feature of the software then a selection (or the whole record) of RR data are analysed for variability using the Polar software itself. The Polar software automatically uses the AR method in the spectral analysis of RR data.

Referring back to the studies of Kingsley *et al.* and Gamelin *et al.*, both these studies have utilised a method analogous to pathway (1) above. By using the selected methodology, HRV analysis was conducted on S810 and ECG RR data with artefacts removed (e.g. in Kingsley *et al.*) or edited using separate criteria (e.g. in Gamelin *et al.*). Corrected S810 and ECG RR data were then analysed using the same spectral analysis technique. In both studies FFT was used. Such a method only assesses the ability of the S810 to record and process RR interval data compared to that of an alternate ECG based system. Neither the study of Kingsley *et al.* (2005) nor Gamelin *et al.* (2006) therefore assessed the validity of the S810 system as a whole (S810 + Polar analysis software).

It is apparent that there is a paucity of data with which to accurately assess the ability of both the Polar S810 system *per se* to determine HRV from RR intervals obtained by the S810. This study proposes to determine the validity of both these methods to determine HRV. The proposed method differs from previous studies assessing the S810 in that HRV will be determined using software specific to the device and the resulting outcomes will be compared with outcomes from a criterion ECG method with established validity and reliability (see Figure 3-1).



**Figure 3-1. Procedures adopted by the present study (A) and those adopted by Kingsley *et al.* (2005) and Gamelin *et al.* (2006) (B) for the recording, editing and analysis of S810 and ECG RR interval data. Italicised words are representative of procedures carried out by Gamelin *et al.* (2006).**

### 3.2. Methods.

#### 3.2.1. Participants.

Thirty three volunteers, 19 males with a median age 34 (range 20 - 59) and 14 females with median age 47.5 (range 25 - 63), were included in the study. The

*mean  $\pm$ SD height and mass for all participants was  $1.73 \pm 0.11$  m and  $74.6 \pm 15.6$  kg. All participants were healthy, defined as being free from illness at the time of testing. None were known to be taking any medication or have any cardiovascular problems that may have influenced the procedures carried out. All procedures were approved by the Ethics Committee of the appropriate university faculty. Informed consent was provided by each participant prior to commencing the experimental procedures.*

### *3.2.2. Instrumentation and data acquisition.*

RR intervals were recorded simultaneously via the CardioPerfect (CP) software (Cardio Control, Delft, The Netherlands) within the Medical Graphics Cardio<sub>2</sub> stress system (Medical Graphics Corporation, St Paul, Minnesota, USA) and a Polar S810 HRM (Polar Electro OY, Kempele, Finland). The CP uses a 12-lead ECG configuration and the S810 consists of a chest strap transmitter plus wrist watch receiver. The CP system was chosen as the criterion measure of HRV as its precision of measurement and reliability has been established (Sandercock et al. 2004a, 2004b). Both CP and S810 were set to record with the same sampling frequency of 1000 Hz, providing a temporal resolution of 1ms for each RR period (Cottin et al. 2004).

The sampling time for CP recordings was set at 300 s and the digitised signal was stored on the hard drive of a PC (Dell Precision 340, Dell Computers, Texas, USA). The RR interval data from CP recordings were edited and subsequently analysed for variability using the automated editing and HRV features of the CP software. The S810 recorded continuously for the duration of the CP recordings. S810 RR interval recordings were transferred to a password protected PC via the Polar Precision Performance 4.03 software. The Polar Precision software was used for both editing and HRV analysis of S810 RR interval recordings.

### *3.2.3. Experimental design.*

*Participants reported to the laboratory on three occasions. The mean period between the first and third experimental day was  $13 \pm 8$  days. Due to the*

*observation that circadian rhythm can significantly influence HRV measures (Lord et al., 2001; Singh et al., 2003), attempts were made to ensure participants reported at similar times on each visit. In accordance with current data capture guidelines of RR interval data for HRV analysis, participants were asked to refrain from eating and smoking two hours prior to testing. Where testing took place in the morning, participants were instructed to eat a light breakfast at least two hours prior to testing. Participants were also asked to abstain from caffeine and alcohol containing foods and beverages on test days, and to avoid heavy physical exertion and alcohol consumption during the 48 hours preceding test days. Where participants failed to meet the protocol requirements an assessment was made on the potential impact of their behaviour on HRV measures and where necessary the test was rescheduled.*

On each occasion (trial) participants underwent two simultaneous RR interval recordings. The reason for the simultaneous use of the two HRV systems was to ensure ECG and S810 signals were synchronised (recording the same intervals) to enable valid analysis of the agreement between the two analysis systems. Preparation for recordings included the cleaning and preparation of the skin for the attachment of surface electrodes (Blue Sensor Medicotest, Olstykke, Denmark). Electrodes were placed in the standard configuration for 12-lead ECG and the leads from the CP module were attached accordingly. *The S810 chest strap (transmitter) was fitted in accordance with manufacturer's instructions. The S810 receiver (watch) was then placed on the participant's wrist and heart rate (HR) checked by depressing the red start button on the S810 watch. Participants next lay on a bed with the head supported by a pillow in a quiet laboratory under thermoneutral conditions. Participants were asked to relax and the researcher monitored their HR visually for two or three minutes until it became stable. Two 5-min ECG and one ~10-min S810 recording were then made simultaneously. Both pieces of equipment were synchronously started by two researchers. At the end of the first ECG recording participants were instructed to remain in the same position. The S810 signal was synchronised with the end of the ECG recording by marking the S810 using the available temporal "event" (lap) marker. The first ECG recording was then saved to the hard drive of the PC. During this time the S810 was still recording. When saving of the first*

ECG was completed (~30-secs), a second ECG recording was then performed. The start and end of the second ECG was marked on the S810 using the synchronisation procedure. This procedure provided S810 recordings of approximately 10 minutes and 30 seconds.

#### 3.2.4. *Raw cardiac data processing.*

Raw RR intervals from both acquisition systems were edited and compared to discriminate error caused by the S810 acquisition or by non-sinus beats. Non-sinus beats were replaced by interpolated data derived from adjacent normal RR intervals via the methods described below.

The CP was set to sample RR intervals from 300 seconds of ECG recording. Editing of the raw RR interval data was carried out using a default automated threshold-detection algorithm. The software rejected abnormal intervals, defined as an interval which differed by more than 20% from the previous interval. Following abnormal interval removal, the system linearly interpolated abnormal intervals with an interval based on preceding intervals. HRV analysis was performed on the corrected data file of normal-to-normal (NN) RR intervals. The RR data were then passed through a Hanning type window to remove baseline trend.

*The Polar software contains an automatic RR interval filtering and interpolation algorithm. Prior to extraction of any segments the entire time series was error corrected using a moderate filter power set at a minimum beat protection zone of six beats·min<sup>-1</sup>. The effects of this interpolation method on spectral measures of HRV obtained from stationary tachograms where <15% of beats are rejected are only minor (Jurca et al., 2004) A more comprehensive description of the beat filtering and interpolation algorithms is available (Huikuri et al., 1996). Following abnormal interval removal, the S810 algorithm substitute's detected errors with interpolated intervals (usually two to four intervals) calculated from differences between previous and subsequent accepted RR intervals. After filtering and correcting, 10-min RR interval time series (corresponding to each of the ECG recordings) were stored on the hard drive of a password protected computer for later HRV analysis using Polar S810 specific software.*

### 3.2.5. *Heart rate variability analysis.*

Following abnormal interval removal, both the CP and Polar software linearly interpolated removed intervals using system specific algorithms. Standard time and frequency domain measures of HRV were then derived from the normal-to-normal (NN) CP and S810 interval data within the software programme for each system. In accordance with current recommendations (Task Force, 1996) only the standard deviation of NN intervals (SDNN) and the root mean square of successive differences (rMSSD) were derived from time domain analysis. Mean RR interval was also obtained as a further index of cardiac autonomic control (Pinna *et al.*, 2007).

By default the CP and S810 software use fast Fourier transformation (FFT) and autoregressive (AR) methods respectively to derive frequency domain HRV measures from the RR interval time series. In accordance with Task Force recommendations, the power spectrum for frequency domain HRV analysis was divided into the following bands for all three systems: VLF (very low frequency; 0.0033-0.04 Hz), LF (low frequency; 0.04-0.15 Hz) and HF (high frequency; 0.15-0.40 Hz). Only LF, HF in absolute and normalised (LFnu, HFnu) units and LF:HF ratio were assessed for agreement.

### 3.2.6. *Statistical Analysis.*

*All statistical analysis was carried out using SPSS version 13.0 (SPSS inc. Chicago, Illinois, USA). Prior to statistical analysis, data were checked for univariate and multivariate outliers using standard Z-distribution cut-offs of  $\pm 3.29$  and Mahalanobis distance tests respectively. Where outliers were found, the corresponding data were corrected and/or noted accordingly. Where data sets were found to contain large numbers of outliers logarithmic transformation ( $\ln$ ) was applied. The normality of data sets was then assessed using a Kolmogorov-Smirnov test. Homogeneity of variance was assessed by doubling the smallest variance within the data set. When this value exceeded the value for the largest variance in the data set, the assumption of homogeneity was violated. Where*

*assumptions for parametric testing were not met this was noted prior to conducted statistical testing.*

To assess differences in RR count between the S810 and CP systems, repeat measures ANOVA were performed. The number of RR intervals recorded by the two systems was assessed for agreement by intraclass correlation coefficient (ICC) with 95% CI. An ICC of  $> 0.80$  is commonly considered as indicating good to excellent agreement and ICCs between 0.60 and 0.80 are taken to represent substantial agreement (Pinna *et al.*, 2007). However, agreement sufficient for the interchangeable use of two methods is suggested only when a lower 95% CI value of  $> 0.75$  is observed (Lee *et al.*, 1989; Sandercock *et al.*, 2004b).

Bland and Altman, (1986) query the use of a single number to summarise agreement and suggest the calculation of 95% CI based on the mean of differences between two methods in addition to the ICC. Plots of average values from both systems versus differences between systems and subsequent limits of agreement (LoA) are recommended. Therefore 95% LoAs were calculated for RR intervals recorded and edited by the S810 and CP systems. The recently described approach by Bland and Altman (2007) was adopted for LoA analysis due to the multiple observations per individual in the present study.

Repeat measures ANOVAs were carried out on all HRV measures to assess systematic bias between the two systems (Bland and Altman, 1986, 1990; Hopkins, 2000). As with the number of RR intervals, agreement between measures of HRV derived by the two systems was assessed using ICC and LoA.

For LoA analysis of log-transformed data, dimensionless ratios were calculated by taking the antilog of the mean of differences and 95% LoA (Bland and Altman, 1986). Outcomes of transformed data are presented and described separately to those of non-transformed data as recommended (Mortensen *et al.*, 2002).

### **3.3. Results.**

#### *3.3.1. Non-transformed data.*

A technical failure with the CP excluded the first trial data of two participants, the second trial data of one participant and the third trial data of eight participants. As a result, data from all three trials were only available for 23 participants. Data from two trials were obtained for nine participants and for one participant data were only available from one trial. Statistical outliers were found for the measures LF and HF. These values, however, were not removed as they were apparent in both systems and were also within the range of reported values for these measures.

There were no differences in the number of RR intervals recorded by the S810 in comparison to the CP for any trial (Table 3-1). There was agreement sufficient to allow interchangeable use of the two systems in the recording and editing of RR intervals, with an average ICC of 0.97 and a lower bound CI > 0.75 across all three trials. 95% LoA revealed the number of RR intervals returned by the S810 following editing is between 22 less than and 25 more than CP, with the S810 returning on average one more RR interval than that of the CP (Table 3-2).

There were no significant differences between values for non-transformed measures of HRV. All four measures showed excellent levels of agreement when assessed by ICC (Table 3-1) but only mean RR interval displayed sufficient agreement across all three trials to allow each system to be used interchangeably (lower 95% CI > 0.75). However, analysis by LoA revealed that mean RR, LFnu, HFnu and LF:HF displayed unacceptable agreement between systems (Table 3-2).

#### *3.3.2. Log-transformed data.*

All measures of HRV except mean RR interval time, LFnu, HFnu and LF:HF showed a marked right-skewed distribution (Kolmogorov-Smirnov test:  $p < 0.05$ ). Subsequent log-transformation of skewed measures provided normality and homoscedasticity (Figures 3-2 and 3-3). Descriptive statistics for log-

transformed HRV measures and their agreement as assessed by ICC are reported in Table 3-3.

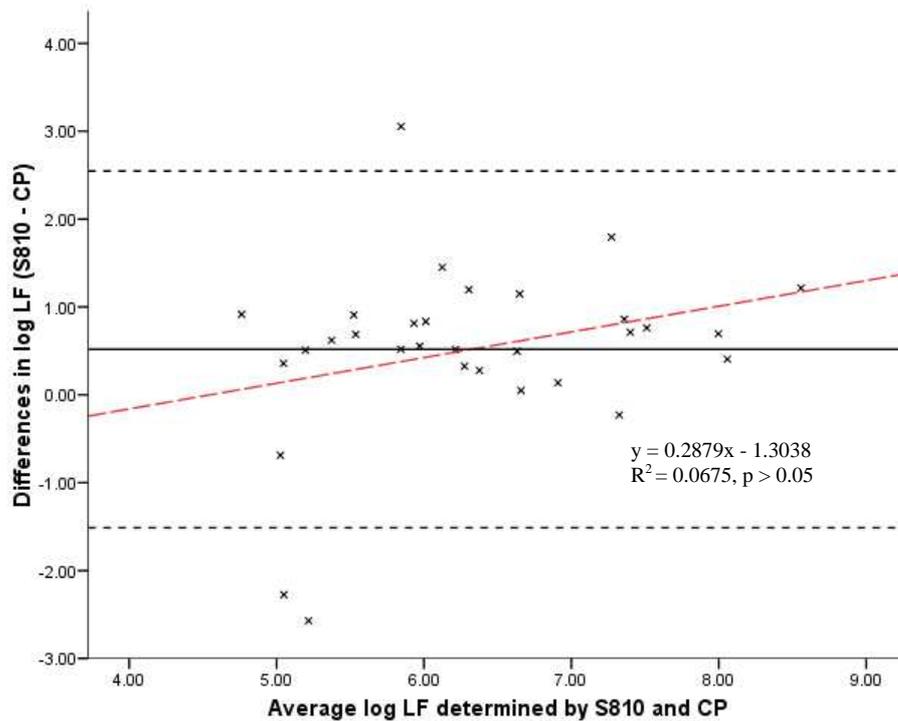
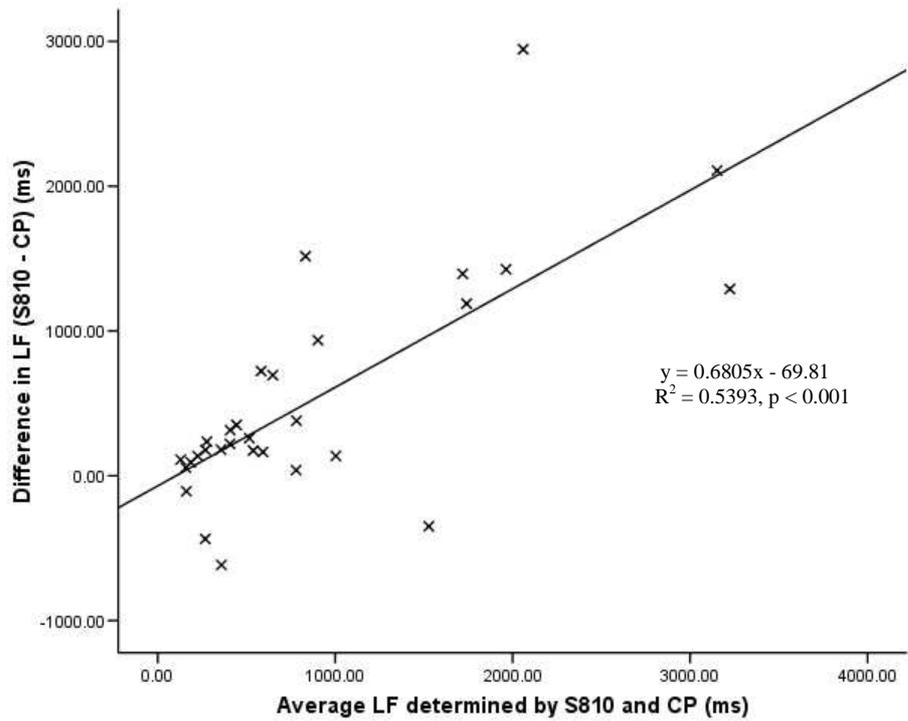
There was no systematic bias between the two systems for log-transformed measures of HRV. Analysis by ICC showed excellent and interchangeable agreement for SDNN and rMSSD across all three trials and for LF trial three and HF trial two (Table 3-3). Good to excellent but not interchangeable agreement was found for LF and HF in their other two trials.

LoA analysis for heteroscedastic HRV measures are reported in Table 3-4. Since statistical analysis of these variables was carried out following log-transformation, the bias and 95% LoA are expressed in log units. To relate these data to the original scale of measurement, antilogarithmic transformation provides dimensionless ratios where a ratio of one is equal to zero. Measurement values from the S810 system can be as small/large as about 0.3/4.4 times those of the CP; with S810 measures averaging 1 to 1.2 times those of the CP.

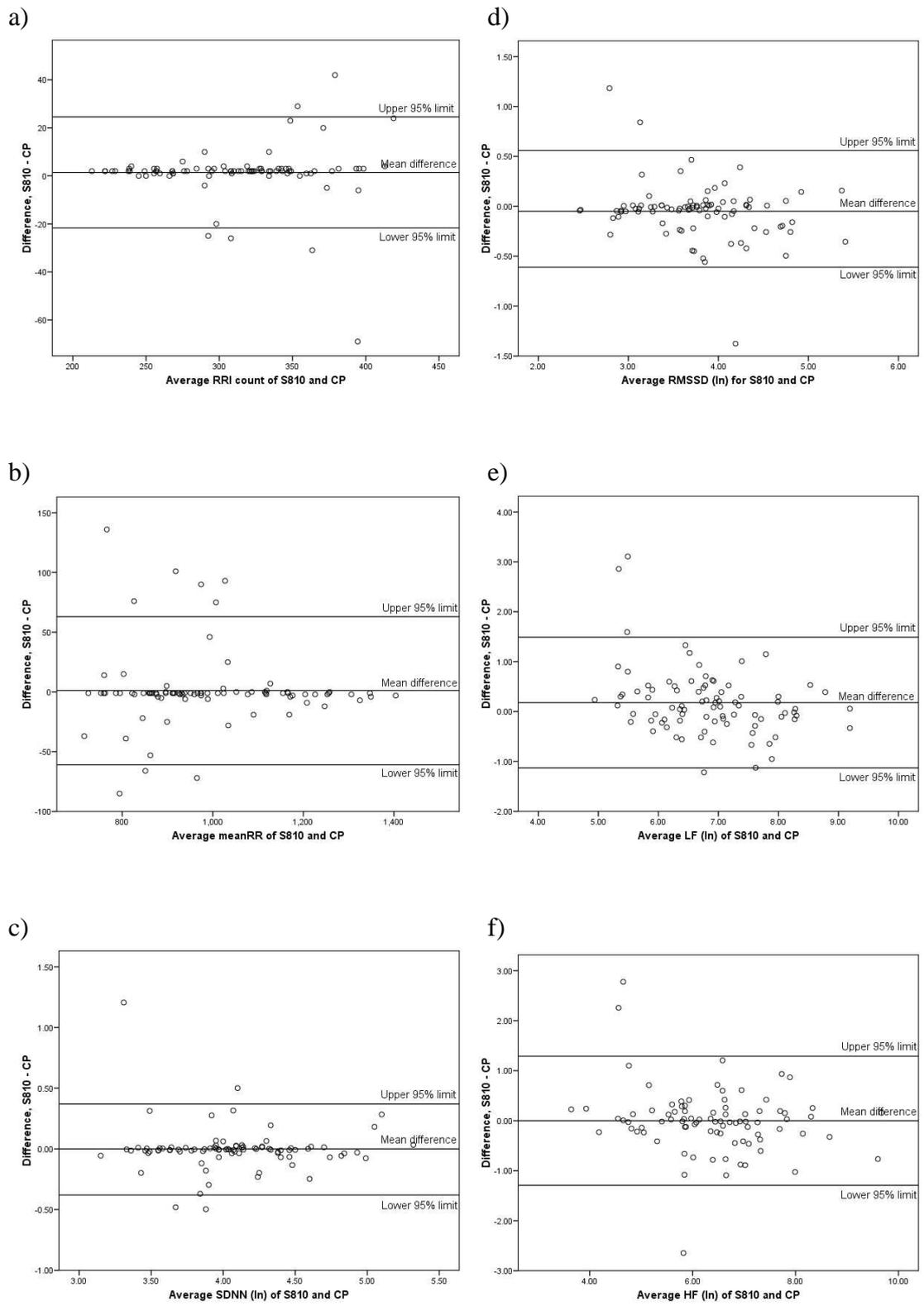
**Table 3-1. Descriptive results and agreement outcomes from analysis by intraclass correlation coefficient for homoscedastic heart rate variability measures obtained by the S810 and CP.**

		S810	CP	<i>P</i> value*	ICC (95% CI)	Interchangeable agreement
RR count	Trial 1	316 ± 54	314 ± 53	0.99	0.98 (0.95 – 0.99)	Yes
	Trial 2	320 ± 53	319 ± 55		0.96 (0.92 – 0.98)	Yes
	Trial 3	299 ± 40	298 ± 39		0.98 (0.97 – 0.99)	Yes
mRR (ms)	Trial 1	980.6 ± 178.6	979.4 ± 176.9	0.99	0.99 (0.98 – 0.99)	Yes
	Trial 2	970.3 ± 167.9	964.7 ± 172.6		0.98 (0.95 – 0.99)	Yes
	Trial 3	1021.8 ± 140.9	1026.3 ± 136.8		0.98 (0.96 – 0.99)	Yes
LF (nu)	Trial 1	62.5 ± 14.5	59.0 ± 17.8	0.59	0.75 (0.54 – 0.87)	No
	Trial 2	62.9 ± 14.5	58.5 ± 18.6		0.73 (0.51 – 0.86)	No
	Trial 3	62.2 ± 16.0	61.3 ± 16.3		0.70 (0.44 – 0.87)	No
HF (nu)	Trial 1	37.5 ± 14.5	41.3 ± 17.7	0.43	0.72 (0.51 – 0.86)	No
	Trial 2	37.1 ± 14.5	42.1 ± 18.7		0.71 (0.48 – 0.85)	No
	Trial 3	37.8 ± 16.0	38.2 ± 15.9		0.74 (0.49 – 0.87)	No
LF:HF	Trial 1	2.2 ± 1.9	2.1 ± 2.1	0.72	0.90 (0.81 – 0.95)	Yes
	Trial 2	2.2 ± 1.5	2.1 ± 1.9		0.87 (0.76 – 0.94)	Yes
	Trial 3	2.1 ± 1.3	2.3 ± 1.9		0.54 (0.19 – 0.76)	No

Data represent the mean ± SD; RR count, number of RR interval data points recorded; mRR, mean time between normal r-waves; LF, low frequency spectral power; HF, high frequency spectral power; LF:HF, the ratio of low to high frequency spectral power; nu, normalised units; \**P* value outcomes from repeated measures ANOVA for group effect; ICC, intraclass correlation coefficient; CI, confidence interval.



**Figure 3-2. Absolute differences in trial 1 LF measured by the Polar S810 and CP against the mean value from both systems indicating heteroscedasticity of data (upper panel); and, successful correction of heteroscedasticity after logarithmic transformation of values (lower panel). Upper panel – solid horizontal line denotes linear trend. Lower panel: solid horizontal line denotes the mean difference; black broken horizontal lines denote upper and lower limits of agreement; red broken horizontal line denotes linear trend.**



**Figure 3-3. Bland Altman plots for RR count (a), mean RR (b), log-transformed SDNN (c), rMSSD (d), LF (e), and HF (f) absolute measures of HRV.**

**Table 3-2. Outcome of limits of agreement analyses between homoscedastic heart rate variability measures obtained by the S810 and CP.**

	Comparison	Bias	Limits of agreement	Acceptable limits
RR count	S810 versus CP	1.4	±23.2	Yes
mRR	S810 versus CP	2.5 ms	±61.8 ms	No
LF (nu)	S810 versus CP	3.1 ms	±23.2. ms	No
HF (nu)	S810 versus CP	-3.3 ms	±23.4 ms	No
LF:HF	S810 versus CP	0.06	2.23	No

RR count, number of RR interval data points recorded; mRR, mean time between normal r-waves; LF, low frequency spectral power; HF, high frequency spectral power; LF:HF, the ratio of low to high frequency spectral power; nu, normalised units; Comparisons are made between values from the former system to values from the second system (e.g. S810 versus CP = values obtained by the CP are subtracted from values obtained by S810); Bias, the mean of differences in participant values between the two systems for each test (three tests n = 23, two tests n = 9, one test n =1, total tests n = 88).

**Table 3-3. Descriptive results and agreement outcomes from analysis by intraclass correlation coefficient for heteroscedastic heart rate variability measures obtained by the S810 and CP.**

		S810	CP	<i>P</i> value*	ICC (95% CI)	Interchangeable agreement
Ln SDNN (ln ms)	Trial 1	4.06 ± 0.49	4.01 ± 0.53		0.87 (0.75 – 0.94)	Yes
	Trial 2	4.10 ± 0.47	4.11 ± 0.45	0.66	0.94 (0.88 – 0.97)	Yes
	Trial 3	4.02 ± 0.41	4.09 ± 0.41		0.97 (0.92 – 0.99)	Yes
Ln rMSSD (ln ms)	Trial 1	3.70 ± 0.61	3.68 ± 0.67		0.88 (0.77 – 0.94)	Yes
	Trial 2	3.75 ± 0.62	3.82 ± 0.70	0.81	0.88 (0.77 – 0.94)	Yes
	Trial 3	3.77 ± 0.58	3.88 ± 0.63		0.94 (0.87 – 0.97)	Yes
Ln LF (ln ms <sup>2</sup> )	Trial 1	6.93 ± 0.92	6.58 ± 1.24		0.64 (0.38 – 0.81)	No
	Trial 2	6.92 ± 0.91	6.82 ± 1.09	0.23	0.84 (0.70 – 0.92)	No
	Trial 3	6.92 ± 0.88	6.87 ± 0.92		0.89 (0.79 – 0.95)	Yes
Ln HF (ln ms <sup>2</sup> )	Trial 1	6.37 ± 1.17	6.20 ± 1.31		0.81 (0.65 – 0.91)	No
	Trial 2	6.34 ± 1.19	6.41 ± 1.42	0.81	0.93 (0.87 – 0.97)	Yes
	Trial 3	6.38 ± 1.16	6.50 ± 1.10		0.81 (0.62 – 0.91)	No

Data represent the mean ± SD; SDNN, the standard deviation of normal-to-normal intervals; rMSSD, root mean square of successive differences; LF, low frequency spectral power; HF, high frequency spectral power; Ln, natural logarithm; \**P* value outcomes from repeated measures ANOVA for group effect; ICC, intraclass correlation coefficient; CI, confidence interval.

**Table 3-4. Outcome of limits of agreement analyses between heteroscedastic heart rate variability measures obtained by the S810 and CP.**

	Comparison	Bias	Upper, lower 95% LoA	Antilog of bias	Antilog of upper, lower 95% LoA	Interpretation of antilog values	
						Bias	Upper, lower 95% LoA
Ln SDNN	S810 versus CP	0.00 ln ms	-0.38, 0.36	0.00	0.68, 1.45	On average S810 yields the same value as CP	S810 may yield between 0.68 and 1.45 times that of CP
Ln rMSSD	S810 versus CP	-0.05 ln ms	-0.61, 0.51	0.95	0.54, 1.66	On average S810 yields 0.95 times CP	S810 may yield between 0.54 and 1.66 times that of CP
Ln LF	S810 versus CP	0.18 ln ms <sup>2</sup>	-1.13, 1.49	1.19	0.32, 4.44	On average S810 yields 1.19 times CP	S810 may yield between 0.32 and 4.44 times that of CP
Ln HF	S810 versus CP	0.00 ln ms <sup>2</sup>	-1.29, 1.29	0.00	0.28, 3.63	On average S810 yields the same value as CP	S810 may yield between 0.28 and 3.63 times that of CP

SDNN, the standard deviation of normal-to-normal intervals; rMSSD, root mean square of successive differences; LF, low frequency spectral power; HF, high frequency spectral power; Ln, natural logarithm; Comparisons are made between values from the former system to values from the second system (e.g. S810 versus CP = values obtained by the CP are subtracted from values obtained by S810); Bias, the mean of differences in participant values between the two systems for each test (three tests n = 23, two tests n = 9, one test n = 1, total tests n = 88); The antilog values are a dimensionless ration, where 1 = zero; A value less than 1 represents a negative bias from one system compared to the other; A value greater than 1 represents a positive bias from one system to the other.

### 3.4. Discussion.

The research and clinical studies assessing cardiac autonomic activity have led to the development of more accessible and user friendly technologies and systems to determine heart rate variability (HRV). One such system is the Polar S810 HRM which provides an alternative means to determine HRV away from the laboratory setting. To ensure comparability between laboratory and field measures of HRV it is important to quantify the agreement between methods and systems being used. In this study we carried out an in-depth assessment of the agreement between measures of HRV obtained by the S810 and by a 12-lead ECG laboratory based system (CP).

There were no significant differences in values for non-transformed or transformed measures of HRV, indicating an absence of systematic bias between the two systems. Analysis by ICC showed that, at worst, agreement between the S810 and CP systems was substantial (LF:HF, trial 3) and at best excellent. All time domain measures display interchangeable levels of agreement across all trials and three frequency domain measures (LF, HF and LF:HF) display interchangeable agreement in at least one trial. However, the sole use of ICC to demonstrate agreement has been questioned, primarily due to fact that values can be exaggerated when data reveal a wide spread of scores, often disguising the true magnitude of variation (Bland and Altman, 1990). Large SD values for the majority of HRV measures (Tables 3-1 and 3-3) indicated large inter-individual variations, a finding not uncommon in HRV analysis (Sinnreich *et al.*, 1998; Pikkujämsä *et al.*, 2001).

Analysis using the Bland and Altman (2007) limits of agreement (LoA) method revealed that agreement between the systems was poor, particularly for absolute measures in the frequency domain (Tables 3-2 and 3-4). On average and for the majority of HRV measurements, the S810 showed a bias for higher values compared to those of the CP. Exceptions to this were found for measures of normalised HF and rMSSD. As an example, when obtained by the S810 the value for a simple measure such as mean RR interval could vary by as much as plus or minus 62 ms compared with that from CP (Figure 3-3, panel b). A more

extreme case is presented for frequency domain measures such as LF, where values from the S810 could be anywhere from one-third to four times those obtained from the CP system. These findings suggest that the S810 and CP systems should not be used interchangeably in the determination of commonly used HRV measures.

The bias presented by S810 can be explained by small discrepancies in the length of RR intervals and differences in frequency domain analysis methods between the CP and S810 systems. The use of differing algorithms for detecting R-wave peaks may have caused the small discrepancies in RR interval length observed between the S810 and CP systems and these were likely to have been further magnified as a result of the calculations performed to assess variability.

The CP system utilises the FFT method to determine frequency domain measures of HRV. By contrast, the S810 relies on autoregressive (AR) methods. Although these methods can create the same measures, values may differ (Fagard, 2001; Chemla *et al.*, 2005; Pichon *et al.*, 2006). Differences in estimates of spectral power outcomes from FFT compared to those estimated by AR methods have been related to the crossover of power between defined bandwidths (Badilini *et al.*, 1998) and the possible inclusion of noise with the FTT method (Fagard *et al.*, 1998). Finally, the use of the elastic electrode belt for the S810 system may induce minor artefacts (Gamelin *et al.*, 2006).

#### 3.4.1. *Comparisons with previous data.*

In the present study the CP and S810 did not display agreement sufficient to allow for their interchangeable use in the determination of HRV. The discrepancies found for both time and frequency domain indices were similar to those reported in a previous study assessing the agreement of HRV indices from 5 minute, supine ECG recordings obtained by three different instruments. Sandercock *et al.* (2004b) demonstrated contrasting findings for agreement depending on the statistical approach. Using ICC, excellent and interchangeable agreement between instruments was shown. In contrast, 95% limits of agreement actually demonstrated poor and non-interchangeable agreement as a result of

wide variations in the outcomes of HRV between all instruments. The authors highlight inconsistencies in data sampling periods between instruments for the finding of bias and a lack of agreement for even the simple measure of RR interval length.

The lack of agreement in RR interval length observed in the present study may have been due to similar data sampling inconsistencies. The CP system determines HRV from 256 normal-to-normal (NN) intervals selected from the 300 s recording. It appears however the S810 calculates HRV from the total number of NN intervals over the 300 s recording period. This may therefore account for the greater variance in RR interval observed between the CP and S810. In addition, in participants who displayed a resting RR interval  $>1.2$  s (heart rate  $<50$  b $\cdot$ min $^{-1}$ ) this translated into a sampling period that in some cases had less than 256 RR intervals over the 300s recording. Therefore the CP system may have underestimated HRV due to an insufficient number of recorded RR intervals.

Contrasting findings to those of the present study have been reported. In a study assessing the agreement of HRV derived from RR intervals obtained using the S810 in comparison to a non-ambulatory (ECG) method, Kingsley *et al.* (2005) showed incredibly good agreement between HRV measures (e.g. LoA for LF and HF =  $\pm 7.3$  ms $^2$  and  $\pm 7.6$  ms $^2$ ) obtained at rest and during lower intensities of exercise, the findings of which have led to the study being referenced by the manufacturer of the S810 (Polar OY). There are, however, methodological concerns with the Kingsley *et al.* (2005) study that may lead to slightly misleading conclusions. A brief description of these concerns may also help to explain the difference in findings to those of the present study.

As already described in the present study, the S810 system has the ability to acquire RR interval data and also to perform correction and subsequent variability analysis of RR data via its software package. In the study of Kingsley *et al.*, the HRV analysis aspect of the S810 system was not assessed for agreement. RR intervals were simultaneously recorded by both methods during a resting period and during an incremental exercise test. A temporal event marker was used in a similar manner to the present study in an effort to synchronise RR

intervals from the two methods. RR interval data from the S810 and the ECG were then exported separately to a spreadsheet. Within the spreadsheet, artefacts for S810 RR data were identified as differences between consecutive RR intervals  $>2000\text{ms}$ . Details as to the detection criteria for artefacts in ECG RR data were not provided. Spectral analysis was performed on detrended RR interval data from both methods via fast Fourier transform (FFT). Finally, data were analysed for strength of association using Pearson's correlation coefficients, for differences using paired *t*-tests and for agreement according to the Bland-Altman method.

The concerns with the methodology described above are that the ability of the S810 and its software to analyse HRV was not directly assessed. The finding of good agreement between RR interval data is not of issue. However, RR interval data from both systems were imported into the same software package and HRV analysis was performed using the same spectral method (FFT). If agreement was found to be good between RR interval data then employment of this methodology would result in similar HRV values. This was found to be the case in the study of Kingsley *et al.* It is important that the findings of Kingsley *et al.* are not misinterpreted as showing that measures of HRV obtained by the S810 *per se* agree well with those of the ECG system. In the present study, the ability of the S810 to acquire and process RR interval data and also to derive HRV from such data using S810 specific software was contrasted to that a criterion ECG system (CP). The effects of differing HRV analysis techniques (e.g. AR or FFT,) was shown as a possible cause of the large variation between scores, a factor made obsolete in Kingsley *et al.* by the use of the same analysis method to derive HRV.

The use of Pearson's coefficients in studies assessing agreement has been criticised (Bland and Altman, 1986), even more so when sample size is  $<15$  (Kautzner, 1995), as was the case in Kingsley *et al.* The Pearson's *r* was used by Kingsley *et al.* to assess strength of association, however strong strength of association may not indicate good agreement. Others, however, support the use of regression analysis to demonstrate validity of measures when used in conjunction with measures of random error (Hopkins *et al.*, 2009).

Comparisons to the present data are also confounded by the fact that resting measures appear to have been taken in a seated position (on the cycle ergometer prior to exercise), although specific details of position and length of resting recordings are not provided by the authors. Indices of HRV such as LF and HF have been shown to differ by as much as 16% to 60% when taken in seated position compared to the supine position, with higher values recorded in the supine position (Pichon *et al.*, 2006). The present study assessed HRV obtained in the supine position as this has previously been shown to yield the most reliable HRV outcomes (Sandercock *et al.*, 2004a) and is recommended for the standard assessment of short-term HRV (Task Force, 1996). When compared to the values of Kingsley *et al.*, values for HF were greater and both LF and HF showed larger variation in the present study. This is possibly the result of supine compared to the seated conditions and/or to variation in the recording duration during the resting period.

Finally, considerable differences in the number and range of participants between both studies may also explain the difference in findings. Kingsley *et al.* used a very small sample of young, similarly aged (28 plus or minus 3 years) men ( $n = 6$ ) and women ( $n = 2$ ). The present study utilised a much larger ( $n = 33$ ) sample of participants with widely varying age (20 – 63 years). Well documented is the finding that HRV diminishes with age (Malik and Camm, 1995; Task Force, 1996). This factor may explain why such large variations were found in the present study in comparison to the much lower variations of Kingsley *et al.*

A recent study assessing the validity of the S810 to measure RR intervals at rest in the supine position has shown similar findings to that of Kingsley *et al.* Using paired *t*-tests (in conjunction with effect size (ES)), Pearson *r* and LoA to assess the (in their own words) “accuracy” of the S810, Gamelin *et al.* (2006) found almost identical values for HRV when compared to those obtained from a two-lead ECG recorder.

The authors also specifically looked at errors from the S810 recordings and found the two most common were either the detection of too few or too many RR intervals compared to ECG. The authors reasoned the former was possible due to

a decrease in R-wave amplitude caused by lack of contact between the skin and elastic electrode belt of the S810 transmitter. Detection of too many RR intervals resulted from multiple triggering during a single cardiac contraction and may have occurred as a result of the S810 registering a T-wave, a P-wave being register as an R-wave or both. The finding of a slightly greater number of RR intervals detected by the S810 in the present study may also be explained by these factors.

Of interest, and somewhat underestimated by Gamelin *et al.*, was the finding that whilst the number of RR intervals did not differ, the mean RR interval time was found to differ significantly. Only *P* value and ES estimates were presented, making it difficult to ascertain the cause of differences, however Bland and Altman plots revealed that these were due to a systematic overestimation of RR interval by the S810. A finding for slight overestimation of RR interval time by S810 compared to the ECG method (CP) was found in the present study, although this was not statistically significant.

It was suggested by Gamelin *et al.* that the number of ECG observations ( $N = 11,353$ ) produced the significant finding as the magnitude of the difference (i.e. ES) was very small (ES  $d < 0.000$ ). The present study used similarly large numbers of observations ( $N = 9,133$ ; mean RR observations over 3 trials) and the magnitude of difference for RR interval from S810 and CP was also very small (ES  $d = 0.004$ ). However, this difference was not found to be significant. The authors argued that narrow LoA, good correlations and small ES indicated the S810 was a valid tool to measure RR intervals, despite significant differences between the two systems. The provision of raw RR interval data by Gamelin *et al.* would have been useful in order that reported magnitude of differences could have been verified.

The study of Gamelin *et al.* also suffers from some of the methodological issues raised in Kingsley *et al.*, mainly the study has similarly compared the ability of the S810 to record and process RR intervals to that of an alternative system and has then gone on to calculate HRV using the same spectral analysis method on both RR signals. The authors therefore wrongly conclude in their abstract that the

Polar S810 (*per se*) provides a valid measure of RR intervals and subsequent HRV analysis. Furthermore, nowhere in the study do the authors provide justification for the ECG method used as the criterion measure.

Finally, the issue of homogeneity of the sample population is again raised in Gamelin *et al.* as this study has assessed HRV in a group of active men. The fact that the group was again similar in terms of age (27 plus or minus 2 years) and physical activity level may have led to the lower variations for HRV observed by Gamelin *et al.* compared to the present study.

Based on the findings of the present study the S810 displays good agreement with a typical 12-lead ECG system (CP) in terms of its ability to record and pre-process RR interval data prior to determination of the variation characteristics of the RR interval series. This finding supports those of previous studies similarly contrasting (Kingsley *et al.*, 2005) and or assessing agreement (Gamelin *et al.*, 2006) of RR data obtained using the S810.

In terms of HRV determination, the present study appears to be the unique in that it assesses the ability of the S810 to record and process RR interval data and to subsequently derive HRV from such corrected RR data using its own software, and then assesses agreement of these HRV values to those obtained from a separate system. This contrasts to previous studies which have compared the ability of S810 to record and process RR data to another ECG based system and have then calculated HRV by applying the same detrending and spectral analysis techniques to the RR data from both systems (see Figure 3-1). When HRV is determined by the S810 *per se*, agreement of measures compared to that of ECG based methods is unacceptably large and is the likely result of differences in analysis techniques and algorithms to determine HRV between systems.

Users of the S810 should be aware that HRV obtained via the use of its own software will yield values for HRV that could disagree with those from an ECG based system when data display heteroscedastic error or not.

The Task Force report highlights several recommendations related to the specification of equipment used to record RR intervals and, where possible,

calculate HRV. These recommendations were provided as an attempt to standardise the methodology for HRV determination within the literature at the time when the report was produced.

The recommendations were likely based on the level of technology available at the time. For example, the report stressed that an ECG must always be available to view and RR intervals should be confirmed/edited manually by a suitably experienced individual. This was the standard procedure at the time the report was published although systems utilising automated algorithms for the detection and editing of RR interval data series were emerging. The Task Force recommended against the use of such automatic filters based on earlier findings of unsatisfactory behaviour leading to potential errors. However, the behaviour and accuracy of more modern systems utilising automated RR interval detection/filtering algorithms has been shown in this study and by others (Ruha *et al.*, 1997; Kinglsey *et al.*, 2005; Gamelin *et al.*, 2006) to be compatible with manual editing. Such modern devices offer greater user-friendliness and potential for rapid, short-term HRV determination. As a result they also offer greater clinical utility compared to more complex methods requiring specifically trained personnel. According to the current Task Force recommendations for short-term HRV determination, few of these systems match the criteria for RR interval recording devices. Indeed this is evident with the two systems used in the present study. Table 3-5 lists a number of the Task Force recommendations for obtaining spectral HRV against which the S810 and CP (automated functions) are contrasted.

It is apparent that for each method, at least one of the recommendations is not met satisfactorily. However, methods such as these offer greatest potential for the regular use of HRV in clinical settings. It would appear that new recommendations on the design and use of modern automated systems to assess HRV are needed. Recommendations could include the need for new systems to specify the type of spectral analysis technique (FFT/AR) used and include the ability to assess the model and model order in the case of AR. The ability to visually assess the RR interval tachogram should be possible. The provision for assessment of the number and duration of RR intervals removed and interpolated,

and the provision of normal values and ranges of HRV should also be available. Until such recommendations are in place, and only when developers adhere to such recommendations, then the affordable, reliable and practical use of HRV in clinical settings is unlikely.

**Table 3-5. A comparison of the S810 and CP in their adherence to Task Force recommendations for the analysis of RR interval data and determination of variation by fast Fourier transformation (FFT) and/or autoregressive (AR) methods.**

<b>Recommendations for RR interval determination/editing</b>	<b>S810</b>	<b>MG</b>
Ability to assess the effect of baseline and trend removal	X	X
Ability to view RR interval tachogram	✓	✓
Ability to view and/or select the fiducial point in QRS complex	X	X
Interpolation of missing, ectopic and/or arrhythmic beats	✓	✓
Ability to assess relative number and duration of RR intervals omitted	✓*	✓*
<b>Recommendations specific to FFT</b>		
Ability to assess frequency of sampling	✓	✓
Ability to assess number of samples for spectral calculations	✓	✓
Ability to assess spectral window employed	X	✓
<b>Recommendations specific to AR</b>		
Ability to assess model used	X	N/A
Ability to assess the value of the model order	X	N/A
Ability to assess central frequency	X	N/A
Ability to assess values for prediction error whiteness test (PEWT) and/or optimal order test (OOT)	X	N/A
Ability to assess employment of at least 512 but preferably 1024 points	X	N/A

\*Not within the software itself; Requires lengthy process of exporting data to spreadsheet for further calculation of relevant values.

The problem of published cut-off values representing depressed HRV are highlighted in both the present study and previous studies (Sandercock *et al.*, 2004a, 2004b). The Task Force published a value of 50 to 100 ms for SDNN as representative of moderately depressed HRV, and a value of SDNN below 50ms representative of severely depressed HRV. Several studies have referenced these values, particular in clinically based trials (Chemla *et al.*, 2005). With reference to data for SDNN from trial 1 observed in the present study, the mean value of 50.4 ms would suggest that participants on average displayed moderately, and almost severely, depressed HRV. Individually, 10 to 16 participants (32% to 52%) displayed moderately depressed HRV and 12 to 19 (39% to 61%)

participants displayed severely depressed HRV depending on whether SDNN was derived from the CP or S810 respectively. The figures presented here are mirrored in other studies assessing HRV in normal, healthy populations (Sandercock *et al.*, 2004a; 2004b)

The participants in the present study were a sample chosen to represent that of the normal population, and therefore HRV would be representative of this population. However, the present and previous findings clearly suggest that the cut-off values for HRV are overestimated. However, it should be pointed out that the cut-off values presented by the Task Force relate to 24 h measure of SDNN and therefore may not relate to those obtained from short recordings.

A slightly different argument for the need of a range of normal HRV is found when analysing the outcomes of LoA and other agreement analysis studies. The majority of the studies show wide LoA for most indices of HRV, particularly those of the frequency domain. However, studies report poor agreement based on wide LoA but often do not provide justification as to how such limits were deemed poor (Chemla *et al.*, 2005), or provide somewhat arbitrary values based on a percentage of the published Task Force normal values (Pichon *et al.*, 2006). Here in lies on of the issues raised by the use of LoA, namely the degree of and reliance on subjectivity in determining their meaning (Lee, 1992). Efforts to provide more quantitative analyses of LoA findings have been made. Sandercock *et al.* (2004b) assessed LoA findings in terms of detecting differences between groups, utilising cross sectional studies from which to draw suitable values. However, such measures to assess LoA are population specific and rely on the reliability and validity of data from individual studies. A value and range for so called normal HRV in healthy adults, based on values obtained across the literature would provide a reference point suitable for the majority of studies assessing HRV and allow for better decisions when using LoA.

Because of their increased use in both clinical and non-clinical population studies, and observations from the present and previous work that current normal values appear to be unrepresentative, there is strong justification for the need of clearly defined values and ranges of short-term HRV indices in normal populations.

### 3.4.2. Study limitations.

In the present study attempts to synchronise the RR interval recording start and end time were made to ensure compatibility of HRV data from the two devices. This was done manually by marking the S810 record with a temporal “event” marker on commencement of the ECG recording. The success of this procedure was confirmed by the finding of a similar number of RR intervals recorded by the CP and S810. However, this method has potential to succumb to experimenter error and may explain the small variation observed in the number of RR intervals and RR interval length observed between CP and S810.

The study assessed HRV obtained from a RR interval segment 300s in length in order to standardise between the two devices. However, on observation it appears that CP calculates HRV from 256 NN intervals from the 300s recording. For the S810, HRV is calculated from the total number of RR intervals within the 300s recording. Calculation of HRV from different numbers of RR intervals may have facilitated differences observed between the CP and the S810.

Sugawara *et al.* (2001) described significant diurnal variation in parasympathetic reactivation following exercise. Our study did not control for this as experimental procedures were performed between 8 AM and 5 PM; therefore the effects of diurnal variation on HRV cannot be discounted.

When assessing agreement, there are many contradictions between interpretations of values for ICC. Studies vary in their classification of ICCs, with some suggesting ICCs of  $r < 0.41$ ,  $R = 0.41 - 0.6$ , and  $r > 0.6$  showing poor/fair agreement, moderate/good agreement and very good/excellent agreement respectively (Gardiner *et al.*, 2004). Others suggest an ICC of below 0.4, between 0.4 and 0.75, and above 0.75 as representative of poor, fair to good and excellent agreement respectively (Quiles *et al.*, 2003). These discrepancies can be somewhat resolved when reference to the original Lee *et al.* (1989) study is made. The values referred to in the present study were selected based on those suggested by Lee *et al.* and by their use in previous similar studies (Sandercock *et al.*, 2004b).

### **3.5. Recommendations.**

The S810 RR interval filtering features are intentionally easy to adjust according to user need. In order for better comparisons and to standardise across studies, authors should provide information on the type of filter settings used and whether or not the additional error correction feature was utilised.

As discussed earlier, the provision of new recommendations pertaining to the use of automated systems/methods to obtain RR interval data and subsequent HRV is warranted in order to ensure standardisation of procedures and facilitate the validity and reliability of values obtained from short RR recordings.

In tandem with the findings presented in chapter two, the present study observed a need for more clearly defined values and ranges for HRV indices within normal, healthy populations. Such values would be of significant use to researchers and clinicians currently using HRV, particularly those addressing the diagnosis and treatment of conditions known to affect the normal function of the autonomic system such as diabetes, coronary artery disease, and heart failure.

It can be argued that knowledge of agreement between instruments is somewhat arbitrary as comparisons across laboratories are a rare occurrence. Furthermore, most researchers would agree that to ensure reliability, the same instruments should be used for each patient and where necessary across repeat trials, thus limiting measurement error and the effects this may have on subsequent dependant variable outcomes.

### **3.6. Conclusions.**

This study assessed the agreement of HRV measurements derived from the S810 and accompanying Polar software. When derived in this manner, and despite high ICCs, measures of HRV obtained by the S810 display unacceptable agreement with those simultaneously obtained by the 12-lead ECG (CP) system. Non-significant differences, interchangeable agreement by ICC and narrow LoA

for the number of RR intervals recorded, suggest that S810 and CP are comparable in their ability to record and process RR interval data. The two systems may, therefore, be used interchangeably in the recording and, where appropriate, the interpolation of RR intervals. These results indicate that HRV results are machine-specific, requiring all studies to specify details of the method of measurement.

Wide variation between individuals illustrates the variable nature of short-term measures of HRV and highlights the need for an established range for normal HRV.

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#### **CHAPTER 4. SHORT-TERM RESTING HEART RATE VARIABILITY AND PROGNOSTIC EXERCISE TEST RESPONSES: ASSOCIATIONS WITH HEART RATE, AEROBIC CAPACITY AND PHYSICAL ACTIVITY.**

##### **Abstract.**

The main purpose of this study was to identify the association between resting heart rate variability (HRV) and prognostic measures of heart rate (HR) obtained before, during and after graded exercise testing (GXT). A strong association could identify HRV as a potential screening tool for GXT. A secondary aim was to identify a role of autonomic function underlying a poorer HR response to exercise.

Resting five minute time and frequency domain HRV and HR measurements were made in 33 volunteers (19 males, median age 34, range 25 – 63 years and 14 females median age 48, range 21 - 63years). Measures of  $\dot{V}O_{2peak}$  and HR obtained during a maximal GXT and HR recovery (HRR), one, two and three min post GXT were assessed for associations with resting HRV. Participants were also divided into groups for increased risk based on established cut-points for resting, exercise and recovery HR responses. Between group differences and effect size ( $d$ ) for measures of HRV were analysed.

Compared with resting HR, resting HRV was equally or better related to all but two exercise HR measures. Controlling for resting HR, measures of HRV were weakly and non-significantly related to GXT HR responses (best  $r$  value = -0.27,  $P > 0.05$ ) but were moderately and significantly related to HRR at all time points (best  $r$  value = 0.46,  $P < 0.05$ ). In contrast to other dependent variables, measures of HRV were consistently able to demonstrate significant and moderate to large ( $d = 0.9 - 2.0$ ) differences between groups based on HR risk cut-points.

In conclusion, weak associations with HR responses to exercise prevent their accurate prediction from resting measures of HRV. Data support the use of vagally mediated resting HRV in predicting a better post-exercise HR response. A lower resting autonomic modulation underlined high risk resting and exercise HR responses. Resting short-term HRV measurements should be considered

when assessing cardiac autonomic health from the HR response before, during and/or after exercise.

ABBREVIATIONS:

The following abbreviations are used throughout this chapter:

- GXT = graded exercise test;
- HR = heart rate;
- $\Delta\text{HR}_{1\text{minute}}$  = HR at one minute of GXT minus the HR at supine rest;
- $\Delta\text{HR}_{1/3\text{exercise}}$  = HR at one third GXT minus the HR at supine rest;
- $\Delta\text{HR}$  = HR at peak exercise (GXT) minus the HR at supine rest.

#### **4.1. Introduction.**

The heart rate (HR) response before, during and after exercise is used to assess the condition and response of the cardiovascular system and are well established prognostic measures in certain cardiovascular diseases (Cole *et al.*, 1999; Nissinen *et al.*, 2003; Falcone *et al.*, 2005; Jouven *et al.*, 2005; Lipinski *et al.*, 2005; Leeper *et al.*, 2007). Likewise, ambulatory and resting measures of heart rate variability (HRV) are well established prognosticators for adverse events in numerous patient populations (Tsuji *et al.*, 1994, 1996; Task Force 1996; La Rovere *et al.*, 1998; Nolan *et al.*, 1998; Guzzetti *et al.*, 2005; Dewey *et al.*, 2007).

During and following exercise, HR response has shown a prognostic and predictive role; including changes in HR at exercise onset, at one-third capacity, peak exercise capacity and within five minutes post-exercise (Savin *et al.*, 1982; Cole *et al.*, 1999; Shelter *et al.*, 2001; Vivekanathan *et al.*, 2003; Falcone *et al.*, 2005; Jouven *et al.*, 2005; Dewey *et al.*, 2007; Leeper *et al.*, 2007). This is due likely to the close association of these measures as indicators of autonomic nervous system (ANS) function and the increased risk of arrhythmias and death observed with impaired ANS function (Jouven *et al.*, 2005). However, the majority of studies using the HR response as a potential indicator of ANS dysfunction or imbalance fail to provide a quantitative measure of ANS activity.

Heart rate variability (HRV) offers the potential to do so and may help to clarify or critique the findings of these studies.

##### *4.1.1. Assessment of cardiac autonomic function from the heart rate response.*

Due to the role the ANS plays in mediating the HR response during and after exercise, a number of studies have utilised measures of HR to assess imbalances between the two branches of the ANS and the effect this may have on cardiovascular health (Savin *et al.*, 1982; Cole *et al.*, 1999; Jouven *et al.*, 2005; Leeper *et al.*, 2007). Attempts to describe the physiological control systems underlying the HR response to exercise are often made by reference to studies

identifying contributions of the ANS under similar conditions using direct, often invasive methods (e.g. assessment of the turnover rate of norepinephrine (Esler *et al.*, 1990) and microneurography, which involves direct placement of electrodes in the peroneal nerve (Wallin *et al.*, 1980). A number of studies have alternatively used non-invasive measures of ANS function such as HRV and baroreflex sensitivity. Table 4-1 presents examples of studies that have referred to papers using invasive and/or non-invasive measures of ANS activity in an attempt to explain the contribution of the autonomic system to specific HR changes observed during and following exercise. Studies which have demonstrated associations between measures of HRV and HR responses to exercise are also presented. Falcone *et al.* (2005) reported a link between reduced vagal and/or increased sympathetic activity and a higher risk for adverse cardiac events in patients with documented coronary artery disease. Simply by recording heart rate at rest and at the onset of exercise, Falcone *et al.* (2005) tested the hypothesis that an abnormally elevated HR response at the onset of exercise would imply rapid vagal withdrawal immediately preceding sympathetic activation, and might predict adverse cardiac events in such populations. The authors noted an increase in HR  $\geq 12$  bpm (the median value for whole group) during the first minute of a stress test of was predictive of adverse cardiac events, including death. Confirmation of the occurrence of parasympathetic withdrawal and/or increased sympathetic activity could not be made as no direct or indirect measures of these parameters were taken.

Jouven *et al.* (2005) assessed the likelihood of sudden death occurring as a result of abnormal HR profiles during exercise and recovery and hypothesised that the mediation of HR during exercise and recovery occurs as a result of the balance between sympathetic and vagal activity. They proposed that known alterations in neural control of cardiac function contribute to the risk of sudden death. In asymptomatic men between the ages of 42 and 53 years, the authors found an increased risk of sudden death from myocardial infarction: i) in those with a resting HR  $> 75$  b·min<sup>-1</sup>, ii) in those with an increase in HR during exercise  $< 89$  b·min<sup>-1</sup>, and iii) in those with a decrease in HR of less than 25 b·min<sup>-1</sup> in the first minute post-exercise. Likewise, only through reference to previous studies could discussion of the proposed activities of the ANS be made. In both of these and

similar studies, the use of HRV could not only have provided indirect quantification of ANS activity, in particular vagal contribution, but may have contributed to the observed predictive value of the HR response during and post exercise.

**Table 4-1. Examples of studies using measures of heart rate, heart rate variability or both for prognostic, risk stratification and/or autonomic assessment purposes.**

Author, date and study type	Participants	Data collection, HR and/or HRV parameters assessed	Use of measures	Main outcomes	Potential parameters to include in present study
Leeper <i>et al.</i> (2007) – Retrospective	1,959 middle aged men and women. Subgroup of 578 patients displaying CAD.	Individualised treadmill GXT to peak capacity with concurrent 12-lead ECG. HR = $\Delta$ HR from pre-test standing assessed at 15 s of exercise, 2 METs, 1 min of exercise, one-third total exercise capacity, peak exercise. Supine HRR at 2 min also taken; HRV = none.	Prognosis and risk stratification for all-cause and CV mortality.	In whole group - Lower value for $\Delta$ HR at 15 s and 1 min and decrease of 1 SD in $\Delta$ HR at one-third exercise capacity associated with increased risk of all-cause and/or CV mortality. HRR at 2 min predicted all-cause and CV mortality. $\Delta$ HR at peak exercise (HR increase) most powerful and accurate predictor of all-cause and CV mortality In CAD - $\Delta$ HR one-third exercise predicted prognosis.	$\Delta$ HR at 1 min $\Delta$ HR at one-third exercise capacity $\Delta$ HR at peak exercise (HR increase) HRR at 2 min.
Dewey <i>et al.</i> (2007) – Retrospective	1,335 middle-aged men and women.	Treadmill GXT to peak capacity. 12-lead ECG recording throughout and supine after GXT. HR = Increase in HR (peak – rest) and HRR at 2 mins taken; HRV = standard time and frequency domain measures obtained only for first and last 2 min of GXT and during 2 min recovery from GXT.	Prognosis and risk stratification for all-cause and CV mortality	Higher rMSSD at peak exercise and higher rMSSD, HF and HF% in recovery associated with increased all-cause and CV mortality. Higher LF, lower LF% and lower LF:HF during recovery predicted all-cause and CV mortality. Faster HR recovery predicted better prognosis	HRR at 2 mins. Time and frequency HRV 2 mins post-exercise.
Davrath <i>et al.</i> (2006) – Prospective	Twenty healthy, middle-aged men and women with repeatedly slow HRR and eight controls.	Bruce treadmill GXT to 90% age-predicted max HR. 12-lead ECG recording seated 10 min before, throughout and seated 10 min after GXT. HR = HRR at 1 min taken; HRV = LF and HF power calculated over entire recording using novel modified CWT method.	Characterise ANS contributions to slow HRR.	Significant differences in resting HR but not HRV between slow and normal HRR groups. Slow HRR (<19 bpm) associated with lower HF and LF fluctuations between 45 s and 2 min of recovery indicating delayed vagal reactivation and abnormal sympathetic deactivation.	Slow HRR (<19 bpm) at 1 min. Normal HRR (19 – 35 bpm) at 1 min. LF and HF 45 s – 2 min post-exercise.
Evrengul <i>et al.</i> (2006) – Prospective	Thirty three CAD patients and thirty eight healthy controls.	Submaximal Bruce treadmill GXT to 85% age-predicted max HR. 1 h supine Holter recording before GXT. HR = HRR at 1-, 2- and 3 min. Only correlations between HRV and HRR at 3 min assessed; HRV = standard time and frequency domain measures.	Characterise differences in ANS and contributions to HRR.	All time domain HRV lower in CAD and positively correlated to HRR at 3 min. HF power reduced in CAD and positively correlated to HRR at 3 min. LF and LF:HF higher in CAD and negatively correlated to HRR at 3 min.	HRR at 3 min.

Table 4-1 continued

Author, date and study type	Participants	Data collection, HR and/or HRV parameters assessed	Use of measures	Main outcomes	Potential parameters to include in present study
Falcone <i>et al.</i> (2005) – Prospective	Four hundred and fifty eight middle-aged CAD patients	Semi-recumbent cycle GXT to peak capacity. 12-lead ECG recording throughout. HR = $\Delta$ HR at 1 min of exercise (2 groups based on $<$ or $\geq$ median value (12 bpm)); HRR at 1 min semi-recumbent - value of $\leq$ 12 bpm considered abnormal; HRV = none.	Prognosis and risk stratification for cardiac events and/or mortality.	$\Delta$ HR at 1 min exercise $\geq$ 12 bpm (median value for whole group) predicted cardiac mortality and non-fatal MI, and risk linearly associated with increased values for $\Delta$ HR at 1 min.  Trend for increased risk based on HRR.	$<$ or $>$ median $\Delta$ HR at 1 min
Jouven <i>et al.</i> (2005) – Retrospective	5,713 middle-aged men	Standardised 10 min cycle GXT at three fixed workloads. Bipolar ECG monitored at rest, every 2 min during and every minute after GXT. HR = resting HR after 5 min supine, $\Delta$ HR from rest to peak ( $\Delta$ HR) and HRR at 1 min; HRV = none.	Prognosis and risk stratification for all-cause and CV mortality	Increased risk of sudden death from myocardial infarction if resting HR $>$ 75 bpm, $\Delta$ HR $<$ 89 bpm and HRR $<$ 25 bpm. HR increase was most powerful predictor.	Cut-offs for resting ( $>$ 75), $\Delta$ HR ( $<$ 89) and recovery ( $<$ 25) HR.
Cole <i>et al.</i> (1999) – Prospective	2,428 middle-aged men and women referred for first GXT	Standard and modified Bruce treadmill GXT to peak capacity. HR = percent HR reserve (difference between predicted max HR and rest HR) used at peak exercise. $<$ 80% HR reserve considered impaired chronotropic response; HRR measured at 1 min during active cool-down period; HRV = none.	Prognosis and risk stratification for all-cause and CV mortality	Cut-off value of 12 bpm strongest predictor of mortality. Smaller increase in HR during exercise and impaired chronotropic response also found to predict mortality.	HRR value of $\leq$ 12 bpm  $<$ 80% HR reserve

CAD, coronary artery disease; MI, myocardial infarction; HR, heart rate; HRV, heart rate variability; HRR, heart rate recovery; GXT, graded exercise test; ECG, electrocardiograph;  $\Delta$ HR, change in HR; CV, cardiovascular; ANS, autonomic nervous system; CWT, continuous wavelet transform; rMSSD, root mean square of successive differences; HF, high frequency power; LF, low frequency power; bpm, beats per minute.

4.1.2. *Assessing autonomic function: heart rate responses and heart rate variability.*

The recovery of HR following exercise and vagal-related HRV measures (e.g. root mean square of successive differences, rMSSD; high frequency power, HF) are presumed to be of parasympathetic origin. This assumption has prompted research assessing the intuitive notion that association between these two measures should be high. However studies have both succeeded (Evrengul *et al.*, 2006) and failed to find a relationship (Javorka *et al.*, 2002; Buchheit and Gindre, 2006).

Evrengul *et al.* (2006) observed a significant positive relationship between resting vagal measures of HRV and the level of HR recovery (HRR) three minutes after completion of a submaximal graded treadmill exercise test (GXT) in coronary artery disease (CAD) sufferers. The authors concluded that the relatively easy measure of HRR can be used to evaluate the basal autonomic function in patients with CAD.

Such a relationship was not observed by Javorka *et al.* (2002). In a cohort of healthy males, Jovarka *et al.* found no correlation between basal HRV measures and the HR recovery level at one minute following eight minutes continuous stepping at 70% maximal power output. However, in a separate study the same authors provided confirmation of a parasympathetic (vagal) contribution to the recovery phase following exercise. Jovorka *et al.* (2003) found that post-exercise vagal measures of HRV, such as power in the HF range (0.15-0.5 Hz.), correlated negatively with the adjustment of HR at the onset of exercise. In other words, a slower initial adjustment at the onset of exercise leads to reduced HRV after exercise. This also implies that a more rapid rise in early HR is important for faster parasympathetic recovery after exercise.

The studies by Javorka *et al.* assessed the relationship between HRV and HR response during and following exercise at 70% of the participants maximal power output. Different exercise intensities, therefore, may have distinct effects on cardiovascular changes during and after exercise. The fact that cardiovascular

function is most often assessed using HR response during and following exercise to peak power output and/or peak oxygen consumption (Cole *et al.*, 1999; Shelter *et al.*, 2001; Vivekanathan *et al.*, 2003; Falcone *et al.*, 2005; Dewey *et al.*, 2007; Leeper *et al.*, 2007) would suggest that the relationship to HRV at such exercise intensities is warranted.

A theme common to the studies listed and discussed above is the use of exercise to elicit a HR response for prognostic purposes or to describe ANS activity. The majority of studies have involved the use of a graded exercise test (GXT) at submaximal and more often maximal intensities as reflective of current clinical practice. Unarguably, GXT performance, particularly maximal, is physiologically stressful. Another important consideration is the increased susceptibility to arrhythmias and an increased risk of cardiac and sudden death during and immediately after vigorous activity (Albert *et al.*, 2000). Arguably perhaps, it can also place undue psychological stress on patients prior to its performance. With these factors in mind, a resting measure that could identify the need for performance of a GXT would be of use within cardiology clinics.

Measures of HRV, in particular a low ultra low frequency (ULF) power and a low very low frequency (VLF) component, obtained from 24 h Holter recordings are routinely found to be the strongest risk factors for mortality in numerous populations (Bigger *et al.*, 1993). From a clinic view point, 24 h Holter monitoring is time consuming and not without its own issues related to the effects of patient activity on HRV outcomes (Task Force, 1996; Roach *et al.*, 2004). More specifically, Roach *et al.* (2004) reported higher values for measures of long-range HRV indexes (e.g. power in the ULF band) when obtained during an “active” compared to a “rest” day. Tulppo *et al.* (2003) demonstrated that steady state and incremental exercise had differing influences on the HRV response, indicating that there is a complex interaction between the type and duration of physical activity, average HR, and measures of long-term HRV.

In contrast, measures of HRV derived from short-term RR interval recordings under controlled conditions are independent of habitual exercise. There is also evidence that such measures may better reflect abnormalities in intrinsic

autonomic regulatory systems and the risk of mortality than long-range HRV measures (Bigger *et al.*, 1993; Ho *et al.*, 1997).

Given that short-term HRV is independent of habitual exercise and considering the known association with exercise related HR responses and prognosis of adverse events and mortality in both healthy and cardiovascular groups, this raises the question “Could easy to use, pre-exercise HRV predict or ‘pre-screen’ patients so that they need not perform a GXT?” Should a strong relationship between prognostic HR measures and resting HRV exist, this could be used to identify patients likely to show chronotropic incompetence and would save the need to perform a stressful GXT.

At this point it is important to consider that, in the clinical setting, a GXT is performed to gather information on the normality/abnormality of other key physiological responses to exercise (e.g. cardiac output, blood pressure). Moreover, a failure to attain a set value (e.g.  $89 \text{ b}\cdot\text{min}^{-1}$ ) for the HR response is not the only criterion for chronotropic incompetence, and indeed any abnormal chronotropic response can be considered a sign of incompetence. It is therefore somewhat over-simplistic to imply that a relationship between resting HRV and the HR response to exercise will guide the decision to perform a GXT. Perhaps then it is when the HR response to exercise is specifically being considered that such a relationship could be of use.

Due to issues of complexity and cost, measures of ANS activity are only slowly entering risk stratification on a routine basis (Falcone *et al.*, 2005). Evolution in technology has seen an increase in more practical and cost effective systems to record and process RR interval data. One such system is the Polar S810 heart rate monitor (HRM) (Polar Electro Oy, Kempele, Finland). The S810 uses an electro-transmitter belt to detect and transmit RR interval data to the HRM for subsequent downloading and HRV analysis.

It has been demonstrated that individuals who perform regular physical activity present with higher values for resting HRV, particular for measures related to parasympathetic activity, compared to sedentary individuals (Dixon *et al.*, 1992;

Rennie *et al.*, 2003; Buchheit *et al.*, 2005; Sandercock *et al.*, 2008). It has been well established amongst the medical and health professions that performance of physical activity and/or exercise reduces the risk of developing cardiovascular disease. Of the studies outlined in Table 4-1, those assessing the prognostic role of HR responses make some referral to a role for exercise and/or physical activity to help shift autonomic balance in a more favourable direction (e.g. Jouven *et al.*, 2005). Whether the improved prognosis that accompanies the increased performance of physical activity is due to autonomic functions underlying HR responses to exercise, to those underlying modulations of resting ANS activity, or both is yet to be fully established. The present study offers the opportunity to at least investigate some of these questions.

The aims of this study were, therefore:

1. To identify the relationship between short-term resting measures of HRV and prognostic HR responses before, during and after graded exercise testing (GXT).
2. To examine the autonomic activity modulations underlying prognostic measures of resting, exercise and recovery HR.
3. To investigate the underlying role of physical activity on autonomic function as assessed by HR response to exercise and resting measures of HRV.

## **4.2. Methods.**

### *4.2.1. Participants.*

*Thirty three volunteers, 19 males with a median age 34 (range 20 - 59) and 14 females with median age 47.5 (range 25 - 63), were included in the study. All participants were healthy, defined as being free from illness at the time of testing. None were known to be taking any medication or have any cardiovascular problems that may have influenced the procedures carried out. All procedures were approved by the Ethics Committee of the appropriate university faculty. Informed consent was provided by each participant prior to commencing the experimental procedures.*

#### 4.2.2. *Instrumentation and data acquisition.*

*RR intervals and heart rate (HR) were recorded via a Polar S810 heart rate monitor (HRM) (Polar Electro OY, Kempele, Finland). The S810 was set to record beat-to-beat RR intervals with a sampling frequency of 1000 Hz providing an accuracy of 1ms for each RR period (Cottin et al., 2004). S810 recordings were transferred to a password protected PC via the Polar Precision Performance 4.03 software (Polar Electro OY, Kempele, Finland). Each downloaded RR interval file was then exported as a .txt file to a separate folder for later HRV analysis using an advanced software package (HRV Analysis Software 1.1, University of Kuopio, Finland).*

Respiratory gas exchanges were measured breath-by-breath using a Medical Graphics Cardio<sub>2</sub> online analysis system (MG) (Medical Graphics Corporation, St. Paul Minnesota, USA). Before each test, the system was calibrated using known reference and calibration gas concentrations.

Physical activity level was assessed using the physical activity rating (PA-R) questionnaire as developed by Jackson *et al.* (1990) and validated for adult males and females between the ages of 19 and 79 by Matthews *et al.* (1999). The PA-R comprises three sections that differentiate from no recreational sport or heavy physical activity, modest physical activity, and heavy physical exercise (see Appendix II). A score of zero to seven is used to describe those who perform activity ranging from no recreational sport or heavy physical activity (i.e. sedentary) to those who perform regular heavy physical activity (e.g. exercise trained). The PA-R was used due to its ease of application and its ability to distinguish between modest and high levels of physical activity.

#### 4.2.3. *Experimental design.*

##### 4.2.3.1. *Resting autonomic control assessments.*

Measurements were performed between 09:00 and 13:00 in a quiet laboratory with ambient temperature conditions. Participants were instructed to abstain from

caffeine and alcohol containing foods and beverages on test days, and to avoid heavy physical exertion and alcohol consumption during the 48 h preceding test days. Participants were instructed to eat a light breakfast at least 2 h prior to testing where appropriate.

After a stable resting heart rate was attained, participants were asked to remain quiet for 10 min and to avoid speaking or making any movement. HR and RR intervals were continuously monitored and recorded during this period. Following 10 min, the end of Polar recording was marked using the temporal “event” (lap) marker feature on the Polar S810.

#### 4.2.3.2. Cardio-respiratory capacity assessment.

Following resting recordings, participants performed a GXT (Bruce protocol) on a motor-driven treadmill (Cardio Control, Delft, The Netherlands) to volitional exhaustion. During the GXT, expired O<sub>2</sub> and CO<sub>2</sub> were monitored continuously. The test was stopped when a participant could no longer maintain the walking/running speed. Maximal oxygen uptake ( $\dot{V}O_{2\max}$ ) was defined as the highest  $\dot{V}O_2$  attained in a 30-sec period. Criteria to establish  $\dot{V}O_{2\max}$  were 1) a plateau in  $\dot{V}O_2$  despite increasing work load, 2) a final respiratory exchange ratio (RER) greater than 1.15, 3) a heart rate within 10 b·min<sup>-1</sup> of age-predicted maximum, and 4) visible exhaustion (Howley *et al.*, 1995; ACSM, 2000). Participants were considered to have reached  $\dot{V}O_{2\max}$  if at least three of these criteria were met. A peak value for  $\dot{V}O_2$  ( $\dot{V}O_{2\text{peak}}$ ) was taken when less than three criteria were obtained.

#### 4.2.3.3. Exercise heart rate measurements.

Measures of HR and RR interval were recorded continuously with the S810 during the 10 min of rest and throughout the GXT. The following HR parameters were obtained as recommended (Cole *et al.*, 1999; Falcone *et al.*, 2005; Jouven *et al.*, 2005; Leeper *et al.*, 2007):

- I. Resting HR - calculated as the mean HR during the last 5 min of the 10 min supine rest;

- II. Change in HR at one min of exercise ( $\Delta\text{HR}_{1\text{minute}}$ ) - calculated as the difference between HR at one min and immediately prior to the start of exercise;
- III. Change in HR at one-third exercise time ( $\Delta\text{HR}_{1/3\text{exercise}}$ ) and the HR immediately prior to the start of exercise
- IV. HR increase was obtained by subtracting the HR immediately prior to exercise (e.g. standing) from HR at peak exercise, and;
- V.  $\Delta\text{HR}$  was calculated as the difference between HR at peak exercise and the resting HR when supine.

In reporting the prognostic role of the HR response to GXT, Jouven *et al.* (2005) established a resting HR  $> 75 \text{ b}\cdot\text{min}^{-1}$  and a change in HR from rest to peak exercise (HR)  $< 89 \text{ b}\cdot\text{min}^{-1}$  as increased risk factors of adverse events. These values were dichotomised from high and low quintiles respectively for each measure. In the present study, participants were grouped first according to the cut-points for resting HR ( $</> 75 \text{ b}\cdot\text{min}^{-1}$ ) and  $\Delta\text{HR}$  ( $>/< 89 \text{ b}\cdot\text{min}^{-1}$ ) as identified by Jouven *et al.* and also study specific dichotomised values from high and low quintiles respectively.

#### 4.2.3.4. Post-exercise heart rate measurements.

On completion of the GXT, participants immediately undertook a 10 min recovery period during which HR and RR interval were recorded. Due to the effects of posture on recovery (Buchheit and Gindre, 2006), participants remained inactive in a seated position. The time to attain the seated position following test termination was also noted. Recovery HR (HRR) and RR recordings began when participants achieved the required recovery position. HRR was calculated as the difference between peak HR and HR recorded one, two and three minutes post-exercise (Cole *et al.*, 1999; Evrengul *et al.*, 2006). Participants were subdivided into groups based on a HRR  $>/< 25 \text{ b}\cdot\text{min}^{-1}$  (Jouven *et al.*, 2005). As with resting and exercise HR measures, groups based on study specific lowest and highest quintiles dichotomised from HRR values were also analysed for comparison.

#### 4.2.3.5. Heart rate variability analysis.

Resting HRV measures were derived from the last 5 min of the 10 min supine RR interval recording. After filtering and correction, all RR interval data were imported into well-validated software (HRV analysis 1.1) and developed in accordance with published recommendations (Task Force, 1996; Ruha *et al.*, 1997; Niskanen *et al.*, 2004). To account for any non-stationarity of the time series, filtered RR data were detrended using the smoothness priors approach (Gersh, 1991). The filtered data were interpolated at a rate of 4 Hz prior to spectral analysis (Niskanen *et al.*, 2004). The HRV measures selected were those currently recommended (Task Force, 1996) that hold prognostic value for adverse cardiac events in healthy individuals (Tsuji *et al.*, 1996, Dewey *et al.*, 2007) or cardiac patients (Bigger *et al.*, 1993; Lucreziotti *et al.*, 2000; La Rovere *et al.*, 2003). From the many HRV measures available, only low frequency spectral power (LF), high frequency (HF) spectral power and the LF:HF ratio and root mean square of the successive differences of normal-to-normal RR intervals (rMSSD) were assessed. Mean RR interval (mRR) was also recorded as an additional marker of overall cardiac autonomic control.

#### *4.2.4. Statistical Analysis.*

*All statistical analysis was carried out using SPSS version 13.0 (SPSS inc. Chicago, Illinois, USA). Prior to statistical analysis, data were checked for univariate and multivariate outliers using standard Z-distribution cut-offs of  $\pm 3.29$  and Mahalanobis distance tests respectively. Where outliers were found, the corresponding data were corrected and/or noted accordingly. The normality of data sets was then assessed using a Kolmogorov-Smirnov test. Where assumptions for parametric testing were not met logarithmic transformation ( $\ln$ ) was applied.*

#### 4.2.4.1. Baseline heart rate variability and exercise test responses.

The relationship between selected exercise test responses and HRV measures was evaluated by Pearson correlation analysis. For non-parametric data,

relationships were analysed using spearman rank correlations. Due to the known association between age and gender with HR and HRV, the relationship between these two characteristics and all dependent measures was assessed. Where associations were found, subsequent analyses for relationships were run with age and/or gender as covariates. The magnitudes of correlations were defined according to Cohen's (1988) description whereby correlations  $\geq 0.5$  are considered large, 0.3 to 0.5 are considered moderate and 0.1 to 0.3 are considered small. To assess the predictive power of baseline HRV, exercise test responses showing significant or close-to-significant relationships with measures of HRV were entered into binary logistic regression analysis.

#### 4.2.4.2. Group comparisons based on heart rate and physical activity.

Between-group differences were assessed using independent *t*-test or Wilcoxon's rank-sum test for continuous data and Chi square test for dichotomised variables. A *P* value  $< 0.05$  was considered statistically significant. The use of *P* values alone has been criticised and the requirement to present precision of estimates is increasingly common in the literature (Gardner and Altman, 2000; Hopkins, 2000). Therefore the magnitudes of effects were assessed and defined as follows: effects  $< 0.2$  were considered trivial, 0.2 to 0.6 small, 0.6 to 1.2 moderate, 1.2 to 2.0 large, and  $> 2.0$  as very large. Precision of estimates of outcome statistics is provided by 95% confidence intervals (CI).

Finally, reductions in the significance level ( $P < 0.05$ ) (i.e. Bonferroni adjustment) to account for inflation of the cumulative Type I error rate was not made for a number of reasons. First, this study purposely looks to explore the possibility of new relationships that have not been identified in the literature. Second, identifying the magnitude of the actual adjusted *P* value is made difficult by the non-independence of HRV and other dependent measures. Third, the study has been designed with consideration to the intended number of analyses *a priori*. Whilst there is a risk of making a Type I error, this study will provide the necessary data with which subsequent studies can make appropriate Bonferonni adjustments.

### 4.3. Results.

The mean  $\pm$ SD stature and mass for all participants was  $1.73 \pm 0.11$  m and  $74.6 \pm 15.6$  kg. The median (1<sup>st</sup> - 3<sup>rd</sup> quartile) PA-R score was 5 (3 - 6), indicating a minimum of regular participant involvement in recreational or vigorous activity for 30 – 60 min per week.

Due to skewed distributions, analysis of all HRV measures except mean RR and LF:HF was performed on log-transformed values. None of the participants satisfied all the criteria for achievement of  $\dot{V}O_{2\max}$  and as a result measures of peak oxygen uptake ( $\dot{V}O_{2\text{peak}}$ ) were taken. The focus of this chapter is aimed at the magnitude of relationships between prognostic measures of HRV and selected prognostic HR, cardiovascular and physical activity parameters. Therefore, only data relating to such relationships are presented in the main body of this chapter.

Significant correlations were found for age and/or gender with resting HR ( $r = -0.41$  for age), HR increase ( $r = -0.48$  for age,  $r = 0.55$  for gender),  $\Delta$ HR ( $r = -0.64$  for age,  $r = 0.54$  for gender),  $\dot{V}O_{2\text{peak}}$  ( $r = -0.60$  for age,  $r = 0.49$  for gender), duration of GXT ( $r = -0.50$  for age,  $r = 0.46$  for gender) and mRR ( $r = 0.39$  for age) (see Appendix I). Subsequent correlation analyses for these measures were made controlling for age and/or gender where appropriate (Table 4-2). Resting HR was significantly and highly negatively correlated with all measures of HRV ( $r$  value range =  $-0.67$  to  $-0.98$ ) except LF:HF ratio ( $r = 0.22$ ,  $P = 0.26$ ). As a result, relationships between resting HRV and GXT responses were re-assessed whilst controlling for resting HR.

#### 4.3.1. *Correlations for prognostic heart rate measures with resting heart rate variability.*

The outcomes of the correlation analysis with and without controlling for resting HR are presented in Table 4-2. When controlled for resting HR, HRR was the only prognostic HR parameter significantly associated with resting HRV. Moderate and positive correlations were observed for ln rMSSD with HRR at two and three minutes and for ln HF with HRR at all three time points. There

were moderate negative correlations between LF:HF and HRR at two and three minutes.

4.3.2. *Correlations for cardiovascular, test performance physical activity measures with resting heart rate variability.*

Peak oxygen consumption was found to correlate with only one HRV measures, displaying a positive moderate association with ln LF power. Non-significant moderate correlations were displayed for peak oxygen consumption and mean RR, ln rMSSD and ln HF. Ln LF displayed a positive moderate association with duration of GXT, although this just failed to reach statistical significance ( $P = 0.06$ ). There were positive moderate correlations between PA-R score and resting HR, mean RR, ln LF and ln HF (Table 4-2). A moderate but none significant correlation was observed for PA-R with rMSSD.

**Table 4-2. Outcome of Pearson’s correlation analyses for measures of resting heart rate variability with prognostic heart rate parameters, aerobic capacity, test duration and physical activity level.**

	mRR		rMSSD ln		LF ln		HF ln		LF:HF	
	Not controlled for rest HR	Controlled for rest HR	Not controlled for rest HR	Controlled for rest HR	Not controlled for rest HR	Controlled for rest HR	Not controlled for rest HR	Controlled for rest HR	Not controlled for rest HR	Controlled for rest HR
Gender	-0.05 (-0.39 to 0.3)	n/a	-0.02 (-0.36 to 0.33)	n/a	0.20 (-0.15 to 0.51)	n/a	0.01 (-0.33 to 0.35)	n/a	0.26 (-0.09 to 0.55)	n/a
Age	0.39* (0.05 to 0.65)	n/a	-0.23 (-0.53 to 0.12)	n/a	-0.23 (-0.53 to 0.12)	n/a	-0.33 (-0.6 to 0.02)	n/a	0.28 (-0.07 to 0.57)	n/a
Rest HR	-0.98***† (-0.99 to -0.96)	n/a	-0.72***† (-0.85 to -0.5)	n/a	-0.66***† (-0.82 to -0.41)	n/a	-0.67***† (-0.82 to -0.41)	n/a	0.22† (-0.13 to 0.52)	n/a
ΔHR <sub>1 minute</sub>	-0.03† (-0.37 to 0.34)	<b>-0.09†</b> (-0.42 to 0.26)	-0.08 (0.41 to 0.27)	<b>-0.15</b> (0.47 to 0.2)	-0.20 (-0.51 to 0.a5)	<b>-0.27</b> (-0.56 to 0.08)	-0.12 (-0.44 to 0.23)	<b>-0.17</b> (-0.49 to 0.18)	-0.05 (-0.39 to 0.3)	-0.04 (-0.39 to 0.3)
ΔHR <sub>1/3 exercise</sub>	0.18† (-0.17 to 0.49)	<u>-0.11†</u> (-0.44 to 0.24)	0.16 (-0.19 to 0.48)	0.10 (-0.25 to 0.43)	0.10 (-0.25 to 0.43)	0.03 (-0.32 to 0.37)	0.18 (-0.17 to 0.49)	0.13 (-0.22 to 0.45)	-0.09 (-0.42 to 0.26)	-0.08 (-0.42 to 0.26)
HR increase	0.29§ (-0.06 to 0.58)	<u>-0.05§</u> (-0.39 to 0.3)	0.18§ (-0.17 to 0.49)	<u>-0.07§</u> (-0.4 to 0.28)	0.04§ (-0.31 to 0.38)	<b>-0.23§</b> (-0.53 to 0.12)	0.20§ (-0.15 to 0.51)	<u>-0.02§</u> (-0.15 to 0.51)	-0.31§ (-0.59 to 0.04)	-0.23§ (-0.53 to 0.12)
ΔHR	0.56**§ (0.27 to 0.76)	0.02§ (-0.27 to 0.76)	0.49**§ (0.18 to 0.71)	0.15§ (0.18 to 0.71)	0.45** (0.13 to 0.69)§	0.15 (0.18 to 0.71)§	0.49**§ (0.18 to 0.71)	0.20§ (0.18 to 0.71)	-0.20§ (-0.51 to 0.15)	-0.09§ (-0.42 to 0.26)
HR reserve at peak	-0.32† (-0.6 to 0.03)	-0.05† (-0.39 to 0.3)	-0.25 (-0.55 to 0.1)	-0.08 (-0.41 to 0.27)	-0.13 (-0.45 to 0.22)	0.05 (-0.3 to 0.39)	-0.20 (-0.51 to 0.15)	-0.06 (-0.51 to 0.15)	0.17 (-0.18 to 0.49)	0.15 (-0.18 to 0.49)
HRR <sub>1 minute</sub>	0.17† (-0.18 to 0.49)	<b>0.28†</b> (-0.07 to 0.57)	0.29 (-0.06 to 0.58)	<b>0.31</b> (-0.04 to 0.59)	0.25 (-0.1 to 0.55)	0.25 (-0.1 to 0.55)	0.35* (0.01 to 0.62)	<b>0.36*</b> (0.01 to 0.62)	-0.23 (-0.53 to 0.12)	-0.22 (-0.53 to 0.12)
HRR <sub>2 minute</sub>	0.16† (-0.19 to 0.48)	<b>0.20†</b> (-0.15 to 0.51)	0.35* (0.01 to 0.62)	<b>0.37*</b> (0.03 to 0.63)	0.19 (-0.16 to 0.5)	0.18 (-0.17 to 0.49)	0.44* (0.11 to 0.68)	<b>0.46*</b> (0.11 to 0.68)	-0.41* (-0.66 to -0.08)	-0.41* (-0.66 to -0.08)
HRR <sub>3 minute</sub>	0.24† (-0.11 to 0.54)	<b>0.31†</b> (-0.04 to 0.59)	0.37* (0.03 to 0.63)	<b>0.38*</b> (0.04 to 0.64)	0.24 (-0.11 to 0.54)	0.22 (-0.13 to 0.52)	0.43* (0.1 to 0.67)	0.43* (0.1 to 0.67)	-0.39* (-0.65 to -0.05)	-0.39* (-0.65 to -0.05)
$\dot{V}O_{2 peak}$	0.30§ (-0.05 to 0.58)	<b>0.39*§</b> (0.05 to 0.58)	0.31§ (-0.04 to 0.59)	0.21§ (-0.14 to 0.52)	0.40*§ (0.07 to 0.65)	0.33§ (-0.02 to 0.6)	0.30§ (-0.05 to 0.58)	0.20§ (-0.05 to 0.58)	0.03§ (-0.32 to 0.37)	<b>0.12§</b> (-0.32 to 0.37)
Duration of GXT	0.24§ (-0.11 to 0.54)	<b>0.26§</b> (-0.09 to 0.55)	0.18 (-0.17 to 0.49)	0.04 (-0.31 to 0.38)	0.33§ (-0.02 to 0.6)	0.28§ (-0.07 to 0.57)	0.18§ (-0.17 to 0.49)	0.06§ (-0.17 to 0.49)	0.09§ (-0.26 to 0.42)	<b>0.17§</b> (-0.26 to 0.42)
PA-R score	0.40*† (0.07 to 0.65)	0.30† (-0.05 to 0.58)	0.32 (-0.03 to 0.6)	0.23 (-0.12 to 0.53)	0.42* (0.09 to 0.67)	0.35* (0.01 to 0.62)	0.38* (0.04 to 0.64)	0.31 (0.04 to 0.59)	-0.04 (-0.38 to 0.31)	<b>0.07</b> (-0.38 to 0.31)

Data in parentheses represent the 95% confidence/likely interval/range for the effect statistic. HR, heart rate; HRR, heart rate recovery; mRR, mean time between normal r-waves; rMSSD, root mean square of successive differences; LF, low frequency spectral power; HF, high frequency spectral power; LF:HF, the ratio of low to high frequency spectral power; ln, natural logarithm; PA-R, physical activity rating; GXT, graded exercise test. **Bold/italicised** data indicate **increased/decreased** effect size from that observed when HR is not controlled for; underline denotes a change in direction of association from that observed when HR is not controlled for. \*\*\*P<0.001, \*\*P<0.01, \*P<0.05; †Correlation also controlled for age; §Correlation also controlled for age and gender.

4.3.3. *Resting heart rate variability as a predictor of exercise test response.*

$\Delta$ HR, HRR, PA-R score, peak oxygen consumption and duration of GXT were found to be associated with one or more baseline HRV measures. To assess the capacity of baseline measures of HRV to predict the outcome values, these parameters were dichotomised according to values for a positive or negative response. When these dichotomised parameters were entered into binary logistic regression analysis, HF (ln) and ln rMSSD were found to independently correctly predict a low risk HRR response in 97% of cases but predicted a high risk response correctly in only 43% of cases (Tables 4-3 and 4-4). No other significant regressions were observed.

**Table 4-3. Summary of binary logistic regression analysis for heart rate recovery.**

Predictor	<i>B</i>	Wald $\chi^2$	<i>P</i>	Odds ratio
HF (ln)	-1.08	4.80	0.029	0.34

**Table 4-4. Specificity and sensitivity of HF (ln) in predicted heart rate recovery outcome.**

		HRR risk		Percentage correct
		Negative	Positive	
HF(ln)	Negative	25	1	96.2
	Positive	4	3	42.8
Overall Percentage				84.8

#### 4.3.4. *Grouping participants according to prognostic heart rate values.*

Differences in characteristics and dependent measures for participants when grouped according to risk cut-points for resting HR,  $\Delta$ HR, HRR at one minute and physical activity rating (PA-R) are presented in Tables 4-5 to 4-8 respectively. Differences between dependant variables in groups based on highest and lowest quintile values for resting HR and HRR are also included in Tables 4-5 and 4-7 respectively. Only data for participants grouped according to high and low quintiles for  $\Delta$ HR are presented in Table 4-6 as all participants achieved a  $\Delta$ HR greater than the cut-point for increased risk ( $\Delta$ HR < 89 b·min<sup>-1</sup>) according to Jouven *et al.* (2005).

Significant differences in age were observed for groups based on quintiles for resting HR and  $\Delta$ HR (Tables 4-5 and 4-6) but not for HRR (Table 4-7). Differences in the proportion of female participants were observed for groups based on quintiles of resting HR (63% versus 40%, low versus high respectively),  $\Delta$ HR (83% versus 0%, low versus high respectively), and risk cut-points for HRR (57% versus 38%, low versus high risk respectively).

Measures of HRV consistently displayed large and significant effect sizes for all groups and across each of the prognostic HR parameters. Participants in the low risk and low quintile (i.e. lower HR) groups for resting HR demonstrated lower values for all HV measurements except LF:HF (Table 4-5). When grouped according to  $\Delta$ HR, those in the highest quintile displayed significantly higher values for ln LF ( $d = 1.3, P = 0.03$ ). Almost significantly higher values for ln HF ( $d = 1.1, P = 0.05$ ) and rMSSD ( $d = 1.0, P = 0.07$ ) were also observed in this group (Table 4-6). Similar findings were observed for groups based on HRR risk (Table 4-7). Participants below the cut-point for increased risk demonstrated significantly lower values for ln rMSSD and ln HF power. Similarly, significantly lower ln HF values were observed for participants in the lowest quintile group and lower values for ln rMSSD ( $d = 1.2, P = 0.06$ ) and ln LF ( $d = 1.0, P = 0.06$ ) were large and almost reached statistical significance.

The only other measures to demonstrate significant effects were the duration of GXT, peak oxygen consumption and HR increase, all of which demonstrate significant differences between groups based on  $\Delta$ HR (Table 4-6). Participants in the low quintile for  $\Delta$ HR demonstrated a significantly lower duration of GXT (10 min and 14 s), peak oxygen uptake ( $27.9 \text{ ml}\cdot\text{kg}\cdot\text{min}^{-1}$ ) and HR increase ( $93 \text{ b}\cdot\text{min}^{-1}$ ) compared to those in the high quintile (13 min and 18 s,  $41.9 \text{ ml}\cdot\text{kg}\cdot\text{min}^{-1}$  and  $120 \text{ b}\cdot\text{min}^{-1}$ ).

Differences in participant characteristics and dependent measures when grouped according to high ( $\geq 4$ ) or low ( $\leq 3$ ) physical activity levels are listed in Table 4-8. There were significant and moderate differences between groups for mRR, LF and HF power with the high activity group demonstrating higher values for all three measures. A moderate but non-significant difference in rMSSD was observed with higher values present in the high activity group. LF:HF was similar between groups. No measures based on HR demonstrated a significant difference between groups.

**Table 4-5. Characteristics, exercise test responses and heart rate variability of participants grouped according to prognostic cut-off points for resting heart rate.**

	Rest HR (Cut-offs from literature)			Effect size ± 95% CI	Rest HR (lowest and highest quintiles)			Effect size ± 95% CI
	≤ 75 b·min <sup>-1</sup> (n = 23)	> 75 b·min <sup>-1</sup> (n = 10)	P Value		< 56 b·min <sup>-1</sup> (n = 8)	> 69 b·min <sup>-1</sup> (n = 10)	P Value	
Age (yr)	41 ± 12	35 ± 11	0.20	0.52 ± 0.82	49 ± 9	35 ± 11	0.01	1.40 ± 1.0
Female sex - no. (%)	10 (44)	4 (40)	0.56*	n/a	5 (63)	4 (40)	0.02*	n/a
Body mass index (kg/m <sup>2</sup> )	24.6 ± 3.8	25.3 ± 3.9	0.64	-0.18 ± 0.79	22.3 ± 3.1	25.3 ± 3.9	0.10	-0.86 ± 1.0
PA-R score	4.7 ± 1.4	3.7 ± 2.3	0.15	0.54 ± 0.75	5.0 ± 0.9	3.7 ± 2.3	0.16	0.81 ± 1.2
Duration of GXT (min:sec)	11:54 ± 2:14	12:07 ± 2:54	0.81	-0.08 ± 0.67	12:18 ± 1:53	12:07 ± 2:54	0.88	0.08 ± 1.1
$\dot{V}O_{2peak}$ (ml·kg <sup>-1</sup> ·min <sup>-1</sup> )	35.2 ± 8.8	36.3 ± 10.7	0.77	-0.11 ± 0.76	34.9 ± 6.2	36.3 ± 10.7	0.74	-0.17 ± 1.0
$\Delta HR_{1\text{ minute}}$ (b·min <sup>-1</sup> )	23 ± 9	19 ± 11	0.24	0.40 ± 0.68	18 ± 7	19 ± 11	0.24	-0.11 ± 0.19
$\Delta HR_{1/3\text{ exercise}}$ (b·min <sup>-1</sup> )	36 ± 10	31 ± 8	0.18	0.56 ± 0.83	30 ± 7	31 ± 8	0.27	-0.13 ± 0.24
HR increase (b·min <sup>-1</sup> )	107 ± 14	105 ± 13	0.78	0.15 ± 1.1	100 ± 14	105 ± 13	0.44	-0.37 ± 0.99
$\Delta HR$ (b·min <sup>-1</sup> )	119 ± 14	115 ± 13	0.46	0.30 ± 0.82	116 ± 12	115 ± 13	0.94	0.03 ± 0.81
HR reserve at peak (%)	99 ± 5	104 ± 12	0.17	-0.59 ± 0.86	95 ± 4	104 ± 12	0.04*	1.1 ± 1.0

Table continued on next page

Table 4-5 continued

	Rest HR (Cut-offs from literature)		<i>P</i> Value	Effect size ± 95% CI	Rest HR (lowest and highest quintiles)		<i>P</i> Value	Effect size ± 95% CI
	≤ 75 b·min <sup>-1</sup> (n = 23)	> 75 b·min <sup>-1</sup> (n = 10)			< 56 b·min <sup>-1</sup> (n = 8)	> 69 b·min <sup>-1</sup> (n = 10)		
HRR <sub>1 minute</sub> (b·min <sup>-1</sup> )	34 ± 11	34 ± 17	0.93	0.03 ± 0.69	37 ± 14	34 ± 17	0.68	0.19 ± 0.96
HRR <sub>2 minute</sub> (b·min <sup>-1</sup> )	63 ± 17	61 ± 15	0.69	0.13 ± 0.66	63 ± 22	61 ± 15	0.82	0.11 ± 0.98
HRR <sub>3 minute</sub> (b·min <sup>-1</sup> )	75 ± 14	73 ± 10	0.73	0.17 ± 0.99	75 ± 18	73 ± 10	0.73	0.14 ± 0.82
mRR (ms)	1047 ± 141	811 ± 42	<0.001	2.6 ± 0.70	1210 ± 89	811 ± 42	<0.001	6.1 ± 1.7
rMSSD (ln ms)	4.0 ± 0.5	3.3 ± 0.4	0.001	1.6 ± 0.39	4.1 ± 0.4	3.3 ± 0.4	0.001	2.0 ± 1.5
LF (ln ms <sup>2</sup> )	6.5 ± 0.8	5.7 ± 0.6	0.003	1.3 ± 0.85	6.7 ± 0.5	5.7 ± 0.6	0.001	1.8 ± 1.3
HF (ln ms <sup>2</sup> )	6.2 ± 1.0	4.9 ± 1.0	0.001	1.3 ± 0.74	6.2 ± 0.9	4.9 ± 1.0	0.001	1.4 ± 0.74
LF:HF	0.5 ± 0.7	0.9 ± 0.6	0.12	-0.62 ± 0.79	0.7 ± 0.6	0.9 ± 0.6	0.45	-0.33 ± 0.90

Data are presented as mean ± SD; HR, heart rate; HRR, heart rate recovery; mRR, mean time between normal r-waves; rMSSD, root mean square of successive differences; LF, low frequency spectral power; HF, high frequency spectral power; LF:HF, the ratio of low to high frequency spectral power; ln, natural logarithm; PA-R, physical activity rating; GXT, graded exercise test; \*Obtained via Chi Square analysis; CI, Confidence interval; HR reserve: predicted max HR minus resting HR; \*same outcome was found when age was controlled for.

**Table 4-6. Characteristics, exercise test responses and heart rate variability of participants grouped according to prognostic cut-off points for delta heart rate.**

	$\Delta$ HR (highest and lowest quintiles)		P Value	Effect size $\pm$ 95% CI
	> 127 b·min <sup>-1</sup> (n = 9)	< 104 b·min <sup>-1</sup> (n = 6)		
Age (yr)	31 $\pm$ 6	51 $\pm$ 13	0.002	-2.1 $\pm$ 1.1
Female sex - no. (%)	0 (0)	5 (83)	<0.001*	n/a
Body mass index (kg/m <sup>2</sup> )	24.5 $\pm$ 2.8	26.5 $\pm$ 4.2	0.29	-0.57 $\pm$ 1.2
PA-R score	4.7 $\pm$ 1.7	3.8 $\pm$ 1.9	0.39	0.50 $\pm$ 1.3
Duration of GXT (min:sec)	13:18 $\pm$ 0:57	10:14 $\pm$ 3:32	0.05	1.4 $\pm$ 1.4
$\dot{V}O_{2peak}$ (ml·kg <sup>-1</sup> ·min <sup>-1</sup> )	41.9 $\pm$ 7.9	27.9 $\pm$ 7.7	0.005	1.8 $\pm$ 1.1
Rest HR (b·min <sup>-1</sup> )	63 $\pm$ 9	66 $\pm$ 10	0.51	-0.32 $\pm$ 1.1
$\Delta$ HR <sub>1 minute</sub> (b·min <sup>-1</sup> )	21 $\pm$ 6	25 $\pm$ 13	0.43	-0.53 $\pm$ 1.5
$\Delta$ HR <sub>1/3 exercise</sub> (b·min <sup>-1</sup> )	39 $\pm$ 5	31 $\pm$ 13	0.10	1.3 $\pm$ 1.6
HR increase (b·min <sup>-1</sup> )	120 $\pm$ 5	93 $\pm$ 4	<0.001	6.0 $\pm$ 0.85
HR reserve at peak (%)	107 $\pm$ 10	95 $\pm$ 5	0.03	1.5 $\pm$ 1.3
HRR <sub>1 minute</sub> (b·min <sup>-1</sup> )	31 $\pm$ 10	35 $\pm$ 18	0.56	-0.29 $\pm$ 1.1
HRR <sub>2 minute</sub> (b·min <sup>-1</sup> )	61 $\pm$ 12	59 $\pm$ 17	0.80	0.14 $\pm$ 1.2
HRR <sub>3 minute</sub> (b·min <sup>-1</sup> )	74 $\pm$ 12	69 $\pm$ 10	0.40	0.45 $\pm$ 1.2
mRR (ms)	978 $\pm$ 159	921 $\pm$ 140	0.49	0.38 $\pm$ 1.2
rMSSD (ln ms)	4 $\pm$ 0.6	3.4 $\pm$ 0.4	0.07	1.0 $\pm$ 1.1
LF (ln ms <sup>2</sup> )	6.6 $\pm$ 0.8	5.6 $\pm$ 0.7	0.03	1.3 $\pm$ 1.2
HF (ln ms <sup>2</sup> )	6.2 $\pm$ 1.1	5.0 $\pm$ 1.0	0.06	1.1 $\pm$ 1.2
LF:HF	0.6 $\pm$ 0.5	0.7 $\pm$ 0.6	0.76	0.18 $\pm$ 1.3

Data are presented as mean  $\pm$  SD. HR, heart rate; HRR, heart rate recovery; mRR, mean time between normal r-waves; rMSSD, root mean square of successive differences; LF, low frequency spectral power; HF, high frequency spectral power; LF:HF, the ratio of low to high frequency spectral power; ln, natural logarithm; PA-R, physical activity rating; GXT, graded exercise test. \*Obtained via Chi Square analysis. CI, Confidence interval.

**Table 4-7. Characteristics, exercise test responses and heart rate variability of participants grouped according to prognostic cut-off points for heart rate recovery.**

	HRR <sub>1 minute</sub> (Cut-offs from literature*)		P value	Effect size ± 95% CI	HRR <sub>1 minute</sub> (highest and lowest quintiles)		P Value	Effect size ± 95% CI
	> 25 b·min <sup>-1</sup> (n = 26)	≤ 25 b·min <sup>-1</sup> (n = 7)			> 39 b·min <sup>-1</sup> (n = 8)	< 25 b·min <sup>-1</sup> (n = 7)		
Age (years)	38 ± 11	42 ± 15	0.50	-0.31 ± 0.93	40 ± 14	42 ± 15	0.78	-0.14 ± 1.1
Female sex - no. (%)	10 (38)	4 (57)	0.002 <sup>‡</sup>	n/a	3 (38)	4 (57)	0.06 <sup>‡</sup>	n/a
Body mass index (kg/m <sup>2</sup> )	24.9 ± 3.8	24.6 ± 4	0.87	0.08 ± 0.99	24.3 ± 3.1	24.6 ± 4	0.89	-0.08 ± 1.3
PA-R score	4.5 ± 1.7	4 ± 2	0.54	0.27 ± 0.89	4.9 ± 2	4 ± 2	0.41	0.45 ± 1.2
Duration of GXT (min:sec)	11:57 ± 2:20	12:00 ± 2:52	0.97	-0.02 ± 1.1	12:08 ± 3:01	12:00 ± 2:52	0.93	0.05 ± 1.3
$\dot{V}O_{2peak}$ (ml·kg <sup>-1</sup> ·min <sup>-1</sup> )	36.5 ± 8.7	31.8 ± 10.8	0.23	0.48 ± 0.8	38.0 ± 7.6	31.8 ± 10.8	0.22	0.67 ± 1.2
Rest HR (b·min <sup>-1</sup> )	63 ± 9	63 ± 13	0.99	0.001 ± 0.16	60 ± 13	63 ± 13	0.67	-0.23 ± 1.2
$\Delta$ HR <sub>1 minute</sub> (b·min <sup>-1</sup> )	22 ± 9	21 ± 11	0.99	0.10 ± 0.29	19 ± 10	21 ± 11	0.77	-0.19 ± 1.5
$\Delta$ HR <sub>1/3 exercise</sub> (b·min <sup>-1</sup> )	35 ± 10	36 ± 11	0.80	-0.10 ± 0.8	34 ± 13	35 ± 11	0.77	-0.08 ± 0.62
HR increase (b·min <sup>-1</sup> )	107 ± 14	102 ± 11	0.32	0.40 ± 0.81	107 ± 10	102 ± 11	0.38	0.48 ± 1.2
$\Delta$ HR (b·min <sup>-1</sup> )	119 ± 13	114 ± 15	0.37	0.36 ± 0.81	117 ± 9	114 ± 15	0.6	0.25 ± 1.1
HR reserve at peak (%)	100 ± 8	100 ± 7	0.78	0.13 ± 0.94	98 ± 5	100 ± 7	0.54	0.33 ± 1.1
mRR (ms)	974 ± 153	982 ± 206	0.91	-0.04 ± 0.72	1045 ± 217	982 ± 206	0.58	0.29 ± 1.2
rMSSD (ln ms)	3.9 ± 0.5	3.4 ± 0.6	0.048	0.91 ± 0.90	4.0 ± 0.4	3.4 ± 0.6	0.06	1.2 ± 1.3
LF (ln ms <sup>2</sup> )	6.4 ± 0.8	5.8 ± 0.7	0.12	0.74 ± 0.94	6.4 ± 0.5	5.8 ± 0.7	0.06	1.0 ± 1.0
HF (ln ms <sup>2</sup> )	6.0 ± 1.0	4.9 ± 1.1	0.02	1.1 ± 0.87	6.3 ± 0.8	4.9 ± 1.1	0.02	1.5 ± 1.2
LF:HF	0.5 ± 0.7	1.0 ± 0.6	0.15	-0.78 ± 1.1	0.4 ± 0.6	1.0 ± 0.6	0.09	-1.0 ± 1.2

Data are presented as mean ± SD; HR, heart rate; HRR, heart rate recovery; mRR, mean time between normal r-waves; rMSSD, root mean square of successive differences; LF, low frequency spectral power; HF, high frequency spectral power; LF:HF, the ratio of low to high frequency spectral power; ln, natural logarithm; PA-R, physical activity rating; GXT, graded exercise test\*Cut-offs taken from Jouven *et al.* (2005); <sup>‡</sup>Obtained via Chi Square analysis. CI, Confidence interval.

**Table 4-8. Characteristics, exercise test responses and heart rate variability of participants grouped according to physical activity level.**

	PA-R score (high or low activity level)		P Value	Effect size ± 95% CI
	≥ 4 (n = 24)	≤ 3 (n = 9)		
Age (yr)	38 ± 11	43 ± 13	0.28	-0.42 ± 0.84
Female sex - no. (%)	9 (38)	5 (56)	0.002*	n/a
Body mass index (kg/m <sup>2</sup> )	23.6 ± 3.3	28.0 ± 3.4	0.002	-1.3 ± 0.67
Duration of GXT (min:sec)	12:38 ± 26	10:11 ± 1:54	0.01	1.3 ± 0.87
$\dot{V}O_{2\text{ peak}}$ (ml·kg <sup>-1</sup> ·min <sup>-1</sup> )	38.1 ± 8.6	28.8 ± 7.7	0.01	1.1 ± 0.78
Rest HR (b·min <sup>-1</sup> )	62 ± 11	67 ± 6	0.17	-0.59 ± 0.96
$\Delta\text{HR}_{1\text{ minute}}$ (b·min <sup>-1</sup> )	20 ± 9	25 ± 11	0.17	-0.50 ± 0.73
$\Delta\text{HR}_{1/3\text{ exercise}}$ (b·min <sup>-1</sup> )	35 ± 10	34 ± 10	0.38	0.10 ± 0.23
HR increase (b·min <sup>-1</sup> )	107 ± 13	103 ± 15	0.38	0.29 ± 0.72
$\Delta\text{HR}$ (b·min <sup>-1</sup> )	120 ± 13	112 ± 14	0.14	0.59 ± 0.83
HR reserve at peak (%)	100 ± 10	102 ± 7	0.44	0.24 ± 0.63
HRR <sub>1 minute</sub> (b·min <sup>-1</sup> )	35 ± 13	31 ± 12	0.36	0.32 ± 0.76
HRR <sub>2 minute</sub> (b·min <sup>-1</sup> )	64 ± 17	57 ± 13	0.29	0.47 ± 0.96
HRR <sub>3 minute</sub> (b·min <sup>-1</sup> )	76 ± 14	70 ± 11	0.29	0.48 ± 0.98
mRR (ms)	1004 ± 174	901 ± 98	0.04	0.75 ± 0.71
rMSSD (ln ms)	3.9 ± 0.5	3.5 ± 0.7	0.08	0.67 ± 0.77
LF (ln ms <sup>2</sup> )	6.5 ± 0.6	5.7 ± 1.0	0.02	1.0 ± 0.70
HF (ln ms <sup>2</sup> )	6.0 ± 0.9	5.1 ± 1.5	0.045	0.75 ± 0.73
LF:HF	0.6 ± 0.7	0.7 ± 0.8	0.70	0.13 ± 0.75

Data are presented as mean ± SD; HR, heart rate; HRR, heart rate recovery; mRR, mean time between normal r-waves; rMSSD, root mean square of successive differences; LF, low frequency spectral power; HF, high frequency spectral power; LF:HF, the ratio of low to high frequency spectral power; ln, natural logarithm; PA-R, physical activity rating; GXT, graded exercise test. \*Obtained via Chi Square analysis; CI, Confidence interval; A PA-R score of ≤ 3 indicates regular performance of physical activity ranging from none at all (0) to over 1 h/wk<sup>-1</sup> (3) of modest recreation or work (e.g. gardening, golf, bowling, weight lifting); a PA-R score ≥ 4 indicates regular performance of heavy physical activity (e.g. running, cycling, swimming, basketball etc.) ranging from less than 30 min to over 3 h/wk<sup>-1</sup>.

#### 4.4. Discussion.

The primary aim of this study was to identify the strength of relationship between prognostic short-term resting HRV measures and literature defined prognostic HR responses during and following a graded exercise test (GXT). If strong relationships do exist, the use of resting HRV to distinguish between individuals requiring a GXT becomes plausible. A secondary aim was to identify

the ability of HRV to distinguish between individuals when grouped according to cut-offs for increased risk based on:

- I) resting HR;
- II) the HR response during and post GXT;
- III) participants level of physical activity.

The main findings of the present study were threefold. First, associations between resting HRV measurements and HR and cardiorespiratory responses to exercise were at best moderate. Moreover, resting HRV was unable to predict the HR and cardiorespiratory response during GXT. Secondly, vagally mediated measures of HRV (rMSSD, HF) were moderately and independently related to the HR response immediately after exercise and were able to predict a better HRR following GXT. Thirdly, resting HRV was singularly and consistently able to distinguish between individuals when grouped according to cut-points and quintiles for prognostic resting and exercise HR response measures.

#### *4.4.1. Correlations between resting heart rate variability and prognostic heart rate measures.*

The correlation coefficients generated for resting measures of HRV and prognostic HR measures revealed the majority of relationships (60%) were trivial to small, 29% were moderate and 11% were large or greater. This indicates that measures of HRV are generally not well associated with prognostic HR measures, particularly those derived during the GXT.

The present study assessed specific HR responses to exercise that have shown prognostic value in both healthy and various patient populations. These included the change in HR at 1 minute ( $\Delta\text{HR}_{1\text{minute}}$ ; Falcone *et al.*, 2005; Leeper *et al.*, 2007), the change in HR at one-third of GXT duration ( $\Delta\text{HR}_{1/3\text{exercise}}$ ; Leeper *et al.*, 2007), the difference between start and peak HR during GXT (HR increase; Lauer *et al.* 1996; Lauer *et al.*, 1999; Leeper *et al.*, 2007) and the difference between baseline resting and peak HR during GXT ( $\Delta\text{HR}$ ; Cole *et al.*, 1999; Jouven *et al.*, 2005). These measures essentially observe the chronotropic response

to exercise and their ability to predict adverse outcomes was related to possible dysfunction of the underlying autonomic control.

It was hypothesised then that higher values for resting HRV, related to better prognosis and/or decreased risk, would relate to a more favourable chronotropic HR response. This was found not to be the case, with only small to weak associations observed between measures of HRV and HR responses to exercise. In addition, where small associations were observed these were often opposite to anticipated direction (e.g. negative correlations for ln LF with  $\Delta\text{HR}_{1\text{minute}}$  and with HR increase).

#### 4.4.2. *Factors underlying poor association between resting HRV and HR response to exercise.*

A number of possible factors can help explain these findings, the most important relating to likely changes in the mechanisms underlying ANS outflow and cardiac control during exercise compared to resting conditions and the nature of HRV and HR as measures of autonomic tone. The generally weak associations may also result from methodological disparities to and between previous studies.

The existence of transient HR fluctuations at the onset of exercise that are not observed at rest illustrates an altered autonomic control on HR during exercise (Fagraeus and Linnarsson, 1976) may extend to measures of HRV, whereby apparent healthy ANS modulatory activities at rest are not representative of the cardiac autonomic response during exercise. During the first few seconds of exercise there is a rapid increase in HR almost exclusively mediated by vagal inhibition that is continued up to a HR of approximately 100 beats per minute (Araújo, 1985). Beyond this point, sympathetic stimulation as well as hormonal and other non-neural mechanisms progressively increases the HR (Robinson *et al.*, 1966; Lauer *et al.*, 1996; Lauer, 2001; Navare and Thompson, 2003).

It is apparent that there is a dynamic interchange between parasympathetic restraint and sympathetic excitation on the sinoatrial node exerting a chronotropic effect on the heart during exercise. Central and peripheral regulatory mechanisms of HR are likely to be altered under exercise conditions

and this will impact the underlying degree of parasympathetic and sympathetic tone. In contrast, under resting conditions a homeostatic control of HR is maintained by an overriding parasympathetic activation which exerts a decreasing effect on the SA node pacemaker rate ( $100\text{-}120\text{ b}\cdot\text{min}^{-1}$ ) and inhibits the effects of the SNS. There is also likely to be a more balanced interaction between central and peripheral (e.g. baroreceptor) regulatory mechanisms under resting conditions (Robinson *et al.*, 1966). This may in part explain the poor association between the HR response to exercise and measures of resting HRV.

Further support for the idea that resting HRV may be measuring differing autonomic factors to those underlying autonomic control of HR during exercise is the observed lack of association between resting and exercise HRV response (Sandercock and Brodie, 2006). The influences of the PNS and the actions of the baroreflex underlying most measures of resting HRV has been well established (Akselrod *et al.*, 1981; Pomeranz *et al.*, 1985; Pagani *et al.*, 1986; Malliani *et al.*, 1991; Montano *et al.*, 1994; Sleight *et al.*, 1995; Task Force., 1996; Warren *et al.*, 1997; Goldberger, 1999; Cevese *et al.*, 2001; La Rovere *et al.*, 2001; Moak *et al.*, 2008).

The established physiological mechanisms underlying resting HRV, particularly vagally mediated measures, do not relate well to the observed HRV changes during exercise. This is especially the case at higher exercise intensities where an expected increase in absolute power within the LF band (as a proposed measure of sympathetic outflow) does not occur (Pereni *et al.*, 2000; Lewis *et al.*, 2006; Sandercock and Brodie, 2006; Dewey *et al.*, 2007). This observation is common in conditions where high levels of sympathetic tone predominate such as in chronic heart failure sufferers. Under such conditions, autonomic saturation of the sinus node can occur, making it less capable of maintaining a rhythmic modulation and leading to defective integrity of sympathetic innervations (Malik and Camm, 1993; Brunner-La Rocca *et al.*, 2006). A similar effect may occur under maximal exercise conditions where sympathetic tone predominates and may explain observations of abolished or severely diminished power in the LF band during heavy to maximal exercise (Casedei *et al.*, 1995; Perini *et al.*, 2000; Lewis *et al.*, 2006). An expected diminished power in the HF band is normally

observed but a greater proportion of the total power is distributed within the supposedly vagally mediated HF band (Arai *et al.* 1989; Casadei *et al.* 1995; Tulppo *et al.* 1998; Perini *et al.*, 2000; Perini *et al.*, 2002; Lewis *et al.*, 2006; Kaikonen *et al.*, 2008). At higher exercise intensities it appears power in the HF band no longer remains purely autonomic in orientation, with greater contributions from non-neural mechanisms such as sinoatrial stretch (Perlini *et al.*, 1995) and mechanical stimuli (Casadei *et al.*, 1996). It appears that exercise elicits a different pattern of autonomic and non-autonomic modulation of beat-to-beat heart periods that prevents extrapolation of current explanations for resting HRV. The same factors exhibiting change in autonomic modulations during exercise are likely to underline cardiac control during exercise and could explain the dissociations between exercise HR responses and resting HRV observed.

In the present study resting HR was equally (HR increase) or better ( $\Delta\text{HR}_{1/3\text{minute}}$ ,  $\Delta\text{HR}$ ) associated with HR responses to exercise than resting measures of HRV. Moreover, where significant associations between resting HRV measures and exercise HR responses were observed (ln rMSSD, HF and LF with  $\Delta\text{HR}$ ), these appeared to be underlined by the resting HR as demonstrated by large reductions in the strength of associations when controlling for resting HR (Table 4-2).

An underlying role of resting HR in the modulatory activity of the ANS was demonstrated by Van Hoogenhuyze *et al.* (1991) who reported moderate correlations between mean HR and 24 h SDNN ( $r = 0.64$ ). These findings actually reflect the association between circadian changes in HR and HRV and cannot be used to show dependence of HRV on HR on an individual basis. To this effect, Coumel and colleagues (1995) present evidence of some independence between HR and spectral measures of HRV as correlations between mean RR and LF ( $r = 0.46$ ) and HF ( $r = 0.38$ ) powers in 17 individuals only just reach the  $P < 0.05$ . In the present study, observed correlations between these measures were higher and easily reached the  $P = 0.05$  level of significance. The more stable recording conditions presented by the methodology employed here compared to the relatively unstable recording conditions in Coumel *et al.* (1995) may in part explain these differences. Factors such as habitual physical activity, sleep and other daily activities can affect measures of HR and HRV to

differing degrees when obtained from 24 h recordings (Task Force, 1996; Roach *et al.*, 2004).

It could be argued then that resting HRV offers no additional benefit to that of HR in assessing the chronotropic response to exercise. It is important to note that whilst variance in resting HR did explain 32% of the variance in  $\Delta HR$ , it explained none of the variance for  $\Delta HR_{1\text{minute}}$  and only 4% and 10% of the variance for the  $\Delta HR_{1/3\text{minute}}$  and HR increase respectively. An alternative view is that an observed association between HR and HRV is evidence of an undisturbed cardiac physiology and a state of 'harmony' between HRV and HR (Coumel *et al.*, 1995). Alteration of the cardiovascular system leads to deterioration of this harmony and may be reflected as reduced association between measures of HRV and resting HR. The strong association between resting HR and HRV, and subsequent associations to exercise HR responses, demonstrated by participants in the present study may be reflective of a harmonic cardiovascular system.

#### 4.4.3. *Heart rate variability and the HR response following exercise.*

It appears that modulations in autonomic outflow as measured by HRV have little association with the chronotropic response of the heart to maximal exercise. The same, however, cannot be said about the association between resting measures of HRV and the response of the heart following exercise. The strongest associations were consistently shown between measures of HRV and HRR at all time intervals and these were independent of baseline HR. Controlling for resting HR actually lead to increases in the strength of associations between measures of HRV and HRR, particularly those representing modulations in vagally mediated ANS activity (e.g. rMSSD and HF). Regression analysis revealed that these measures significantly and independently predicted a negative HRR response. This finding is of particular significance as it supports the use of resting HRV to identify those less likely to record a low risk HRR response to GXT.

The findings also support the proposal of a vagally mediated control in the decrease in HR following exercise (Robinson *et al.*, 1966; Arai *et al.*, 1989; Imai *et al.*, 1994; Cole *et al.*, 1999; Kannankeril *et al.*, 2004). On cessation of high-

intensity exercise there is an immediate decrease in HR associated with cessation of the primary exercise stimulus from the cerebral cortex of the brain followed by further decreases resulting from parasympathetic reactivation (Ewing *et al.*, 1980; Imai *et al.*, 1994; Nishime *et al.*, 2000). Decreases in HR beyond the first minute after exercise are believed to relate to a metabaroreceptor and baroreceptor-mediated withdrawal of sympathetic activity (Perini *et al.*, 1989). This suggests that vagal measures of HRV should relate better to the degree of HR during this period but this was not found to be the case. Whilst spectral measures of vagal activity (HF) were significantly related to HRR at one min, the vagal time domain measure rMSSD was not. As recovery progressed there was a concomitant increase in associations with both HF and rMSSD. This can be explained by the fact that time domain measures of HRV obtained from short recordings provide less reliable physiological correlates and may be best reserved for longer recordings (Fei *et al.*, 1996; Task Force, 1996). In addition, there is evidence for a lack of parasympathetic effect on HRR from high exercise intensities (Buchheit *et al.*, 2007a). A diminished vagal tone or a reduced effect of vagal activity on HR was attributed to upregulation of sympathetic activity as a result of the exercise demand. A stronger relationship between vagal measures of HRV and HRR following submaximal exercise has also been reported (Evrengul *et al.*, 2006). Combined with those of the present study, such findings suggest the relationship between vagal HRV and early HRR may have been affected by high levels of sympathetic activity. The relationship appeared to be augmented progressively during the recovery period, possibly as a result of increasing parasympathetic and decreasing sympathetic predominance during a return to homeostasis. Alternatively, there are suggestions that the parasympathetic system is not the unique determinant of HRR and a dissociation phenomenon between efferent vagal outflow and its effect of HR could exist (Buchheit *et al.*, 2007b). This could help explain why associations between all measures of HRV and the HRR were no better than  $r = 0.46$ .

The present findings relate to supine measures of HRV and HR responses to upright exercise and seated recovery. Canales *et al.* (2006) provide evidence for a larger post exercise decrease in HR in the supine position compared to standing and relate this to conditions favouring parasympathetic reactivation. In the

present study, a seated position for the recovery period was adopted due to its use by Jouven *et al.* (2005). Others have shown strong prognostic power of HRR when obtained both from supine (Evrengul *et al.*, 2006) and active (Cole *et al.*, 1999) recovery protocols. It is possible that the associations between resting HRV and HRR observed here will differ under such conditions and this warrants further investigation. Findings of the present study are also limited to HRR obtained in the seated position.

An important consideration for the findings present here is the repeatability of HRR. Individuals displaying slow (abnormal) HRR after a first GXT demonstrated normal HRR after a one week follow-up GXT (Davrath *et al.*, 2006). This has implications for the association between resting HRV and HRR which may not be reproducible on each occasion even within the same individual.

#### 4.4.4. *Relationship between aerobic capacity, physical activity and resting heart rate variability.*

Due to the known association between aerobic capacity and physical activity levels with resting HRV (Kenney, 1985; Buchheit *et al.*, 2005; Sandercock *et al.*, 2008) these measures were also assessed in the present study. A higher  $\dot{V}O_{2peak}$  was mildly associated with a higher LF power at rest. Moreover, a greater level of physical activity was mildly associated with a longer RR interval time and higher LF and HF power. Although the strength and significance of relationships were lowered when controlling for resting HR (due in part to a small association between  $\dot{V}O_{2peak}$  and physical activity with resting HR), there was a small association of sympathetic and vagal mediated measures of HRV with aerobic capacity and physical activity independent of age and gender.

There is a general consensus that global (e.g. SDNN) and spectral (e.g. HF) measures of HRV related purely to vagal control of HR are higher in trained compared to untrained individuals (Sandercock and Brodie, 2006). This has been suggested as one of the mechanisms responsible for an observed bradycardia in trained individuals (Ekblom *et al.*, 1973; Smith *et al.*, 1989). It also indicates that those with a higher aerobic capacity demonstrate higher values for resting HRV.

The present findings add some support for this phenomenon. Moreover, the fact that measures of HRV were better related to aerobic capacity suggests modulations in parasympathetic activity and the mechanisms underlying these are better related to aerobic fitness compared to measures of basal vagal tone (i.e. HR). In the present study, resting HR was poorly associated with the aerobic capacity which is perhaps reflective of the homogeneity of participants in terms of training status. It is likely that in a group of less homogenous participants, a wider range in training status would have been reflected in stronger associations with resting HR.

In this group of non-trained individuals, the level of habitual physical activity was significantly related to measure of both purely vagal and mixed sympathovagal mediated HRV. This is in agreement with previous findings whereby higher levels of habitual physical activity were indicative of higher vagal related HRV indexes (Dixon *et al.*, 1992; Rennie *et al.*, 2003; Buchheit *et al.*, 2005) and increased RR interval length (Sandercock *et al.*, 2008). Several clinical studies have demonstrated a cardioprotective effect with a background high in parasympathetic activity (Tsuji *et al.*, 1996; Billman, 2002). The present findings provide moderate support for a plausible link between a higher habitual physical activity level and decreased cardiovascular disease risk based on an increased vagally mediated cardioprotective effect.

The finding of a better association of LF with  $\dot{V}O_{2peak}$  and physical activity perhaps indicates a better sympathovagal mediation of cardiac control relating to a better exercise sympathetic response, the ability to achieve a maximal sympathetic response or both.

In common with the outcomes for prognostic HR responses to exercise, associations between measures of HRV and aerobic capacity and physical activity were at best only moderate. The largest association was found between mRR and  $\dot{V}O_{2peak}$  and LF with PA-R but the two measures of HRV only explained 16% and 12% of the variance in  $\dot{V}O_{2peak}$  and PA-R respectively. Making inferences from these findings would be tenuous at best. There is also

lack of support for reliance on cardiac autonomic activity at rest to identify the peak cardiovascular response to exercise in a healthy adult population.

4.4.5. *Ability of heart rate variability to distinguish between groups based on prognostic heart rate and physical activity groups.*

A well known phenomenon is that acute exercise may elicit cardiovascular abnormalities not present at rest, hence its diagnostic usefulness (Fagraeus and Linnarsson, 1976; Navare and Thompson, 2003). It may also be the case that the magnitude in modulations of ANS activity at rest may underline differences in prognostic HR responses. To assess whether this was the case, resting HRV measurements were compared across groups based on a resting HR less or greater than  $75 \text{ b}\cdot\text{min}^{-1}$ ,  $\Delta\text{HR}$  lower or higher than  $89 \text{ b}\cdot\text{min}^{-1}$  and a HRR lower or higher than  $25 \text{ b}\cdot\text{min}^{-1}$  (Tables 4-5, 4-6 and 4-7). The cut-off values for each of the above measures were taken from the seminal study of Jouven *et al.* (2005) who demonstrated an increased risk of sudden death from myocardial infarction when individuals demonstrated values in the highest (resting HR) and lowest ( $\Delta\text{HR}$ , HRR) quintiles for each measure. Study specific quintiles were also determined for this chapter in an effort to relate findings to the present participant cohort and also due to none of the participants in the present study demonstrating a  $\Delta\text{HR}$  below  $92 \text{ b}\cdot\text{min}^{-1}$ .

Measures of HRV were consistently found to differ between groups based on resting HR and HRR cut-offs and quintiles (Tables 4-5 and 4-7). Participants with a resting HR greater than  $75 \text{ b}\cdot\text{min}^{-1}$  and/or in the highest quintile for resting HR demonstrated significantly lower HRV. The same findings were observed for participants in the lowest quintile (smallest change) for  $\Delta\text{HR}$  (Table 4-6). Those with a HRR below  $25 \text{ b}\cdot\text{min}^{-1}$  and/or in the lowest quintile also had significantly lower HRV. Few other dependant measures were found to differ between groups and no other measure differed consistently across all prognostic HR groups.

Interestingly, a closer look at the data reveals a pattern whereby effects for measures of HRV mediated by parasympathetic activity (e.g. rMSSD, HF) are greater between groups based on parasympathetic mediated HR responses (e.g.

resting HR and HRR). Where groups are compared based on quintiles for  $\Delta$ HR, considered a measure of maximal sympathetic response (Leeper *et al.*, 2007), effects are largest for HRV measures mediated by both sympathetic and parasympathetic activities (e.g. LF).

These findings:

- i) indicate a role for increased modulations in autonomic outflow underlying a better HR response at rest and during and after exercise;
- ii) provide support for the parasympathetic and sympathovagal orientations of standard time and frequency domain measures of HRV;
- iii) offer support to studies promoting the concept that abnormalities in autonomic balance may precede cardiovascular disease (Jouven *et al.*, 2005).

Previous studies reporting a link between poor HR response and risk of developing cardiovascular disease, myocardial infarctions and even sudden death speculate an underlying role of autonomic imbalance resulting in an increased risk (Cole *et al.*, 1999; Jouven *et al.*, 2005). Associations between abnormal resting HR and altered HR response to exercise with sudden cardiac death following myocardial infarct (MI) led Jouven *et al.* (2005) to conclude a susceptibility to cardiac arrhythmias underlined by lower vagal and higher sympathetic outflows respectively. This conclusion was based on referral to previous data demonstrating an increased risk of sudden death and reduced vagal or increased sympathetic activity as measured by HRV and baroreflex responses (Schwartz *et al.*, 1988, 1992 and 1998). The present study provides more direct evidence that supports the speculations of Jouven *et al.* Participants who demonstrated a resting HR greater than the cut-off value for increased risk of  $75 \text{ b}\cdot\text{min}^{-1}$  had significantly lower HRV than those with a resting HR below  $75 \text{ b}\cdot\text{min}^{-1}$ . The fact that the largest differences were found for rMSSD and HF does indeed imply a reduced vagal orientation for an abnormal resting HR. Individuals demonstrating a high risk post-exercise HR response (e.g.  $\text{HRR} < 25 \text{ b}\cdot\text{min}^{-1}$ ) also presented with significantly lower HRV values; again rMSSD and HF showed the largest effects. This supports the idea of greater modulations in vagal

activity (indicative of a healthier ANS) underlying a better HR recovery and a reduced risk profile.

When dichotomised into quintiles, Jouven *et al.* reported individuals with a  $\Delta\text{HR}$  of less than  $89 \text{ b}\cdot\text{min}^{-1}$  (lowest quintile) were four times likely to die from sudden cardiac death compared to the highest quintile group ( $\Delta\text{HR} > 113 \text{ b}\cdot\text{min}^{-1}$ ). The authors suggest that impaired baroreflex sensitivity involving both sympathetic and parasympathetic responses favours circulatory collapse during ventricular tachycardia and manifests as a reduced ability to increase HR during exercise. Our findings for larger differences in LF power between groups based on lowest and highest quintiles for  $\Delta\text{HR}$  may support this view. This is the case particularly when considering recent evidence for a baroreflex-cardiovagal mediation of the LF component of HRV (Moak *et al.*, 2008). It may be that individuals with a greater sympathovagal function at rest have a better capacity to attain maximal sympathetic activation during exercise, possibly due to an exercise response that prevents or minimises the circulatory collapse as hypothesised by Jouven *et al.*

#### 4.4.5.1. Groups based on physical activity level.

There is much interest in measuring cardiac vagal activity due to the observation that it may exert a cardio-protective effect through enhanced cardiac electrical stability (Billman, 2002). Measures associated with vagal outflow such as HRV and HRR are able to provide information as to any impairment of the PNS and as a result have also been related to cardiovascular risk (Tsuji *et al.*, 1996; Cole *et al.*, 1999). To this effect, there is a growing body of evidence demonstrating a positive association between increased physical activity and improved parasympathetic mediated autonomic function as assessed by HRV (Dixon *et al.*, 1992; Rennie *et al.*, 2003; Buchheit *et al.*, 2005) and HRR (Hagberg *et al.*, 1980; Cole *et al.*, 1999; Jouven *et al.*, 2005), thus suggesting a cardio-protective role for physical activity.

The above findings are equivocal however, and a number of studies provide mixed results (Davy *et al.*, 1996; Melanson, 2000; Aubert *et al.*, 2001). Paradoxically, it seems that extremely high levels of physical training are

associated with lower values for parasympathetic indices compared with moderately physically active and sedentary individuals (Buchheit *et al.*, 2004). To identify a possible mechanism for such findings, Buchheit and Gindre (2006) argued that there would be separate associations between HRV and HRR as measures of parasympathetic function with cardiorespiratory fitness and training load. The authors reported that vagally mediated measures of HRV were related to cardiorespiratory fitness but not physical activity level (training load). HRR response showed the opposite relationship.

More recently, Sandercock and colleagues (2008) demonstrated lower levels of cardiac vagal modulation and shorter mean RR in less active compared to more active healthy individuals. The authors also report the paradox of an association between physical activity and RR interval length but no such association for physical activity and measures of HRV when participants are grouped according to tertiles of physical activity. The authors postulate a link between physical activity and RR interval mediated by mechanisms that are not measurable with HRV.

Whilst not directly comparable due to methodological differences, the findings of the present study are somewhat conflicting to those of Buchheit and Gindre (2006) and Sandercock *et al.* (2008). Firstly, when looking at the association between physical activity and measures of HRV, there was a significant, albeit small, positive correlation for PA-R with LF ( $r = 0.35$ ,  $P < 0.05$ ) and a trend for a positive association with HF ( $r = 0.31$ ,  $P = 0.09$ ). Secondly, when grouped according to high and low physical activity levels (Table 4-8), there was a significant and large effect for the difference in LF and a moderate effect for differences in HF. There were no such associations (see Appendix I) or differences for measures of HRR when grouped in the same manner. These findings indicate that the amount of physical activity performed is linked to the magnitude of modulations of ANS activity. Furthermore, the data suggest that the link is not only limited to parasympathetic mediated measures but is present between measures mediated by baroreflex and sympathetic activities.

When considering the cardiorespiratory fitness of each group as assessed by  $\dot{V}O_{2\text{peak}}$ , the high activity group did demonstrate a significantly higher fitness level compared to the low activity group. The fact that magnitude of the effect was large may indicate that the greater cardiorespiratory fitness in part underlines the higher HRV values observed in the high active group. One way to assess this would have been to divide participants into high and low cardiorespiratory fitness categories as in the study of Buchheit and Gindre (2006). In their study, Buchheit and Gindre classified low (“Unfit”) fitness as a  $\dot{V}O_{2\text{max}}$  of less than 50  $\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ . A high (“Fit”) fitness level was classified as a  $\dot{V}O_{2\text{max}}$  of 55  $\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$  or more. In the present study, only two individuals attained a  $\dot{V}O_{2\text{peak}}$  of greater than 50  $\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$  and none higher than 52  $\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ . It was therefore not possible to compare measures of HRV between groups based on cardiorespiratory fitness in a similar manner to that of Buchheit and Gindre (2006). This also highlights the greater homogeneity of the present subject cohort than that of Buchheit and Gindre. The fact that large effects were observed for measures of HRV in such a homogenous group also indicates its discriminative power over other measures of autonomic control such as HRR.

As mentioned, the present findings both contrast and support some of those reported by Sandercock *et al.* (2008). Unlike Sandercock *et al.*, physical activity was equally associated with measures of HRV and RR interval length (Table 4-8). When controlling for resting HR, the association between HRV and physical activity was less affected compared to that of physical activity and RR interval. As already discussed, the low activity group showed significantly lower HRV compared with their more active counterparts. There was also a moderate effect for differences in RR interval between these two groups. These findings are in agreement with Sandercock *et al.* (2008) who demonstrated significantly higher levels for rMSSD and SDNN (standard deviation of normal-to-normal intervals) in moderate compared to lower physically active young adults. The authors reported a trend increased HF power in the higher activity groups whereas the present study found significant differences for both LF and HF.

There are two factors that may explain the differences observed between this study and that of Sandercock *et al.* (2008). Firstly, a difference in group allocation methodologies is one likely factor. Sandercock *et al.* (2008) compared measures of HRV between groups based on “lower”, “moderate” and “higher” physical activity levels as obtained by the Baecke questionnaire (Baecke *et al.*, 1982). This method is comparable to other similar studies (Buchheit and Gindre, 2006). In the present study, groups were formed of high and low activity based on a PA-R score of below or above three. This was a somewhat arbitrary figure selected on the basis that those with a value of three or less would be low to moderately physically active. Moreover, the PA-R questionnaire itself is largely subjective with little objectivity as to the activities relating to a particular score. As a result, there was likely to have been a larger range of physical activity levels in the two groups formed by the present methodology. This may have attenuated the differences in HRV measures observed.

An additional factor that may explain the discrepancies between the two studies is differences in the age of participants. There is a well documented decrease in values of the majority of HRV measures with increasing age (Task Force, 1996; Antelmi *et al.*, 2004). Sandercock *et al.* used a homogenous group of participants with an age range of just 15 years (18 to 33) and therefore results were unlikely to be affected by age. A much wider age range of participants was assessed in the present study (20 to 63) and an effect of age was more likely. Only RR interval showed a significant association with age, but there were trends for a lower HRV with increasing age. When grouped according to physical activity, participants in the high activity group were younger but not significantly. 95% CI reveal that the small effect could have been positively large or negatively moderate. Based on the data for the present study cohort, differences in HRV as a result of physical activity levels appear to be independent of age. However, methodological differences again imply caution when making direct between-study comparisons (Sandercock *et al.*, 2008).

The findings observed suggest that the inclusion of measures of HRV where the HR response before, during and following exercise is being assessed for risk stratification is warranted. It also presents with the intriguing possibility of

strategies to increase the magnitude of modulations in resting autonomic activity as a means to reduce the risk profile when based on the HR response during and after exercise.

#### **4.5. Study limitations and recommendations.**

The present study assessed the relationship between resting HRV and measures of resting, exercising and post-exercise HR in a healthy adult cohort. Whilst the majority of studies demonstrating the prognostic value of these HR measures did so in healthy cohorts, they were often limited to specific and higher risk age groups. The findings of this study may not relate to other, particularly clinical populations.

Recent evidence points to a decreased HRV in obese individuals (Emdin *et al.*, 2001; Kim *et al.*, 2005; Piestrzeniewicz *et al.*, 2007). This may have implications for obese populations whereby a reduced resting HRV could present as a result of abnormal BMI, body fat percentage or due to altered breathing mechanics. One could speculate that the cardiorespiratory and HR response would be poor and is indicative of the increased risk of cardiovascular disease observed in this population (Eckel, 1997). A link between decreased body fat percentage, BMI or both with increased HRV (Emdin *et al.*, 2001) and an improved physiological response to exercise is plausible. It is possible that in obese populations the association between resting HRV and the physiological response to exercise is more pronounced, particularly when weight loss is being sought. Alternatively, in obesity the mechanisms of breathing itself can be altered, whereby the capacity of the thorax to expand is reduced due to an increase in abdominal fat (Enright, 2009). Such alteration in breathing mechanics is likely to affect measures of HRV, particularly those associated with respiratory sinus arrhythmia (e.g. HF power). A decreased vital capacity will result in a lesser Hering-Breuer reflex response which in turn could manifest as a reduced power of HR oscillations at the 0.2 to 0.25 Hz frequency range. However, there is evidence to suggest the Hering-Breuer reflex plays only a minimal role in establishing rate and depth of breathing under resting conditions but becomes more evident during

exercise (West, 2005). This has implications for the measurement of vagally mediated HRV responses to exercise in obese populations.

The use of self-reported physical activity remains a limitation. The PA-R questionnaire may have lacked the power to discriminate between low and high physical activity levels. Participants in both groups may have falsely assigned themselves by under- or over-estimating physical activity due a degree of ambiguity in determining the exercise intensity. The PA-R questionnaire also includes in its estimation of physical activity the performance of non-aerobic activities such as resistance training. Moreover, this type of activity falls into the low physical activity category only (e.g. PA-R score  $\leq 3$ ) and is not considered for those in the high category where only aerobic activities are considered. The influence of mixed aerobic and anaerobic activities on HRV is less pronounced compared to aerobic activity alone (Aubert *et al.*, 2001). The findings for lower HRV in the low physical activity group may be due to the nature of exercises performed by participants in this group.

The PA-R also only considers the level of physical activity for the month preceding its completion. Alternative questionnaires afford longer periods of assessment and greater distinction between sporting and non-sporting activities (e.g. Baecke questionnaire) but are not without limitations (Buchheit and Gindre, 2006; Sandercock *et al.*, 2008). The use of motion measuring devices (e.g. accelerometers) to offer a more accurate measure of exercise intensities has been put forward by a number of authors (Buchheit and Gindre, 2006; Sandercock *et al.*, 2008) and such a notion is echoed by this study.

The precision of the estimates, indicated by 95% CI, was found to be poor for the majority of correlations. Wide 95% CIs not only mean greater uncertainty as to where the true effect estimate lies, but also impacts on the significance of the effect. When the CI (positive or negative) of a correlation includes zero, the effect will be classed as statistically non-significant ( $P > 0.05$ ). The opposite occurs when the CI does not include zero. Where trivial or small effects are observed, then having more precise estimates of the effect are unlikely to change the fact that there is only minor association between two variables. However,

where moderate to large effects exist, then the precision of estimates becomes of greater importance as potentially important effects can be dismissed (due to a  $P$  value  $> 0.05$ ). In addition, it becomes harder to make definite conclusions when CIs are wide. Combined with available resources (Hopkins, 2007), data presented in this study affords future studies the means to calculate required sample sizes for improved precision of effect size estimates from which stronger conclusions could be made.

#### **4.6. Conclusions.**

Measures of resting HRV are not strongly related with prognostic measures of HR obtained during exercise. This is possibly due to changes in the mechanisms underlying autonomic control of the heart under resting and exercising conditions. Heart rate recovery following maximal exercise is related to vagally mediated measures of HRV at rest. This provides support for the parasympathetic orientation of the post-exercise reduction in heart rate and indicates a cardioprotective effect afforded with higher values of vagally mediated HRV. Even in a relatively homogenous participant sample, HRV was the only measurement able to distinguish between participants grouped according to risk based on resting and exercise heart rate and levels of physical activity. This potentially indicates a role of resting autonomic function underlying the poor prognosis from increased resting and decreased exercise HR response. Such a finding warrants the inclusion of HRV measurements in studies assessing the prognostic role of various HR parameters and also presents the possibility of strategies aimed at increasing autonomic modulation as a means to reduce risk through an improved HR response during and after exercise.

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## **CHAPTER 5. THE RANGE OF NORMAL SHORT-TERM HEART RATE VARIABILITY IN HEALTHY ADULTS: A COMPARISON WITH PUBLISHED NORMS AND FACTORS UNDERLYING DISPARATE VALUES.**

### **Abstract.**

The 1996 Task Force paper “Heart rate variability: Standards of measurement, physiological interpretation and clinical use” presents values for normal short-term heart rate variability (HRV). However, these data were approximated from a limited number of small scale studies available at that time. The aim of this study was to review data published since the 1996 Task Force paper and compare these with Task Force norms and with “real-life” data obtained from a large healthy cohort in a clinical setting.

Data from studies published from January 1997 to September 2008 and reporting short-term measures of HRV obtained in normally healthy individuals were collated and factors underlying discrepant values were identified. Retrospective data were also obtained from 1050 healthy adults (717 males and 333 females) assessed for HRV from 2004 to 2006. These data were analysed for gender and age related differences and compared to norm and published data.

Only 44 (12%) of the publications returned met the pre-set inclusion criteria. Short-term HRV values from the literature were lower than Task Force norms. A degree of homogeneity for common measures of HRV in healthy adults was shown across studies. A number of studies demonstrate large inter-individual variations (up to 260,000%), particularly for spectral measures. Both publication and retrospective data demonstrated known gender and age related differences in HRV, however retrospective absolute values were incompatibly high. Explaining this finding was made difficult by the lack of transparency in operating procedures of the device used to obtain the retrospective HRV data.

Data presented here can be used to identify reference ranges for HRV in healthy adult populations but should be done with reference to methodological factors underlying disparate values. These include a systematic failure of studies to recognise the importance of RR data recognition/editing procedures and to query

disparate HRV values observed in normally healthy individuals. There is still a need for large-scale population studies of short-term HRV that cover the full age spectrum. A review of the standards for HRV measurement and updating of the recommendations set out by the 1996 Task Force is also required. These should include methodological transparency for all new technologies.

## 5.1. Introduction.

The aim of the present study was to review the normal range in short-term HRV in light of the significant increase in publications related to HRV throughout the last decade.

Over 12 years ago, the European Society for Cardiology and the North American Society of Pacing and Electrophysiology supported a Task Force which issued a seminal paper: “Heart rate variability: Standards of measurement, physiological interpretation and clinical use” (*Circulation*, 1996; 93, 1043 – 1065). Reference normal values for measures of HRV in healthy adults were published as an appendix to the paper. Some of these values however were approximations from smaller studies involving low subject numbers. This was particularly true for values obtained from stationary, supine 5 min recordings. As a result these data are considered “unsuitable for definite clinical conclusions to be drawn from” (Task Force, 1996, p.380) despite their referral to in the literature (Pichon *et al.*, 2006). The Task Force group stressed the need for large prospective population studies to establish normal HRV standards that should include various age and gender subsets. This need was considered greatest for HRV values obtained from short-term recordings.

Since the 1996 paper, there has been a significant increase in the number of publications assessing and reporting 24 h and short-term HRV in both healthy and clinical populations. A number of recent publications document the role of HRV as an established non-invasive research and clinical tool and point to the growth in the number of articles involving HRV as evidence of such (Chandra *et al.*, 2003; Tulppo and Huikuri, 2004; Cerutti *et al.*, 2006). Cerutti *et al.* (2006) note over 8000 papers related to HRV were published in the period 30 years prior to 2006. Likewise, Pinna *et al.* (2007) report an increase in the number of yearly publications from 391 to 584 in the period 2000 to 2006 respectively. Taylor and Studinger (2006) reported an average of 10 articles related to HRV published weekly during 2005.

### 5.1.1. *Study justification and hypotheses.*

The interest in HRV as a measurement of autonomic function lies in its clinical importance. A reduced HRV is a powerful and independent predictor of an adverse prognosis in patients with heart disease (Kleiger *et al.*, 1987; Nolan *et al.*, 1999; La Rovere *et al.*, 2003) and in the general population (Tsuji *et al.*, 1996; Rennie *et al.*, 2003). Despite the important prognostic power of HRV, it is still not a widely used tool in clinical settings. Key issues relating to this fact include the most appropriate analysis method(s), the recommended length of ECG recordings and the conditions in which they should be assessed (Perkiömäki, 2002). Others relate to the identification of cut-points for prognostic and risk stratification purposes and the expected benefits of HRV analysis in patients' evaluation and treatment. Arguably an additional key factor is the obscurity as to norm values for HRV, without which classifying "abnormal" HRV remains difficult. In the majority of other clinically health related measures (e.g. blood pressure, heart rate, forced vital capacity), established norms are routinely compared to provide an indication of current health status. The question remains as to why this is not the case for the autonomic nervous system and measures of HRV.

The importance of establishing the normal range in HRV values was recognised by the Task Force who stressed the need for large population based studies in healthy individuals of both sexes and across age groups. The variety of articles involving such populations published since the original 1996 Task Force paper may reveal the existence of such data for short-term measures of HRV. By selecting those publications in healthy populations that demonstrate homogeneity based on RR interval recording position and duration, it is possible to determine cross publication means and ranges in values for common measures of HRV. Moreover, by comparing and contrasting the values from each publication, factors contributing to publications demonstrating substantial deviations can be identified.

Two more sources of short-term HRV data obtained in healthy participants were available for use in this study. The first source was "in-house" HRV data

obtained in a small cohort of healthy adults as part of chapters two, three and four of this thesis. Data from chapter two and three have been recently published (Nunan *et al.*, 2008, 2009). Both these provide additional published HRV data with relevance to the current chapter. The second source of HRV data was retrospective data obtained from patients of a private UK hospital who had undergone HRV assessments as part of their routine general health assessment(s). Data from this source would provide HRV values obtained using a commercially available device (NerveExpress<sup>®</sup>, Heart Rhythm instruments, Inc., New Jersey, USA) and in accordance with current clinical practice. With this information comparisons between short-term HRV values observed in the literature and those obtained in a “real-life” situation can be made.

Therefore the present study consists of two parts; Part one involves a critical systematic review of published values for Task Force approved/recommended short-term measures of HRV obtained in healthy adults. Part two consists of the retrospective analysis of HRV measures obtained in a large cohort (n = 1051) of adult clients of a UK private healthcare hospital.

The present study aims to investigate a number of hypotheses based upon previous findings:

- 1) Values for simple mathematical measures of HRV (i.e. time-domain) demonstrate greater homogeneity between studies;
- 2) Measures of HRV demonstrate large inter-individual variation;
- 3) Values for measures of HRV differ by gender and age; females demonstrate higher resting values in vagally related measures of HRV and values for all HRV parameters decrease with age;
- 4) Paced breathing will elicit larger HRV values, particular for measures representing vagal modulations;
- 5) Spectral measures obtained via autoregressive (AR) methods will not differ from those obtained using fast Fourier transformation (FFT);

## **5.2. Methods – Part one.**

### *5.2.1. Search strategy.*

The PubMed and Ovid databases were searched using the mesh term ‘heart rate variability’ and: ‘short’ ‘term’ ‘short-term’ and ‘five’. A second search using 13 terms in conjunction with the previous search terms was then performed. Full text articles were then obtained and their bibliographies searched for further studies not identified electronically. The full set of search strategy terms are illustrated in Figure 5-1.

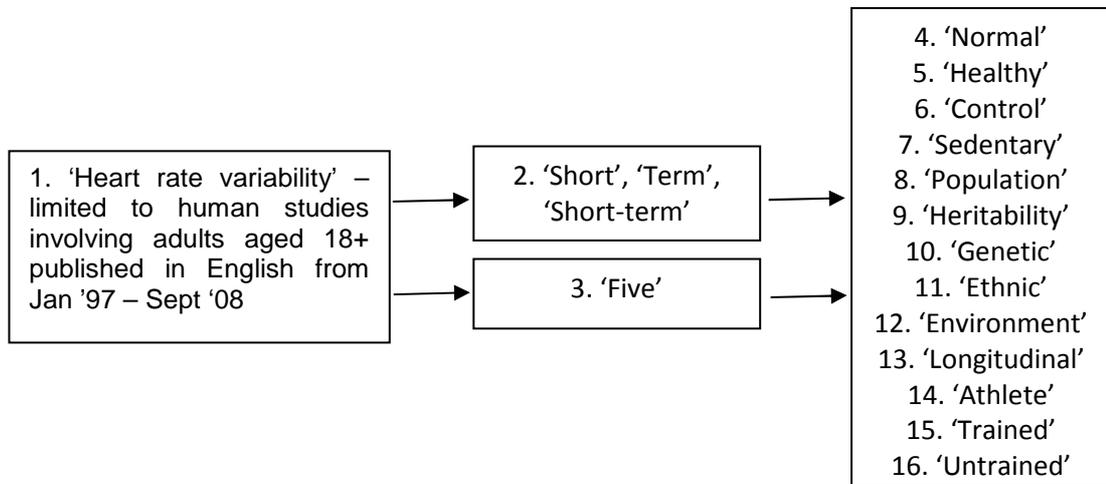
### *5.2.2. Criteria.*

Only English language publications involving healthy adults of at least 18 years were included. As this study was only interested in short-term HRV, publications reporting 24 h measures of HRV were excluded. A sample size greater than 50 was originally an inclusion criterion but was later lowered to 30. The requirement for all publications to present the mean RR interval was also an original criterion but was later revoked. These two actions were performed as only 22 papers were eligible for inclusion when these criterion were applied. Where publications present values for HRV other than in Task Force standardised formats of absolute, log-transformed or back transformed units, these were also excluded.

**Phase 1 (3141 returns)**

**Phase 2**

**Phase 3**



**Figure 5-1. Schematic of search “strings” added to the PubMed and Ovid databases for retrieval of citations assessing short-term measures of HRV in healthy adults.**

### 5.2.3. *Review process.*

The outcome of the search for papers related to short-term HRV in healthy adults is presented in Table 5-1. Presented are the numbers of citations returned, the number of papers accepted and rejected, with the reasons for rejection from each of the search strings outlined in Figure 5-1. From all search strings a total of 630 papers were returned, of which 254 were duplicates leaving a total of 376 original papers. Three hundred and thirty two (88%) of these did not meet the criteria for inclusion in the present study. More specifically, 90 (24%) papers were rejected because they did not measure short-term HRV, 134 (36%) had too small a sample size, 78 (21%) of the papers did not assess healthy subjects, 29 (8%) did not present values for, or did not measure, traditional time and/or frequency domain HRV and finally less than 1% were review articles. Therefore only 44 (12%) of the 376 papers met the inclusion criteria. The sum of the sample sizes from these 44 papers was 21438.

**Table 5-1. Outcome of database search for literature relating to short-term heart rate variability measures in healthy adult participants.**

Search string*	Number of returns	Number accepted	Number rejected	Dup	24h	Reason for rejection			
						Sam	Sub	Meas	Rev
1 and 2 plus:									
4	77	5	72	0	24	26	15	7	
5	113	13	100	22	14	43	7	13	1
6	120	2	118	70	9	16	22	1	
7	4	0	4	3		1			
8	35	3	32	22	6		3	1	
9	0								
10	4	1	3	3					
11	0								
12	4	0	4	4					
13	8	0	8	6	1			1	
14	1	0	1	1					
15	7	0	7	7					
16	2	0	2	2					
1 and 3 plus:									
4	57	7	50	1	22	15	9	3	
5	78	9	69	27	9	27	4	2	
6	62	1	61	39	3	4	15		
7	5	1	4	3		1			
8	22	1	21	17	2		2		
9	1	0	1	1					
10	5	0	5	5					
11	0								
12	8	0	8	7			1		
13	5	0	5	4				1	
14	1	0	1	1					
15	8	1	7	6		1			
16	3	0	3	3					
<b>TOTALS</b>	<b>630</b>	<b>44</b>	<b>586</b>	<b>254</b>	<b>90</b>	<b>134</b>	<b>78</b>	<b>29</b>	<b>1</b>

\*See Figure 5-1 for search terms corresponding to each number; Dup, duplicated return; 24 h, paper reports HRV from 24 h Holter analysis; Sam; sample size  $n < 30$ ; Sub, subjects not free from disease/medication affecting ANS, not adults or both; Meas; indicates i) measures were not taken supine, ii) measures were from RR data greater than 10 min in length, iii) traditional measures were not reported and/or iv) raw values were not presented; Rev, paper is a review article.

### 5.3. Methods– Part two.

#### 5.3.1. Retrospective data analysis.

As well as obtaining data for normal HRV from appropriate previous studies, this paper also includes retrospective HRV data obtained from a large cohort of clients of a British regional private hospital over a two year period dating from 2004 – 2006. The analysis of HRV was performed on over 1000 clients as part of

overall health assessment provisions provided by the hospital at numerous sites located throughout the UK. All assessments were carried out by hospital trained staff. In some cases, a second assessment was conducted and less frequently a third assessment may also have been carried out. The mean time between assessments was  $12.5 \pm 3.8$  months. Stored HRV data were retrieved by the study investigator on a weekly basis from a password protected PC housed at a London based site of the hospital. In order to ensure adherence to the data protection act, the investigator in this study was made an honorary employee of the hospital on a temporary contract basis.

The protocol utilised by the hospital for the recording and analysis of HRV and also for retrieval of retrospective data is described next.

### 5.3.2. *Clients.*

1054 (720 male and 333 female) private hospital clients were assessed for heart rate variability over a two year period from 2004 to 2006. The median and range in age of the male clients was 43 and 23 – 70 years respectively. The median age for the female clients was 42 and ranged from 21 – 60 years. All clients were believed to be of good health, with no known cardiovascular conditions, diabetes or other conditions affecting the heart and/or autonomic nervous system.

### 5.3.3. *Heart rate variability analysis.*

Heart rate variability was assessed using a fully automated system (NerveExpress<sup>®</sup>, Heart Rhythm instruments, Inc., New Jersey, USA) which consists of the patented recording system and analysis software. This system calculates the variability of 192 recorded RR intervals using proprietary algorithms based on 'Frame' theory (Minsky, 1972). The algorithms used by the NerveExpress<sup>®</sup> system have been validated in both healthy and heart disease individuals (Bigger, 1998). Data from the NerveExpress<sup>®</sup> recording system are uploaded to the PC containing the software in real time during the RR interval recordings. The NerveExpress<sup>®</sup> automatically provides the following measures from each RR interval data recording: mean heart rate (HR), the mean squared standard deviation (MSSD), total power (TP), spectral power in the low

frequency (LF) and high frequency (HF) bands and the HF:LF ratio. Resting RR interval data used in the present study were obtained from recordings made in the supine position that lasted the time it took to record 192 RR intervals (approximately 3 minutes 20 seconds when resting HR is 60 b·min<sup>-1</sup>).

#### 5.3.4. *Data retrieval.*

Data stored on a password protected, stand alone PC system and based on cite at the hospital was accessed on a weekly basis over the period from January 2007 to May 2007. Retrieval of data involved access to the PC system which was provided by hospital employees over seeing the conduction of the data retrieval. Once access to the data files was obtained, individual client files were accessed and the required data was extracted. The nature of the programme used to obtain and store the original HRV data did not allow for direct exportation of data. Therefore, a separate Windows Excel<sup>®</sup> spreadsheet was created to which original data were inputted manually. The Excel<sup>®</sup> data file was stored on the same password protected PC as the original data files. A duplicate of the Excel<sup>®</sup> data file was also transported via a portable data storage device to another password protected PC located in the investigator's university office. Once transported, the data stored within the portable device were erased. A hardcopy of each client file was also produced. Where sensitive client information was present, this was screened accordingly. Hardcopy of patient files were stored in a locked filing cabinet within the investigator's university office.

In order to ensure subject anonymity and in accordance with privacy law, client data files were assigned a number starting 01 for the first extracted file. A separate worksheet was created providing client identification according to their corresponding number. This worksheet was created to facilitate obtaining additional client information should a need to do so have arisen. A hardcopy of this file was kept in a secure, lockable filing cabinet housed within a university office separate to that of the investigator and the client data files.

#### 5.3.5. *Statistical analyses.*

The statistical analyses performed differed according to the two parts of this study. Part one involved descriptive analysis of values for HRV measures

reported in the literature which was divided into two sections. In the first section, data are presented for time and frequency measures of HRV most commonly reported within the literature. Measures of HRV often demonstrate skewed distributions thus violating the conditions of normal distribution. In an attempt to ensure normality of data, logarithmic transformation is often performed. Therefore absolute and log-transformed units are presented for the following measures:

1. Standard deviation of normal-to-normal (NN) intervals (SDNN);
2. Root mean square of successive differences between NN intervals (rMSSD);
3. Proportion of successive NN intervals greater than 50 ms (pNN50%);
4. Very low frequency power (VLF), and;
5. TP, LF and HF ( $\text{ms}^2$  and normalised) and the ratio of LF power to HF power (LF:HF).

It is necessary to note that the use of TP and VLF are not recommended by the Task Force due to doubts as to their physiological meaning from short RR recordings. The Task Force also prefers the use of rMSSD to pNN50 due to its mathematical robustness. The inclusion of TP, VLF and pNN50 data is to present the reader with a complete view of the discrepancy between studies in relation to both the Task Force recommendations and norm values. For the reasons given, TP, VLF and pNN50 were not presented in the second section of data analyses involving distribution statistics.

The nature of the data (i.e. analysis of means) for part one of this study do not allow for difference/correlation analyses. As a result standard descriptive statistics are presented including: mean, standard deviation (SD), median and range. Measures such as the coefficient of variation ( $\text{CV} = \text{SD}/\text{mean} \times 100$ ) provide an index of the dispersion of the data. To identify factors underlying between-study differences, values for measures equating to greater than 1.5 SD from the mean publication value were considered as discrepancies. A value of 1.5 SD was chosen to provide a more conservative reference range for consideration of discrepant values. Assessment of possible factors underlying discrepant values was then made on a study-by-study and measure-by-measure

basis. In addition, whilst it is not possible to assess differences between groups using inferential statistics, the use of percentages does allow for relative comparisons between groups. This was applied to the analysis of groups based on gender, differences in spectral decomposition technique (autoregressive versus fast Fourier transformation) and the application of paced breathing versus normal breathing rates.

Retrospective data relating to part two of this study were analysed using both descriptive statistics described above and inferential statistics. The Kolmogorov-Smirnov test was used to assess normality of data sets. Data grouped according to gender were assessed for differences using independent *t*-tests. The Mann-Whitney U test was used to analyse non-parametric data. Data grouped according to age were assessed for differences using one-way analysis of variance (ANOVA). Specific group differences were assessed *post-hoc* using the least significant difference (LSD) test. Only LF power, HF power and the LF:HF ratio were analysed statistically. This was due to a number of reasons. First, the units of measurement for MSSD were not reported and difficult to ascertain from observation alone. This prevented the calculation of the rMSSD. Secondly, the NerveExpress<sup>®</sup> does not report actual interval times from the 192 RR interval recording. This also meant it was not possible to calculate the SDNN parameter. Furthermore, the LF:HF ratio was calculated manually as NerveExpress<sup>®</sup> fails to report this measure automatically. These are some major concerns with the NerveExpress<sup>®</sup> that are discussed later in more detail.

#### **5.4. Results.**

To aid the reader, the results section has been split according to the two parts of the study as follows:

Data related to part one are presented in the following tables:

- Table 5-2 – Participant demographics and details of the methodologies employed for all publications that met the inclusion criteria;
- Table 5-3 – Values for the HRV measures corresponding to each study in Table 5-2;

- Table 5-4 – Summary data including the overall mean, SD, CV and range in values (both absolute and/or log-transformed as appropriate) for each of the HRV measures in Table 5-3;
- Table 5-5 – Compares data in Table 5-4 based on gender;
- Table 5-6 – Compares data in Table 5-4 based on breathing protocol and spectral method;
- Table 5-7 – studies demonstrating data for the inter-individual range in a number of HRV measures.

Readers may notice that Table 5-3 does not contain data related to the study of Rajendra Acharya *et al.* (2004) listed in Table 5-2. This study only presented the range in values for measures of HRV without providing mean data and therefore is only included in Table 5-7 to demonstrate the individual variability of HRV.

For part two of the study, HRV data obtained in a clinical setting using a commercially available system (NerveExpress<sup>®</sup>) are presented. The outcomes for the analysis of differences between groups based on gender are also presented and compared to data observed in the literature. Performing this analysis provides information on “real-life” measures of HRV from current practice and allows for direct comparison to values of research orientated measures of HRV.

#### 5.4.1. *Part one – analysis of short-term HRV data from the literature.*

The outcomes of descriptive statistics performed on data from all included publications are presented in Table 5-3. As hypothesised, time domain measures of HRV demonstrated less variation than those in the frequency domain. The least variable measure was the mean RR interval and the most variable measure was HF power in absolute units. Apart from mean RR, the magnitude of variation was large for all measures of HRV. The magnitude of variation for log-transformed values was smaller than for absolute values but still followed the lower-higher pattern for time-frequency domain measures observed in absolute units. There was a massive range in values across the studies, with ranges for log-transformed measures between 5% (rMSSD) and 8600% (HF) and from 100% (LFnu) to 5200% (LF) for absolute measures.

Compared to males, females demonstrated slightly lower values (< 11%) for all time domain measures of HRV expressed in absolute units (Table 5-5). In the frequency domain, males demonstrated a similar magnitude for lower values in LF (14%) and HF (8%) power. Males showed higher values for LFnu (17%) but HFnu was similar between genders. When expressed in log units, values for LF and HF power were lower (20% and 18% respectively) in females compared to males. Females also demonstrated a lower LF:HF ratio regardless of the unit expressed.

When compared with AR, spectral measures of HRV derived using the FFT method were markedly different (Table 5-6). Studies utilising the FFT method demonstrate lower LF power (in  $\text{ms}^2$  and normalised units) and LF:HF ratio and higher HF power ( $\text{ms}^2$  and normalised).

There were large discrepancies in values for HRV measures when obtained under paced versus normal breathing conditions (Table 5-6). When conducted under the former conditions, values were higher for all measures of HRV except LF power which was higher when breathing rate was not controlled.

Finally, a number of studies revealed large inter-subject variation for the majority of HRV measures, with values for one measure (HF) differing by as much as 260,000% between individuals within the same study (Fagard *et al.* 1998; Table 5-7).

**Table 5-2. Publications reporting short-term measures of heart rate variability in normally healthy adults from 1996 to September 2008: comparison of methodologies.**

Author and date	Participants		Population and nature/criteria of/for inclusion/exclusion	HRV assessment protocol <sup>#</sup>
	Number & gender <sup>b</sup>	Age in years*		
Ho <i>et al.</i> (1997)	23 males 18 females	72 (±8)	Control group to compare against CCHF. No history of CHD, CHF, hypertension, ICP, or use of cardiovascular (CV) health related drugs.	Ambulatory; 2 h; NB; Holter ECG; FFT on 15 min segments, segments excluded if >20% error intervals or duration rejected; TP (0.001 – 0.05), VLF (0.001 – 0.01), LF (0.01 – 0.15), HF (0.15 – 0.5), LF:HF; Only In units; Male and female results combined.
Agelink <i>et al.</i> (1998)	69 (gender NR)	NR	Healthy volunteer controls similar in demographics to that of alcoholic experimental group.	Position NR; 5 min; NB; ECG; Sample rate NR; Artefact identification/removal NR; FFT on 1024 points; rMSSD, LF (0.01 – 0.05), MF (0.05 – 0.15), HF (0.15 – 0.5), LF:HF; Absolute units, spectral parameters reported in Hz <sup>2</sup> ; Male and female results combined.
Fagard <i>et al.</i> (1998)	286 males 301 females		Population based sample.	Supine; 15 min; NB; 12-lead ECG; Sample rate 300 Hz; Ectopic and artefact free section used but method NR; FFT and AR (model 6 – 16) on 512, 256 or 128 beats; mRR; TP (0.05 – 0.50), LF (0.05 – 0.15), HF (0.15 – 0.5), LFnu <sup>1</sup> , HFnu <sup>1</sup> , LF:HF; Absolute units; Male and female results combined
Kageyama <i>et al.</i> (1998)	223 males	31 (±5) Range 21 – 42	Male Japanese white-collar workers from private Tokyo company. Excluded if under medical care, drugs consumed on day of test and < 2 h since previous meal or beverage.	Supine; 3 min; NB; ECG; Sample rate NR; Artefact identification and/or removal NR; AR (model NR); LF (0.05 – 0.15), HF (0.15 – 0.35); Only In units reported.
Piccirillo <i>et al.</i> (1998)	22 males 90 females	Range 20 – 107	Range of healthy subjects not presenting with any medical condition and with normal cognitive status.	Supine; 15 min; NB; ECG; Sample rate 500 Hz; Manual identification and interpolation of artefacts; ECG with >1% artefacts not used; AR (model order 15) on 10 min segment; TP (0.04 – 0.4), VLF (<0.04), LF (0.04 – 0.15), HF (0.16 – 0.4); LFnu <sup>1</sup> , HFnu <sup>1</sup> , LF:HF; Absolute and In units; males and female results combined.

Table 5-2. continued.

Author and date	Participants		Population and nature/criteria of/for inclusion/exclusion	HRV assessment protocol <sup>#</sup>
	Number & gender <sup>b</sup>	Age in years*		
Sinnreich <i>et al.</i> (1998)	147 males <b>147 females</b>	52 ( $\pm 8$ ) <b>51 (<math>\pm 8</math>)</b> Range 35 – 65	Communal kibbutz members. Background information and inclusion/exclusion criteria NR.	Supine, 5 min; NB and PB; 2 channel ECG; RR-I editing NR but referred to elsewhere; AR (model order 16); SDNN, rMSSD, TP (0.0033 – 0.4), VLF (0.0033 – 0.04), LF (0.04 – 0.15), HF (0.15 – 0.4), LF:HF; Only In units; Male and female results separated.
Steinberg <i>et al.</i> (1998)	10 males <b>23 females</b>	49 ( $\pm 13$ )	Control group matched by age to patients with end-stage renal disease.	Supine; 5 min; NB; ECG; Sample rate NR; Artefact identification/removal NP; PSD method referred to; LF (0.04 – 0.15), HF (0.15 – 0.4), LF:HF; Only In units; Male and female results combined.
Kuo <i>et al.</i> (1999)	473 males <b>598 females</b>	Range 40 – 79	Taiwanese volunteers from normal population. Excluded if history or presence of hypo- or hypertension, diabetic neuropathy, ICP, AF, PVC, arrhythmias.	Supine; 5 min; NB; Precordial ECG; Sample rate 256 Hz; Rejection of non-stationary or erroneous RR-I but method NR; Interpolation of RR-I at 7.11 Hz; FFT on 288 s segments; mRR, VLF (0.003 – 0.04), LF (0.04 – 0.15), HF (0.15 – 0.4), LFnu <sup>1</sup> , HFnu <sup>1</sup> , LF:HF; Absolute and In units, only In units analysed; Male and female results separated.
Notarius <i>et al.</i> (1999)	33 males <b>1 female</b>	47 ( $\pm 2$ )	Healthy age-matched control against CHF. No adverse medical history or medications.	Supine; 7 – 10 min; NB; analogue ECG, Sample rate NR; Linear interpolation of missing beats; CGSA on average of 256 beats from 400 – 500 beats; TP (0 – 0.5), LF (0.0 – 0.15), HF (0.15 – 0.5), LF:HF, HF:TP; Absolute units; Male and female results combined.
Dekker <i>et al.</i> (2000)	385 males <b>471 females</b>	53 Range (45 – 64)	Participants from the ARIC study assessing longitudinal atherosclerosis sequelae in a North American probability sample of 15,792 mixed race individuals.	Position NR; 2 min; NB; 12-lead ECG; Sample rate NR; manual abnormal beat identification and removal; only time domain measures assessed. SDNN, rMMSD, SDSD, pNN50; Absolute units; Male and female results combined.

Table 5-2. continued.

Author and date	Participants		Population and nature/criteria of/for inclusion/exclusion	HRV assessment protocol <sup>#</sup>
	Number & gender <sup>b</sup>	Age in years*		
Fagard (2001)	202 males <b>222 females</b>	50 ( $\pm 14$ ) <b>48 (<math>\pm 12</math>)</b> Range 25 – 89	Random sample of healthy adults free from history of MI, diabetes, hypertension, antihypertensive medications.	Supine; 15 min; NB; 12-lead ECG; Sample rate 300 Hz; Manual detection of artefacts/ectopic beats; Outliers considered $> \pm 3$ SD of mRR; FFT and AR (model order 4 – 16) on 512, 256 or 128 beats; mRR; LF (0.05 – 0.15), HF (0.15 – 0.5); LFnu <sup>1</sup> , HFnu <sup>1</sup> , LF:HF; Log units and back-transformed geometric mean; Male and female results separated; Range in values also given.
Melanson (2000)	37 males	Range 25 – 49	Non-smoking, healthy cohort free from CV and other physical diseases/disorders. Grouped according to high, moderate or low activity levels.	Supine, 10 min; PB at 0.17 Hz; ECG; Sample rate 200 Hz; Automated RR detection; Manual detection of error free 5 min segment; RR-I interpolation with 1024-point cubic spline and re-sampled at 5 Hz; FFT; RR-I, SDNN, rMSSD, pNN50, TP (0.04 – 0.3), LF (0.04 – 0.12), HF (0.12 – 0.3), Absolute and I <sub>10</sub> units.
Pikkujämsä <i>et al.</i> (2001)	192 males <b>200 females</b>	50 ( $\pm 6$ ) <b>51 (<math>\pm 6</math>)</b> Range 40 – 59	Age and sex matched healthy middle-aged controls free from hypertension, other cardiac and respiratory diseases and diabetes.	Supine and seated; 13 min; NB; ambulatory ECG; Sample rate NR; Autonomic and manual removal of premature beats; $< 15\%$ removed beats included in analysis; Linear detrend applied; AR (model order 20); LF (0.04 – 0.15), HF (0.15 – 0.4), LFnu <sup>2</sup> , HFnu <sup>2</sup> , LF:HF; Absolute and ln units; Male and female results separated and combined; range in values provided for combined data.
Tulppo <i>et al.</i> (2001)	30 males	29 ( $\pm 6$ )	Healthy volunteers	Supine; 15 – 25 min; PB; ECG and Polar HRM; Sample rate 1000 Hz; manually editing of artefacts; AR (model NR); TP (0.04 – 0.4), LF (0.04 – 0.15), HF (0.15 – 0.4), LFnu and HFnu method NR, LF:HF; Absolute and ln units.
Sucharita <i>et al.</i> (2002)	94 males	Range 18 – 80	Healthy cohort free from history of asthma, diabetes, hypertension, and other CV disease and not taking medication.	Supine, 10 – 12 min; NB; Sample rate 1000 Hz; Automated RR detection, RR-I re-sampled at 2 Hz, linear trend removal; FFT on eight data sets of 256 points; HF (0.15 – 0.4), HFnu <sup>1</sup> ; Absolute units.

Table 5-2. continued.

Author and date	Participants		Population and nature/criteria of/for inclusion/exclusion	HRV assessment protocol <sup>#</sup>
	Number & gender <sup>b</sup>	Age in years*		
Yildirim <i>et al.</i> (2002 – part 1)	43 females	29 (±6) Range 20 – 38	Young health personnel free from cardiac or neurological symptoms and use of hormone replacement, CV or other medications. HRV obtained during the follicular phase of the menstrual cycle.	Supine; 8 min; NB; ECG; Sample rate NR; Automated identification of RR-I marked manually or interpolated; artefacts identified manually; AR on 5 min segment; LF (0.03 – 0.15), HF (0.15 – 0.4), LFnu & HFnu method NR; LF:HF; Absolute units.
Yildirim <i>et al.</i> (2002 – part 2)	As part 1	As part 1	As part 1 except HRV assessed during luteal phase of menstrual cycle and compared to results in part 1	As part 1
Geelen <i>et al.</i> (2003)	36 males <b>38 females</b>	59 (±5)	50 – 70 year old healthy individuals with no history of CV disease, diabetes, asthma, high blood pressure. Females all post-menopause.	Position NR; 10 min; PB; 12-lead ECG; Sample rate NR; Manual artefact identification/removal; Linear trend removal and zero padding then FFT on 4 - 10 min RR-I data; SDNN, rMSSD, LF (0.05 – 0.15), HF (0.15 – 0.5); Absolute and log 10 <sup>-2</sup> units; Male and female results combined.
Gerritsen <i>et al.</i> (2003)	98 males <b>93 females</b>	62 (±7) <b>63 (±7)</b> Range 50 – 75	Healthy older volunteers with normal glucose tolerance and free from neurological disorders and adverse pulmonary, CV, and hypertensive history.	Supine; 3 min; NB; Bipolar ECG; Sample rate NR; Artefact detection/interpolation NR; Spectral analysis method NR; mRR, SDNN, LF (0.04 – 0.12), HF (0.12 – 0.4), LFnu <sup>2</sup> ; log units back-transformed to geometric mean; Male and female results separated.
Jurca <i>et al.</i> (2004)	88 females	57 (±6)	Sedentary postmenopausal who were non-smokers, normotensive, had no history of respiratory or cardiac diseases and with a stable HRT status.	Supine; last 10 min of 25 min; PB at 0.2 Hz; Polar Advantage HRM; Manual and automated RR filtering of artefacts/ectopic beats, removed RR interval replaced with average; AR (model order NR); SDNN, TP (0.00 – 0.04), LF (0.04 – 0.15), HF (0.15 – 0.4). LFnu <sup>1</sup> , HFnu <sup>1</sup> ; Absolute and ln units.
Rennie <i>et al.</i> (2003)	2,334 males <b>994 females</b>	56 <b>57</b> Range 45 – 68	Non-industrial UK civil servants originally recruited for epidemiological study between 1985 and 1988 then assessed for HRV between 1997 and 1999 (UK Whitehall study II)	Supine; 5 min; NB; 12-lead ECG; Sample rate 500Hz;; automated extraction/interpolation of ectopic beats; rejected if >10% ectopic beats; AR; LF (0.04 – 0.15), HF (0.15 – 0.4); Absolute units; Male and female results separated.

Table 5-2. continued.

Author and date	Participants		Population and nature/criteria of/for inclusion/exclusion	HRV assessment protocol <sup>#</sup>
	Number & gender <sup>b</sup>	Age in years*		
Virtanen <i>et al.</i> (2003)	71 males <b>79 females</b>	47 (±8) 48 (±8)	Residents of southwest Finish town free from diseases and medications affecting the ANS.	Supine; 5 min; PB; 12-lead ECG; Manual artefact identification and removal; Data excluded if absence of ≥4 min artefact free segment, detrend and interpolation method NR, RR-I resampled at 5 Hz; FFT; LF (0.04 – 0.15), HF (0.15 – 0.4); Absolute units; Male and female results separated.
Rajendra Acharya <i>et al.</i> (2004)	75 males <b>75 females</b>	Range 5 – 70	Healthy Chinese individuals grouped into four age groups; 10 ± 5 (n=25), 25 ± 10 (n=50), 40 ± 15 (n=40) and 60 ± 5 (n=35) years.	Supine; 20 min; NB; ECG in lead II configuration; Sample rate of 400 Hz; Artefact editing NR; FFT used to calculate ULF (<0.003) and VLF (0.003 – 0.04), AR (model NR) used for LF (0.04 – 0.15) and HF (0.15 – 0.4), SDNN, rMSSD, pNN50; Non-linear methods also used; Only variation in values shown; Male and female results combined.
Laitinen <i>et al.</i> (2004)	29 males <b>34 females</b>	Range 23 – 77	Healthy volunteers able to tolerate HUT without cardioneurogenic reflex syncope. Free from hypertension and other systemic disease and non-smokers.	Supine following 3 h bed rest; 5 min, PB at 0.2 Hz; 12-lead ECG, Sample rate 200 Hz, RR-I re-sampled at 5 Hz; Smoothed FFT on last 2.5 min; TP (0 – 0.4), LF (0.04 – 0.15), HF (0.15 – 0.4), LF:HF as a percentage; Absolute units; Male and female results separated.
Liao <i>et al.</i> (2004)	2,917 males <b>3,867 females</b>	62 (±6) Range 45 - 64	Participants from the ARIC study assessing longitudinal atherosclerosis sequelae in a North American probability sample of 15,792 mixed race individuals.	Supine; 5 min; NB; 3-lead ECG; Sample rate 1000 Hz; manual and automated RR-I artefact identification and re-sampling; FFT; SDNN, LF (0.04 – 0.15), HF (0.15 – 0.4), Absolute units for SDNN and log units for LF and HF. Male and female results combined.
Piccirillo <i>et al.</i> (2004)	105 males <b>85 females</b>	54 (±1)	Healthy normotensive controls.	Supine; 5 min; PB; Single lead ECG; Sample rate 500 Hz; Automated identification of normal RR-I, artefact removal NR; AR (model NR); mRR; TP (NR), VLF (<0.03), LF (at 0.1), HF (at 0.25); LF:HF; Back transformed median and inter-quartile range; Male and female results combined.

Table 5-2. continued.

Author and date	Participants		Population and nature/criteria of/for inclusion/exclusion	HRV assessment protocol <sup>#</sup>
	Number & gender <sup>b</sup>	Age in years*		
Sandercock <i>et al.</i> (2004)	20 males <b>10 females</b>	34 ( $\pm$ 9) <b>27 (<math>\pm</math>8)</b> Range 19 – 54	Healthy volunteers defined by absence of CV disease and medications affecting HRV.	Supine; 5 min; NB and PB; Simultaneous recordings with 12-lead ECG, ambulatory 5-lead ECG and bipolar 2-lead chest strap; system specific automated artefact removal and interpolation; FFT for all three systems; mRR, SDNN, rMSSD, LF (0.04 – 0.15), HF (0.15 – 0.4), LFnu & HFnu method NR, LF:HF; Absolute units; Male and female results combined
Schroeder <i>et al.</i> (2004)	32 males <b>31 females</b>	52 Range 45 – 64	Healthy middle-aged volunteers without history of diabetes, CHF, renal disease, pacemaker, and antiarrhythmic medications.	Supine; 6 min; NB; 3-lead ECG; automated artefact identification and interpolation; Smoothed FFT; mRR, SDNN, rMSSD, LF (0.04 – 0.15), HF (0.15 – 0.5), LFnu <sup>2</sup> , HFnu <sup>2</sup> , LF:HF; LF and HF presented using scientific notation; Absolute and ln units; Male and female results combined.
Hemingway <i>et al.</i> (2005)	2,197 males	Range 45 - 68	Non-industrial white European civil servants at phase 5 of UK Whitehall II study (between 1997 and 1999).	Supine; 5 min; NB; 12-lead ECG; Sample rate 500 Hz; automated extraction/interpolation of ectopic beats; rejected if >10% ectopic beats; AR; LF (0.04 – 0.15), HF (0.15 – 0.4); Absolute units.
Lucini <i>et al.</i> (2005)	50 males <b>82 females</b>	42 ( $\pm$ 2)	Healthy middle-aged cohort as control group for comparison to psychologically stressed patients.	Supine; 10 min; NB; 2-way wireless ECG; sample rate 300 samples/sec; editing for artefacts NR; AR (model NR); mRR, VAR, LF (0.03 – 0.14), HF (0.15 – 0.35), LFnu <sup>1</sup> , HFnu <sup>1</sup> , LF:HF; Absolute values; Male and female results combined.
Mörner <i>et al.</i> (2005)	64 males <b>57 females</b>	Range 20 – 90	Healthy controls free from hypertension, LVH, respiratory or ECG disorder and HD. Divided into three age groups: young (<40), middle-aged (40 – 60), old (>60).	Supine; 2 min; NB; 12-lead ECG; Sample rate NR; Artefact identification/removal NP; Cubic spline interpolation at 2 Hz; mean and linear trends removed; AR (model NR); TP (0.003 – 0.45), LF (0.04 – 0.15), HF (0.15 – 0.45), LF:HF; Only ln units; Male and female results combined.
Buchheit and Gindre (2006)	55 males	34 ( $\pm$ 2)	Healthy middle-aged volunteers with no history or clinical signs of CV or pulmonary disease, use of medications and ECG abnormalities. Grouped according to fitness level and training load.	Supine, 5 min, PB; Polar S810 HRM; Sample rate NR; Manual artefact identification; interpolation procedure NR; detrend but NR; FFT; mRR, SDNN, rMSSD, pNN50, LF (0.04 – 0.15), HF (0.15 – 0.5), HFnu <sup>2</sup> ; Absolute and ln units.

Table 5-2. continued.

Author and date	Participants		Population and nature/criteria of/for inclusion/exclusion	HRV assessment protocol <sup>#</sup>
	Number & gender <sup>b</sup>	Age in years*		
Evrengul <i>et al.</i> (2006)	21 males <b>17 females</b>	48 (±8)	Healthy adults with atypical angina pectoris, negative exercise test and normal angiograms enrolled as a control group in CAD study.	Supine; 1 h; NB; 3-channel Holter ECG; Sample rate NR; Artefacts/ectopic beats excluded from analysis but method of detection/removal NR; Detrend applied to HR series but method NR; FFT; SDNN, SDANN, rMSSD, pNNS50, TP (0.003 – 0.5), LF (0.004 – 0.15), HF (0.15 – 0.5), LF:HF; Absolute units; Male and female results combined.
Park <i>et al.</i> (2006)	413 males	73 (±7)	Original participants from the Normative Aging Study recruited in 1963 assessed for HRV from 2000 to 2004. Participants were free from chronic medical conditions.	Seated; 7 min; NB; 2-channel ECG; Sample rate 256 Hz; manual identification of artefacts; FFT on 4 min RR-I data; SDNN, LF (0.04 – 0.15), HF (0.15 – 0.4), LFnu <sup>1</sup> , HFnu <sup>1</sup> ; LF:HF; Absolute units.
Pichon <i>et al.</i> (2006)	41 males <b>15 females</b>	Range 18 – 64	Health volunteers free from known cardiac, circulatory, respiratory or other diseases.	Seated; 7 min; NB; Polar Vantage NV HRM; manual interpolation/extrapolation of artefacts and re-sampled at 2H; detrend but method NR; FFT and AR (model order 12) on 256 RR-I; LF (0.045 – 0.15), HF (0.15 – 0.4) HFnu <sup>2</sup> ; Absolute units; Male and female results combined.
Britton <i>et al.</i> (2007)	1,417 males <b>582 females</b>	56 (±7) Range 44 – 69	Non-industrial UK civil servants originally recruited for epidemiological study between 1985 and 1988 then assessed for HRV between 1999 and 2004 (UK Whitehall II study).	Supine; 5 min; NB; 12-lead ECG; Re-sampled at 500 Hz; Artefact detection/removal/interpolation NR; AR (model NR); SDNN, LF (0.04 – 0.15), HF (0.15 – 0.4); In units back-transformed to geometric mean; Male and female results separated.
Kobayashi (2007)	75 males	Range 20 – 61	NR	Supine; 4 min; NB; Polar S810i HRM; RR-I correction and rejection criteria NR; FFT from 1024 points; Only LF (0.04 – 0.15), HF (0.15 – 0.35); Absolute and log-transformed units.
Kurosawa <i>et al.</i> (2007)	66 females	Range 19 – 20	College students in Akita, Japan not suffering from CV disease, diabetes or using medication.	Supine, 5 min; NB; ECG; Sample rate 1000 Hz; Artefact identification/removal NP; AR (model NR); LF (0.01 – 0.15), HF (0.15 – 0.4), LF:HF; Absolute units and range shown.

Table 5-2. continued.

Author and date	Participants		Population and nature/criteria of/for inclusion/exclusion	HRV assessment protocol <sup>#</sup>
	Number & gender <sup>b</sup>	Age in years*		
Pinna <i>et al.</i> (2007)	18 males <b>21 females</b>	38 Range 22 – 56	Healthy volunteers free from chronic and acute disease and use of medication.	Supine; 8 min; PB at 0.2 5Hz; ECG; RR-I re-sampled at 2 Hz by cubic spline interpolation and detrended via least-square second-order fitting; AR (model order 26) and BT on middle 5 min; LF (0.04 – 0.15), HF (0.15 – 0.45), LFnu <sup>2</sup> ; LF:HF; Absolute and ln units analysed ; Male and female results combined.
Uusitalo <i>et al.</i> (2007 – part 1)	208 males	53 (±8) Range 40 – 73	Monozygotic (MZ) twins from the Twin Spine Study. 104 considered healthy as free from physiological and/or psychological diseases/disorders. Medication not controlled for.	Supine; 5 min; PB at 0.2 Hz; ECG; Sample rate NR; second-order polynomial interpolation; AR (model order 14) on ectopic free region of RR-I; mRR, rMSSD, LF, HF, LF:HF; Absolute units.
Uusitalo <i>et al.</i> (2007 – part 2)	296 males		Dizygotic (DZ) twins from the Twin Spine Study. 173 considered healthy as free from physiological and/or psychological diseases/disorders. Medication not controlled for.	As part 1
Huang <i>et al.</i> (2008)	33 females	36 (±13)	Age-matched control group.	Supine; 15 min; NB; ECG; Sample rate 500 Hz; patient excluded if deleted arrhythmias >5%; FFT on 512 stationary RR-I; mRR, SDNN, VLF (0.01 – 0.04), LF (0.04 – 0.15), HF (0.15 – 0.40), LFnu <sup>3</sup> , HFnu <sup>3</sup> , LF:HF; Absolute units.
Mehlsen <i>et al.</i> (2008)	15 males <b>20 females</b>	32 (±2)	Age and sex matched controls in cardioinhibitory syncope study showing normal response to head-up tilting.	Supine; 10 min; NB; 12-lead ECG; Sample rate 1000 Hz; Artefact identification/removal NP; FFT with 1024 points on 300 cardiac cycles; RR-I, SDNN, LF (0.04 – 0.15), HF (0.15 – 0.4); Only normalised units; Male and female results combined.

Table 5-2. continued.

Author and date	Participants		Population and nature/criteria of/for inclusion/exclusion	HRV assessment protocol <sup>#</sup>
	Number & gender <sup>b</sup>	Age in years*		
Sandercock <i>et al.</i> (2008)	47 males <b>45 females</b>	23 ( $\pm$ 2) Range 18 – 33	Young, healthy and moderately active volunteers, classed as neither sedentary nor highly active.	Supine; 10 min; PB at 0.25 Hz; Polar S810 HRM; automated artefact filtering and interpolation at 4 Hz; FFT on 300 s sample; RR-I, SDNN, rMSSD, LF (0.04 – 0.15), HF (0.15 – 0.4), LFnu <sup>2</sup> , HFnu <sup>2</sup> , LF:HF; Absolute and In units; Male and female results combined.
Nunan <i>et al.</i> (2008)	19 males <b>14 females</b>	36 Range 20 – 59 <b>48</b> <b>Range 25 - 63</b>	Healthy adult population as defined by absence of CV and other chronic diseases used to identify agreement between two different HRV systems	Supine, 10 min; NB, 12-lead ECG and Polar S810 HRM; Sample rate 1000 Hz; Automated artefact identification and interpolation; FFT and AR on last 5 min; RR-I, SDNN, rMSSD, LF (0.04 – 0.15), HF (0.15 – 0.4), LFnu <sup>2</sup> , HFnu <sup>2</sup> , LF:HF; Absolute and In units; Male and female results combined.
Nunan <i>et al.</i> (2009)	19 males <b>14 females</b>	36 Range 20 – 59 <b>48</b> <b>Range 25 - 63</b>	Healthy adult population as defined by absence of CV and other chronic diseases used to identify the validity of the Polar S810 HRM.	Supine, 10 min; NB, 12-lead ECG and Polar S810 HRM; Sample rate 1000 Hz; Automated artefact identification and interpolation; FFT and AR on a 5 min segment; RR-I, SDNN, rMSSD, LF (0.04 – 0.15), HF (0.15 – 0.4), LFnu <sup>2</sup> , HFnu <sup>2</sup> , LF:HF; Absolute units; Male and female results combined.

<sup>b</sup>Bold letters and values refer to female participants; \*Values are mean ( $\pm$ SD) unless otherwise stated; <sup>#</sup>Left to right relates to recording position; recording duration; Paced (PB) or natural breathing (NB); RR interval recording device; sampling rate for RR-I recordings; data correction and interpolation procedure; spectral decomposition method; time domain and frequency domain HRV measures reported; mode of data presentation; and finally, the use of data by gender. <sup>1</sup>Method for calculation:  $LF/(TP - VLF) \times 100$  and/or  $HF/(TP - VLF) \times 100$ ; <sup>2</sup>Method for calculation:  $LF/(LF + HF) \times 100$  and/or  $HF/(LF + HF) \times 100$ ; <sup>3</sup>Method for calculation:  $LF/(LF + TP)$  and/or  $HF/(HF+TP)$ ; NR, not reported; NP, not performed; ECG; electrocardiogram; HRM, heart rate monitor; ANS, autonomic nervous system; PB, paced breathing; FFT, fast Fourier transformation; AR, autoregressive; BT, Blackman-Tukey; RR-I, RR interval(s); mRR, mean RR interval; SDNN, standard deviation of normal-to-normal intervals; rMSSD, root mean square of successive differences; pNN50, proportion of normal-to-normal interval differences greater than 50 ms; VAR, variance; TP; total spectral power; ULF, ultra low frequency spectral power; VLF, very low frequency spectral power; LF, low frequency spectral power; MF, mid frequency spectral power; HF, high frequency spectral power; LF:HF, ratio of low frequency power to high frequency power; HF:TP, ratio of high frequency power to total power; nu, normalised units; ln, natural logarithm; HUT, head-up tilt; HRT, hormone replacement therapy; CHF, congestive heart failure; CCHF, chronic congestive heart failure; CAD, coronary artery disease; HD, heart disease; LVH, left ventricular hypertrophy; ICP, implanted cardiac pacemaker; AF, atrial fibrillation; PVC, premature ventricular contractions.

**Table 5-3. Publications reporting short-term measures of heart rate variability in normally healthy adults from 1996 to September 2008: heart rate variability measurement values.**

Author and data	Heart rate variability measure										
	mRR (ms)	SDNN (ms)	rMSSD (ms)	pNN50 (%)	TP (ms <sup>2</sup> )	VLF (ms <sup>2</sup> )	LF (ms <sup>2</sup> )	LFnu	HF (ms <sup>2</sup> )	HFnu	LF:HF
Ho <i>et al.</i> (1997)	NR	NR	NR	NR	3.13 ln	1.94 ln	2.05 ln	NR	0.08 ln	NR	1.98 ln
Agelink <i>et al.</i> (1998)	NR	NR	32	NR	NR	309 <sup>#</sup>	256 <sup>#</sup>	NR	266 <sup>#</sup>	NR	2.0
Fagard <i>et al.</i> (1998)	942	NR	NR	NR	1143	691	<u>229</u> <u>194</u> <sup>§</sup>	<u>38</u> <u>34</u>	<u>290</u> <u>222</u>	<u>47</u> <u>38</u>	
Kageyama <i>et al.</i> (1998)	NR	NR	NR	NR	NR	NR	5.78 ln	NR	5.69 ln	NR	NR
Piccirillo <i>et al.</i> (1998) ( <i>data are for three age groups: ≤40, ≥41≤60, ≥61≤80</i> )	NR	NR	NR	NR	8.01 ln 6.90 ln 6.90 ln	7.32 ln 6.39 ln 6.45 ln	6.59 ln 5.21 ln 4.84 ln	56 55 51	6.15 ln 4.83 ln 4.46 ln	38 38 36	2.0 1.7 1.8

Table 5-3. continued.

Author and data	mRR (ms)	SDNN (ms)	rMSSD (ms)	pNN50 (%)	TP (ms <sup>2</sup> )	VLF (ms <sup>2</sup> )	LF (ms <sup>2</sup> )	LFnu	HF (ms <sup>2</sup> )	HFnu	LF:HF
Sinnreich <i>et al.</i> (1998)	NR	3.71 ln <b>3.57 ln</b>	3.26 ln <b>3.26 ln</b>	NR	6.61 ln <b>6.33 ln</b>	5.80 ln <b>5.44 ln</b>	5.40 ln <b>5.02 ln</b>	NR	4.84 ln <b>4.85 ln</b>	NR	5.19 ln <sup>†</sup> <b>4.78 ln</b>
Steinberg <i>et al.</i> (1998)	NR	NR	NR	NR	NR	NR	5.78 ln	NR	5.51 ln	NR	1.0 ln
Kuo <i>et al.</i> (1999)	792 <b>794</b>	NR	NR	NR	NR	5.65 ln <b>5.67 ln</b>	4.61 ln <b>4.59 ln</b>	50 <b>46</b>	3.96 ln <b>4.15 ln</b>	27 <b>30</b>	0.65 ln <b>0.45 ln</b>
Notarius <i>et al.</i> (1999)	NR	NR	NR	NR	980	NR	199	NR	98	NR	11.6
Dekker <i>et al.</i> (2000)	NR	34	22	8	NR	NR	NR	NR	NR	NR	NR
Fagard (2001)	978 909	NR	NR	NR	1379 <sup>G</sup> 3.14 ln <b>1189<sup>G</sup></b> <b>3.08 ln</b>	NR	261 <sup>G</sup> 2.42 ln <b>193<sup>G</sup></b> <b>2.29 ln</b>	38 <b>31</b>	229 <sup>G</sup> 2.36 ln <b>279<sup>G</sup></b> <b>2.45 ln</b>	34 <b>44</b>	1.14 <sup>G</sup> 0.06 ln <b>0.69<sup>G</sup></b> <b>-0.16 ln</b>
Melanson (2000) ( <i>data are listed for groups as low, moderate or highly physically active</i> )	968 1160 1120	51 93 85	42 93 87	10 25 21	1231/2.91 l <sub>10</sub> 4251/3.50 l <sub>10</sub> 4285/3.30 l <sub>10</sub>	NR	312/2.36 l <sub>10</sub> 1009/2.76 l <sub>10</sub> 655/2.61 l <sub>10</sub>	NR	919/2.72 l <sub>10</sub> 3242/3.38 l <sub>10</sub> 3630/3.16 l <sub>10</sub>	NR	NR
Pikkujämsä <i>et al.</i> (2001)	897 <b>884</b>	52 <b>46</b>	NR	NR	NR	NR	<u>747</u> <b><u>566</u></b>	65 <b>62</b>	<u>416</u> <b><u>351</u></b>	29 <b>34</b>	2.9 <b>2.4</b>

Table 5-3. continued.

Author and Date	mRR (ms)	SDNN (ms)	rMSSD (ms)	pNN50 (%)	TP (ms <sup>2</sup> )	VLF (ms <sup>2</sup> )	LF (ms <sup>2</sup> )	LFnu	HF (ms <sup>2</sup> )	HFnu	LF:HF
Tulppo <i>et al.</i> (2001)	NR	NR	NR	NR	8.3 ln	NR	7.0 ln	56	6.8 ln	44	1.7
Sucharita <i>et al.</i> (2002)	NR	NR	NR	NR	NR	NR	NR	NR	1113	54	NR
Yildirim <i>et al.</i> (2002 – part 1)	785	NR	NR	NR	NR	NR	482	54	385	40	1.6
Yildirim <i>et al.</i> (2002 – part 2)	796	NR	NR	NR	NR	NR	559	58	396	37	2.1
Geelen <i>et al.</i> (2003)	NR	34	27	NR	NR	NR	228	NR	244	NR	NR
Gerritsen <i>et al.</i> (2003)	989 <b>956</b>	37 <sup>G</sup> <b>35<sup>G</sup></b>	NR	NR	NR	NR	354 <sup>G</sup> <b>213<sup>G</sup></b>	41 <b>46</b>	189 <sup>G</sup> <b>175<sup>G</sup></b>	NR	NR
Jurca <i>et al.</i> (2004)	NR	28	19	NR	6.53 ln	NR	4.84 ln	46	4.96 ln	52	NR
Rennie <i>et al.</i> (2003)	NR	34 <b>32</b>	NR	NR	NR	NR	324 <b>240</b>	NR	116 <b>138</b>	NR	NR

Table 5-3. continued.

Author and Date	mRR (ms)	SDNN (ms)	rMSSD (ms)	pNN50 (%)	TP (ms <sup>2</sup> )	VLF (ms <sup>2</sup> )	LF (ms <sup>2</sup> )	LFnu	HF (ms <sup>2</sup> )	HFnu	LF:HF
Virtanen <i>et al.</i> (2003)	NR	NR	NR	NR	NR	NR	400 258	NR	357 435	NR	NR
Laitinen <i>et al.</i> (2004)	NR	NR	NR	NR	2039 1759	NR	436 479	NR	787 723	NR	184% 129%
Liao <i>et al.</i> (2004)	NR	37.5	NR	NR	NR	NR	5.00 ln	NR	4.54 ln	NR	NR
Piccirillo <i>et al.</i> (2004)	882	NR	NR	NR	743	NR	225	NR	82	NR	5.0
Sandercock <i>et al.</i> (2004) ( <i>data are listed for three different instruments as Bipolar, Holter, 12-lead ECG</i> )	944 938 946	53 63 54	46 46 48	NR	NR	NR	918 962 987	46 47 46	1194 1185 1246	55 51 52	1.6 1.5 1.5
Schroeder <i>et al.</i> (2004)	1032	50	39	NR	NR	NR	DR	64	DR	36	NR
Hemingway <i>et al.</i> (2005)	NR	33	NR	NR	NR	NR	304	NR	105	NR	NR
Mörner <i>et al.</i> (2005) ( <i>data are for three age groups: young, middle-aged and old</i> )	NR	NR	NR	NR	3.4 ln 2.9 ln 2.7 ln	NR	2.9 ln 2.4 ln 2.1 ln	NR	3.0 ln 2.3 ln 1.9 ln	NR	-0.1 ln 0.0 ln 0.2 ln

Table 5-3. continued.

Author and Date	mRR (ms)	SDNN (ms)	rMSSD (ms)	pNN50 (%)	TP (ms <sup>2</sup> )	VLF (ms <sup>2</sup> )	LF (ms <sup>2</sup> )	LFnu	HF (ms <sup>2</sup> )	HFnu	LF:HF
Lucini <i>et al.</i> (2005)	933	NR	NR	NR	2249	NR	683	52	466	37	2.6
Buchheit and Gindre (2006)	1007	61	49	12	NR	NR	6.70 ln	NR	6.50 ln	46	NR
Evrengul <i>et al.</i> (2006)	NR	90	48	17	NR	NR	NR	52	NR	49	1.2
Park <i>et al.</i> (2006)	NR	39	NR	NR	NR	NR	194	54	290	46	2.1
Pichon <i>et al.</i> (2006)	801	55	NR	NR	1739 <u>1567</u>	NR	880 <u>903</u>	NR	364 <u>207</u>	26 <u>16</u>	4.2 <u>10.2</u>
Britton <i>et al.</i> (2007)	NR	35 <b>32</b>	NR	NR	NR	NR	<u>332</u> <sup>G</sup> <u>246</u> <sup>G</sup>	NR	<u>118</u> <sup>G</sup> <u>136</u> <sup>G</sup>	NR	NR
Kobayashi (2007)	NR	NR	NR	NR	NR	NR	523 6.26 ln	NR	74 4.30 ln	NR	NR

Table 5-3. continued.

Author and Date	mRR (ms)	SDNN (ms)	rMSSD (ms)	pNN50 (%)	TP (ms <sup>2</sup> )	VLF (ms <sup>2</sup> )	LF (ms <sup>2</sup> )	LFnu	HF (ms <sup>2</sup> )	HFnu	LF:HF
Kurosawa <i>et al.</i> (2007)	NR	NR	NR	NR	NR	NR	706	NR	1196	NR	1.4
Pinna <i>et al.</i> (2007)	919	45 3.69 ln	37 3.41 ln	NR	NR	NR	<u>744</u> 4.13 ln	63	<u>491</u> 5.60 ln	NR	2.5 0.58 ln
Uusitalo <i>et al.</i> (2007 – part 1)	866	NR	21	NR	NR	NR	<u>257</u>	NR	<u>343</u>	NR	156%
Uusitalo <i>et al.</i> (2007 – part 2)	858	NR	21	NR	NR	NR	<u>246</u>	NR	<u>299</u>	NR	132%
Huang <i>et al.</i> (2008)	835	39	NR	NR	NR	193	199	30	247	32	1.2
Mehlsen <i>et al.</i> (2008)	887	87	NR	NR	NR	NR	NR	54	NR	36	2.4
Nunan <i>et al.</i> (2008)* ( <i>data are listed as the three trial mean for two different instruments</i> )	991 990	4.06 ln 4.07 ln	3.74 ln 3.79 ln	NR	NR	NR	6.92 ln 6.79 ln	63 60	6.36 ln 6.37 ln	37 40	2.2 2.2

Table 5-3. continued.

Author and Date	mRR (ms)	SDNN (ms)	rMSSD (ms)	pNN50 (%)	TP (ms <sup>2</sup> )	VLF (ms <sup>2</sup> )	LF (ms <sup>2</sup> )	LFnu	HF (ms <sup>2</sup> )	HFnu	LF:HF
Sandercock <i>et al.</i> (2008) ( <i>data are for tertiles based on physical activity levels</i> )	852	55	56	NR	NR	NR	6.95 <u>ln</u>	58	6.59 <u>ln</u>	42	2.0
	924	75	78				7.26 <u>ln</u>	57	6.95 <u>ln</u>	43	1.7
	935	64	60				7.31 <u>ln</u>	65	6.60 <u>ln</u>	35	2.6
Nunan <i>et al.</i> (2009)** ( <i>data are listed for two different instruments</i> )	1001	56 <sup>bt</sup>	41 <sup>bt</sup>	NR	NR	NR	960 <sup>bt</sup>	63	557 <sup>bt</sup>	37	2.0 <sup>bt</sup>
	1004	58 <sup>bt</sup>	44 <sup>bt</sup>				904 <sup>bt</sup>	61	608 <sup>bt</sup>	40	1.9 <sup>bt</sup>

Data in bold refers to female participant values; <sup>†</sup>Method for calculation not reported; <sup>#</sup>Values transformed from Hz<sup>2</sup> to ms<sup>2</sup> via 1/Hz<sup>2</sup> × 1000; <sup>%</sup>Value is a percentage; <sup>§</sup>Underlined value calculated using AR spectral method; <sup>¶</sup>Value is geometric mean; <sup>\*</sup>Copy of study in appendix III; <sup>\*\*</sup>Copy of study in appendix IV; <sup>bt</sup>Value is back-transformed following log-transformation; NR, not reported; DR, Difficult to report due to nature of data presentation; mRR, mean RR interval; SDNN, standard deviation of normal-to-normal intervals; rMSSD, root mean square of successive differences (values for this measure have been round up or down to nearest whole number); pNN50, proportion of normal-to-normal interval differences greater than 50 ms (values for this measure have been round up or down to nearest whole number); TP; total spectral power; ULF, ultra low frequency spectral power; VLF, very low frequency spectral power; LF, low frequency spectral power; HF, high frequency spectral power; LF:HF, ratio of low frequency power to high frequency power; nu, normalised units; ln, natural logarithm; l<sub>10</sub>, decadic logarithm.

**Table 5-4. Summary of data from Table 5-3: cross study overall mean and range values for approved Task Force measures of short-term heart rate variability.**

HRV measure	N <sup>o</sup> of studies	Absolute values					Log-transformed values					
		Mean*	SD*	CV* (%)	Median*	Range*	N <sup>o</sup> of studies	Mean*	SD*	CV* (%)	Median*	Range*
<b>mRR (ms)</b>	30	926	90	10	933	785 – 1160	n/a	n/a	n/a	n/a	n/a	n/a
<b>SDNN (ms)</b>	27	50	16	32	51	32 – 93	4	3.82	0.23	6	3.71	3.57 – 4.07
<b>rMSSD (ms)</b>	15	42	15	37	42	19 – 75	4	3.49	0.26	7	3.26	3.26 – 3.41
<b>LF (ms<sup>2</sup>)</b>	35	519	291	56	458	193 – 1009	18	5.01	1.76	35	5.02	2.05 – 7.31
<b>LFnu</b>	29	52	10	19	54	30 – 65	n/a	n/a	n/a	n/a	n/a	n/a
<b>HF (ms<sup>2</sup>)</b>	36	657	777	118	385	82 – 3630	18	4.76	1.78	37	4.96	0.08 – 6.95
<b>HFnu</b>	30	40	10	25	38	16 – 60	n/a	n/a	n/a	n/a	n/a	n/a
<b>LF:HF</b>	25	2.8	2.6	93	2.1	1.1 – 11.6	7	0.69	0.73	106	0.58	-0.16 – 1.98

n/a, non-applicable; SD, standard deviation; CV, coefficient of variation (SD/mean × 100), \*values from across studies; mRR, mean RR interval; SDNN, standard deviation of normal-to-normal intervals; rMSSD, root mean square of successive differences; LF, low frequency spectral power; HF, high frequency spectral power; LF:HF, ratio of low frequency power to high frequency power; nu, normalised units; ln, natural logarithm.

**Table 5-5. Comparison of absolute and log-transformed heart rate variability values from included publications according to gender.**

HRV measure	Mean absolute values from all studies according to gender*					Mean log-transformed values from all studies according to gender				
	N <sup>o</sup> of studies		M	F	Difference (%)	N <sup>o</sup> of studies		M	F	Difference (%)
	M	F				M	F			
mRR (ms)	9	7	922	885	8			No data <sup>¥</sup>	No data	No data
SDNN (ms)	3	4	40 <sup>†</sup>	36 <sup>†</sup>	9			No data	No data	No data
rMSSD (ms)	2	1	21 <sup>†</sup>	19 <sup>†</sup>	11			No data	No data	No data
LF (ms <sup>2</sup> )	9	8	356	414	14	8	4	5.04	4.19	20
LFnu	6	9	53	46	17			No data	No data	No data
HF (ms <sup>2</sup> )	10	8	475	516	8	8	4	4.86	4.10	18
HFnu	7	7	39	38	3			No data	No data	No data
LF:HF	3	6	2.3	1.2	91	2	1	0.36 <sup>£</sup>	0.15 <sup>£</sup>	140

\*Data are means regardless of spectral method; M; males; F, females; <sup>†</sup>Data from AR studies only; <sup>£</sup>Data from FFT studies only. <sup>¥</sup>Refers to the fact that no comparable data between males and females were available from any of the included studies; mRR, mean RR interval; SDNN, standard deviation of normal-to-normal intervals; rMSSD, root mean square of successive differences; LF, low frequency spectral power; HF, high frequency spectral power; LF:HF, ratio of low frequency power to high frequency power.

**Table 5-6. Comparison of absolute heart rate variability values from included publications according to breathing protocol and spectral decomposition methods.**

HRV measure	Mean absolute values according to normal or paced breathing pattern <sup>£</sup>					Mean absolute values according to spectral decomposition method <sup>§</sup>				
	N <sup>o</sup> of studies		NB	PB	Difference (%)	N <sup>o</sup> of studies		AR	FFT	Difference (%)
	NB	PB				AR	FFT			
<b>mRR (ms)</b>	20	6	928	948	2	12	14	881	943	7
<b>SDNN (ms)</b>	20	5	49	59	17	11	14	42	59	29
<b>rMSSD (ms)</b>	8	4	43	55	22	5	10	26	44	40
<b>LF (ms<sup>2</sup>)</b>	26	15	500	440	12	17	13	484	441	10
<b>LFnu</b>	25	3	51	58	12	13	13	55	47	18
<b>HF (ms<sup>2</sup>)</b>	27	16	434	963	54	17	14	348	647	45
<b>HFnu</b>	27	2	39	43	9	13	16	36	40	10
<b>LF:HF</b>	21	6	2.72	2.76	<1	12	12	2.9	1.7	71

<sup>£</sup>Values are means from all studies using normal breathing (NB) and paced breathing (PB) protocols without accounting for gender or spectral decomposition method;

<sup>§</sup>Data are means from all AR or FFT studies without accounting for gender. mRR, mean RR interval; SDNN, standard deviation of normal-to-normal intervals; rMSSD, root mean square of successive differences; LF, low frequency spectral power; HF, high frequency spectral power; LF:HF, ratio of low frequency power to high frequency power.

**Table 5-7. Publications presenting inter-individual variation in approved Task Force short-term measures of heart rate variability.**

Author and Date	Number of Participants	mRR (ms)	SDNN (ms)	rMSSD (ms)	LF (ms <sup>2</sup> )	LFnu	HF (ms <sup>2</sup> )	HFnu	LF:HF
Agelink <i>et al.</i> (1998)	69	NR	NR	6.9 – 99.4	NR	NR	NR	NR	0.29 – 11.00
Fagard <i>et al.</i> (1998)	587	NR	NR	NR	4 – 6397 <sup>G</sup> 1 – 6924 <sup>G</sup>	NR	4 – 10751 <sup>G</sup> 2 – 7513 <sup>G</sup>	NR	NR
Sinnreich <i>et al.</i> (1998)	293	NR	3.39 – 4.05 ln*	2.88 – 3.57 ln*	4.63 – 6.24 ln*	NR	4.07 – 5.49 ln*	NR	NR
Pikkujämsä <i>et al.</i> (2001)	392	573 – 1402	13 – 168	NR	35 – 5941 3.56 – 8.69 ln	11 – 98	10 – 7231 2.30 – 8.89 ln	3 – 72	0.24 – 17.10
Sucharita <i>et al.</i> (2002)	93	NR	NR	NR	NR	NR	13- 6830	19 - 93	NR
Rajendra Acharya <i>et al.</i> (2004) ( <i>mean lower and upper values from three age groups</i> )	125	NR	41 - 67	53.6 – 70.4	NR	NR	NR	NR	1.6 – 1.9
Kurosawa <i>et al.</i> (2007)	66	NR	NR	NR	86 – 1874**	NR	98 – 3938**	NR	NR

\*Values are 25<sup>th</sup> – 75<sup>th</sup> percentile; \*\*Values are 5 and 95 percentiles; <sup>G</sup>Value is geometric; NR, not reported; mRR, mean RR interval; SDNN, standard deviation of normal-to-normal intervals; rMSSD, root mean square of successive differences; LF, low frequency spectral power; HF, high frequency spectral power; LF:HF, ratio of low frequency power to high frequency power; nu, normalised units; ln, natural logarithm.

5.4.2. *Part two – analysis of ‘real-life’ HRV data.*

The outcomes from the analyses of NerveExpress<sup>®</sup> retrospective data are presented in Table 5-8. The size of the data set meant that there was inevitably some data missing for a number of clients. These included:

1. Age for 15 male and 12 female clients;
2. Gender for one client in the 23 – 29 age group and one client in the 30 – 39 age group;
3. HRV data for three male clients, one from the 23 – 29 age group and two from 40 – 49 age group;
4. HRV data for 1 female client from the 30 – 39 age group
5. Age analysis data for the group aged 60 – 70 are from male clients only.

Therefore, HRV data are presented for a total of 1050 clients of which 717 are male and 333 are female. Data for all measures of HRV were found to violate the assumptions of normality and were transformed using natural logarithm. The reader is presented with both absolute and log-transformed values to facilitate comparisons to values observed within the literature.

Based on analysis of the total data set, values for absolute and log-transformed LF and HF obtained by the NerveExpress<sup>®</sup> were massively higher compared with the mean value obtained from data within the literature. Mean absolute values for LF and HF over 1000% greater than mean literature values and indicates a systematic overestimation of these measures by the NerveExpress<sup>®</sup>. The dispersion of values, represented by the CV, was also greater for measures obtained by the NerveExpress<sup>®</sup>, with LF and HF power demonstrating a 95% and 29% higher CV compared to that observed for LF and HF values from the literature.

When analysed by gender, both absolute and log values for HF obtained by the NerveExpress<sup>®</sup> were higher in females compared to males ( $P < 0.001$ ). Females also demonstrated a significantly lower resting LF:HF ratio compared to males ( $P < 0.001$ ). Both male and female values for LF and HF measures from the NerveExpress<sup>®</sup> differed massively to the average published values for these

measures. NerveExpress<sup>®</sup> male and female values for the LF:HF ratio were similar to the mean publication values.

There were significant effects for age in all three measures of HRV, whereby LF and HF measures decreased with age and LF:HF increased with age (see Figure 5-2). Only two groups did not to show significantly lower LF and HF power for each decade decrease in age group. These were the 23 – 29 versus 30 – 39 age groups for LF power (Figure 5-2 left panel) and the 50 – 59 versus the 60 – 70 age groups for both LF and HF measures (Figure 5-2 left and middle panels). Likewise, the same sets of age groups showed no significant differences in LF:HF (Figure 5-2, right panel)

**Table 5-8. Comparison of supine, resting short-term heart rate variability values obtained in healthy adults from a commercially available instrument (NerveExpress<sup>®</sup>) with those from included published studies.** Presented are outcomes from the analysis of the complete data sets (upper section) and from gender based groups (lower section)).

<b>Analysis of total data sets</b>						
<b>HRV measure</b>	<b>NerveExpress<sup>®</sup></b>				<b>Published data</b>	<b>NerveExpress<sup>®</sup> vs. published data</b>
	<b>Mean</b>	<b>SD</b>	<b>CV</b>	<b>Range</b>	<b>Mean</b>	<b>Difference (%)</b>
LF (ms <sup>2</sup> )	7840	8841	113	20 – 99978	519	7321 (1411)
HF (ms <sup>2</sup> )	5051	6385	126	10 – 78223	657	4394 (669)
LF:HF	2.4	2.3	96	0.2 – 17.5	2.8	-0.4 (14)
LF ln	8.51	0.98	12	3.0 – 10.1	5.01	3.50 (70)
HF ln	7.96	1.14	14	2.3 – 9.79	4.76	3.20 (67)
LF:HF ln	0.53	0.86	162	-1.69 – 2.86	0.69	-0.16 (23)

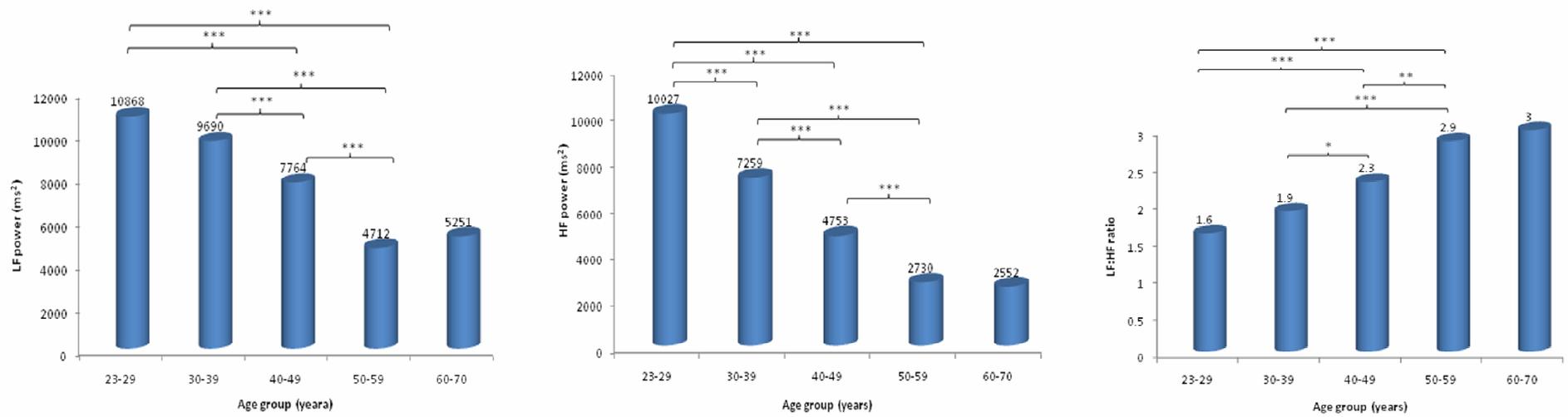
LF, low frequency spectral power; HF, high frequency spectral power; LF:HF, ratio of low frequency power to high frequency power; SD, standard deviation; CV, coefficient of variation (SD/mean × 100); ln, natural logarithm.

Table 5-8. continued

**Analysis of data according to gender**

HRV measure	NerveExpress <sup>©</sup>			Published data <sup>†</sup>			NerveExpress <sup>©</sup> vs. published data Difference (%)	
	Male	Female	Male – female difference (%)	Male	Female	Male – female difference (%)	Males	Females
LF (ms <sup>2</sup> )	7878	7767	1	356	414	14	7522 (2113)	7353 (1776)
HF (ms <sup>2</sup> )	4333	6591	34*	475	516	8	3858 (812)	6075 (1177)
LF:HF	2.7	1.8	50*	2.3	1.2	91	0.4 (17)	0.6 (50)
LF ln	8.52	8.49	1	5.04	4.19	20	3.48 (69)	4.30 (103)
HF ln	7.81	8.29	6**	4.86	4.10	18	2.95 (60)	4.19 (102)
LF:HF ln	0.69	0.18	283**	0.36	0.15	140	0.33 (92)	0.03 (20)

<sup>†</sup>Values represent cross study averages; LF, low frequency spectral power; HF, high frequency spectral power; LF:HF, ratio of low frequency power to high frequency power; SD, standard deviation; CV, coefficient of variation (SD/mean × 100); \**P* < 0.001 from Mann-Whitney U Test; \*\**P* < 0.001 from independent *t*-test.



\* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ .

20 – 29,  $n = 100$ ; 30 – 39,  $n = 305$ ; 40 – 49,  $n = 382$ ; 50 – 59,  $n = 232$ ; 60 – 70,  $n = 31$

**Figure 5-2. Differences in LF and HF power and their ratios obtained in a clinical setting and from participants grouped according to age decades.**

## 5.5. Discussion.

This study is the first to assess values systematically from publications (with  $n \geq 30$ ) reporting short-term HRV since the 1996 Task Force publication and found that:

1. Only a small number of studies (44) were able to match the study inclusion criteria;
2. Mean publication values for most measures of HRV differ massively to those published by the Task Force;
3. The majority of studies demonstrated HRV values within 1.5 SD of mean values;
4. Time domain measures were less variable than frequency domain measures;
5. For most measures of HRV paced breathing and FFT protocols present with higher values;
6. Values differ between males and females, with females demonstrating higher values for vagally related measures of HRV;
7. A number of studies reported large within-study ranges for measures of HRV;
8. When compared to published data, spectral measures of HRV obtained in a “real-life” clinical setting demonstrate known gender and age differences but values are unexpectedly high.

Further discussion of these findings is subdivided according to the separate parts and addressed with reference to the study hypotheses and previous data.

### 5.5.1. *Results of literature retrieval for normal values of short-term HRV.*

This study sought to determine the range in normal values for measures of short-term HRV and to compare them with current published norm values (Task Force, 1996). It was believed that the wealth of studies related to HRV published since the 1996 Task Force report would provide the necessary data. It was somewhat surprising and alarming that out of 3,141 PubMed/Ovid publications citing HRV since 1996, only 44 reported short-term linear measures of HRV in healthy adult

samples and/or populations with an  $n \geq 30$  and in accordance with Task Force methodological standards/recommendations. The source of data from which to derive a normal range in short-term HRV is therefore limited and also highlights:

1. The use of short-term recordings is not widely utilised in the study of HRV, and/or;
2. Studies tend to use small samples without inclusion of a healthy cohort and/or reference to healthy values, and/or;
3. Adherence to Task Force methodological recommendations is poor.

Some of the factors pertaining to the above findings can be more easily explained than others. A preferred use of 24 h measurements to that of short-term measurements could lie in their greater predictive power (Schwartz *et al.*, 1992; Bigger *et al.*, 1993; Fei *et al.*, 1996; Nolan *et al.*, 1999, Kleiger *et al.*, 2005) or the additional information such as night:day ratios that can only be determined by 24 h monitoring.

The fact that studies utilise only a small sample size may be explained by the nature of the study, limitations in resources and/or the calculations for effect power. An example of the latter is found in the study of Gujit *et al.* (2007) who calculated that 23 subjects provided sufficient power in their reliability of HRV study. Other factors, such as the failure to report the actual values for measures of HRV, were found to occur when studies were interested in change scores (Reland *et al.*, 2005) or preferred to present results graphically (Buchheit *et al.*, 2005). The sole presentation of outcomes graphically makes determination of the actual values difficult and requires a degree of guesswork.

The failure to report mean RR interval by 54% of the studies is a concern. Because of the reciprocal nature of HR and mean RR interval, studies reporting measures of HRV often choose to report only mean HR (Sugawara *et al.*, 2001; Hemingway *et al.*, 2005; Britton *et al.*, 2007) or in some cases, neither (Sucharita *et al.*, 2002, Park *et al.*, 2006). This error can be likened to reporting basal metabolic index (BMI) without providing data on height and/or weight. Thirty six percent of included studies reported TP and VLF which is not recommended from short RR recordings. The use of units that differ to standard units (e.g. bpm/ $\sqrt{\text{Hz}}$  used by Fluckiger *et al.*, 1999) further limited the number of eligible

studies. The fact that studies such as these have been published reflects a weakness in adherence to Task Force recommendations and a lack of coherence between authors, editors or both as to how and what to present when reporting short-term measures of HRV. It may also reflect the fact that short-term HRV is an easy-to-obtain measure of autonomic modulatory activity and can be simply added to a study as an ‘interesting adjunct’ without proper consideration to methodological standards and/or its physiological meaning.

5.5.2. *Comparisons between literature and published norm heart rate variability values.*

The Task Force do not provide norm values for short-term time domain measures of HRV and therefore comparisons can only be made between spectral measures. The Task Force published figures of 1170 ms<sup>2</sup> for LF power, 975 ms<sup>2</sup> for HF power, 54 and 29 for normalised LF and HF and 1.5 – 2.0 for the LF:HF ratio. The norm LF value is greater than 1.5 SD of the mean literature value (519 ms<sup>2</sup>) with norm HF also higher compared to literature values (657 ms<sup>2</sup>). Task Force and literature normalised measures of LF and HF power are more homogenous but the Task Force value for LF:HF (1.5 – 2.0) is considerably lower than that from the literature (2.8).

Reasons for these discrepancies could be due a number of factors including heterogeneity of participants and spectral decomposition methods. The studies from which the norms were obtained were not presented by the Task Force so comparisons in terms of participants are not possible. Comparisons in terms of the spectral methods used (i.e. autoregressive or FFT) are also not possible. The Task Force does provide details as to the frequency bandwidths used for determining LF and HF power distributions. Oscillations in RR intervals occurring at LF were assessed between 0.04 – 0.15 Hz and at HF between 0.15 – 0.4 Hz. Forty seven percent of the included studies presented here report values for LF and HF power obtained at frequency bandwidths differing from those of the Task Force. Some considered oscillations in heart periods at frequencies as low as zero to 0.003 as part of the LF component (Notarius *et al.*, 1999; Evrengul *et al.*, 2006) and others utilised much lower cut-off values (e.g. 0.3 Hz for the HF

component in Melanson (2000)). Discrepancies in LF and HF frequency bands could lead to the inclusion and/or exclusion of additional spectral power in these bandwidths that would result in varying values for LF, HF and/or both. It is both interesting and somewhat telling then that these studies report some of the largest discrepancies for spectral measures of HRV. The findings also reveal a large discrepancy within the literature for LF and HF frequency bandwidths that differ from Task Force standards for measures obtained under resting, supine conditions.

It is important to recall that the norm values are approximations based on values presented in a number of small studies and the Task Force warn against basing clinical conclusions upon these values. The Task Force stressed the need for large prospective population based studies to establish normal HRV standards and that such studies should involve the full age spectrum and both genders. Looking at included studies in Table 5-3, it appears that the following six population based studies report values for short-term HRV measurements from large samples (~1000):

- Kuo *et al.* (1999)
- Dekker *et al.* (2000)
- Rennie *et al.* (2003)
- Liao *et al.* (2004)
- Hemingway *et al.* (2005)
- Britton *et al.* (2007)

On closer examination a number of these studies were based upon ongoing longitudinal and/or cross sectional assessments of the same participant populations. Whilst these studies respectively used different sized samples and were investigating different hypotheses, a large proportion of the values from these studies were likely to have been obtained from the same individuals. This may explain the similarity in values between Dekker *et al.* and Liao *et al.* and between Rennie *et al.*, Hemingway *et al.* and Britton *et al.* (Table 5-4). For these reasons it could be argued that only three populations, including the separate population of Kuo *et al.*, have been assessed since the 1996 Task Force report.

Moreover, the lowest participant age across these three populations was 40 years. This means that there are currently no published data for short-term HRV measures obtained in a population based study and in adults aged less than 40. This may also explain the relatively low values for HRV measures observed by these studies and the impact of these data on the mean publication values.

5.5.3. *Homogeneity of short-term measures of heart rate variability between studies.*

When assessed in terms of deviations from mean publication values, approximately 85% of the included studies demonstrated values within 1.5 SD of the mean publications value for one or more measure of short-term HRV. This indicates a degree of homogeneity for mean values of short-term HRV in healthy participants and that these measures are robust to methodological differences in terms of participant age and/or gender, RR interval device, data recording, and/or editing protocols and HRV analysis methods. Closer scrutiny of the 15% of studies demonstrating values greater than 1.5 SD can help identify conditions leading to disparate values for short-term measures of HRV.

5.5.4. *Studies reporting discrepant absolute heart rate variability values.*

Discussion of studies demonstrating discrepant values will adopt a measure-by-measure approach. Upon review it was found that studies displaying discrepancies often did so for similar values. Time and frequency domain measures of HRV are known to correlate highly both within and between their respective domains (Kleiger *et al.*, 1991). A discussion of factors underlying those studies demonstrating discrepancies on a measure-by-measure basis will therefore be subject to a degree of repetition. Six studies demonstrated values greater than 1.5 SD from the mean absolute value for at least one measures of HRV. These studies and their discrepant values were:

1. Melanson (2000) – mean RR, SDNN, rMSSD, LF, HF
2. Sandercock *et al.* (2004) – LF
3. Evrengul *et al.* (2006) – SDNN
4. Mehlsen *et al.* (2008) – SDNN

5. Sandercock *et al.* (2008) – SDNN, rMSSD
6. Nunan *et al.* (2009) – LF

A closer look at the characteristics of the above studies revealed a number of similarities and differences related to study participants, RR interval data recording, artefact identification and interpolation and spectral decomposition protocols. As these factors can have differing effects depending on the measure, they will be discussed separately for time and frequency domain measures respectively.

#### 5.5.4.1. Time-domain measures.

##### 5.5.4.1.1. Mean RR.

Technically mean RR is not a measure of the variability in autonomic modulation but rather it is an indication of the underlying level of autonomic tone. High and low mean RR interval values reflect greater and lesser parasympathetic tone respectively. The majority of studies displayed homogeneity and this is reflected by the relatively low coefficient of variation (CV) for mean RR interval (10%). The only publication to demonstrate heterogeneous values was that of Melanson (2000). A closer look at the characteristics of participants and the study protocol can explain this finding. Melanson (2000) assessed the effect of habitual activity level on measures of HRV in a young ( $\leq 34$  years) male cohort of university students, ~50% of which were considered moderately to highly trained. It was in these latter two groups that values above 1.5 SD of the mean were observed (1160 ms and 1120 ms respectively). There is strong evidence of a training induced bradycardia and subsequently an increased mean RR interval, particularly in younger compared to older individuals (Sandercock *et al.*, 2005). Although the relative autonomic contribution to this increase has not been determined, it none the less helps to explain the above average values observed by Melanson (2000).

#### 5.5.4.1.2. SDNN.

Only the studies of Melanson (2000), Evrengul *et al.* (2006), Mehlsen *et al.* (2008) and Sandercock *et al.* (2008) present values greater than 1.5 SD of the mean SDNN, with all four studies demonstrating higher values compared to the mean value. The SDNN measure is known as a global index of HRV and reflects the combined influence of many physiological systems including the SNS, PNS, renin-angiotensin and respiratory systems, chemoreceptor function and habitual physical activity. With regards to the latter, the larger values for SDNN observed by Melanson (2000) and Sandercock *et al.* (2008) may simply reflect higher levels of habitual physical activity. More specifically, individuals with moderate and/or high levels of physical activity demonstrated discrepant values whereas those with a low physical activity level did not.

There is a well established link between age and HRV, with a decrease in HR for increasing age (Task Force, 1996; Kuo *et al.*, 1999, Ramaekers *et al.*, 1999; Migliaro *et al.*, 2001). Commonly therefore younger individuals demonstrate higher values (Sinnreich *et al.*, 1998). The discrepant value observed for SDNN in the study by Mehlsen *et al.* (2008) may have resulted from the use of a younger group that was very homogenous in age (mean age  $32 \pm 2$ ).

SDNN is also a function of the recording length, with longer analysed recordings producing larger values (Saul *et al.*, 1988). For this reason the Task Force recommends a standardised duration of 5 min for short-term SDNN (and other measures of HRV). These factors most likely explains the larger values observed by Evrengul *et al.* (2006), who determined the SDNN of RR interval data recorded over a 1 h period. No justification for such a recording length was given by the authors. Furthermore, participants within the so called 'healthy' control group suffered from atypical angina. Whilst the origins of the angina may not be cardiac in nature, it suggests a dysfunction of one of the physiological and/or neurological systems of the body. These participants therefore cannot be classed as normally healthy and this could also explain the discrepant values for SDNN observed by Evrengul *et al.* (2006).

#### 5.5.4.1.3. rMSSD.

Parasympathetic nerve traffic enacts its effects at a much faster ( $< 1$  s) rate than sympathetic outflow ( $> 5$  s), and as a result is responsible for beat-to-beat changes in RR intervals. The rMSSD is a measure of beat-to-beat changes in HR and is therefore considered by some as a reflection of vagal tone (Bigger *et al.*, 1989; Kleiger *et al.*, 1995). Because of these close associations, rMSSD is highly influenced under conditions where vagal outflow is enhanced (Óri *et al.*, 1992). One such condition is presented during paced breathing, particularly in the supine position. In addition, the bradycardia observed for more highly trained individuals (as discussed in 5.5.2.1.1) is commonly accompanied by augmented markers of cardiac vagal modulation (Puig *et al.*, 1993; Shin *et al.*, 1997), although this relationship is not always observed (Sandercock *et al.*, 2005). The studies of Melanson (2000) and Sandercock *et al.* (2008) present discrepant values for rMSSD derived from RR data obtained under paced breathing conditions and discrepancies were again observed only for moderately and/or highly trained individuals (Melanson, 2000; Sandercock *et al.*, 2008). The combination of young, trained individuals, with possibly higher baseline vagal tone and a more parasympathetic favourable condition, is likely to reflect the higher values presented by these studies.

#### 5.5.4.2. Frequency-domain measures.

##### 5.5.4.2.1. LF power.

Observed increases in both animal and human intervention studies utilising protocols to enhance sympathetic activity (e.g. postural changes such as tilt and standing, physical stress, baroreceptor unloading by nitroglycerin infusion, coronary occlusion) have led some to believe in an underlying sympathetic orientation of the LF power spectrum component (Guzetti *et al.*, 1984; Pomeranz *et al.*, 1985; Brown *et al.*, 1989, Rimoldi *et al.*, 1990; Malliani *et al.*, 1991). However, there is also a significant parasympathetic influence on LF oscillations as revealed by clearly augmented and diminished LF power under enhanced vagal and parasympathetic blockade conditions respectively (Akselrod *et al.*,

1981). This has implications for studies where vagal conditions are enhanced, such as during paced breathing. The higher values observed by Melanson (2000) may be due to a vagally mediated augmentation of LF power resulting from the paced breathing condition.

Spectral measures are highly sensitive to technical errors with RR data such as artefacts, misplacement of missing data, poor pre-processing and non-stationarity. Information regarding error detection methods for 1 h Holter RR interval data was not provided by Evrengul *et al.* (2006) and no indication as to the number of errors observed and/or removed was given. The fact that Mehlsen *et al.* (2008) do not report the performance of any error identification, removal and/or correction procedures suggests a failure to understand the importance of correct RR interval data in the analysis of its variation. RR intervals were also considered to be 'within normal range' yet the authors provide no reference for this so called 'normal' range.

Melanson (2000) report care was taken to ensure that measures of HRV were obtained from manually selected error free RR data. This may have resulted in significant selection bias as can occur when employing such a strategy (Task Force, 1996).

Data for LF power from Nunan *et al.* (2009) and Sandercock *et al.* (2004) are very similar (908 versus 987 ms<sup>2</sup>) and may be related to similarities in methodology. Both studies utilised participants with similar demographics and also used the same RR interval recording devices (MeRdgraphics Cardio CP stress system: Medical Graphics Corporation, St Pauls, MN USA) and automated HRV analysis software (CarioPerfect ST). They also provide details of similar RR interval error detection and correction procedures, with Nunan *et al.* (2009) also providing information on exclusion criteria for RR time series data (e.g. < 20% total errors within the RR time series). It is possible that the strict criteria adopted by these two studies ensured that HRV was derived from correctly determined RR interval data and represent an accurate measure of LF power from short-term recordings. Finally, these two studies present values similar to the Task Force for LF power (1170ms<sup>2</sup>) using completely automated RR interval data analysis methods. This is in direct opposition to Task Force recommendations that stress the need for manual editing of RR interval data.

Evidence of a strong prognostic value for fully automated measures of HFV (Ho *et al.*, 1997) and the similarity of values from Nunan *et al.* and Sandercock *et al.* with norm values suggests that the Task Force recommendations may be outdated. At the very least they require updating to account for the computational power of current automated RR recording and HRV analysis devices.

#### 5.5.4.2.2. HF power.

Early and more recent animal studies demonstrating peak HF amplitudes at the respiratory frequency and depressed HF power following vagotomy and muscarinic receptor blockade have established the relationship between the HF component, parasympathetic activity, and respiration (Chess *et al.*, 1975; Rimoldi *et al.*, 1990). In humans the relationship is equally well established (Pomeranz *et al.*, 1985; Vibyral *et al.*, 1989). The HF component is very sensitive to changes in both breathing rate and frequency, a factor that is often ignored (Brown *et al.*, 1993). Akselrod (1995) presents evidence of greater power in the HF band at lower breathing frequencies, with highest values occurring at frequencies closer to 2 Hz and progressively decreasing with increased frequencies from 2 to 5 Hz. Combined with the factors underlying discrepancies for other measures of HRV, values for HF observed by Melanson (2000) could also be augmented by the pacing of breathing rate at 0.17 Hz.

Another factor could relate to the occasional and unexplained findings of comparably low HRV, particularly low HF power, in otherwise healthy individuals (Akselrod, 1995). This factor may underline values at the lower end of the range and inadvertently influence the overall mean publication value for HF power. In healthy normotensive controls, a value of 82 ms<sup>2</sup> was reported by Piccirillo *et al.* (2004). Moreover, this value was used to determine ‘abnormal’ HF power in chronic heart failure (CHF) patients. Inclusion of these values may explain the lower overall mean value for HF power. An important observation is that these values are considerably lower than the Task Force norm value and the mean studies value presented here. As is common throughout the literature, consideration as to the ‘normality’ of actual healthy values is ignored.

#### 5.5.4.2.3. Normalised LF and HF power.

Factors underlying discrepancies in normalised LF and HF measures are likely to be masked by the confounding issue of publication differences in methods for the calculation of these measures. This factor is an important illustration of the disparity between studies in the calculation of normalised frequency domain measures. One reason for this disparity could relate to conflicting information from the Task Force report itself. In their report, the Task Force provides the calculation of LF and/or HF in normalised units from short-term RR recordings as:  $LF / (\text{Total power} - \text{VLF}) \times 100$  and/or  $HF / (\text{Total power} - \text{VLF}) \times 100$ . These two equations clearly include the use of total power (TP) and power distributed in the very low frequency (VLF) range yet the Task Force simultaneously recommends against the assessment of TP and VLF from short-term recordings (e.g.  $\leq 5$  min). As a result, numerous studies have utilised normalisation methods that differ from those of the Task Force to account for omitting TP and VLF data (Pikkujämsä *et al.*, 2001; Gerritsen *et al.*, 2003; Buchheit and Gindre, 2006; Pichon *et al.*, 2006; Pinna *et al.*, 2007; Huang *et al.*, 2008; Nunan *et al.*, 2008, Sandercock *et al.*, 2008; Nunan *et al.*, 2009). Despite this, values from these studies are similar to norm values published by the Task Force and perhaps illustrate an insignificant contribution of VLF power to the spectral density of short-term RR interval modulations in healthy participants.

#### 5.5.5. *Studies reporting discrepant log-transformed heart rate variability values.*

Of the studies reporting log-transformed measures of HRV, only one demonstrated discrepant values for HRV measures (Ho *et al.*, 1997). In the study by Ho *et al.* data for spectral measures of HRV were obtained in a healthy control group matched for age and sex to a group of patients suffering from CHF. The participants in the control group were 44% female, with a mean age of 72 years and a resting HR of  $76 \text{ b}\cdot\text{min}^{-1}$ . As discussed earlier, there is a well known age related decline in HRV that particularly affects measures related to vagal modulations of HR in females (Kuo *et al.*, 1999). Data presented in chapter four as part of this thesis and by others (Coulmel *et al.*, 1995) demonstrate a negative

correlation between HR and spectral measures of HRV. These two factors alone may explain the low values for LF (2.05 ln ms<sup>2</sup>) and particularly for HF power (0.08 ln ms<sup>2</sup>) observed by Ho *et al.* As with the majority of studies utilising a control ‘reference’ group, the values presented in the control group are not questioned by the authors as to their normality/abnormality.

5.5.6. *Summary of main factors underlining discrepant values in short-term heart rate variability from healthy individuals.*

The measure-by-measure analysis performed in 5.5.4 for those studies reporting discrepant values revealed a number of underlying factors including:

1. Moderate to high level of participant habitual physical activity;
2. The use of paced breathing protocols, particularly when performed in participants with moderate to high physical activity levels;
3. Where younger participants are measured, values for HRV are typically higher;
4. Poor reporting and/or performance of RR interval error recognition, removal and/or correction procedures;
5. The use of differing frequency bandwidths and normalisation methods for LF and HF spectral measures;
6. Wide variation in HRV measures between healthy participants of the same study;
7. The misclassification of participants as healthy;
8. A failure of studies to recognise the normality/abnormality of values obtained in healthy participants.

Some of the points above (1, 2, 3 and 6) were not unexpected. Of some surprise was the failure to perform error correction procedures by a number of studies and the poor reporting of these procedures by others. The last three summary points are particularly important and highlight the inherent problem of defining a so called ‘normal’ HRV.

These points are also inter-related in that the failure to question the normality of data when obtained in healthy participants possibly stems from the fact that even

in homogenous healthy groups, measures of HRV can display wide inter-individual variations (as high as 260,000%, Fagard *et al.*, 1998; Table 5-7).

It is important however to recognise that at least one or more of the factors outlined above are also present within those studies that do not present with discrepant values for HRV. Other factors could influence discrepancies between studies. Measures of HRV are influenced by diet (caffeine and alcohol intake), medications (beta-blockers) and physical and mental stress. Very few of the studies included here include information on these factors and their impact on values presented cannot be determined. When assessing studies reporting so called normal HRV, readers should employ close scrutiny of the factors outlined above as well as potential other factors (e.g. diet, stress) related to the individual aspects of each study. With consideration of these factors, the data presented in this study may provide users of HRV with reference ranges by which to determine disparate values for common measures of short-term HRV.

#### 5.5.7. *Reasons for disparate 'real-life' heart rate variability values.*

The second part of this study aimed to assess values for spectral HRV measurements obtained in a real-life and current clinical practice setting. These values were obtained in over 1000 clients of a private UK hospital who underwent measurement of HRV as part of their routine health care. The higher HF and lower LF:HF ratio values for females mirrored publication findings (Table 5-8). The data also demonstrate very well the age related decrease in HRV (Figure 5-3). As this cohort consists of adults aged 23 to 70 years, it represents for the first time measures of short-term HRV obtained in a large population involving a broad age spectrum.

It was disappointing then to find that values for absolute measures of short-term LF and HF HRV were not comparable with those from the literature. Mean and range values of 7840 ms<sup>2</sup> and 20 – 99978 ms<sup>2</sup> have not been seen elsewhere and suggest a massive overestimation of the power spectrum density. The only plausible reasons for such findings all relate to the measurement device used, namely the NerveExpress<sup>®</sup> (Heart Rhythm instruments, Inc., New Jersey, USA).

Determining the exact methods (e.g. algorithms) used for the detection, removal and/or interpolation of RR intervals and spectral HRV analysis is not possible from any of the literature made available by the developers of the NerveExpress<sup>®</sup>. There are also many spurious and ill or even unreferenced claims within the NerveExpress<sup>®</sup> literature. These include claims that LF and HF measures respectively represent SNS and PNS tone (as opposed to modulations in their activity) and that the device is able to ‘accurately and reliably’ quantify 74 states of the ANS.

Some features that can be commented upon directly are the fact that the NerveExpress<sup>®</sup> a) derives HRV from a set number of RR intervals (192), b) uses proprietary algorithms and artificial intelligence theories (Minsky, 1972) to determine spectral measures of HRV and c) that frequency bandwidths for LF (0.033 to 0.15) and HF (0.15 to 0.5) differ to those recommended by the Task Force. For an individual with a resting heart rate greater than 80  $b \cdot \text{min}^{-1}$  the NerveExpress<sup>®</sup> would determine HRV parameters from approximately two minutes of RR interval data. This is similar to the cut-off time required for the correct determination of the LF component (Task Force, 1996). The spectral decomposition methodologies employed by the NerveExpress<sup>®</sup> only adds to the disparate values presented.

The most important observation from this part of the study is the ambiguity in the information made available to users of the NerveExpress<sup>®</sup>. The developers fail to provide sufficient detail of the self-developed spectral analysis methods and for their preferred use over well established methods. Parts of the wordings related to the physiological meaning and underlying ANS influence of spectral measures are misleading and evidence of good agreement for algorithms used by the NerveExpress<sup>®</sup> are mistakenly interpreted as indications of good reliability. In order to be able to determine accurately the factors underlying the disparate values and in order to assess its validity, full details of the QRS and RR interval detection and spectral decomposition algorithms used by the NerveExpress<sup>®</sup> need to be made available.

## **5.6. Limitations.**

It is possible that some papers meeting the inclusion criteria for the present study would have been missed by the search strategy employed. Arbitrary selection of the selected search terms may have meant that studies reporting short-term HRV in healthy adults may have been missed. Alternatively, it could be argued that studies missed despite the comprehensive list of search terms may be too ambiguous in terms of the context in which short-term measures of HRV were used.

A number of original inclusion criteria had to be removed as a result of small study numbers when these criteria were applied. This included a minimum sample size of 50 and the inclusion of only those studies reporting mean RR interval data alongside the HRV values. Therefore the mean publication values, and subsequently those found to be discrepant, are obtained in part from small-scale studies. Whether the samples used in these studies are truly representative of the normal adult population is open to speculation. The results presented here therefore need to be considered with this in mind.

The arbitrary and uniform use of a value 1.645 SD greater than mean values to determine discrepancies may be considered too conservative or too strict depending on the HRV measure. Relative SD for some measures is greater than that of others (e.g. HF versus SDNN) as a result of large discrepancies in relative inter-individual variations. To account for the greater degree of uncertainty presented by such differing variations, a value of 1.5 SD was chosen as this equates to a more conservative reference range for measures displaying wide variations. The use of a less conservative and more conventional value (e.g. 1.96 SD) could be used to identify the likely range for discrepant values in measures demonstrating less variation (e.g. mRR, SDNN, rMSSD).

## **5.7. Recommendations.**

The studies and data presented in Tables 5-2, 5-3 and 5-4 can be used to provide reference values for common time- and frequency domain measures of HRV

derived from short-term ( $\leq 10$  min) RR interval recordings. Studies intending to report measures of HRV can use the findings from this study to minimize and/or explain discrepant values.

To facilitate between-study comparisons and aid standardisation of measurements, studies need to report the outcomes of RR interval data editing procedures. In addition, measures of stationarity or measures taken to address non-stationary signals should be provided. Moreover, journal editors and reviewers need to adopt greater diligence in ensuring that papers submitting data related to HRV provide details of data treatment before accepting the paper(s) for publication.

Despite the call for large population based studies to determine normal HRV standards by the 1996 Task Force paper there are no studies with participants from the full age spectrum. Whilst retrospective data in part two of this study include population measures from the full age spectrum and also reconfirm the known gender and age differences for spectral measures of HRV, values are incompatible with data presented throughout the literature. There is still a need for a prospective population based study assessing short-term HRV measurements and involving the full age spectrum. A multicentre approach may be the most feasible approach. Such a study would require stringent methodological standards and participant inclusion criteria. Awareness and/or control of methodological and participant factors known to affect HRV, including environmental (time, temp, noise etc), demographic (age, gender, smoker, caffeine consumption etc), and participants physical and mental well-being would also need to be given.

It is important to consider that no one is likely to be in the exact same autonomic state on two occasions. The range in intra-individual HRV may indicate its sensitivity to this fact. Therefore, the concept of this measurement having an expected range etc may not be feasible. None-the-less, studies referring to so called “normal” HRV should indicate awareness to the issues when presenting such data.

There is a need for a revision of current recommendations and standards for the measurement of short-term HRV. These should be made in light of significant developments in the computational power and accuracy of automated RR interval and HRV analysis systems. There is a particular need to stress clarity and transparency by the manufacturers as to the QRS, RR interval and HRV analysis procedures of new technologies. Strong re-iteration of the methodological standards that studies should adhere to, particularly for RR interval data treatment and appropriate frequency bandwidths, is also required.

## **5.8. Conclusions.**

Only a small number of large scale studies reporting short-term HRV measurements in healthy adults have been published since 1996 and highlights issues related to its ease-of-use. Compared to Task Force norms, mean values for frequency domain measures of HRV from the literature were noticeably lower and could relate to differences in spectral methods.

When compared across studies, values for short-term HRV in healthy adults demonstrate a degree of homogeneity and appear robust to slight differences in methodologies. Factors underlying discrepant values were related to participant demographic characteristics including age, gender and habitual physical activity levels. Poor RR interval data editing procedures, poor classification of healthy participants and a failure to recognise values as disparate were found to be additional factors. Studies reporting HRV need to recognise the normality of data even when obtained in supposedly normally healthy individuals.

Values for HRV measures obtained in a current clinical setting were found to differ from both norm and publications mean values. A lack of transparency as to the methodologies employed by the automated analysis system and the nature of software algorithms for RR interval and HRV analysis exacerbated this finding.

Twelve years after the Task Force recommendation, the need for large-scale population studies assessing short-term HRV in normally healthy adults still remains. Current recommendations also need updating to account for the era of completely automated HRV analysis and a clarification of measurement standards in light of discrepancies observed between studies is also needed.

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## **CHAPTER 6. MEASURES OF HEART RATE VARIABILITY FROM THE POLAR S810 AND HRV ANALYSIS SOFTWARE 1.1: A VALIDITY AND RELIABILITY STUDY IN CHRONIC HEART FAILURE PATIENTS.**

### **Abstract.**

The present study aimed to assess the Polar S810 and HRV analysis systems in terms of their reliability and validity to determine heart rate variability (HRV) in chronic heart failure (CHF) patients and using appropriate statistical procedures.

Five min R wave interval (RR) data for 16 male and four female CHF patients during 10 min of quiet rest on two separate occasions at 1 week intervals were obtained using the Polar S810. Separate measures of HRV were obtained from the same RR data using Polar specific software (version 4.03, Polar Electro OY, Kempele, Finland) and two different settings (with or without detrend) in the HRV analysis software (HRV Analysis Software 1.1., University of Kuopio, Finland). Measures of validity of HRV analysis software settings without detrend were estimated by regression analysis, and measures of reliability of the Polar S810 and HRV analysis software with detrend were estimated by analysis of change scores and coefficient of variation (CV). Linear measures of the SD of normal-to-normal intervals (SDNN), the root mean square of successive differences (rMSSD), the low-frequency (LF) and high-frequency (HF) spectral power and their ratio (LF:HF) and non-linear Poincaré plot measures (SD1 and SD2) were analysed after log-transformation. Mean RR, LF and HF in normalised units (nu) were analysed without transformation.

Data from 16 patients were available for analysis. Measures of HRV from the Polar S810 demonstrated similar reliability compared to estimates in healthy participants. There were marginal differences between the Polar and the HRV 1.1 analysis software without detrend mean for all time-domain and non-linear measures of HRV, uncertainty in the differences was small and high correlations ( $> 0.98$ ) indicated near-perfect validity for these measures. Normalised and log-transformed LF and HF power were underestimated by the HRV analysis software, uncertainty in differences was large and small for the former and later measures respectively and this is reflected by low (0.66 and 0.38, LFnu and HFnu) and high correlations ( $> 0.98$  for Ln LF and Ln HF). Except for LFnu and

HFnu, the HRV analysis software with a detrend applied did not add any substantial technical error to the within-subject variability in repeated measures of HRV. Measures from both systems demonstrated large inter- and intra-individual variation.

When obtained in CHF patients, measures of HRV obtained with the Polar S810 system are as reliable as those obtained by the same and criterion systems in healthy adults. Using the HRV analysis software without a detrend (i.e. settings best matching those of the Polar S810 software) applies no appreciable bias or additional random error to time-domain and non-linear Polar S180 measures of HRV. Spectral measures are underestimated but bias is only consistent for raw and not normalised measures. Applying a smoothness priors detrend before analysis of RR data results in measures of HRV that are equally as reliable as those from the Polar S810 but, as in healthy cohorts, measures are inherently unreliable over a 1 week period. Log-transformation of measures, however, improves reliability estimates and should be considered for intervention and/or management studies involving HRV.

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## 6.1. Introduction.

The empirical work that follows in this and subsequent chapters looks at measures of HRV in chronic heart failure (CHF) patients. Assessments of HRV will be made for the first time using the Polar S810 heart rate monitor to record RR interval data and the HRV analysis software 1.1 (University of Kuopio, Finland) to derive measures of HRV from such data. In Chapters two and three of this thesis the reliability and agreement of measures from and between the Polar S810 system (including its own HRV software) and HRV analysis software were assessed in healthy participants.

The initial analyses revealed that measures from both systems demonstrated large inter- and intra-individual variation and lacked sufficient agreement to allow them to be used interchangeably. Subsequent knowledge gained in the process of submitting these chapters for publication (Nunan *et al.*, 2008 and 2009) revealed that original statistical analyses limited the findings. Extensive review work in conjunction with journal editors revealed that the Polar S810 system gives both valid and reliable measures when compared to those obtained from a criterion (Nunan *et al.*, 2009).

One of the points highlighted in chapters two and three and also in Nunan *et al.*, (2009) was the fact that the reliability of short-term measures of HRV may differ in clinical patient populations, including CHF sufferers (Van Hoogenhuyze *et al.*, 1991; Piepoli *et al.*, 1996; Ponikowski *et al.*, 1996; Lord *et al.*, 2001). Combined with the fact that the present study will utilise measures from the Polar S810 system and HRV analysis software for the first time, the reliability of these systems for use in CHF populations requires determination.

In the previous chapters, only traditional linear measures of HRV (e.g. SDNN, LF, etc) were assessed. There is strong opinion that cardiac systems are non-linear in their function (Guevara *et al.*, 1981, Krstacic *et al.*, 2007). Others state that at the very least non-linearities are an integral part of biological systems that are often ignored, or, that assessment of linear measures is partly invalidated due to heart-rate dynamics seldom meeting the assumption of stationarity required for

their derision (Huikuri *et al.*, 1996; Maestri *et al.*, 2007). A realistic presumption is that HRV also contains non-linear properties. These non-linear characteristics can be addressed by the use of non-linear analysis techniques. Recent estimates suggest over 30 such available techniques (Stein and Reddy, 2005). It is beyond the remit of this chapter to review all of these, but the utility of some of these techniques lies in their independent prognostic and risk stratification power which has been shown to equal or even better that of traditional linear measures. One such technique is the Poincaré plot which represents the underlying structure of the RR interval time series. Woo *et al* (1994) first described how a plots shape could distinguish amongst CHF patients those likely to have higher sympathetic activation and demonstrate an increased risk profile. A quantitative approach was later developed involving the fitting of an ellipse centred on the middle of the points and plotting two axes that describe the short- (SD1) and long-term (SD2) variability of the data. Measures of SD1 and SD2 have been shown to be strong indicators of all-cause and sudden death, especially in CHF patients (Kamen and Tonkin, 1995; Brouwer *et al.*, 1996; Maestri *et al.*, 2007).

Both the Polar S810 system and HRV analysis software provide SD1 and SD2 measures. The reliability of these systems to obtaine Poincaré measures in CHF patients would also be assessed for the first time.

A second aim of this study was to assess measures of HRV obtained from the HRV analysis software but when different parameter settings are applied. As described in greater detail in chapter two (section 2.1), users of the HRV analysis software can adjust a number of parameters by which HRV values are determined. This feature is not apparent with the Polar S810 system. The ability to adjust parameters is afforded by the software developers to account for situations where short-term RR interval data present with a very low frequency trend. To account for this, detrending options are available including removal of the first or second order linear trend or a smoothness priors method (Niskanen *et al.*, 2004). The smoothness priors detrend method acts like a time-varying finite impulse response high-pass filter and is easily applied to different occasions through the adjustment of only one parameter. The application of a detrend to RR interval data is particularly evident in diseased populations, particularly CHF,

where there is often an observed shift in spectral power distribution into the very low-frequency (VLF) region (Saul *et al.*, 1988). Where short-term recordings are being made, it is often therefore necessary to account for this trend so as to obtain adequate spectral measures from the LF and HF regions. The effect of applying this method to the reliability of HRV was also assessed in chapter two and it was found to display similar outcomes to those for the Polar S810. The same analysis is required in CHF patients as the likelihood of using detrend methods is more prominent.

Application of a smoothness priors detrend has differing effects according to the spectral decomposition method whereby for fast Fourier transform (FFT) methods the VLF component is properly removed without adversely affecting the higher components (Niskanen *et al.*, 2004).

Due to the varying nature in which data from the HRV analysis software will be assessed, the aims and objectives of this chapter are divided as follows:

- i. To compare the reliability of Polar S810 HRV measurements obtained in CHF with measures obtained using the Polar S810 and criterion systems in healthy participants;
- ii. To assess the validity of HRV measurements obtained in CHF patients using the HRV 1.1 analysis software with settings that most closely match those of the Polar S810;
- iii. To assess the reliability of repeat measures of HRV obtained in CHF patients using the HRV 1.1 analysis software with application of a smoothness priors detrend.

Lessons learned during the publishing process for chapters two and three will be applied to the statistical analyses best suited to address the above aims. A graphical illustration of the RR and HRV analysis procedures to be carried out in is provided in Figure 6-1.

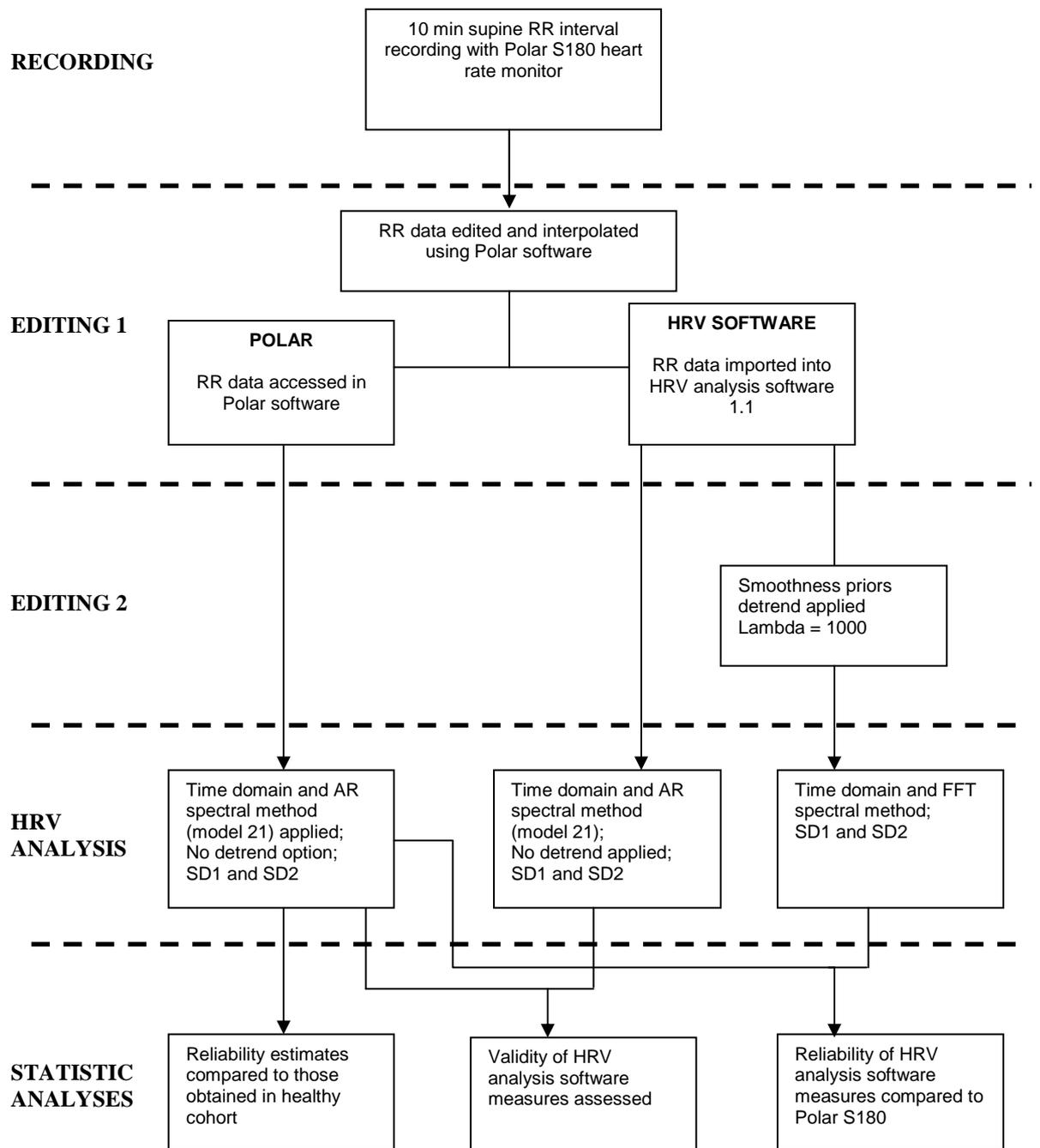


Figure 6-1. Schematic of the procedures followed to meet the study aims.

## **6.2. Methods.**

### *6.2.1. Patient Recruitment.*

Patients from the Hillingdon Hospital NHS Trust heart failure clinic were recruited for this study in accordance with approval received by the local government research ethics committee. Following an initial phone conversation, volunteers were sent an information pack containing:

1. The scope, aims and methodology of the study
2. An information sheet detailing what was required of the participant prior to and during each visit to the laboratory
3. A detailed informed consent form

Participants were requested to read and complete the documents provided in the information pack and to adhere to the pre-testing instructions prior to their initial visit to the laboratory.

### *6.2.2. Patient sample.*

Sixteen males with median age 65 (range = 41 – 81) and four females with median age 68 (range = 58 – 78) gave full written informed consent to participate in the study. Heart failure was confirmed in all patients by the supervising cardiologist. The aetiology of disease included dilated cardiomyopathy (DCM), ischaemic heart disease (IHD) and myocardial infarct (MI). New York Heart Association (NYHA) classification ranged from I to II across the patient cohort.

### *6.2.3. Instrumentation and data acquisition.*

RR intervals and heart rate (HR) were recorded via a Polar S810 heart rate monitor (HRM) (Polar Electro OY, Kempele, Finland). The S810 was set to record beat-to-beat RR intervals with a sampling frequency of 1000 Hz providing an accuracy of 1ms for each RR period (Cottin *et al.*, 2004). S810 recordings were transferred to a password protected PC via the Polar Precision Performance software version 4.03 (Polar Electro OY, Kempele, Finland). Each downloaded RR interval file was exported as a .txt file to a separate folder for later HRV analysis using an advanced software package (HRV Analysis Software 1.1., University of Kuopio, Finland)

#### 6.2.4. Protocol.

##### 6.2.4.1. RR interval recordings.

On two separate occasions heart rate variability measures were derived from seven minutes of stationary ECG obtained supine and at rest using the S810. On each occasion a two minute RR recording was first obtained under normal conditions to determine baseline HRV values. Following the initial two minute recording, a five minute recording was made whilst controlling breathing at a rate of 12 breaths·min<sup>-1</sup> (0.2 Hz) via standardized instruction and metronome pacing. The S810 recordings were filtered for errors using the Polar software automated RR interval filtering algorithm set at medium filter power and minimum beat protection zone of 6 b·min<sup>-1</sup>. The interpolation of beats via this method has only minor effects on spectral measures of HRV measured from stationary tachograms (Jurca *et al.*, 2004) in which <15% of beats are rejected. Only data from the second five minute (i.e. paced breathing) condition were entered into validity and reliability analyses.

##### 6.2.4.2. Heart rate variability analysis.

###### 6.2.4.2.1. Linear heart rate variability.

Linear measures of HRV were obtained from the filtered RR interval data according to recommended standards (Task Force, 1996) using both Polar Precision software and HRV analysis software 1.1 as described earlier (chapters two and three). The HRV analysis software affords users the ability to adjust certain parameter settings to account for differing RR interval time series data. In the present study, RR interval data were analysed using two distinct and separate parameter settings including:

1. Settings one: autoregressive (AR) model 21, no detrend and interpolation rate set at 2 Hz;
2. Settings two: fast Fourier transform (FFT), smoothness priors detrend, interpolation rate set at 4 Hz and  $\lambda$  set at 1000.

Settings one were used to provide data that best matched data from Polar which does not have a detrend feature and uses AR (model 21) decomposition methods to determine spectral measures of HRV. Settings two were used to account for often non-stationary RR interval time series (see 7.2.4.2.2. below) and the more commonly applied FFT spectral analysis technique. It is not uncommon for non-stationary signals to be present in the RR interval time series of diseased patients, such as CHF (Tulppo *et al.*, 1996; İşler and Kuntalp, 2007). Such signals can distort values of HRV, particularly those in the frequency domain towards greater power in the very low frequency (0.0033 – 0.04 Hz; VLF) regions. Therefore it is often necessary to remove trends in the series via some form of detrending procedure. The advanced HRV analysis software incorporates several options including a smoothness priors detrend. This form of detrend acts like a time varying finite impulse response high-pass filter that removes the low frequency trend whilst not to severely effecting the LF and HF. The RR interval time series was subjected to smoothness priors detrend prior to HRV analysis. From both settings in the HRV analysis software and from the Polar Precision software, the time domain measures SDNN and rMSSD were derived. In the frequency domain, low frequency power (LF, 0.04 – 0.15 Hz) and high frequency power (HF, 0.15 – 0.40 Hz) were measured in raw and normalised units. The ratio between LF and HF power (LF:HF) was determined. Data were transformed, if necessary, to allow parametric analysis.

#### 6.2.4.2.2. Non-linear heart rate variability.

In addition to the linear measures above non-linear measures were also obtained. As mentioned, heart rate dynamics often violate the assumptions of stationarity required for traditional linear HRV analysis methods and present with non-linear characteristics (Tulppo *et al.*, 1996; Kleiger *et al.*, 2005; Contreras *et al.*, 2007). This is particularly true in cardiovascular disease where several methods for analysing these non-linear aspects have been proposed (İşler and Kuntalp., 2007; Maestri *et al.*, 2007). The Poincaré plot, a graph of each RR interval plotted against the next interval, is a simple technique taken from non-linear dynamics to quantify the RR data. By fitting an ellipse to the shape of plotted points, two standard deviations, referred to as SD1 and SD2, are obtained. These are related

to the fast beat-to-beat and longer-term variability respectively. Moreover, these quantitative measures have been shown to independently predict all-cause and sudden cardiac death in CHF patients (Brouwer *et al.*, 1996). Both the Polar and the HRV analysis software automatically derive SD1 and SD2 and these measures were included in this chapter.

#### 6.2.5. *Statistical Analysis.*

All statistical analysis was carried out using SPSS version 13.0 (SPSS inc. Chicago, Illinois, USA). Normality of data sets was assessed using a Kolmogorov-Smirnov test. Where assumptions for parametric testing were not met data were subjected to transformation (natural logarithm - ln).

##### 6.2.5.1. *Validity of heart rate variability from HRV analysis software.*

The validity of non-detrended data from the HRV analysis software with settings one were assessed using Pearson correlation coefficient between Polar S810 and the HRV analysis software. In addition, the standard error of the estimate (SEE) was derived from the regression analysis and provided a measure of the random error (noise) in the prediction of Polar HRV from the HRV analysis software. The uniformity of error was assessed by visual analysis of regression plots to identify any differences in the degree of error over the range of participant measurement values. Trivial error or noise is indicated when SEE is lower than the smallest worthwhile effect (0.2 of the between subject SD as defined by Cohen (1988)) which is equal to a validity correlation greater than 0.98. To provide more precise estimates, mean bias, and SEE were derived for each trial and then averaged (Hopkins, 2000). The estimate of uncertainty was provided by averaging the 95% confidence intervals (CI).

Finally, 95% limits of agreement (LoA) were obtained to assess agreement of measures between Polar and HRV analysis software. For LoA analysis of log-transformed data, dimensionless ratios were calculated by taking the antilog of the mean of differences and 95% LoA (Bland and Altman, 1986).

#### 6.2.5.2. Reliability of measurements from Polar and HRV analysis software.

Experiences gained as a result of undergoing the peer review process during the successful submission of chapter two for publication have identified alternative statistical methods to determine reliability. For these reasons, the standard error of measurement (SEM) was derived from values obtained by the HRV analysis software with settings two and then compared to Polar SEM values. Uniformity of error was assessed by visual analysis of regression plots for between-trial change scores to identify any differences in error over the range of values. The use of SEM was preferred to other statistical methods of precision and reliability, as they are unaffected by changes in mean values, are robust to sample size bias and best enable cross study comparisons (Hopkins, 2000).

In addition, both between- and within-subjects coefficient of variation (CV) were obtained to enable comparisons with data obtained in chapters two and three for normal healthy adults. Finally, intraclass correlation coefficient (ICC) with 95% CI (Marks and Lightfoot, 1999) was calculated between each trial as an additional measure of within-subject reliability and to allow for comparison to previous reliability studies. A random effects mixed model ICC (3.1) was chosen as it is unaffected by sample size bias (Shrout and Fleiss, 1979). There is no universal standard for classifying the magnitude of ICC. Hopkins (2000) suggests retest reliability of at least 0.81 for decisions related to criterion-referenced assessments.

### **6.3. Results.**

#### *6.3.1. Validity of heart rate variability from the HRV analysis software using settings one.*

Due to unforeseen personal circumstances four patients were unable to perform repeat HRV and exercise testing meaning that data from 16 patients were entered into the final analyses.

The outcomes of validity and agreement analyses are presented in Table 6-1. Natural logarithms (ln) of all measures except mRR, LFnu and HFnu were used

owing to skewed distributions. Descriptive data for these measures are presented as back-transformed means with a times/divide factor for the standard deviation. The SEE for these measures is presented as a factor difference with times/divide confidence limits.

A mean difference of less than 0.1 ms, narrow CI, a trivial SEE ( $< 0.01$  of the between-subjects SD) and perfect correlations with values from the Polar indicates perfect validity for measures of mean RR interval obtained from the HRV analysis software with settings one. Agreement in measures was also demonstrated by relatively small LoA.

The outcomes for validity statistics indicate that values for normalised LF and HF measurements demonstrate poor validity, with the HRV analysis software underestimating Polar values on average by 12 to 15 units for LFnu and HFnu respectively. Poor agreement between systems was also demonstrated by large limits of agreement for both measurements.

A mean ratio ranging from 0.33 (-67%) to 1.06 (6%) was observed between Polar and HRV analysis software log-transformed measures of HRV. Observed CI indicate the true ratio was trivial for SDNN (0% to 1%), rMSSD (-2% to 3%) and SD2 (-3% to 1%), small for SD1 (-5% to 4%) and large for LF (-70% to -62%) and HF (-71% to -61%) power and LF:HF ratio (-14% to 31%). The SEE for these measures show error ranged from trivial (0.01 SD, SDNN) to small (0.27 SD, LF:HF). Validity correlations ranged from 0.91 (LF:HF) to 1.00 (SDNN) indicating good to perfect validity of measures (i.e. values are either the same or differences are consistent). Analysis of agreement revealed that values for HRV measures from the HRV analysis software can be as small/large as about 2%/116% of those from the Polar S810.

**Table 6-1. Summary (mean and SD) and validity statistics (mean difference or ratio, standard error of estimate and correlation coefficient, with confidence interval) for measures of heart rate variability from Polar S810 and HRV analysis software (settings one) derived in chronic heart failure patients.**

	<b>Polar S810</b> (mean $\pm$ SD or mean $\times/\div$ SD)	<b>HRV analysis software - S1</b> (mean $\pm$ SD or mean $\times/\div$ SD)	<b>Mean difference or ratio<sup>a</sup></b> (95% CI)	<b>Standard error of estimate</b> (95% CI)	<b>Pearson correlation</b> (95% CI)	<b>95% Limits of agreement</b>
<b>Measures analyzed raw</b>						
mRR	972 $\pm$ 162 ms	972 $\pm$ 162 ms	-0.06 ms (-0.14 to 0.14)	0.23 ms (0.17 to 0.36)	1.00 (1.00 to 1.00)	$\pm$ 20.1 ms
LFnu	44 $\pm$ 16	39 $\pm$ 21	-5.4 (-16.4 to 5.7)	12.4 (9.1 to 19.5)	0.66 (0.25 to 0.87)	$\pm$ 28.8
HFnu	56 $\pm$ 16	42 $\pm$ 19	-14.3 (-22.1 to -6.4)	15.2 (11.2 to 24.1)	0.38 (-0.14 to 0.74)	$\pm$ 40.5
<b>Measures analyzed via log-transformation</b>						
SDNN	43 ms $\times/\div$ 2.01	43 ms $\times/\div$ 2.01	1.01 (1.00 to 1.01)	1.01 (1.01 to 1.02)	1.00 (1.00 to 1.00)	$\times/\div$ 1.02
rMSSD	36 ms $\times/\div$ 2.25	36 ms $\times/\div$ 2.23	1.01 (0.98 to 1.03)	1.04 (1.03 to 1.07)	0.99 (1.00 to 1.00)	$\times/\div$ 1.08
LF	324 ms <sup>2</sup> $\times/\div$ 5.75	110 ms <sup>2</sup> $\times/\div$ 5.87	0.34 (0.30 to 0.38)	1.25 (1.17 to 1.42)	0.99 (0.98 to 1.00)	$\times/\div$ 1.54
HF	428 ms <sup>2</sup> $\times/\div$ 4.10	142 ms <sup>2</sup> $\times/\div$ 3.60	0.33 (0.29 to 0.39)	1.29 (1.20 to 1.51)	0.98 (0.95 to 0.99)	$\times/\div$ 1.72
LF:HF	0.76 $\times/\div$ 2.05	0.80 $\times/\div$ 2.51	1.06 (0.86 to 1.31)	1.34 (1.25 to 1.62)	0.91 (0.76 to 0.97)	$\times/\div$ 2.16
SD1	25.8 ms $\times/\div$ 2.25	25.5 ms $\times/\div$ 2.23	0.99 (0.99 to 1.01)	1.03 (1.02 to 1.04)	0.99 (0.98 to 1.00)	$\times/\div$ 1.19
SD2	53.5 ms $\times/\div$ 1.97	53.0 ms $\times/\div$ 1.97	0.99 (0.99 to 1.00)	1.01 (1.01 to 1.02)	0.99 (1.00 to 1.00)	$\times/\div$ 1.07

For raw data measures of centrality and dispersion are mean  $\pm$  SD; For log-transformed measures the mean shown is the back-transformed mean of the log-transform, and the dispersion is a  $\times/\div$  factor SD; Statistics derived on each of the two testing occasions for the 16 participants were averaged; mRR, mean time between normal r-waves; SDNN, the standard deviation of normal-to-normal intervals; rMSSD, root mean square of successive differences; LF, low frequency spectral power; HF, high frequency spectral power; nu, normalised units; LF:HF, the ratio of low to high frequency spectral power; SD1, standard deviation of points on the short-axis of the Poincaré ellipse; SD2, standard deviation of points on the long-axis of the Poincaré ellipse; CI, confidence interval.

<sup>a</sup>HRV analysis software-Polar or HRV analysis software/Polar.

6.3.2. *Systematic bias and coefficient of variation for Polar S810 and HRV analysis software 1.1. measurements of heart rate variability.*

In the present study, a number of individuals presented with unusually high values for spectral measures of HRV. This was often the result of large values for VLF components of the power spectrum. To account for these non-stationary signals smoothness priors detrending was applied to all RR interval time series which removes the VLF component without significantly altering the LF and HF components. An example case is presented in Figure 6-2 and the effects of applying detrend procedures are displayed in Table 6-2. Changes in VLF, LF and HF before and after detrend application were analysed by paired *t*-tests. The VLF component was successfully removed without statistically altering the values for LF and HF.

Values for initial and repeat raw and log-transformed measurements of HRV from the HRV analysis system with settings two (see 6.2.4.2) are presented along with outcomes of paired *t*-test analysis in Table 6-3. Systematic bias was not present in any measure from either Polar or HRV analysis software as indicated by the non-significance for differences in initial and repeat scores.

To allow for comparisons to data obtained in healthy patients in chapter three of this thesis and data within the literature, between-subjects' coefficient of variation (CV) in initial and repeat trials as well as within-subjects CV were calculated. The results of these analyses are presented in Figure 6-3. The main finding from this analysis was that measures of HRV obtained from the Polar were as variable as those from healthy participants. The second main finding was that log-transformation reduced the variation by > 50% for the majority of measures. The HRV analysis software demonstrated similar between- and within-subject CVs to those from the Polar. As expected, values for CV between-subjects were larger than those for within-subjects and spectral measures in raw and log units demonstrated the largest CVs. Non-linear SD1 and SD2 measures in both raw and log units demonstrated CVs similar to those for time domain measures of HRV.

### RR Interval Time Series

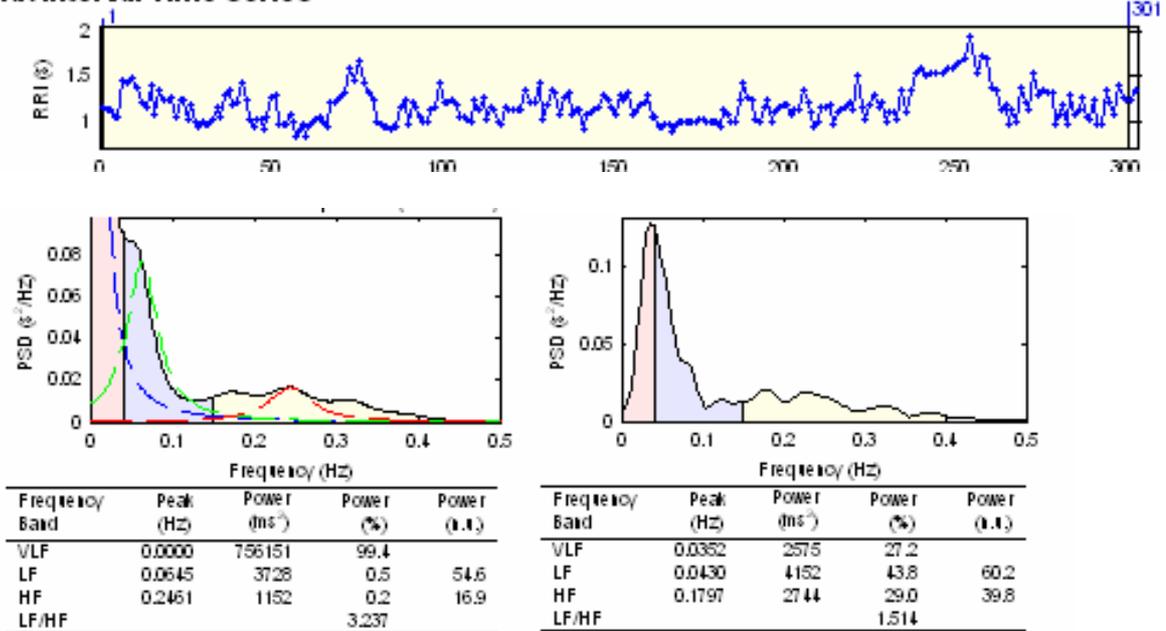


Figure 6-2. RR interval time series from one patient demonstrating non-stationary characteristics (upper panel) and a very low-frequency trend (VLF) (lower left panel). This can be corrected for in the HRV analysis software by using the smoothness priors detrend function which removes the VLF frequency component without adversely affecting the LF and HF components (lower right panel).

Table 6-2. Effects of application of the smoothness priors detrend to frequency domain HRV measures.

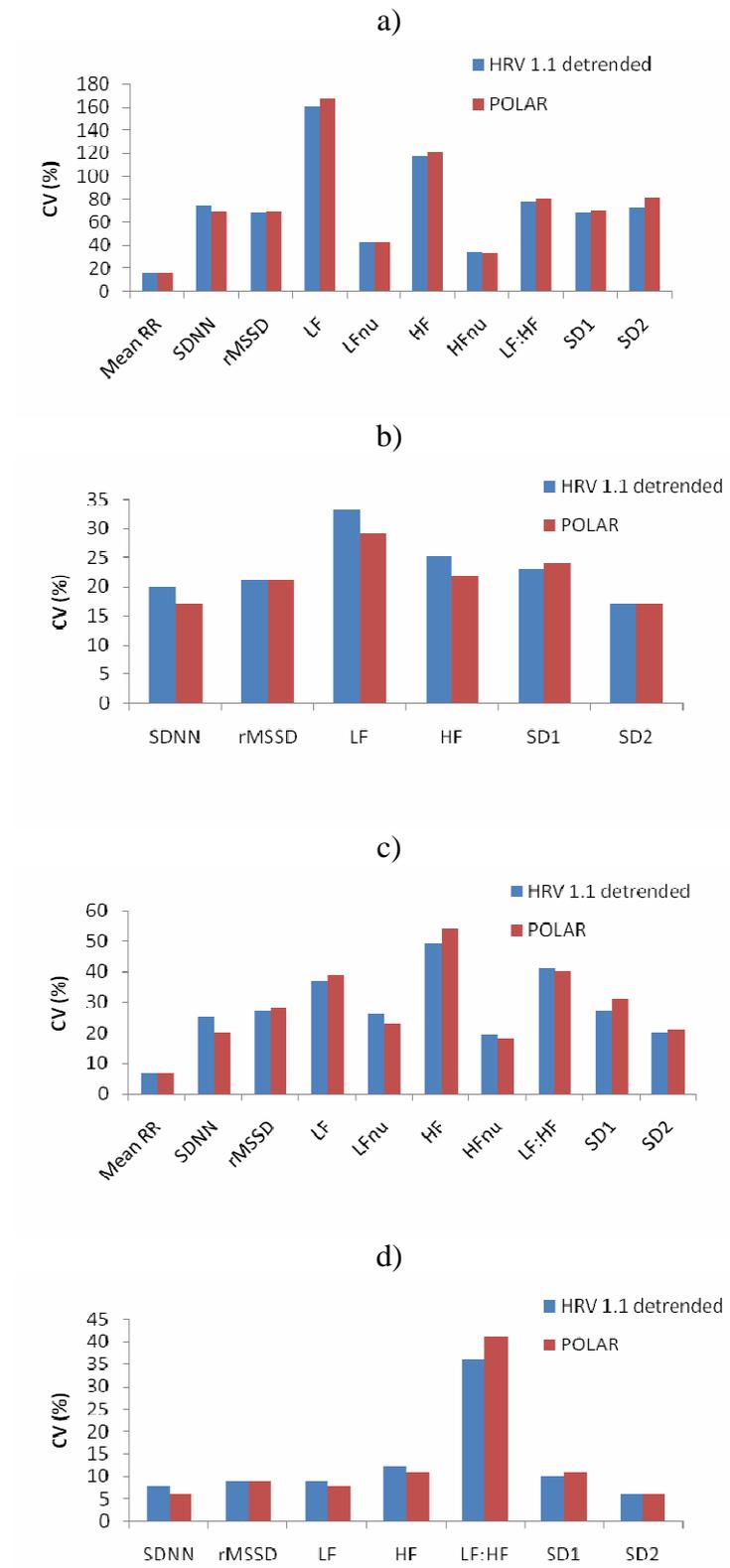
	HRV analysis software Settings 1 (mean ± SD)	HRV analysis software Settings 2 (mean ± SD)	Mean difference <sup>a</sup> (95% CI)	P value	Effect Size
VLF	702420 ± 907909 ms <sup>2</sup>	358 ± 751 ms <sup>2</sup>	702062 (125162 to 1278962)	0.005	1.54
LF	747 ± 1104 ms <sup>2</sup>	878 ± 1243 ms <sup>2</sup>	-131 (-276 to 14)	0.12	-0.08
HF	331 ± 319 ms <sup>2</sup>	593 ± 761 ms <sup>2</sup>	-262 (-554 to 29)	0.15	-0.48

VLF, very low frequency (0.00 – 0.04 Hz); LF, low frequency spectral power; HF, high frequency spectral power; CI, confidence interval.

**Table 6-3. Systematic bias for repeat measures of heart rate variability from the Polar S810 and HRV analysis software with settings two in chronic heart failure patients.**

HRV Measure	POLAR			HRV analysis software – settings 2		
	Initial	Repeat	<i>P</i> value	Initial	Repeat	<i>P</i> value
mRR (ms)	948 ± 167	950 ± 131	0.93	948 ± 167	950 ± 131	0.93
SDNN (ms)	49 ± 33	45 ± 32	0.40	40 ± 27	34 ± 27	0.21
rMSSD (ms)	42 ± 25	39 ± 31	0.49	42 ± 25	39 ± 30	0.44
LF (ms <sup>2</sup> )	1014 ± 1493	785 ± 1475	0.45	445 ± 659	349 ± 606	0.30
LFnu	44 ± 18	45 ± 19	0.85	43 ± 18	46 ± 20	0.58
HF (ms <sup>2</sup> )	668 ± 640	665 ± 967	0.99	321 ± 338	293 ± 377	0.60
HFnu	56 ± 18	55 ± 19	0.87	57 ± 18	54 ± 19	0.58
LF:HF	1.01 ± 0.80	1.05 ± 0.86	0.86	0.95 ± 0.72	1.13 ± 0.91	0.44
SD1 (ms)	31.7 ± 20.0	27.3 ± 21.5	0.28	29.9 ± 18.0	27.5 ± 21.4	0.45
SD2 (ms)	62.9 ± 44.2	56.2 ± 40.5	0.34	61.9 ± 44.3	56.4 ± 40.7	0.42
<b>Analysis following log-transformation</b>						
SDNN	3.68 ± 0.67	3.63 ± 0.56	0.63	3.47 ± 0.73	3.32 ± 0.63	0.27
rMSSD	3.52 ± 0.75	3.42 ± 0.71	0.42	3.52 ± 0.76	3.42 ± 0.68	0.45
LF (ms <sup>2</sup> )	5.63 ± 1.73	5.48 ± 1.45	0.51	4.82 ± 1.68	4.76 ± 1.41	0.79
HF (ms <sup>2</sup> )	5.91 ± 1.26	5.74 ± 1.25	0.52	5.12 ± 1.20	4.98 ± 1.27	0.38
LF:HF	-0.29 ± 0.82	-0.26 ± 0.86	0.90	-0.32 ± 0.79	-0.23 ± 0.94	0.67
SD1 (ms)	3.21 ± 0.79	3.06 ± 0.71	0.30	3.18 ± 0.75	3.08 ± 0.68	0.45
SD2 (ms)	3.92 ± 0.69	3.86 ± 0.56	0.61	3.90 ± 0.68	3.86 ± 0.56	0.69

mRR, mean time between normal r-waves; SDNN, the standard deviation of normal-to-normal intervals; rMSSD, root mean square of successive differences; LF, low frequency spectral power; HF, high frequency spectral power; nu, normalised units; LF:HF, the ratio of low to high frequency spectral power; SD1, standard deviation of points on the short-axis of Poincaré ellipse; SD2, standard deviation of the long-axis of the Poincaré ellipse; Ln, natural logarithm.



**Figure 6-3. Between- and within-subjects coefficient of variation (CV) for measures of heart rate variability obtained by Polar and HRV analysis software (settings two) in chronic heart failure patients. Between-subjects CV for raw and log-transformed data are presented in panels a and b respectively. These statistics were calculate for each trial and then averaged. Within-subjects CV for raw and log-transformed data are presented in panels c and d respectively.**

6.3.3. *Comparisons of reliability estimates for heart rate variability from the Polar S180 and HRV analysis software 1.1 with settings two.*

Estimates for reliability of HRV measures in raw and log-transformed units are presented for Polar and HRV analysis software in Table 6-4. Values for ICC and SEM for raw measures obtained from the HRV analysis software were similar and indicated that reliability was not high as no measure demonstrated an ICC greater than 0.81. Reliability statistics for log-transformed values were also very similar between Polar and the HRV analysis software and if anything SEM was slightly lower (i.e. better) for HRV software measurements. Of the seven log-transformed measures, six demonstrated ICCs greater than 0.81 when obtained by the HRV analysis software. Conversely, four measures displayed ICCs greater than 0.81 from the Polar. The least reliable measure for both systems was the LF:HF ratio.

**Table 6-4. Standard errors of measurement (in raw or factor units) and intraclass correlation coefficients derived from repeat measures of heart rate variability by the Polar S810 and the HRV analysis software.**

	Standard error of measurement		Intraclass correlation coefficient	
	Polar S810	HRV analysis software Settings 2	Polar S810	HRV analysis software Settings 2
<b>Measures analyzed raw (error in raw units)</b>				
mRR	79 ms (57 to 124)	79 ms (57 to 124)	0.74 (0.41 to 0.90)	0.74 (0.41 to 0.90)
LFnu	11 (8 – 18)	12 (9 – 19)	0.63 (0.22 to 0.85)	0.58 (0.14 to 0.83)
HFnu	11 (8 – 18)	12 (9 – 19)	0.63 (0.22 to 0.85)	0.58 (0.14 to 0.83)
<b>Measures analyzed via log-transformation (error in factor units)</b>				
SDNN	1.33 (1.23 to 1.56)	1.40 (1.28 to 1.69)	0.85 (0.62 to 0.94)	0.81 (0.55 to 0.93)
rMSSD	1.43 (1.31 to 1.75)	1.41 (1.30 to 1.72)	0.82 (0.58 to 0.94)	0.83 (0.60 to 0.94)
LF	1.78 (1.52 to 2.45)	1.73 (1.49 to 2.34)	0.90 (0.75 to 0.96)	0.91 (0.77 to 0.97)
HF	2.08 (1.72 to 3.06)	1.90 (1.60 to 2.69)	0.78 (0.49 to 0.92)	0.82 (0.57 to 0.93)
LF:HF	1.73 (1.49 to 2.34)	1.78 (1.54 to 2.44)	0.58 (0.15 to 0.83)	0.56 (0.12 to 0.82)
SD1	1.49 (1.34 to 1.84)	1.41 (1.30 to 1.72)	0.79 (0.51 to 0.92)	0.83 (0.60 to 0.94)
SD2	1.36 (1.26 to 1.63)	1.35 (1.25 to 1.58)	0.81 (0.55 to 0.93)	0.83 (0.60 to 0.94)

Data in parentheses are 95% confidence intervals; mRR, mean time between normal r-waves; SDNN, the standard deviation of normal-to-normal intervals; rMSSD, root mean square of successive differences; LF, low frequency spectral power; HF, high frequency spectral power; nu, normalised units; LF:HF, the ratio of low to high frequency spectral power; SD1, standard deviation of points on the short-axis of Poincaré ellipse; SD2, standard deviation of the long-axis of the Poincaré ellipse.

## 6.4. Discussion.

The present study sought to examine traditional linear and non-linear measures of short-term HRV obtained using the Polar S810 system and the HRV analysis software 1.1 package for their valid and reliable use in CHF patients. Moreover, the effects on reliability of measures derived using different HRV parameter settings within the HRV analysis software were also assessed. The findings will be discussed separately in relation to each of the study aims with reference to data from chapters two and three and those from previous studies where applicable.

### 6.4.1. *Reliability of heart rate variability from Polar S810 in chronic heart failure.*

In chapter two, assessment of the validity of Polar S180 measures was made possible by concurrent derivation of criterion measures from a laboratory based ECG system (CardioPerfect ST module, Cardio Control, Delft, The Netherlands). Due to unforeseen circumstances the same ECG system was unavailable and thus prevented validity assessments of the Polar S180 in the present study. This limitation is referred to later in section 6.5. Only the reliability, therefore, of the Polar S810 system could be assessed. A combination of methods to assess reliability was used in order that comparisons to data in chapters two and three and to previous studies could be made. Comparisons for some reliability statistics (e.g. standard error of measurement (SEM)) could only be made with the study of Nunan *et al.* (2009) as this is the one study providing such estimates.

The data provided by Nunan *et al.* allows for comparisons of reliability estimates of Polar S810 HRV measures in CHF patients with measures from both the Polar S810 and criterion measures in healthy participants. Values for the SEM and ICC reliability estimates for linear measures of HRV were similar to those observed for healthy individuals. The study of Nunan *et al.* does not report reliability estimates for non-linear indices but in the present study, SD1 and SD2 were found to display similar reliability to time-domain measures of HRV. In fact for all linear measures except mean RR, the ICC values (0.58 to 0.90) for Polar S810 HRV data in the present study exceeded those observed for Polar (0.45 to 0.84)

and criterion (0.36 to 0.92) estimates in healthy participants (Nunan *et al.*, 2009). The ICC estimate for SD1 (0.79) and SD2 (0.81) were similar to those observed for linear measures in the present study.

In an earlier study assessing the stability of HRV in CHF patients, Stein *et al.* (1995) demonstrated similarly high ICCs for 24 h time domain and frequency domain measures of HRV with values ranging from 0.86 to 0.91 for measures obtained two weeks apart.

Taken together these data suggest that 24 h and short-term linear and short-term non-linear measures of HRV are inherently more reproducible in CHF patients. However, the sole use of ICC to demonstrate reliability is questionable, primarily due to fact that values can be exaggerated when data reveal a wide spread of scores (e.g. large SD) often disguising the true magnitude of variation (Bland and Altman, 1990). When compared with the healthy participants of Nunan *et al.* (2009), the SD for most measures was larger in the current cohort of CHF patients (Table 6-1) and could explain the slightly better ICCs reported for this group.

Confirmation of this is provided when reliability estimates from the SEM are considered. The SEM is an estimate of the noise that tends to obscure changes in repeated measures (Hopkins, 2000). When log-transformed, SDNN in the time-domain and all frequency-domain measures in CHF demonstrated larger SEM values compared with healthy individuals. Exceptions were found for rMSSD and measures analysed using raw data (mean RR, LFnu and HFnu), all of which had similar SEM values to those reported in Nunan *et al.* (2009). Non-linear measures demonstrated SEMs matching those of time-domain measures. These findings indicate a slightly higher degree of error for linear measures from the Polar S810 when obtained in CHF patients.

Between-subject coefficient of variation (CV) was calculated as a simple means to identify the degree of variation between patients and revealed that Polar S810 measures demonstrate no worse variation between CHF patients compared to Polar measures in healthy participants (chapter two, section 2.3.1.2). In both

healthy and CHF patients, spectral measures demonstrate the largest CVs but the pattern of variation differs, whereby in the former group the CV for HF power (168%) was larger than that for LF power (119%). In CHF patients, an opposite pattern was found, with both raw LF and ln LF measures demonstrating larger variation (168% and 29%) compared with raw and ln HF power (121% and 22%).

Measures of within-subject CV provide an estimate of the variation between repeat measures. The findings for this estimate in the present study are different according to whether measures are assessed raw or following log-transformation. Where raw measures are used, Polar S810 measures are the same and only moderately reliable in CHF patients as they are in healthy participants (chapter two, section 2.3.1.2). However, when log-transformed measures are used, CVs are improved by a factor of two or more for both linear and non-linear measures and all values were below 12% except for LF:HF ratio which remained unchanged (Figure 6-3).

These findings are mirrored somewhat in an earlier study assessing reliability of short-term HRV measures in CHF. In sixteen patients, Ponikowski *et al.* (1996) reported CVs for SDRR (standard deviation of RR intervals) ranging from 25 – 30% and from 45 – 111% for spectral measures of HRV, with LF recording the higher values. Ponikowski *et al.* also assessed reliability after log-transformation and they too demonstrate improved CVs with values ranging from 8 – 61%. An obvious difference is the values for CVs presented here and by Ponikowski *et al.* Even after log-transformation, Ponikowski *et al.* still demonstrated poor reliability for spectral measures of HRV. Reasons for this could relate to the fact a longer period between measures (mean of 25 days) was adopted in Ponikowski *et al.* which would have afforded greater time for changes in underlying biological systems to occur.

The only other similar study assessing the reproducibility of short-term, resting HRV in CHF occurred in patients following a cardiac transplant (Lord *et al.*, 2001). Assessing measures of LF power only, the authors report a CV of 76% for repeat measures made one week apart. Healthy adults demonstrated a CV of

45%. Greater variance in the patient group was attributed to the presence or absence of autonomic reinnervation. The authors also note that the time of day recordings took place explained some, but not all, of the variation observed. Other factors related to familiarity with the measurement were presented. Nunan *et al.* (2009) also report a small familiarity effect between measures from the first and second but not the second and third trials. The use of a larger number of repeat measures may have improved reliability estimates (Vickers *et al.*, 2002).

Overall, when used in CHF patients, the Polar S810 system is no less reliable than when the same system is used in healthy populations. Linear measures of HRV are as equally unreliable in CHF patients as they are in healthy participants but the degree of within-subject variation may be improved when log-transformed measures are considered rather than absolute units. This finding is particularly important for studies assessing the influence of intervention and/or management on the HRV profile.

#### 6.4.2. *Validity of the HRV analysis software 1.1 in chronic heart failure.*

To assess the validity of the HRV analysis software, parameter settings were set to match as close as possible those of the Polar S810 software. This included the application of an autoregressive (AR) model (order 21) to determine spectral measures and the removal of the default detrend option. When assessed in this manner, the HRV analysis software provided near perfect validity for measures of mean RR. This finding was expected due to the fact that the HRV analysis software uses the exact same RR data series and does not apply any different mathematical processes for RR interval determination.

Normalised spectral measures were underestimated by the HRV analysis software and demonstrated large random variation, poor validity correlations and wide limits of agreement (LoA). There is a simple explanation for this finding that relates to the way these measures are determined by the two systems. The HRV analysis software calculates normalised LF as a percentage value over the total power (TP) after subtraction of the very low frequency (VLF) component as follows:  $LF_{nu} = LF / (TP - VLF) \times 100$ . The same equation is used to determine

HFnu, substituting HF as appropriate. Normalised measures are calculated from the Polar S810 using a different equation that does not account for the VLF component as follows:  $LFnu$  or  $HFnu = LF$  or  $HF / (LF + HF) \times 100$ . The equation used by the HRV analysis software will always produce normalised values lower than those from the Polar S810 unless the VLF component is zero.

The validity of both time-domain and non-linear measures from the HRV analysis software was excellent, with no bias, perfect to near perfect correlation, trivial random error (SEE). Limits of agreement (LoA) ranged from  $\times/\div$  2% to 19% for SDNN to SD1, indicating interchangeable agreement for SDNN only. Time-domain measures are simply the outcomes of standard mathematical techniques (e.g. standard deviation, square-root etc) and unlike frequency-domain measures; they do not require the use of algorithmic functions. When derived from the same RR time series, time-domain measures are therefore likely to demonstrate the same findings. Simple mathematical differences such as the amount of decimal places applied to values by the two systems may explain the trivial error observed.

Measures in the frequency-domain did not demonstrate the same level of validity as those for time-domain and non-linear indices. The HRV analysis software showed a large underestimation for LF and HF power and accompanying LoA were wide ( $\times/\div$  54% and 72%). This finding was surprising, as both systems were set to apply the same AR model for spectral decomposition and therefore would be expected to demonstrate similar values. One explanation for the findings relates to the nature of the spectral method employed. The AR method is a complex second order approach involving linear modelling and coefficients to describe the power spectral density at the high and low frequencies. Both *a priori* (e.g. model order) and *post-priori* (e.g. Anderson test) assessments need to be carried out to ensure the model and coefficients used provide reliable and valid estimates. A fault with the overall model can cause an excess of spurious peaks in the spectrum resulting in inaccurate and differing estimates (Cerutti *et al.*, 1995). Whilst the same model order (21) was applied by the two systems, there may be subtle differences in coefficients and *post-priori* assessments. The Polar

and HRV analysis software developers do not provide full details of the AR models applied but it is unlikely they utilise the exact same parameters or *post-priori* assessments.

Despite the above findings for lower spectral values from the HRV analysis software, the SEE indicates that the degree of error was trivial in comparison to the inherent variation in these measures (i.e. SEE was less than 0.2 SD). High correlations also indicate that underestimations are consistent and not the result of a few spurious patient values.

The analysis of limits of agreement (LoA) were included as a commonly used measure of agreement. The degree to which limits are considered unacceptable is a subjective judgement and consideration to the spread of scores should be given (Hopkins *et al.*, 2009). In the present study, LoA values for measures in raw units are similar to those reported in healthy participants (Nunan *et al.*, 2008) and indicate good agreement between Polar S810 and HRV analysis software measures of mean RR but not LFnu and HFnu. Spectral measures actually demonstrate better LoA than those reported in Nunan *et al.* (2008). The use of two differing RR recording and HRV analysis systems explains the higher degree of error between measures reported by Nunan *et al.* (2008).

An important caveat is the fact that LoA observed in the present study suggest that even mean RR demonstrate limits in disagreement with findings for SEE and validity correlations. In a recent paper, Hopkins *et al.* (2009) argue that LoA provide inferior statistics in validity studies. The paper describes the situation where the SEE and validity correlation show a measure to be suitable for clinical assessments but LoA suggest the same measure would not be interchangeable with a criterion. In addition, LoA in a method-comparison study of a new measure with an existing imprecise measure offer little information about the validity of the new measure, whereas regression validity statistics can be combined with published validity regression statistics for the imprecise measure to correctly estimate validity regression statistics for the new measure (Hopkins *et al.*, 2009). In the context of the present study, regression validity estimates for the HRV analysis software were the same or better than regression statistics for

the Polar S810 in healthy individuals (Nunan *et al.* 2009) indicating its valid use in CHF patients. The same conclusion could not be made if inferences were made from LoA estimates.

#### 6.4.3. *Reliability of heart rate variability when altering parameter settings in the HRV analysis software 1.1.*

The CV estimates for measures of HRV obtained using the HRV analysis software with parameter settings two (smoothness detrend applied, FFT spectral method) are equal to those observed for the Polar S810 (Figure 6-3, a-d). Any discussion of these data would be a replication of the discussion that took place for the Polar S810. Therefore, the reliability of measures from the HRV analysis software will not consider CVs other than to say that between- and within-subjects variation is no different for data applied with a detrend compared to Polar S810 measures obtained in CHF, and by default, healthy participants.

As described earlier in the introduction and methods section, the HRV analysis software provides the option to apply a detrend to the RR time series in an effort to remove the VLF component that often presents in short-term recordings. The developers of the software published an article describing the process of applying a smoothness prior detrend and how this effectively removes the VLF component without affecting spectral power of the higher frequency bands (e.g. LF and HF). This facet has already been utilised in patient population and intervention studies (Sandercock *et al.*, 2007).

In chapter three, the effect of applying a smoothness priors detrend on linear measures of HRV was assessed using inferential statistics for the first time and showed that all measures were significantly altered. These differences were related to differences in interpolation rates. The present study aimed to assess whether the same finding occurred in CHF patients. Using an interpolation rate similar to that used in an example provided by the developers (Niskanen *et al.*, 2004), the VLF component was successfully diminished whilst LF and HF components remained relatively unaffected following application of the smoothness priors detrend (Table 6-2). Establishing that LF and HF measures were not adversely affected by detrending in the HRV analysis software was necessary prior to the assessment of its reliability.

In terms of reliability, the SEM and ICC reliability statistics were at least equal to those of the Polar S810 for all measures and in some cases were better than those of the HRV analysis software (e.g. HF and SD1). These findings indicate that the effect of HRV analysis software (with a smoothness detrend applied) technical error on the uncertainty of change scores is negligible (Table 6-4).

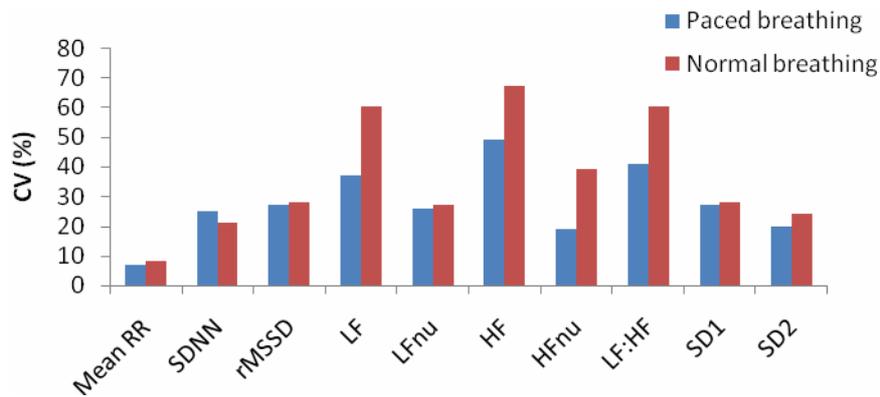
The findings presented here provide support for the use of the HRV analysis software with/without application of smoothness priors detrending to derive HRV measurements from RR interval data obtained using the Polar S810. The data presented here also provide information for making decisions when monitoring individuals. According to Hopkins (2000), the threshold for deciding if a real change has occurred is 1.5 to 2.0 times the SEM. Using current data, the ratio SEM for LF:HF obtained by the HRV analysis software (with settings two) was 1.78 (78%), indicating that an observed change of at least 2.67 (167%) to 3.56 (256%) would be needed for a real change to be likely. Smaller changes would be required for time-domain and non-linear measures. The implications of these findings will be considered in subsequent chapters involving interventions in CHF patients.

## **6.5. Limitations and recommendations.**

The lack of criterion measures of HRV due to an equipment fault prevented validity assessments of the Polar S810 and therefore weakens the outcomes for validity estimates for the HRV analysis software. There remains a need to determine the validity of the Polar S180 and HRV analysis software systems *per se* to assess HRV in CHF. Concurrent criterion, Polar and HRV analysis software measures obtained and analysed in a design similar to that of Nunan *et al.* (2009) would be sufficient for this purpose.

Theoretically, spectral analysis requires rigorous stationary conditions which are unknown to biology and medical science (Malliani, 1999). A reasonable and practical compromise is the analysis of 5-min resting ECG but recordings must

be made under controlled conditions (Task Force, 1996; Malik, 1998). Sandercock *et al.* (2004, 2005) provide evidence that measures obtained under supine and controlled breathing conditions offer greatest reliability estimates. Whether this applied to CHF patients was assessed in the present study and the outcomes reveal a similar finding whereby controlling breathing improves reliability of measures, particularly those in the frequency-domain (Figure 6-4, below).



**Figure 6-4. The effect of controlled breathing on reliability of heart rate variability measures in CHF patients.**

Results for data obtained using HRV analysis software with the smoothness priors detrend and interpolation rate of 4 Hz are specific to these settings and reliability coefficients may differ for data obtained using alternative parameter settings to those in the present study. Studies utilising differing parameter settings in the HRV analysis software may need to determine specific reliability estimates for resulting values.

## 6.6. Conclusions.

When obtained in CHF patients, measures of HRV obtained with the Polar S810 system are as reliable as those obtained by the same and criterion systems in healthy adults. Using the HRV analysis software without a detrend (i.e. settings

best matching those of the Polar S810 software) applies no appreciable bias or additional random error to time-domain and non-linear Polar S180 measures of HRV. Spectral measures are underestimated by the HRV 1.1 software and bias is consistent for raw not normalised measures. Applying a smoothness priors detrend before analysis of RR data successfully removes low frequency trends and the resultant measures of HRV are as reliable as repeat measures from the Polar S810. As in healthy cohorts, measures are inherently unreliable over a 1 week period. The use of paced breathing and log-transformation of measures improves reliability estimates and should be considered in intervention and/or management studies involving HRV.

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## **CHAPTER 7. HEART RATE VARIABILITY IN HEART FAILURE: ITS ROLE IN DIAGNOSIS, PROGNOSIS AND AS A THERAPEUTIC TARGET.**

### **Abstract.**

There is a known derangement of the autonomic nervous system (ANS) in heart failure patients, characterised by depressed parasympathetic and marked increase in sympathetic activity. Studies assessing this dysfunction have utilised 24 h and, less so, short-term heart rate variability (HRV). The overall consensus from these studies is that HRV is attenuated in heart failure patients, and the level of attenuation is reflected by the severity of disease. Paradoxically, patients demonstrating greater activation of sympathetic neural drive (i.e. NYHA class III and IV) often fail to demonstrate low frequency (LF) spectral power, a measure often seen as a non-invasive marker of sympathetic modulations.

Reasons for this paradox relate to dissociation between high levels of sympathetic drive and LF oscillations in CHF, reduced responsiveness of the failing heart to sympathetic modulation and a decreased capability of the SA node to maintain a rhythmic modulation as a result of autonomic saturation of the SA node. There is some indication that functional denervation and impairment of sympathetic nerve terminals may play a role. It is also plausible that patients presenting with LF oscillations may represent less severe condition or disease progression.

Despite ambiguity over the physiological meaning for certain HRV measures, patients with attenuated values generally demonstrate increased risk. Particularly, a decreased overall HRV (SD of RR intervals - SDNN) or LF spectral power appear to be the stronger risk predictors of all-cause mortality and cardiac events, whereas high frequency (HF) spectral power and the LF:HF ratio are predictors of sudden cardiac death.

Current treatments for heart failure have been shown to have a beneficial effect on HRV, including pharmacological and exercise therapies. Gaps in the literature are present, with a need to identify the effects of differing modes of exercise and mechanical support devices on autonomic dysfunction in heart failure patients.

Recent advances in technology allow for the assessment of standard and non-linear measures of HRV that would fit well into normal clinical practice.

## 7.1. Introduction.

In the chapters preceding this one, empirical work relating to resting measures of short-term HRV was carried out in and/or related to healthy, adult populations. In the remaining chapters of this thesis, work will be directed towards the measure of short-term heart rate variability in chronic heart failure (CHF) patients. Procedures and data obtained in healthy participants will be transferred and compared to empirical work in this patient population.

In this chapter a brief introduction to CHF and the effects the condition has on the autonomic nervous system (ANS) is given. This is followed by an in-depth, systematic review of literature related to measures of HRV in CHF, with particular focus on its effectiveness as a diagnostic and prognostic tool and its use as a therapeutic target in CHF. Due to the relatively small number of studies involving short-term measure of HRV in this population, data from papers reported 24 h measures will also be reviewed. A final consideration will be given to current treatment strategies according to disease severity with reference to HRV as a tool to monitor their effectiveness.

It is intended that this review will form the basis for empirical work carried out in subsequent chapters (eight to ten). The format for the introduction section of the remaining empirical chapters will therefore mainly consist of a rationale whilst referring back to information presented here for their justification.

### 7.1.1. *Heart failure: definitions, prevalence and its acute and chronic effects.*

Over the last 50 years many definitions for heart failure have been offered each highlighting one or more features of this complex syndrome including haemodynamic, oxygen consumption, or exercise capacity factors (Poole-Wilson, 1997). A current definition describes heart failure as “a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricles to fill with or eject blood” (Hunt *et al.*, 2005; pp.e158-e160). The syndrome is diagnosed when patients present the following:

1. Symptoms of heart failure: breathlessness at rest or on exercise, fluid

- retention (ankle swelling), and,
2. Signs of heart failure: tachycardia, pulmonary rales, raised jugular pressure, peripheral oedema, and,
  3. Evidence of structural or functional abnormality of the heart at rest: third heart sound, cardiac murmurs, echocardiogram abnormality, raised natriuretic peptide concentration. (Dickstein *et al.*, 2008).

Heart failure can be classified according to the time or rate of occurrence and the severity of structural abnormalities or its effect on functional capacity. New- or recent-onset heart failure is considered when the condition is first presented, acute or has a slow onset (Dickstein *et al.*, 2008). Symptomatic heart failure over a limited period is considered transient, examples of which may include myocardial infarct patients who require diuretics during hospitalisation but in whom long-term treatment is not necessary. Chronic, or decompensated, heart failure is the most common form of the syndrome. A distinction based on left ventricular ejection fraction (LVEF) is also made, with an EF >40-50% indicating heart failure with preserved LVEF (European Study Group on Diastolic Heart Failure, 1998).

Mild, moderate, or severe heart failure is used to describe clinical symptoms. Mild applies to patients with no important limitations of dyspnoea or fatigue, severe for highly symptomatic patients requiring frequent medical treatment, and moderate for patients not fitting either of the other two categories. The New York Heart Association (NYHA) classification of severity is routinely used due its clinical utility and is based on functional classification as follows (The Criteria Committee of the NYHA, 1994):

- Class I: no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnoea.
- Class II: slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoea.
- Class III: marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in fatigue, palpitation, or dyspnoea.
- Class IV: unable to carry on any physical activity without discomfort.

Symptoms at rest. If any physical activity is undertaken, discomfort is increased.

It is generally considered a disease of the elderly and as such an ever aging population contributes to the increased prevalence of heart failure (Hunt *et al.*, 2005). An estimate of the prevalence of heart failure across all European Union (EU) countries is between 2 and 3% of the population; this rises to between 10 and 20% in those from 70 to 80 years of age (Allender *et al.*, 2008; Dickstein *et al.*, 2008). In the UK, an estimated 912, 000 people (or 1.5% of the population) have definite or probable heart failure and around 63,000 new cases are diagnosed each year (Petersen *et al.*, 2002; Heartstats, 2008). The prognosis for heart failure is poor, approximately 40% of patients die within the first year of diagnosis and it is estimated that 5% of all deaths in the UK are due to heart failure (Petersen *et al.*, 2002). The National Health Service in the UK spends just over £625 million annually on patients suffering with heart failure.

#### 7.1.2. *Chronic heart failure and its effects on the autonomic nervous system.*

As described earlier, chronic heart failure (CHF) is a complex, multifactorial syndrome characterised by signs and symptoms relating to: inadequate tissue perfusion, fluid retention, skeletal muscle abnormalities, abnormal immune response, neurohormonal reactions, immune response (Adamopoulos *et al.*, 2003). Chronic heart failure is also characterised by severe autonomic nervous system (ANS) derangement (Leimbach *et al.*, 1986; Saul *et al.*, 1988; Nolan *et al.*, 1992; Tuininga *et al.*, 1994). Specifically, CHF is characterised by chronic sympathetic hyperactivation, (Cohn *et al.*, 1984; Pagani *et al.*, 1988; Saul *et al.*, 1988; Smith *et al.*, 1989; Pilati *et al.*, 1992) and decreased peripheral responsiveness to adrenergic input (Bristow *et al.*, 1982).

This chronic sympathetic activation manifests itself as severely altered (attenuated) heart rate variability (Casolo *et al.*, 1989; van de Borne *et al.*, 1997a; Scalvini *et al.*, 1998; Burger and Aronson 2001; Malfatto *et al.*, 2001; De Tommasi *et al.*, 2003; Arora *et al.*, 2004). Reduced heart rate variability is an

important marker of autonomic dysfunction in CHF patients and has significant, independent prognostic value for mortality in this population (Binder *et al.*, 1992; Takase *et al.*, 1992; Mortara *et al.*, 1994; Brouwer *et al.*, 1996; Nolan *et al.*, 1998; Galinier *et al.*, 2000; Hayano *et al.*, 2001; La Rovere *et al.*, 2003).

### 7.1.3. Heart rate variability as a diagnostic tool in chronic heart failure.

In addition to attenuated levels of overall variability, CHF patients also display specific derangements in their HRV profiles (Mortara *et al.*, 1994; van de Borne *et al.*, 1997a). Patients with severe CHF commonly show little or no variability in the low frequency (LF, 0.04 – 0.15 Hz) peak in the power density spectrum.

The first study to compare HRV in CHF patients with normal subjects used 24 h RR interval variability histograms and hourly standard deviation of RR intervals (Casolo *et al.*, 1989). These authors found significant reductions in both measures for CHF patients compared with controls and lower values for CHF patients who died within six months of the study ( $P = ns$ ). Simple time-domain measures of RR interval variability can give estimates of overall HRV. However, they provide little information regarding interaction of sympathetic and vagal branches of the ANS.

Mortara *et al.* (1994) were the first to describe patterns in spectral measures of HRV in CHF patients. They found reduced overall spectral power in all patients. In 16 patients, no LF spectral peak was evident. This subgroup of patients were found to have a lower overall RR interval and higher plasma noradrenaline concentrations. These authors concluded that spectral measures of HRV may be able to identify subgroups of CHF patients with more advanced disease progression and possibly a poorer prognosis. The authors did not, however, address the paradoxical findings of markers of increased sympathetic drive and decreased (or absent) LF spectral component.

This paradox was, however, later addressed by van de Borne *et al.*, (1997b). Frequency domain analysis of RR interval in CHF patients revealed a reduced overall variability and the absence of a low frequency peak in spectral power.

The authors also simultaneously measured RR interval variability (HRV) and direct intraneural recordings of muscle sympathetic nervous activity (MSNA). Power spectral density values of both these signals were analysed and coherence between the signals determined. As expected, low (~ 0.1 Hz) and high (~ 0.2 Hz) frequency peaks were evident for MSNA and HRV in control subjects. Patients with CHF had significantly higher MSNA (bursts·min<sup>-1</sup>) compared with controls indicating increased sympathetic activation. However, spectral power of HRV in the LF band was significantly decreased in the CHF patients. This difference was evident when LF power was expressed in raw units (55 ± 34 ms<sup>2</sup> vs. 863 ± 407 ms<sup>2</sup>) or normalised units (11 ± 5 vs. 55 ± 7). In raw units, the absolute powers of HF oscillations in MSNA and RR interval were similar between groups. When expressed in normalised units both values were significantly elevated in the CHF patients.

In normal subjects, the HF power of RR interval oscillations is associated with vagal modulation of the SA node. Conditions of relaxation and sympathetic inhibition increase HF power (Pagani *et al.*, 1986; Furlan 1987; Rimoldi *et al.*, 1990; Malliani *et al.*, 1991; Rimoldi *et al.*, 1992; Montano *et al.*, 1994; Pagani *et al.*, 1995; Pagani *et al.*, 1997). Conversely these studies also show that conditions known to increase sympathetic tonic activity increase the relative predominance of LF variability. Such observations particularly hold true for measurements made between individuals, within the same session (Pagani *et al.*, 1997).

The problem encountered with the findings from van de Borne *et al.* (1997b) was that if findings from normal subjects were to hold true for CHF patients in whom ANS activity is known to be predominantly sympathetically mediated, then oscillations in RR interval and MSNA should have both been predominated by low frequency oscillations. These, and previous authors (Mortara *et al.*, 1994) seem to have found a paradox insofar as increased sympathetic drive (bursts·min<sup>-1</sup>) is accompanied by power spectral characteristics indicating vagal predominance. In normal subjects, increased MSNA and LF RR oscillations have been coherent under conditions of sympathetic activation (Pagani *et al.*, 1997). This has not been found to be the case in CHF patients (Notarius *et al.*, 1999) and

there appears to be a dissociation between high levels of sympathetic drive and LF oscillations in MSNA and RR interval. Van de Bourne *et al.* (1997b) stated that the relationship between LF oscillations and sympathetic activation may only hold for a given physiological range and that it may not be extrapolated to conditions characterised by sympathetic hyperactivity such as in CHF. In addition, diminished cardiovascular variability observed in these patients was related to the absence of, or very depressed, low frequency oscillations as there was some preservation of respiratory modulation of autonomic drive. Others have shown a similar finding (Porter *et al.*, 1990).

These authors and others (Guzzetti *et al.*, 2001) have suggested that reductions in LF oscillations may be due to either reduced responsiveness of the failing heart to sympathetic modulation (Bristow *et al.*, 1982), to increased stretch of the SA node (Horner *et al.*, 1996) or to an increase in the very low frequency (VLF, < 0.04 Hz) component in HRV (Ponikowski *et al.*, 1996). A decreased capability of the SA node to maintain a rhythmic modulation as a result of autonomic saturation of the SA node due to chronic sympathetic hyperactivity has also been suggested (Malik and Camm, 1993). An additional mechanism might be suggested from evidence of a progressive denervation of the heart and an apoptosis related reduction in sympathetic nerve terminals in severe (NHYA IV) cardiomyopic patients (Machado *et al.*, 2000).

Low or absent LF oscillations in CHF may be able to distinguish the severity of disease. Patients with a less severe condition, presenting with a lower degree of sympathetic drive, higher parasympathetic outflow or a combination of the two, are likely to present with fewer of the factors underlying the LF paradox. In these patients, there may well be an increase in LF oscillations indicating a more normalised autonomic modulatory activity. The exact point in terms of severity of disease at which LF becomes diminished is unknown.

There is also an argument to suggest that a methodological problem may be present. Under conditions causing maximal sympathetic drive, such as heavy exercise there is very little variation in the RR interval and therefore little or no spectral power, particularly of the LF component (Sandercock and Brodie, 2006). Spectral analysis of MSNA and RR interval only provide measures of autonomic

oscillations and therefore, overall variability of the system (Eckberg, 1997; Notarius *et al.*, 1999). Where no variability is present no inference can be made from such recordings regarding the mean level of sympathetic drive.

On this basis, it may seem that spectral analysis of HRV can provide little information regarding cardiac autonomic control. This is, however, not the case. Overall variability of the cardiovascular system is an indicator of good health and absence of any variation (especially in the LF band) is evidence of a lack or reserve to maintain variability due to sympathetic hyperactivity. This paradox will be addressed again later in this chapter where a further, pharmacological explanation for reduced/absent LF oscillations will be put forward.

It should be noted that the above discussion of HRV in CHF patients relates only to measures of RR interval variability made under resting conditions. In an attempt to make inferences regarding autonomic control mechanisms in CHF patients using spectral HRV analysis, a number of authors have used manoeuvres designed to test autonomic reactivity (Scalvini *et al.*, 1998; Malfatto *et al.*, 2001; La Rovere *et al.*, 2003).

Scalvini *et al.* (1998) found similar values for LF ( $\text{ms}^2$ ) in patients with asymptomatic left ventricular dysfunction (LVD) and CHF values to those reported previously (van de Borne *et al.*, 1997a). Unfortunately, a quantitative comparison of LF in normalised units (nu) is difficult as this value was calculated using differing methods. Despite this, a clear predominance of power in the HF band was evident at rest in both groups. Under conditions of autonomic vagal stimulation (controlled breathing), CHF patients displayed attenuated autonomic responsiveness compared with LVD patients and healthy controls. Additionally, LF ( $\text{ms}^2$ ) and LFnu failed to respond to conditions designed to elicit sympathetic activation (HUT) in CHF patients. The authors concluded that autonomic modulation was attenuated in symptomatic and asymptomatic left ventricular dysfunction and that spectral analysis can provide information on the nature and severity of this condition.

Data concerning baseline values and autonomic responsiveness to stimuli are not entirely consistent. Malfatto *et al.* (2001) also investigated the responsiveness of the ANS to vagal (controlled breathing) and sympathetic (active standing) stimuli in patients with ischaemic heart failure and idiopathic dilated cardiomyopathy. At rest, spectral power in both these groups was predominantly located in the LF band. The LF to HF ratio (LF:HF) was 11.5 ( $\pm 1.1$ ) and 5.6 ( $\pm 0.9$ ) for ischaemic and idiopathic patient groups respectively. The LF:HF of the ischaemic group was responsive (reduced) to vagal stimulation due mainly to an increase in the HF component but remained unchanged from rest to standing. The LF:HF of the idiopathic group was unresponsive to either vagal or sympathetic stimuli. The predominance of LF power in both groups directly contradicts previous findings (Mortara *et al.*, 1994; Guzzetti *et al.*, 1995; van de Borne *et al.*, 1997b; Scavini *et al.*, 1998) indicating a reduced or absent LF spectral component in similar NYHA class CHF patients. However, patients in three of these previous studies (Mortara *et al.*, 1994; Guzzetti *et al.*, 1995; Scavini *et al.*, 1998) were not treated with ACE inhibitors and  $\beta$ -blockers. Most patients in these studies were treated with diuretics, and a varying proportion also received digitalis. In another study, no information is given concerning patient medication except that it was withheld on the morning of testing (van de Borne *et al.*, 1997b). However, the date of this study suggests that patients would have received diuretic therapy, possibly with digitalis. In keeping with what was thought to be best practice in managing CHF at that time, they may have received ACE inhibitors, but are unlikely to have been treated with  $\beta$ -blockers.

In line with more recent guidelines for the treatment of CHF, patients in Malfatto *et al.* (2001) were treated with combinations of ACE inhibitors and (50%) with  $\beta$ -blockers. Although still routinely prescribed, no patients in this study were treated with digitalis. ACE inhibitors and  $\beta$ -blockers not only profoundly affect clinical conditions and survival of CHF patients but also improve cardiovascular autonomic control. There is some evidence that the use of these drugs may allow the sinus node to regain responsiveness to circulating catecholamines and central commands (Pagani *et al.*, 1997; Cooley *et al.*, 1998). This may then show more clearly the excessive sympathetic outflow to the sinus node, in turn manifesting

itself as an increase in proportional LF spectral power despite reduced overall RR variance (Malfatto *et al.*, 2001).

#### 7.1.4. *Heart rate variability as a prognostic tool in chronic heart failure.*

A recent paper offers an excellent review of the utility of HRV in prognosis from several different modes of death in CHF (Sandercock and Brodie, 2006). The general consensus from this review was that global (SDNN) and slow oscillatory (LF) measures of HRV were the strongest risk predictors for all cause mortality and cardiac events, whereas short-term oscillations (HF) and sympathovagal interaction measures (LF:HF) were better predictors of sudden cardiac death (SCD). The number of studies reporting HRV from short-term analyses and non-linear measures was low, a fact the authors stressed needs addressing.

The present review will therefore focus on some of the main studies addressing measures of HRV identified previously but will also consider studies that have been published in the three years post Sandercock and Brodie (2006).

Using simple time domain analyses of HRV, SDNN has been found to be an independent predictor of mortality (Nolan *et al.*, 1998). Similarly, the time domain indices SDNN and the standard deviation of 5 minute RR intervals (SDANN) from 24 h ambulatory recordings were both found to independently predict death in CHF patients (Ponikowski *et al.*, 1997). These authors also applied spectral analysis and found that a reduced LF component was also a significant independent predictor.

A larger (n = 190) subsequent study provided results homogeneous with those reported previously in which global time domain measures were associated with increased risk of all cause mortality and specifically sudden death in CHF patients (Galinier *et al.*, 2000). Along with cardio thoracic ratio and presence of ischaemic heart disease, lower 24 h SDNN values (< 67 ms) were found to predict all cause mortality as well as being related to CHF progression. Low daytime LF power values (< 3.3 ln ms<sup>2</sup>) predicted sudden cardiac death.

During regulated breathing, a number of HRV measures were found to predict increased mortality in univariate analysis. In multivariate analysis a reduced ( $< 13 \text{ ms}^2$ ) LF spectral component during controlled breathing was identified as a significant independent predictor of mortality in moderate (NYHA II) CHF patients (La Rovere *et al.*, 2003). This finding in the development population ( $n = 202$ ) was also confirmed in a consequent investigation of a large validation population ( $n = 246$ ).

These data are supported by an earlier study in 75 CHF patients (NYHA II - IV) resulting from dilated or ischaemic cardiomyopathy. Using heart transplantation or cardiac death as end-points, LF and LF:HF demonstrated univariate risk. In multivariate analysis an LF:HF  $< 0.70$  was identified as the only significant predictor of heart transplantation or death (Lucreziotti *et al.*, 2000).

In a similar (NYHA III or IV) group of patients ( $n = 199$ ) admitted to hospital for decompensated congestive heart failure, Aronson *et al.* (2004) reported relative risk ratios of 2.2 and 2.6 for SDNN and ultra low frequency (ULF) oscillations from 24 h Holter recordings; demonstrating useful prognostic information in correlation with a 1-year total mortality.

There are some data providing equivocal findings for the use of HRV as a significant prognostic measure, particularly for identifying risk of sudden cardiac death (SCD).

Animal studies demonstrate both no (Hull *et al.*, 1995) and a decreased (Hull *et al.*, 1994) risk of SCD associated with an improved HRV profile.

In humans, Fauchier *et al.* (1997) showed that reduced SDNN  $< 100 \text{ ms}$  was independent risk predictor of SCD and arrhythmic events in patients with dilated cardiomyopathy.

Fifty two CHF patients with chronic congestive heart failure secondary to ischaemic or idiopathic dilated cardiomyopathy were assessed in a prospective study of HRV and iodine-123-metaiodobenzylguanidine myocardial uptake

(Anastasiou-Nana *et al.*, 2005). Time and frequency domain measures of HRV were similar between survivors and non-survivors, except that decreased HF power was associated with an increased risk of SCD but not all-cause mortality.

A recent paper by Tekiner *et al.* (2007) was published in Turkish but an English version of the abstract was made available. The authors report both 24 h and short-term measures of HRV in mild-to-moderate (NYHA I – III) heart failure patients. Following 466 days follow-up, LF:HF ratio from 24 h measures of HRV predicted cardiac mortality and morbidity, short-term measures of HRV (e.g. HF) were not able to predict either.

The abstract of an article published ahead of print assessed the prognostic role of HRV and ventricular arrhythmias in CHF patients (Smilde *et al.*, 2009). During a 13 year follow-up, 24 h holter recordings were used to assess the prognostic value of ventricular arrhythmias and HRV in 90 patients with mild-to-moderate CHF. Using cardiovascular (CV) death and SCD as end-points, a total power in the frequency domain spectrum  $> 2500 \text{ ms}^2$  was found to be an important risk marker for CV death but not SCD. Unfortunately the abstract does not provide indication as to whether this value was indicative of an increase or decrease in CV mortality risk.

The paucity of clear evidence for the association between depressed 24 h and short-term HRV parameters and SCD might be due to the difficulty in categorizing the sudden or arrhythmic nature of death, but also could be due to lack of strong evidence for this association. The autonomic nervous system operates differently in various patients depending not only on the disease but also on the advancement of the disease process. Heart failure is a continually progressive process of autonomic imbalance and as such presents difficulty to find the reference point to define the timing of HRV measurements in heart failure patients. Comparisons of HRV determined in heart failure even with homogenous clinical conditions are difficult and these limitations are likely to underline the variable and disparate predictive value of HRV in this patient population.

The studies reviewed so far utilise traditional measures of HRV based on linear properties. The use of such measures implies stationarity of the RR interval time series, an assumption that is rarely met in heart-rate dynamics (Huikuri *et al.*, 1996; Maestri *et al.*, 2007). Non-linearities are considered by some as an integral part of biological systems, particularly in diseased conditions such as CHF where autonomic neurological activity is abnormal (Maestri *et al.*, 2007). To this effect, several studies have shown that non-linear indices of HRV, either individually or combined with standard measures of HRV, may be of prognostic use in CHF.

By plotting each successive normal-to-normal interval from any tachogram (short-term or 24-hour) a Poincaré plot can be constructed. This gives a non-linear estimation of RR interval variability which can provide information on both long- and short-term RR interval oscillations (Kamen and Tonkin, 1995). These plots display distinctive distribution patterns in normal subjects and a variety of clinical populations (Woo *et al.*, 1994; Tulppo *et al.*, 1998; Ziegler *et al.*, 1999; Lerma *et al.*, 2003).

Brouwer *et al.* (1996) found abnormal Poincaré plots to be predictive of all cause mortality and sudden cardiac death. In the 95 NYHA class II - III patients studied, the risk associated with abnormal plot geometry (RR = 5.7 (range 1.6 – 20.6) was found to be greater than that for all other predictors including the presence of ventricular premature contractions, ventricular tachycardia and low (<30%) left ventricular ejection fraction (Brouwer *et al.* 1996).

Recently Maestri *et al.* (2007) aimed to compare several non-linear HRV methods in predicting mortality in patients with CHF. The authors of this study demonstrated that despite differences in prognostic values, assessment of non-linear indices from 24 h Holter recordings provides important prognostic information in addition to clinical data.

All the above data suggest that HRV and specifically overall variability (SDNN) and the LF spectral component are important predictors of survival in CHF patients. They also suggest that claims regarding problems associated with using spectral measures of HRV to study autonomic regulation in CHF patients may be

pharmacologically influenced. If, as it seems, reduced HRV and specifically LF spectral power are prognosticators of consequent cardiac event and mortality, then they may also serve as targets for therapy. The following section is a brief review of how some current therapies used in the treatment of CHF have been found to influence HRV.

#### 7.1.5. *Treatment of chronic heart failure.*

Medical diagnosis and management of CHF is a complex phenomenon dependent on disease type (e.g. ischaemic vs. idiopathic) and severity (NYHA classification). A review of current recommendations and recent medical progress is beyond the scope of this chapter and the reader is directed to recent reviews of this topic (Adamopoulos *et al.*, 2003; Jessup and Brozena, 2003). A brief review is, however, pertinent. This will be followed by closer examination of the effects of specific interventions on autonomic function, sympathetic over-activation and heart rate variability.

##### 7.1.5.1. *Pharmacological treatment.*

Therapeutic goals for heart failure patients with low ejection fractions are the slowing of disease progression, alleviation of symptoms and minimization of risk factors with an end goal of increasing survival (Jessup and Brozena 2003). Patients are advised to avoid excessive alcohol intake and non-steroidal anti-inflammatory drugs, the latter being associated with incidence of decompensated heart failure and hospitalisation. Angiotensin converting enzyme (ACE) inhibitors decrease the degradation of bradykinin by decreasing the conversion of angiotensin one to angiotensin two. Bradykinin promotes vasodilation of the vascular endothelium and thus causes natriuresis in the kidney. Although not shown to unequivocally reduce incidence of sudden death, ACE inhibitors at low doses can be beneficial in the treatment of CHF with only moderate and reversible side effects (Gullestad *et al.*, 1999; Tang *et al.*, 2002). Positive effects include improvements in hospitalisation rates, symptoms, cardiac performance, neurohormonal control (measured by noradrenaline levels), reverse-modelling and overall survival (Garg and Yusuf, 1995; Gullestad *et al.*, 1999).

In addition to ACE inhibitors (such as Lisinopril) there are also angiotensin subtype 1 receptor agonists (such as Valsartan). These two types of drugs were compared directly in CHF patients and found to have similar effects on SDNN derived from ambulatory 24 h ECGs (De Tommasi *et al.*, 2003). Therefore, examining further responses ascribable to a specific therapy in the background of one that already mediates a significant autonomic and clinical effect is problematic and patients' current treatment is an important consideration for intervention studies assessing measures of HRV.

$\beta$ -blockers are currently prescribed for all stable CHF patients without significant fluid retention. These drugs exert similar outcomes to those described for ACE inhibitors (Farrell *et al.*, 2002). In the short term,  $\beta$ -blockers actually tend to exacerbate symptoms. In the long-term, however, effects are uniformly beneficial. There is evidence for increased systolic function and reverse modelling from placebo controlled trials of >12 week duration (Bristow, 2000). Early experimental data show improved baroreflex gain and improved HRV in stable CHF patients treated with the non-selective blocking agent Carvedilol (Mortara *et al.*, 2000). More recent data show mixed results.

In a 6-month controlled trial of CHF patients receiving Carvedilol, Akdeniz *et al.* (2006) observed no changes in autonomic dysfunction despite a significant decrease in QT dispersion and improved ventricular repolarisation characteristics. The degree of autonomic dysfunction (SDNN = 77ms) was considered moderate by the authors but no reference values were provided. The mean dose of Carvedilol was lower from that of Mortara *et al.* (2000) (23 versus 40 mg) and may have been too low to have a detectable effect on 24 h measures of HRV.

In a trial carried out over a 12 month period, the effect on risk factors for SCD from the addition of Carvedilol to current pharmacological treatment was assessed by Nessler *et al.* (2007). Amongst other structural and ECG risk factors, an SDNN < 100 ms was considered a risk factor based on the published values (Priori *et al.*, 2001). After 12 months, an improved SDNN was found to be statistically insignificant. However, the number of patients with an SDNN < 100 ms significantly decreased following Carvedilol treatment, thus supporting a

decreased risk of SCD with chronic beta-adrenergic blockade. Dosages used in this study were similar to those of Mortara *et al.* (2000). It may be there is a dose-response relationship between Carvedilol treatment and HRV in CHF and this warrants further elucidation.

Data from animal models (rabbit) suggest that hydroxymethylglutaryl-CoA reductase inhibitors or statins may also be useful in the partial reversal of autonomic dysfunction. Evidence for this includes significantly reduced plasma noradrenaline levels and more recently, partial reversal of derangement in TP, LF and HF measures of HRV (Pliquett *et al.* 2003).

A recent study also suggest the use of angiotensin-II receptor blockers (ARB), common in current treatment for CHF, may facilitate an improved autonomic function in patients already receiving  $\beta$ -blocker and ACE inhibition treatment (Özdemir *et al.*, 2007). Significant increases in SDNN, SDANN, triangular index and rMSSD were indicative of an improved autonomic profile but the effect of these changes in future risk prediction was not investigated.

#### 7.1.5.2. Exercise therapy.

Chronic heart failure is a multifactorial syndrome affecting not only the heart and supporting vasculature but also causing abnormalities in skeletal muscle, neurohumoral and immunological function (Adamopoulos *et al.*, 2003). Exercise training can improve prognosis and enhance functional outcomes and quality of life in CHF patients (Belardinelli *et al.*, 1999). Belardinelli *et al.* also found that increases in  $\dot{V}O_{2\text{peak}}$  and anaerobic threshold were paralleled by increased quality of life scores.

The most recent guidelines on the management of CHF describe how exercise training improves autonomic control via an enhanced vagal tone and a reduced sympathetic activation (Dickstein *et al.*, 2008). Evidence for this stems from a number of sources involving both invasive and non-invasive methods. In a number of animal models of CHF, exercise has been shown to reduce levels of

circulating catecholamines and renal sympathetic nerve activity (Liu *et al.*, 2000; Pliquett *et al.*, 2003). In humans, significant reductions in muscle sympathetic nerve activity by direct technique have been observed following four months exercise training (Fraga *et al.*, 2007). More specific to the present context, a number of papers employing measurements of HRV as a less invasive, non direct technique to assess autonomic status have shown similar findings.

The pioneering study of exercise in heart failure and its effects on sympathovagal balance was carried out prior to publication of the American Heart Association Guidelines (Hunt *et al.*, 2001) when diuretic prescription was still considered optimal pharmacotherapy in CHF (Coats *et al.*, 1992). Only 75% of patients in the study used ACE inhibitors and none were  $\beta$ -blocked. Using 24 h ambulatory recordings, Coats *et al.* (1992) showed augmented global HRV (SDNN) and a strong shift in the degree of parasympathetic activity manifested as reduced LF and increased HF components of HRV.

More recently, changes in short-term measures of HRV under resting conditions, vagal stimulation (controlled breathing) and sympathetic stimulation (standing) have been reported following exercise training. The baseline characteristics of this population have been discussed previously. After three months of low intensity, home-based rehabilitation, Malfatto *et al.* (2002) found greatly improved autonomic reactivity. At baseline, LF:HF ratio remained mostly unchanged during conditions of supine rest ( $8.4 \pm 2.0$ ), to controlled breathing ( $6.5 \pm 1.7$ ) and active standing ( $8.0 \pm 2.1$ ). After three months, resting values were decreased ( $7.0 \pm 2.2$ ) indicating a shift toward greater vagal activation. Additionally, the decrease and increase from this value due to controlled breathing ( $4.4 \pm 0.9$ ) and active standing ( $10.2 \pm 2.5$ ) respectively were much greater.

By using LF:HF, the relative contribution of the sympathetic and vagal nerves to heart rate can be assessed. LF:HF changes act in a manner concordant with that of a sympathetic marker during pharmacological blockade, orthostatic challenge, physical and mental stress (Pagani *et al.*, 1986; Jokkel *et al.*, 1995; Pagani *et al.*, 1997; Pumprla *et al.*, 2002) and correlates with direct measures of sympathetic

nervous activity in normal, healthy subjects (Pagani *et al.*, 1997). The use of this ratio, along with normalised units controls for the large inter-individual variations in TP, LF and HF commonly observed (Task Force, 1996).

The largest study-to-date concerning the effects of exercise on HRV in CHF patients (European Heart Failure Training Group, 1998) reviewed the progress of 134 patients who undertook exercise rehabilitation in a number of randomised controlled trials. They found a significant increase in  $\dot{V}O_{2peak}$  (13%) and exercise capacity (17%). In a subgroup of patients from one study, these improvements were accompanied by decreases in noradrenaline spillover and increased HRV measured in the time domain as SDNN (Coats *et al.*, 1992).

As with pharmacological intervention, there is clearly an important role for exercise in the management of some CHF patients. It seems that in addition to certain pharmacological treatments, exercise may be able to partially reverse the increased sympathetic activity associated with CHF. HRV may be a useful way to measure such a response. Increased noradrenaline spillover and reduced HRV are both associated with poor prognosis in CHF patients (Cohn *et al.*, 1984). Therefore increasing HRV and specifically attempting to reverse or even normalise measures of sympathovagal balance should be a therapeutic target for any intervention used with CHF patients. What should be noted is that all these interventions are ‘management strategies’, aimed at reducing hospitalisations and slowing disease progression (Jessup and Brozena, 2003). By their very nature, management strategies offer no ‘cure’ for the CHF patient. Moreover, data concerning exercise interventions are generally restricted to less severe heart failure. In order to cause significant reversal of heart failure, surgical interventions may be required. Following such an intervention it may then be possible for the patient to gain benefit from an exercise programme.

#### 7.1.5.3. Pacing, revascularisation and surgical therapies.

In certain patient subgroups (severe systolic dysfunction, left bundle-branch block) cardiac resynchronisation (CRS) therapy can increase exercise tolerance,

quality of life and reduce hospitalisations. Physiological effects include reverse remodelling, decreased heart size and ventricular volumes, increased ejection fractions and decreased mitral regurgitation (Jessup and Brozena, 2003).

In patients diagnosed with myocardial ischaemia, percutaneous transluminal cardiac angioplasty and stenting can both improve ischaemic symptoms, improve cardiac performance and reduce sudden death risk (Baumgartner, 2001). The effects of these procedures on HRV in ischaemic patients without CHF generally show improvements in HRV indices although results are somewhat mixed (Tseng *et al.*, 1996; Osterhues *et al.*, 1998; Szydlo *et al.*, 1998; Ozcan *et al.*, 1999; Bonnemeier *et al.*, 2000; Wennerblom *et al.*, 2000).

In CHF, a similar finding of improved HRV has been demonstrated (Adamson *et al.*, 2003). CRS therapy with biventricular pacing has been shown to improve survival in patients with severe heart failure (Cleland *et al.*, 2005). In a similar patient cohort, Fantoni *et al.* (2005) demonstrated an improved SDNN four weeks after CRS was associated with improved outcomes compared to patients with less pronounced HRV responses.

#### 7.1.5.4. Left ventricular assisting devices.

Originally designed to temporally ‘bridge’ CHF, and in particular dilated cardiomyopathy (DCM) patients to transplantation, left ventricular assisting devices (LVADs) have repeatedly demonstrated that they can restore heart function to various degrees (Frazier *et al.*, 1996; Hetzer *et al.*, 2001). The worldwide number of patients who have been implanted with LVADs is not known, but thought to be small. Early prototypes were available in the 1960s and the use of LVAD implantation as a ‘bridge to transplantation’ has grown steadily from then to the 1990’s where it plateaued. In recent years however, due to technological advances and clinical evidence of the efficacy of LVADs, implantation rates have increased sharply (Hertz *et al.*, 2002).

The original and still most common application of LVAD implantation is as a ‘bridge-to-transplantation’ (Matsuda and Matsumiya, 2003). However, the

observation of spontaneous improvements in a number of factors in implanted patients awaiting transplantation and in some cases continued recovery or 'normalisation' after consequent explantation have led to the use of LVADs as a 'bridge-to-recovery' (Birks *et al.*, 2007).

It was stated earlier that heart failure is a multifactorial disease. However, the progressive remodelling (hypertrophy) of the myocardium appears to be a centrally important factor in disease severity progression and ultimately patient mortality (Katz 1990; Gerdes *et al.*, 1992; Gerdes and Capasso, 1995; Gerdes *et al.*, 1996; Francis 1998; Onodera *et al.*, 1998; Zafeiridis *et al.*, 1998; Sugden, 1999; Lorell and Carabello, 2000).

In myocardial hypertrophy, changes take place in a number of different components of the myocardium. Very briefly, the cardiomyocytes enlarge markedly, particularly about their long axis, a change associated with reduced contractility and relaxation. This alteration in phenotype activates a number of genes including groups associated with sarcomeric and cytoskeletal proteins, metabolic enzymes, ion channels, cytokines, growth factors and enzymes involved in the apoptic pathway (Yacoub, 2001). A full review of all these physiological mechanisms is beyond the scope of this chapter.

A major effect of LVAD implantation is to promote 'reverse remodelling' or demodelling of the myocardium. Successful treatment allows the myocytes to partially revert both in geometry and function toward more normal values (Young, 2001). Again, numerous factors seem to play a part in this reverse remodelling and although mechanical unloading of the myocardium plays a major role, it is insufficient stimulus for such change alone. Pharmacotherapy used in the treatment of CHF can aid in the unloading (and consequent reverse remodelling) of the myocardium. Beneficial effects of  $\beta$ -blocker, angiotensin converting enzyme (ACE) inhibitors and angiotensin-1 receptor agonist therapy have all been clinically demonstrated (Pitt, 1998; McKelvie *et al.*, 1999).

It should be noted that, even with optimal mechanical and pharmacological therapy, bridge-to-recovery rates are not high. The initial observations of spontaneous recovery in patients being bridged to transplantation were only

made in a small number of implanted patients (Frazier *et al.*, 1996). Those who could be weaned off mechanical assistance (consequently explanted) were even smaller (Sun *et al.*, 1999; Hetzer *et al.*, 2001). On this basis, closely monitoring markers of disease state in implanted and explanted LVAD patients through all stages of treatment and recovery is paramount.

One therapeutic approach combines the reduction of pathological hypertrophy followed by promotion of physiological hypertrophy of the myocardium (and inevitably skeletal muscle) using the  $\beta$ -2 agonist clenbuterol (Wong *et al.*, 1997, Wong *et al.*, 1998; Yacoub, 2001). Early findings in patients following this treatment strategy showed consistent 'normalisation' of cardiac structure and function (Yacoub, 2001).

A group from the same centre that demonstrated the positive early findings have recently provided evidence of the long-term efficacy of combination therapy in end-stage heart failure patients. Following 320 days of ventricular support, Birks *et al.* (2007) demonstrated sufficient recovery to allow explantation of a LVAD in 11 patients. The remaining four patients underwent transplantation due to a lack of myocardial recovery or other structural complications. One of the main outcomes was that there were no deaths during the course of the therapy and survival rate 1 and 4 years after explantation was 91% and 82% respectively. Freedom from recurrence of heart failure was 89%, considerably higher than previous LVAD studies. Significant clinical improvements to haemodynamic, exercise capacity, quality of life and functional changes in myocardium were reported. These improvements were maintained in the majority of patients during the 4 year follow-up period.

These findings are somewhat replicated by Miller *et al.* (2007) who demonstrated 75% survival at 180 days of mechanical support with an LVAD in 133 patients. The authors also report and improved functional status and quality of life.

A number of measurements have been reported while monitoring the recovery of LVAD patients. Numerous measures concerning cardiac dimensions and function are derived from echocardiography. In implanted patients, measures are

also made with the pump switched off. A test of exercise capacity (6-min walk test) may also be carried out; this is dependent on the implanted subject's tolerance of being unassisted. Other measurements include: cardiac output (measured via catheterisation) and a battery of tests using ventricular biopsies (taken during catheterisation).

The above treatments and measures differ between clinics, and the brief review above is based on the treatment and monitoring reported previously for the patients investigated in chapter 10. Despite the abundance of literature concerning the role of autonomic measures as risk factors in CHF, there are no published data concerning changes or normalisation of invasive (cardiac noradrenaline spillover) or indirect (heart rate variability) measures of autonomic activity in patients receiving LVAD combination therapy.

## **7.2. Summary.**

Measures of HRV, particular 24 h, demonstrate strong prognostic power in CHF. A need for more studies assessing short-term HRV is required, but evidence points to an increased risk related to depressed short-term HRV in CHF. Non-linear measures show potential and possibly high prognostic value in CHF.

On the whole, modern treatments for CHF, particularly pharmacological therapies have a beneficial effect on HRV but there are some gaps in the literature. The evidence for an improved HRV following exercise training in CHF indicates a beneficial effect, particularly from aerobic exercise. Despite its inclusion in a number of trials and its recommended use in exercise therapy, the effect of resistance exercise on measures of HRV has not been investigated.

There is evidence that resting the myocardium in patients with severe HF via a left ventricular assist device (LVAD) improves quality of life, mortality rate and can lead to recovery. There are no data as to the effect of this treatment on the underlying autonomic dysfunction presented in this patient population.

In chapters two and six, new technologies capable of providing both traditional and non-linear measures of HRV were shown to be reliable in both healthy and HF patients respectively. Moreover, the methodologies used can be applied to a clinical setting in a manner that fits with current operational practice. There is scope to investigate the gaps identified here.

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## **CHAPTER 8. ALTERATIONS IN HEART RATE VARIABILITY OF MILD-TO-MODERATE HEART FAILURE PATIENTS FOLLOWING 12 WEEKS AEROBIC OR RESISTANCE BASED EXERCISE TRAINING.**

### **Abstract.**

New evidence has emerged that definitively identifies a positive role for exercise in the management and care of patients suffering from chronic heart failure (CHF) and it is likely exercise will become standard in cardiac rehabilitation (CR) of these patients. Performance of regular, continuous aerobic exercise has been shown to improve ANS imbalances often observed in CHF. European and UK guidelines also recommend CR programmes incorporate combined intermittent aerobic (AR) and resistance (RT) modes of exercise. The effects of these differing modes of exercise on ANS function in CHF are not well understood. The aim of this study was to assess the effects of CR employing AR only or RT only on ANS function in mild-to-moderate CHF patients.

Seventeen, mild-to-moderate (mean New York Heart Association grade: 2.0) CHF patients were randomly assigned to a 12 week AR (n = 9) or RT (n = 8) exercise programme. Both programmes consisted of one weekly supervised and four home based sessions. Prior to and following the 12 week programme, patients underwent assessments of short-term resting heart rate variability (HRV) during normal and paced breathing. Cardio-respiratory and vascular responses to graded treadmill testing (GXT) were also assessed. The change in values for all measures was assessed within and between groups using repeated measures ANOVA and both paired and independent *t*-tests.

HRV data from 14 patients (7 in AR and 7 in RT) were available for analysis. There was a non-significant but meaningful trend for a favourable and non-favourable change in absolute HRV values in the AR and RT groups respectively. The small sample size and relatively high baseline levels of HRV may have resulted in these findings. Analysis of responses to autonomic stimuli revealed a greater response of sympathetic and baroreflex mediated measures of HRV in the AR group and vagally mediated measures in the RT group. Normalisation of these measures resulted in dissociations to underlying physiology, cautioning against its use without reference to absolute values. There

is a dissociation between the effects of cardiac rehabilitation based on current guidelines on cardiorespiratory and autonomic indices in CHF patients with already preserved HRV.

## **8.1. Introduction.**

### *8.1.1. Efficacy of exercise as a beneficial therapy in chronic heart failure.*

The majority of studies assessing the effects of physical training in CHF patients have been conducted using aerobic exercise as the model training programme (Smart and Marwick *et al.*, 2004). Only a small number of studies report data pertaining to effects following the prescription of resistance based exercise. The efficacy of these two modes of exercise in improving clinical variables will be assessed separately.

#### 8.1.1.1. Aerobic exercise.

As previously identified in chapter seven, CHF is a multifactorial syndrome affecting not only the heart and supporting vasculature but also causing abnormalities in skeletal muscle, neurohumoral and immunological function (Adamopoulos *et al.*, 2003). Exercise training can improve prognosis and enhance functional outcomes and quality of life in CHF patients (Kiilavouri *et al.*, 1995; Belardinelli *et al.*, 1999, Hambrecht *et al.*, 2000; Maiorana *et al.*, 2000), yet a lack of definitive data as to its safety and efficacy have prevented the widespread adoption of exercise in the care of heart failure (Smart and Marwick, 2004; Hunt *et al.*, 2005; Pedersen and Saltin, 2006; Dickstein *et al.*, 2008).

A recent study now presents data aimed at providing a definitive answer to the question: “Should patients with CHF participate in exercise training?” The HF-ACTION (Durham, 2008) is the largest clinical trial to date examining the value of exercise in treatment of heart failure. In a multicentre approach, 2331 patients with moderate to severe heart failure were randomised into normal care or normal care plus 30 minutes bicycle or treadmill walking. The same exercise was later progressed to 40 minutes in a home based setting. Over a two and a half year period, investigators tracked clinical measures of heart failure,

hospitalisation, cardiac events and death. After adjusting for clinical characteristics, a significant 11% reduction in the risk of hospitalisation and a 15% lower risk of death from cardiovascular disease was observed in the exercise group. A modest reduction in clinical events was also reported for patients in the exercise group. The findings that aerobic exercise was both safe and improved clinical outcomes are highly likely to mean the adoption of this type of exercise as standard in the care of both new and chronic heart failure.

The mechanisms underlying the findings have somewhat surprisingly been shown to relate to improvements in peripheral abnormalities even in the absence of central haemodynamic alterations. A number of studies not only report an improved peak oxygen uptake but also increased arteriovenous oxygen difference, decreased lactate accumulation and increased blood flow (Sullivan *et al.*, 1988).

#### 8.1.1.2. Resistance exercise.

The main body of evidence for the benefits of physical activity in cardiovascular disease relates to findings involving predominantly aerobic or mixed (aerobic and resistance) exercise regimens. This was due to the belief that aerobic exercise results in greater improvements in functional capacity and improved quality of life (Johnson *et al.*, 1998), and because the safety and efficacy of resistance exercise is yet to be established (Haskell, 1994). Continuous aerobic exercise may not optimally stress the peripheral muscles, which in CHF patients tend to be atrophied and have fewer muscle fibres, oxidative enzymes and capillary densities (Larsen *et al.*, 2002). Several studies report not only expected increases in muscle strength but also in muscular and aerobic endurance capacities following strength conditioning in heart failure (Hare *et al.*, 1999; Meyer, 2006; Feiereisen *et al.*, 2007). Mechanisms underlying these findings are similar to those observed for responses following aerobic training and relate to increased oxidative enzyme activities, improved peripheral blood flow and increases in muscle fibre area (Pu *et al.*, 2001; Selig *et al.*, 2004; Feiereisen *et al.*, 2007); these improvements are often less significant than those observed following aerobic training (Smart and Marwick, 2004).

The consensus from agencies prescribing exercise guidelines for heart failure groups is that a mixture of aerobic combined with resistance exercise, administered perhaps in the form of a circuit training programme, may be the optimal exercise prescription. In addition, during intermittent aerobic exercise the total cardiac stress is lowered as a result of afforded rest breaks, and allows patients with compensated heart failure to complete short periods of work at higher intensities than would be possible with a continuous protocol (Smart and Marwick, 2004). For this reason, the use of intermittent exercise is also recommended when prescribing exercise training in heart failure (The European Heart Failure Training Group, 1998; SIGN., 2002; Hunt *et al.*, 2005; Balady *et al.*, 2007). These recommendations, however, are based on evidence prior to the HF-ACTION paper and may well undergo revisions as a result of its findings.

#### 8.1.2. *Effects of exercise training on heart rate variability in chronic heart failure.*

The most recent guidelines on the management of CHF describe how exercise training improves autonomic control via an enhanced vagal tone and a reduced sympathetic activation (Dickstein *et al.*, 2008) Evidence for this stems from a number of sources involving both invasive and non-invasive methods. In a number of animal models of CHF, exercise has been shown to reduce levels of circulating catecholamines and renal sympathetic nerve activity (Liu *et al.*, 2000; Pliquet *et al.*, 2003). In humans, significant reductions in muscle sympathetic nerve activity by direct techniques (e.g. muscle sympathetic nerve activity - MSNA) have been observed following four months exercise training (Fraga *et al.*, 2007). More specific to the present context, a number of papers employing measurements of HRV as a less invasive, non-direct technique to assess autonomic status have shown similar findings. The majority of data in CHF are related to measures of HRV derived predominantly from 24 h with only a few studies reporting short-term RR interval recordings.

#### 8.1.2.1. Twenty four hour measurements.

The pioneering study of exercise in heart failure and its effects on sympathovagal balance was carried out prior to the publication of the American Heart Association (AHA) Guidelines (Hunt *et al.*, 2001) when diuretic prescription was still considered optimal pharmacotherapy in CHF (Coats *et al.* 1992). Only 75% of patients in the study used ACE inhibitors and none were beta-blocked. Using 24 h ambulatory recordings, Coats *et al.* (1992) showed improved global HRV (SDNN) and a strong shift toward greater parasympathetic activity as a result of reduced LF and increased HF components of HRV. Moreover, these findings were matched by a significantly reduced norepinephrine spillover. In the pre beta-blocker era others have demonstrated a similar favourable shift in 24 h measures of HRV following aerobic exercise training in CHF (Adamopoulos *et al.*, 1995; Kiilavouri *et al.*, 1995).

The incorporation of beta-blockers in standard therapy is a recent development (Foody *et al.*, 2002) but there are data demonstrating a positive effect on measures of HRV from beta-blockers in numerous pathologies (Guzzetti *et al.*, 1988; Coumel *et al.*, 1991) and in CHF (Mortara *et al.*, 2000). In the context of exercise, studies have documented its efficacy despite beta-blocker therapy (Forissier *et al.*, 2001; Lloyd-Williams *et al.*, 2002). Studies assessing the effect exercise on ANS function in the beta-blocker era have also shown positive effects for 24 h global HRV measures, albeit in patients following a myocardial infarct (Tygesen *et al.*, 2001).

There are no studies assessing the effects of resistance only exercise on 24 h measures of HRV.

#### 8.1.2.2. Short-term measurements.

The amount of data available from assessments of short-term measures of HRV in CHF patients and following prescribed exercise is small and conflicting. Literature searches revealed only three published studies (Piepoli *et al.*, 1996;

Duru *et al.*, 2000; Selig *et al.*, 2004). One of these studies specifically looked at ergoreflex activity, which is greatly heightened in heart failure patients. An increased ergoreflex response to metabolic abnormalities resulted in exaggerated increases in ventilatory, haemodynamic and sympathetic nervous system activity during exercise. These exaggerations were reduced following a six week localised forearm training programme. An important observation was that spectral analysis techniques were unable to identify any differences in autonomic balance between CHF and control subjects following training. Unfortunately no substantive reasons for this finding were given. It may be that indirect measurements of cardiac autonomic modulatory activity are not sensitive or well enough related to detect changes in ergoreceptor contributions to autonomic responses following such specific and local muscle training.

Following a more traditional exercise model involving what the authors describe as “high intensity exercise”, Duru *et al.* (2000) observed improved values for short-term measures of HRV in the time (SDNN) but not the frequency domain. The same findings were observed in a non-exercising control group and negated any differences between groups. Data were obtained in post MI patients with recently diagnosed or “new onset” heart failure and this may in part explain findings. There is evidence that the autonomic derangements observed following MI recover spontaneously in the few weeks and months following MI (Bigger *et al.*, 1991). In the study of Duru *et al.*, initial testing took place just 36 days after the myocardial event. The effects of exercise, whilst greater than those in the control group, were likely masked by a naturally occurring autonomic recovery in both patient groups.

The only other peer reviewed paper assessing the effects of exercise on short-term measures of HRV in CHF claimed to specifically address resistance based exercise. In a control study, Selig *et al.* (2004) assessed measures of HRV before and after 12 weeks moderate resistance training in mild-to-moderate heart failure patients and observed a fall in the ratio of low- to high-frequency spectral power (LF:HF). These findings were matched by increases in peak oxygen uptake, peripheral blood flow and muscular strength and endurance. There were no differences for change in time domain measures of HRV (SDNN, rMSSD). A

number of methodological issues are presented in the study of Selig *et al.* The first relates to nature of the exercise programme. The programme adopted by Selig *et al.* consisted of three graduated resistance exercises alternated with three aerobic based exercises performed in a circuit with periodic rest intervals between exercises. Aerobic exercises performed from anywhere between 0.5 to 2 minutes were considered to be of short duration and moderate intensity as indicated by heart rate monitoring (data not provided) in an effort to minimise aerobic training effects. Several studies (e.g. The European Heart Failure Training Group, 1998; Maiorana *et al.*, 2000) report a beneficial effect following intermittent and mixed mode exercise programmes such as those utilised in Selig *et al.* A facilitative effect of the aerobic exercise performed in Selig *et al.* cannot therefore be discounted. Another important observation is that significant effects were reported between post-training LF:HF values and those obtained at familiarisation but not baseline testing. It is surprising that the authors did not consider this factor, especially when a significant familiarisation effect was observed for normalised LF values. A more robust approach would have been to obtain statistical outcomes for each comparison (e.g. familiarisation with post-training and baseline with post-training) and then taken the average.

In the light of these observations, it is apparent there remains no study assessing the effects of solely resistance training on measures of HRV from 24 h or short-term recordings.

### 8.1.3. *Study justification and aims.*

Overall, the consensus from studies assessing the effects of exercise on 24 h measures of HRV in CHF is one of a beneficial effect. There is much less certainty of the effects of exercise on short-term measures of HRV in this population. Improvements in resting measures of HRV demonstrate potential prognostic significance due to observed associations with low values of global HRV (SDNN) and increased mortality risk in heart failure (Nolan *et al.*, 1998). As with pharmacological intervention, there is clearly an important role for exercise in the management of some CHF patients. It seems that with certain pharmacological treatments, exercise may be able partially to reverse the

increased sympathetic activity associated with CHF. HRV may be a useful tool to measure such a response. Increased noradrenalin spillover and reduced HRV are both associated with poor prognosis in CHF patients (Cohn *et al.*, 1984). Therefore increasing HRV and specifically attempting to reverse or even normalise measures of sympathovagal balance should be a therapeutic target for any intervention used with CHF patients.

Despite the prognostic implications however, HRV is not a routinely sought clinical tool. A number of reasons relating to physiological interpretation and standardised protocols partly explain this finding. Additional factors include equipment costs and personnel requirements involved in the processing and analysis of 24 h Holter and ECG recordings which are often impractical in many clinical settings. In recent years, technological advances in ECG telemetry and software development have seen the introduction of wireless heart rate monitors and specific software that allow for easy and efficient capture of RR interval and subsequent HRV data. In chapter six, the validity and reliability of two such new technologies (the Polar S810 and HRV analysis software 1.1.) has been confirmed for use in CHF patients. This presents for the first time the opportunity to assess short-term measures of HRV following exercise training in CHF patients in a cost-effective and resource efficient manner.

A key outcome of cardiac rehabilitation is to return patients to a fully active lifestyle and such an outcome requires improvements in muscle strength as well as aerobic endurance (Scottish Intercollegiate Guidelines Network (SIGN), 2002). Improvements in strength, cardiovascular function, coronary artery risk factors and psychological well being have been observed following resistance (strength) training (Smart and Marwick, 2004). There have been no studies contrasting the effects of aerobic and resistance only exercise on HRV measurements in CHF.

Little work has been conducted on tools that identify patients most likely to respond favourably to training (Hunt *et al.*, 2005). Measures of HRV potentially offer such a tool and when assessed from short-term recordings are also clinically practical. Malfatto *et al.* (1998) have shown decreases in the baseline LF:HF ratio to relate to improvements in exercise capacity. Moreover, the change in LF:HF

was later found by the same authors to positively relate to baseline LF:HF values (Malfatto *et al.*, 2000). This indicates a potential use of the LF:HF ratio in identifying responders to training. By using this measure, the relative contribution of sympathetic and vagal activity to heart rate fluctuations can be assessed. LF:HF changes act in a manner concordant with that of a sympathetic marker during pharmacological blockade, orthostatic challenge, physical and mental stress (Jokkel *et al.*, 1995; Pagani *et al.*, 1986; Pagani *et al.*, 1997; Pumprla *et al.*, 2002) and correlates with direct measures of sympathetic nervous activity in normal, healthy subjects (Pagani *et al.*, 1997). The use of this ratio can be used to assess the responsiveness or reactivity of fluctuations in autonomic cardiac control. There are no data as to the association between resting LF:HF and the change in LF:HF nor autonomic reactivity following CR in CHF patients.

The aims of the present study were therefore:

1. To assess the effect of aerobic only and resistance only modes of exercise training on measures of resting heart rate variability in chronic heart failure patients;
2. Assess autonomic reactivity and changes thereof following different modes of exercise training in chronic heart failure patients;
3. Identify a role for the low-frequency to high-frequency spectral ratio in identifying patients likely to demonstrate a favourable response to exercise training.

## **8.2. Methods.**

### *8.2.1. Patient Recruitment.*

Patients from the Hillingdon Hospital NHS Trust heart failure clinic were recruited for this study in accordance with approval received by the local government research ethics committee. Following an initial phone conversation, volunteers were sent an information pack containing:

1. The scope, aims and methodology of the study
2. An information sheet detailing what was required of the participant prior to and during each visit to the laboratory

### 3. A detailed informed consent form

Participants were requested to read and complete the documents provided in the information pack and to adhere to the pre-testing instructions prior to their initial visit to the laboratory.

#### 8.2.2. *Patient sample.*

Outcomes from a priori power analysis on the basis of work by Nolan *et al.* (1998) revealed the requirement of 32 participants in the treatment and control group to observe a large effect size ( $d > 1.2$ ) for change in standard deviation of RR intervals (SDNN). A change of 14 ms in SDNN in CHF sufferers following eight weeks cardiac rehabilitation (CR) was observed by Adamopoulos *et al.* (1995). A similar value for change in SDNN is expected in the present study due to the employment of higher exercise intensities and a longer training period.

##### 8.2.2.1. Treatment groups.

Seventeen non-diabetic CHF patients gave full written informed consent to participate in the study. Random allocation provided nine and eight patients for the aerobic and resistance exercise rehabilitation groups respectively. Heart failure was confirmed in all patients by the supervising cardiologist. The aetiology of disease included dilated cardiomyopathy (DCM, 53%), ischaemic heart disease (IHD, 40%) and myocardial infarct (MI, 7%). New York Heart Association (NYHA) classification ranged from I to II across the patient cohort. More detailed characteristics are outlined in section 8.3.1 below.

##### 8.2.2.2. Control group.

So as to avoid unethical denial of a potentially efficacious therapy, only those patients responding with a negative answer as to their inclusion in the treatment group were invited to act as controls. This method was adopted in awareness of possible differences between-groups at baseline and would have been accounted for by appropriate statistical procedures. The fact that only three patients volunteered to participate as controls and two of these withdrew from repeat

testing negated these concerns and meant only the efficacy of aerobic versus resistance training could be assessed in the current study.

### 8.2.3. *Instrumentation and data acquisition.*

RR intervals and HR were recorded via a Polar S810 heart rate monitor (HRM) (Polar Electro OY, Kempele, Finland). The S810 was set to record beat-to-beat RR intervals with a sampling frequency of 1000 Hz providing an accuracy of 1ms for each RR period (Cottin *et al.*, 2004). S810 recordings were transferred to a password protected PC via the Polar Precision Performance 4.03 software (Polar Electro OY, Kempele, Finland). Each downloaded RR interval file was exported as a .txt file to a separate folder for later HRV analysis using an advanced software package (HRV Analysis Software 1.1, University of Kuopio, Finland)

Respiratory gas exchanges were measured breath-by-breath using a Medical Graphics (MG) Cardio<sub>2</sub> analysis system (Medical Graphics Corporation, St. Paul Minnesota, USA). A 12-lead ECG recording was simultaneously made using the CardioPerfect ST 2001 module (Cardio Control, Delft, The Netherlands) of the MG system and blood pressure was obtained by manual sphygmomanometry.

Exercises in the aerobic training group were performed on treadmill, cycle and ski exercise based ergometers. A mixture of patients own body mass and ankle and wrist weights were used to provide resistance.

### 8.2.4. *Protocol.*

#### 8.2.4.1. RR interval recordings.

Heart rate variability measures were derived from seven minutes of stationary ECG obtained supine and at rest using the S810 on two separate occasions, one week apart. On each visit and following a familiarisation period, a five minute RR interval recording was made whilst controlling breathing at a rate of 12 breaths·min<sup>-1</sup> (0.2 Hz) via standardized instruction and metronome pacing. The S810 recordings were filtered for errors using the Polar software automated RR interval filtering algorithm set at medium filter power and minimum beat protection zone of 6 b·min<sup>-1</sup>. The interpolation of beats via this method has only

minor effects on spectral measures of HRV measured from stationary tachograms (Jurca *et al.*, 2004) in which <15% of beats are rejected.

#### 8.2.4.2. Heart rate variability analysis.

##### 8.2.4.2.1. Linear heart rate variability.

Linear measures of HRV were obtained from each of the baseline filtered RR interval data recordings according to recommended standards (Task Force 1996) using the HRV analysis software 1.1 as described earlier (chapters two and three). In the present chapter all HRV data were obtained from the HRV analysis software 1.1 after subjection to smoothness priors detrend and interpolation at 4 Hz. This was to account for non-stationary signals in the RR interval time series that often distorted LF and HF spectral measures. In the time domain, SDNN and rMSSD were calculated. Fast Fourier transformation was applied to determine low frequency power (LF, 0.04 – 0.15 Hz) and high frequency power (HF, 0.15 – 0.40 Hz) in the frequency domain. The ratio between LF and HF power (LF:HF) was also determined. Data were transformed, if necessary, to allow parametric analysis.

##### 8.2.4.2.2. Non-linear heart rate variability.

*In addition to the linear measures above non-linear measures were also obtained. RR interval time series often violate the assumptions of stationarity required for traditional linear HRV analysis methods (e.g. FFT) and present with non-linear characteristics (Tulppo et al., 1996; Kleiger et al., 2005; Contreras et al., 2007). This is particularly true in cardiovascular disease where several methods for analysing these non-linear aspects have been proposed (İşler and Kuntalp., 2007; Maestri et al., 2007). The Poincaré plot, a graph of each RR interval plotted against the next interval, is a simple technique taken from non-linear dynamics to quantify the RR data. By fitting an ellipse to the shape of plotted points, two standard deviations, referred to as SD1 and SD2, are obtained. These are related to the fast beat-to-beat and longer-term variability respectively. Moreover, these quantitative measures have been shown to*

*independently predict all-cause and sudden cardiac death in CHF patients (Brouwer et al., 1996). The HRV analysis software 1.1 automatically derives SD1 and SD2 and these measures were included in this chapter.*

For both linear and non-linear measures, the average from the two pre-rehabilitation assessments was taken as the baseline HRV measurement. This value was then compared with values obtained post-rehabilitation.

#### 8.2.4.3. Treadmill graded exercise test protocol.

Following resting recordings, participants performed a GXT (modified Bruce protocol) on a motor-driven treadmill (Cardio Control, Delft, The Netherlands) to volitional exhaustion. A familiarisation session was provided to those patients unfamiliar with walking on a treadmill. During the GXT,  $\dot{V}O_2$  and  $\dot{V}CO_2$  were monitored breath-by-breath, heart rate was continuously recorded and blood pressure and ratings of perceived exertion (RPE) were obtained two minutes into each stage of the modified Bruce protocol. The same measurements were performed upon completion of the 12 week exercise training/control period.

#### 8.2.4.4. GXT termination and oxygen uptake criteria.

The GXT was stopped when patients could no longer maintain walking on the treadmill or observation of a sustained ST segment depression  $> 2$ mm, acute chest pain or achievement of  $\dot{V}O_{2\max}$ . Maximal oxygen consumption was defined as the highest  $\dot{V}O_2$  attained in a 30-sec period. Criteria to establish  $\dot{V}O_{2\max}$  were based on the ACSM (2001) guidelines. These were:

- i. a plateau in  $\dot{V}O_2$  (increase of  $< 2 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) despite increasing work load;
- ii. a final respiratory exchange ratio (RER) greater than 1.15;
- iii. an RPE  $> 17$ .

Participants were considered to have reached  $\dot{V}O_{2\max}$  if at least two of these criteria were met. A peak value for  $\dot{V}O_2$  ( $\dot{V}O_{2\text{peak}}$ ) was taken when less than two

criteria were obtained. Respiratory data were also analysed *post-hoc* using automated software (Breeze Suite. Medical Graphics Corporation, St. Paul Minnesota).

#### 8.2.4.5. Group allocation and exercise protocols.

Patients were randomly allocated to one of two conditions: supervised and home based aerobic training (AR) or supervised and home based resistance training (RT). A non-exercising control (CT) group was formed of patients who declined cardiac rehabilitation but were happy to perform HRV and exercise test procedures. Patients were recruited as they became available to participate. As a result, differences in patient characteristics (e.g. disease aetiology) between groups were likely. Supervised exercise sessions took place at the hospital once a week on the same day. During each session, patients in the AR group were required to complete a 40 minute circuit involving alternation between one minute of aerobic exercise and one minute of active recovery. Patients in the RT group were also required to complete a 40 minute circuit which involved alternating performance of one min of resistance based exercises separated by a one minute active recovery period. Intensity of exercise was assessed via RPE. A value of 11-13 was used to determine ergometer speed/resistance and weight lifted for the AR and RT groups respectively. To account for improvements in exercise tolerance, the intensity of exercise was monitored upon each visit and altered to maintain the required RPE level where appropriate. Both AR and RT sessions started and ended with a 10 minute warm up and cool down period respectively. Prior to any exercise patients were asked to report on their general health, changes to medication and adherence to home based exercise. Measures of blood pressure and resting heart rate were also recorded. To reduce experimenter bias, data obtained following each session were filed for analysis upon completion of the trial. In addition, patients were given no feedback as to changes in measures until the end of the study.

For the home-based programme patients were asked to complete a selection of either AR or RT exercises according to group allocation. The AR group was required to perform a 30 minute walk four times a week for the duration of the study. The RT group was required to perform a shortened circuit consisting four

of the six hospital based RT exercises, three times per week. Both groups were given an exercise diary with a copy of the RPE scale and the required exercises to perform. Patients in the CT group were only given verbal information regarding the safety and efficacy of walking exercise.

Exercise intensities, types and durations were based on current recommendations for CR in the United Kingdom (British Association of Cardiac Rehabilitation (BACR), 2007; Scottish Intercollegiate Guidelines Network (SIGN), 2002).

#### 8.2.5. *Statistical Analysis.*

All statistical analysis was carried out using SPSS version 13.0 (SPSS inc. Chicago, Illinois, USA). Normality of data sets was assessed using a Kolmogorov-Smirnov test. Where assumptions for parametric testing were not met data were subjected to logarithmic transformation (ln).

##### 8.2.5.1. Changes in cardiac autonomic modulations following cardiac rehabilitation.

In a similar manner to other chapters of this thesis, statistical analysis was only performed on those measures that are recommended from short-term recordings (Task Force, 1996) and those demonstrating prognostic value. This included SDNN and rMSSD in the time domain and LF, HF and LF:HF ratio in the frequency domain. As non-linear measures, SD1 and SD2 were obtained from Poincaré plot analysis. Selecting measures for analysis *a priori* reduces the number of comparisons made and reduces Type II inflation errors. The differing effects of aerobic and resistance CR programmes on HRV measures was assessed using a 2 x 2 mixed repeated measures ANOVA (rm-ANOVA) for pre- and post-test scores. Where significant baseline differences in HRV were observed, differences were assessed whilst controlling for initial HRV using analysis of covariance (ANCOVA). Necessary checks for assumed homogeneity of variance and regression were performed prior to analysis of differences.

Due to large confidence intervals resulting from the small samples sizes the use of effect size statistics were also used to indicate the magnitude of effects regardless of statistical significance. Magnitudes were evaluated using the

following scale:  $< 0.2$  represents a trivial effect; 0.2 to 0.5 represents a small effect; 0.6 to 1.1 represents a moderate effect; 1.2 to 1.9 represents a large effect; and  $> 2.0$  represents a very large effect (Hopkins, 2002).

The use of rm-ANOVA can present difficulties with interpretation of effects, particularly when trying to identify time points for significant group effects. Analysis of change scores for measures of HRV following AR or RT avoids this problem and identifies the degree to which changes are either positive or negative. Significance of differences in change scores between AR and RT groups was analysed using independent *t*-tests. Effect size statistics were again used to identify the magnitude of effects using the same scale outlined above.

#### 8.2.5.2. The LF:HF ratio as a measure of ANS reactivity.

Baseline LF:HF ratio under paced breathing conditions was derived from the five minute tachogram, as described above and natural logarithms of this measure were taken. The relationship between LF:HF and  $\Delta$ LF:HF was assessed using a Pearson's product moment correlation coefficient. A significant or close to significant relationship allowed prediction analysis using stepwise regression.

To assess the reactivity of ANS modulations, LF:HF values were obtained during normal (NB) and paced breathing (PB) conditions. The later condition is used to induce parasympathetic activation whereby an expected decrease in the LF:HF ratio would be indicative of a normal ANS response. The changes in reactivity before and after CR were assessed using paired *t*-tests. The difference in reactivity change between groups was assessed using independent *t*-tests.

#### 8.2.5.3. Individual changes underlying group outcomes.

Due to the known large inter-individual variations in HRV, even in homogenous groups, values for measures were plotted for each individual along with group mean values obtained pre- and post-CR. This allowed for the identification of abnormal individual variations that may have inflated mean change scores.

### **8.3. Results.**

One patient from the AR group dropped out of the study prior to a second baseline test citing personal reasons. In the same group, a second patient demonstrated HRV values that differed substantially to mean values and as a result severely skewed mean outcomes even after transformation. One patient from the RT group was unable to complete the full twelve weeks due to a non-exercise related injury. The AR group therefore consisted of seven patients for measures of HRV and eight patients for physiological measures. The RT group consisted of seven patients for both sets of measurements.

#### *8.3.1. Patient baseline descriptive characteristics.*

Table 8-1 shows the baseline descriptive characteristics of patients in the AR and RT cardiac rehabilitation groups. The two groups were similar in terms of age and mass. Unexpectedly differences in terms of proportion of females and disease aetiology were observed. The AR group contained a higher proportion of females and the largest proportion of disease aetiology was due to dilated cardiomyopathy (DCM). Ischaemic heart disease was the predominant cause of heart failure in the RT group. The possible bearing these differences may have had on results of this study will be discussed later.

**Table 8-1. Baseline descriptive characteristics of patients undertaking cardiac rehabilitation.**

	Aerobic Training Group (n = 8)	Resistance Training Group (n = 7)
Age in years	64.8 (11.2)	63.0 (12.0)
Gender (%)	Male 5 (62%) Female 3 (38%)	Male 6 (86%) Female 1 (14%)
Mass (kg)	82.8 (18.7)	78.7 (20)
Disease aetiology or surgical procedures (%)	Dilated cardiomyopathy 6 (75%) Ischaemic heart disease 2 (25%) Myocardial infarct 0 (0%) Surgical procedure 4 (56%)	Dilated cardiomyopathy 2 (29%) Ischaemic heart disease 4 (57%) Myocardial infarct 1 (14%) Surgical procedure 2 (29%)
New York Heart Association class	2.0 (0.8)	2.0 (0.6)
Left ventricular ejection fraction (%)	32	32
β-Blockers	Yes = 6 (75%) No = 2 (25%)	Yes = 6 (86%) No = 1 (14%)
Digoxin	Yes = 4 (50%) No = 4 (50%)	Yes = 5 (71%) No = 2 (29%)
Statins	Yes = 4 (50%) No = 4 (50%)	Yes = 6 (86%) No = 1 (14%)
Aspirin	Yes = 5 (63%) No = 3 (38%)	Yes = 5 (71%) No = 2 (29%)
Other	Yes = 2 (25%) No = 6 (75%)	Yes = 3 (43%) No = 4 (57%)

All values are mean ( $\pm$  SD) for continuous measures and number of cases (percent) for categorical measures.

### 8.3.2. *Changes in physiological and exercise response measures following differing cardiac rehabilitation programmes.*

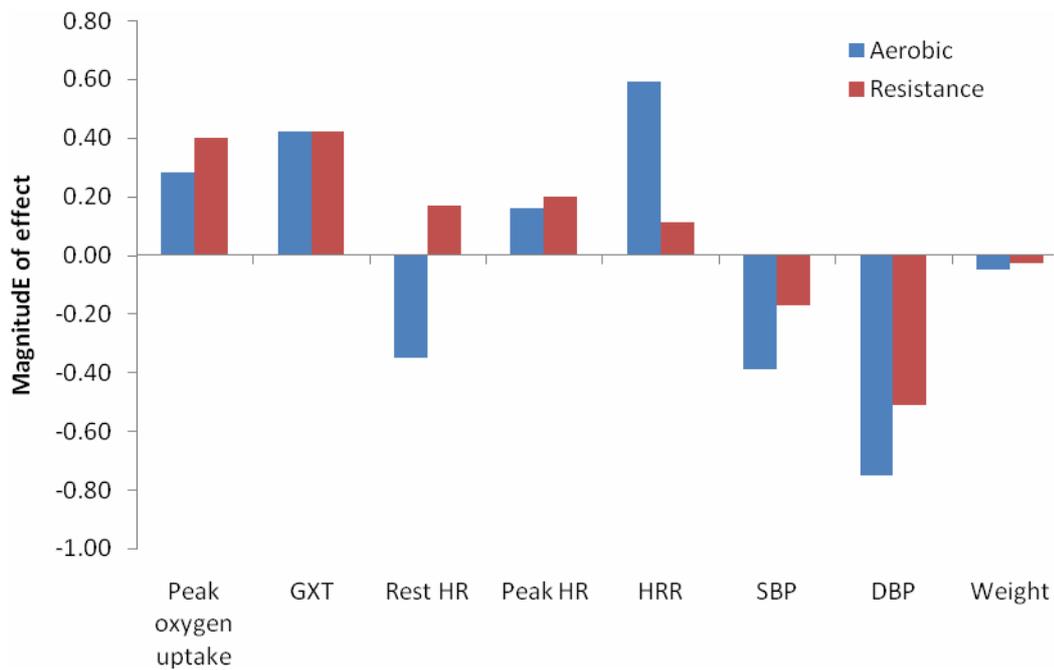
Table 8-2 shows values for physiological and exercise test response measures taken at entry into the CR programmes and again at patient's 12 week exit assessment. Statistically significant time effects were observed for  $\dot{V}O_{2\text{peak}}$  ( $P < 0.05$ ), duration of GXT, and diastolic blood pressure (DBP;  $P < 0.01$ ). Non-significant interaction and group effects indicate that both types of exercise statistically lead to equal increases in  $\dot{V}O_{2\text{peak}}$  and duration of GXT and a similar decrease in DBP.

**Table 8-2. Statistical analysis outcomes for physiological effects of two differing cardiac rehabilitation programmes.**

	Aerobic (n = 8)		Resistance (n = 7)		Significance of effects		
	Pre-CR	Post-CR	Pre-CR	Post-CR	Time	Interaction	Group
$\dot{V}O_{2\ peak}$ (ml·kg <sup>-1</sup> ·min <sup>-1</sup> )	22.3 ± 8.1	24.5 ± 7.8	19.9 ± 4.6	21.8 ± 3.7	0.011	0.622	0.343
Duration of GXT (secs)	614 ± 295	739 ± 273	749 ± 115	798 ± 88	0.002	0.136	0.487
Rest HR (b·min <sup>-1</sup> )	62 ± 8	59 ± 6	64 ± 9	66 ± 8	0.502	0.119	0.290
Peak HR (b·min <sup>-1</sup> )	127 ± 22	130 ± 22	132 ± 16	135 ± 18	0.342	0.714	0.816
HR recovery (b·min <sup>-1</sup> )	20 ± 9	27 ± 11	27 ± 12	29 ± 10	0.177	0.338	0.475
SBP (mm/hg)	120 ± 17	112 ± 11	121 ± 6	120 ± 12	0.074	0.947	0.888
DBP (mm/hg)	74 ± 8	67 ± 10	76 ± 8	72 ± 6	0.003	0.575	0.706
Weight (kg)	78.3 ± 19.8	77.7 ± 18.7	71.7 ± 16.1	71.4 ± 15.8	0.217	0.527	0.338

Data are mean ± SD; CR, cardiac rehabilitation;  $\dot{V}O_{2\ peak}$ , peak oxygen uptake; GXT, graded exercise test; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Observations for the magnitude of effects demonstrated that increases for  $\dot{V}O_{2\ peak}$  were slightly greater in the RT group (Figure 8-1). However, lower between-subject variation in the RT group explained this finding (Table 8-1). A similar effect size for change in duration of GXT was observed for AR and RT groups despite a greater absolute change in the AR group (123 versus 49 s, respectively). Smaller between-subject variations in the RT group again explained this observation. Despite larger between-subject variations, the magnitude of change for the remaining measures was greater in the AR group. This group was also the only one to demonstrate a favourable direction of change score across all measures (Figure 8-1).



**Figure 8-1. Size and direction of effects on physiological measures following 12 weeks exercise training.**

8.3.3. *Changes in heart rate variability measures following differing cardiac rehabilitation programmes.*

Table 8-3 shows values for measures of HRV at baseline and post 12 weeks cardiac rehabilitation according to exercise type. Independent *t*-tests revealed no significant differences in the baseline value for any measure of HRV. Pre- and post-CR values were therefore analysed using rm-ANOVA.

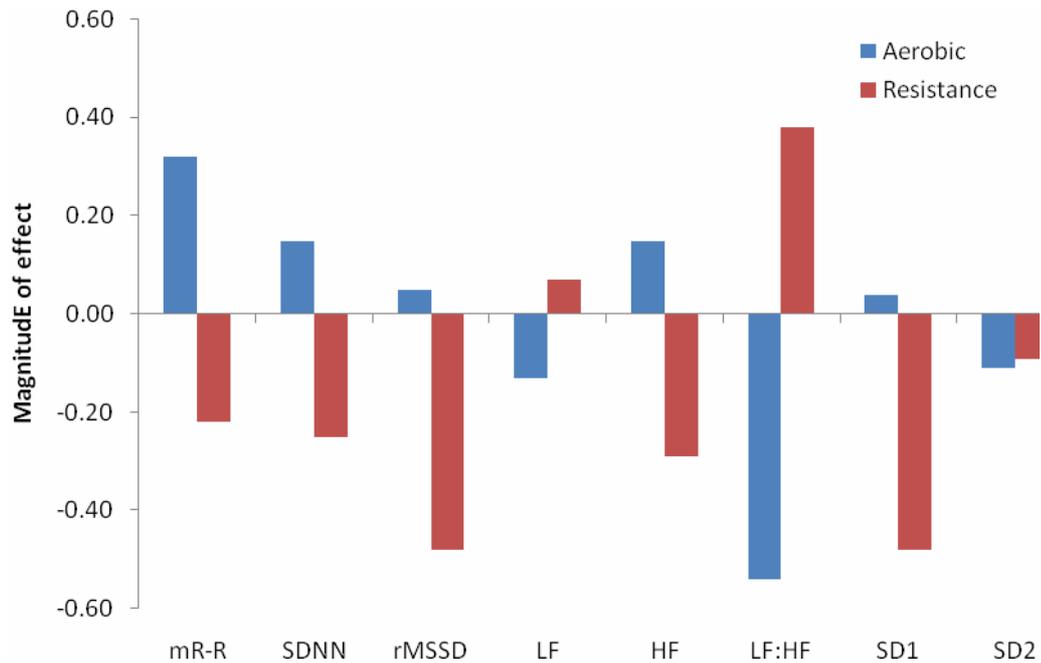
In both the AR and RT groups, there was no significant time or group effect for any measure of HRV indicating that neither CR programme statistically altered HRV. An almost significant interaction effect was observed for LF:HF ( $P = 0.09$ ) whereby the change in LF:HF over time showed a trend toward differing between groups. However, actual values pre- and post-CR were not statistically different between groups.

**Table 8-3. Statistical analysis outcomes for effects on heart rate variability of two differing cardiac rehabilitation programmes.**

	Aerobic (n = 7)		Resistance (n = 7)		P-value of effects		
	Pre-CR	Post-CR	Pre-CR	Post-CR	Time	Interaction	Group
mRR (ms)	985 ± 112	1025 ± 97	956 ± 128	925 ± 105	0.836	0.111	0.267
SDNN (ln)	3.36 ± 0.49	3.45 ± 0.71	3.37 ± 0.64	3.23 ± 0.55	0.868	0.401	0.738
rMSSD (ln)	3.61 ± 0.66	3.64 ± 0.71	3.49 ± 0.62	3.18 ± 0.56	0.277	0.188	0.385
LF (ln)	5.04 ± 1.59	4.82 ± 1.78	4.76 ± 1.50	4.87 ± 1.11	0.753	0.337	0.886
HF (ln)	5.38 ± 1.14	5.57 ± 1.12	4.89 ± 1.25	4.51 ± 0.91	0.624	0.166	0.194
LF:HF*	1.0 ± 0.7	0.63 ± 0.62	1.2 ± 0.7	1.5 ± 0.7	0.961	0.091	0.132
SD1 (ln)	3.27 ± 0.67	3.30 ± 0.71	3.15 ± 0.62	2.84 ± 0.56	0.278	0.189	0.389
SD2 (ln)	3.97 ± 0.62	3.89 ± 0.66	3.88 ± 0.58	3.82 ± 0.47	0.473	0.905	0.777

Data are mean ± SD; CR, cardiac rehabilitation; mRR, mean time between normal r-waves; SDNN, the standard deviation of normal-to-normal intervals; rMSSD, root mean square of successive differences; LF, low frequency spectral power; HF, high frequency spectral power; nu, normalised units; LF:HF, the ratio of low to high frequency spectral power; SD1, standard deviation of points on the short-axis of Poincaré ellipse; SD2, standard deviation of the long-axis of the Poincaré ellipse; ln, natural logarithm; \*Data reported from measures obtained during paced breathing.

When assessed in terms of effect magnitude and direction, changes to measures of HRV differed noticeably between groups (see Figure 8-2). Except for SD2, all measures of HRV in the AR group changed in the opposite direction to that of the RT group. The magnitude of change was greater for mRR, LF, LF:HF and SD2 in the AR group whilst for the RT group SDNN, rMSSD, HF and SD1 showed larger changes. Importantly, the more favourable direction of change was observed for measures in the AR group.



**Figure 8-2. Size and direction of effects on heart rate variability measurements following 12 weeks exercise training.**

For reasons of clarity, secondary analysis of differences in change scores was performed, the outcomes of which are presented in Table 8-4. Independent *t*-test revealed that no change score values differed significantly between groups. There was an almost significant difference in the change score between groups for LF:HF ( $P = 0.07$ ). All HRV measures displayed favourable shifts in their values in the AR group compared with only one (SD2) in the RT group. Despite lack of statistical significance, the magnitude of difference in change scores was moderate to large for most measures except SDNN and SD2.

**Table 8-4. Statistical and magnitude of effect analysis outcomes for change in HRV measurements following differing cardiac rehabilitation programmes.**

HRV Measure	$\Delta$ HRV Aerobic (n = 7)	$\Delta$ HRV Resistance (n = 7)	Difference	P value†	Effect size
mRR (ms)	39.7 (-22.6 – 102.0)	-31.0 (-110.1 – 48.1)	71.0 (-18.8 – 160.8)	0.11	0.93
SDNN (ln)	0.09 (-0.47 – 0.66)	-0.14 (-0.48 – 0.20)	0.23 (-0.36 – 0.82)	0.41	0.47
rMSSD (ln)	0.03 (-0.37 – 0.44)	-0.31 (-0.74 – 0.13)	0.34 (-0.19 – 0.87)	0.19	0.72
LF (ln)	-0.22 (-0.67 – 0.23)	0.11 (-0.56 – 0.78)	-0.33 (-1.04 – 0.39)	0.32	-0.54
HF (ln)	0.19 (-0.50 – 0.87)	-0.38 (-0.485 – 0.381)	0.57 (-0.18 – 1.41)	0.17	0.78
LF:HF*	-0.45 (-0.89 – 0.08)	0.33 (-0.32 – 1.12)	-0.78 (-1.62 – -0.13)	0.07	-1.08
SD1 (ln)	0.03 (-0.38 – 0.44)	-0.31 (-0.74 – 0.13)	0.34 (-0.19 – 0.87)	0.19	0.74
SD2 (ln)	-0.08 (-0.39 – 0.24)	-0.06 (-0.35 – 0.24)	-0.02 (-0.40 – 0.36)	0.92	-0.06

Data are mean values with 95% confidence interval in parentheses; †Obtained from independent *t*-test; mRR, mean time between normal r-waves; SDNN, the standard deviation of normal-to-normal intervals; rMSSD, root mean square of successive differences; LF, low frequency spectral power; HF, high frequency spectral power; nu, normalised units; LF:HF, the ratio of low to high frequency spectral power; SD1, standard deviation of points on the short-axis of Poincaré ellipse; SD2, standard deviation of the long-axis of the Poincaré ellipse; ln, natural logarithm; \*Data for this measure analysed using non-parametric Mann-whitney test of differences.

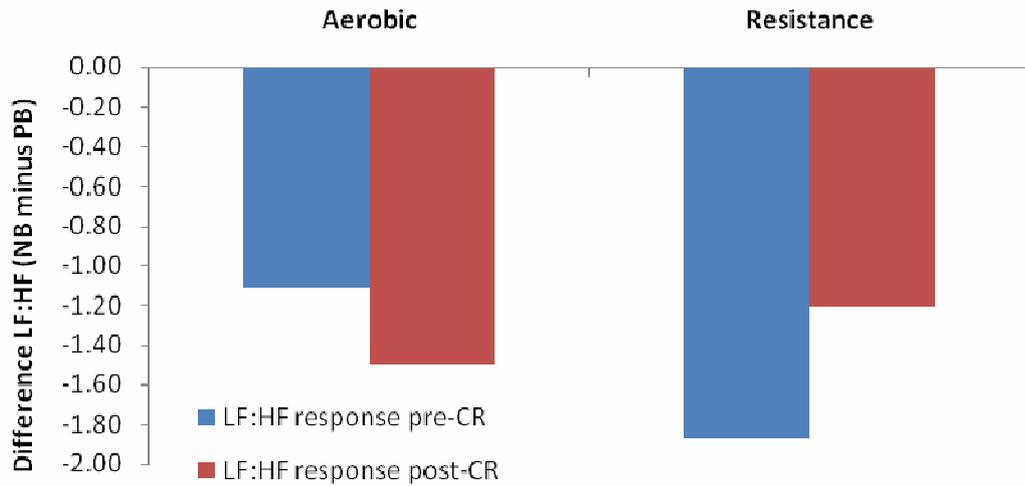
8.3.4. *Reactivity of LF:HF in AR and RT group before and after training.*

A negative association between baseline LF:HF and  $\Delta$ LF:HF was observed in both groups and almost reached statistical significance in the AR ( $r = -0.53$ ,  $P = 0.10$ ) and RT group ( $r = -0.64$ ,  $P = 0.06$ ). When entered into regression analysis, LF:HF was not able to statistically predict  $\Delta$ LF:HF (Table 8-5).

**Table 8-5. Summary of stepwise regression analysis for  $\Delta$ LF:HF in the AR and RT groups.**

		$\Delta$ LF:HF		
		$\beta$	$R^2$	$P$
AR group	LF:HF	-0.635	0.403	0.126
RT group	LF:HF	-0.526	0.277	0.283

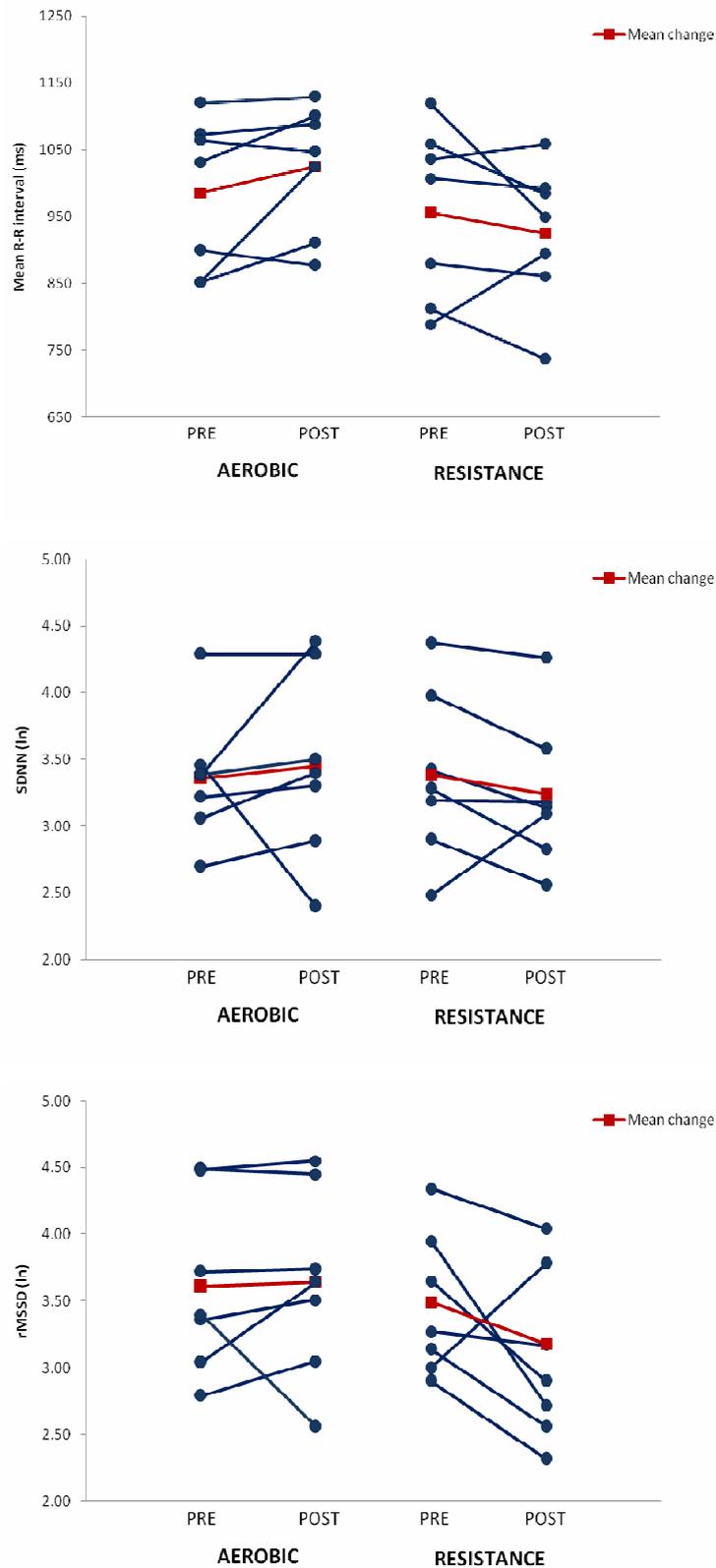
A trend for an improved response of the LF:HF ratio under controlled breathing conditions was observed following AR but not in RT training. The former group demonstrated a more favourable parasympathetic mediated response to paced breathing whereas in the RT group, a decline in reactivity towards a lesser parasympathetic and/or greater sympathetic/baroreflex mediated response was observed (Figure 8-3).



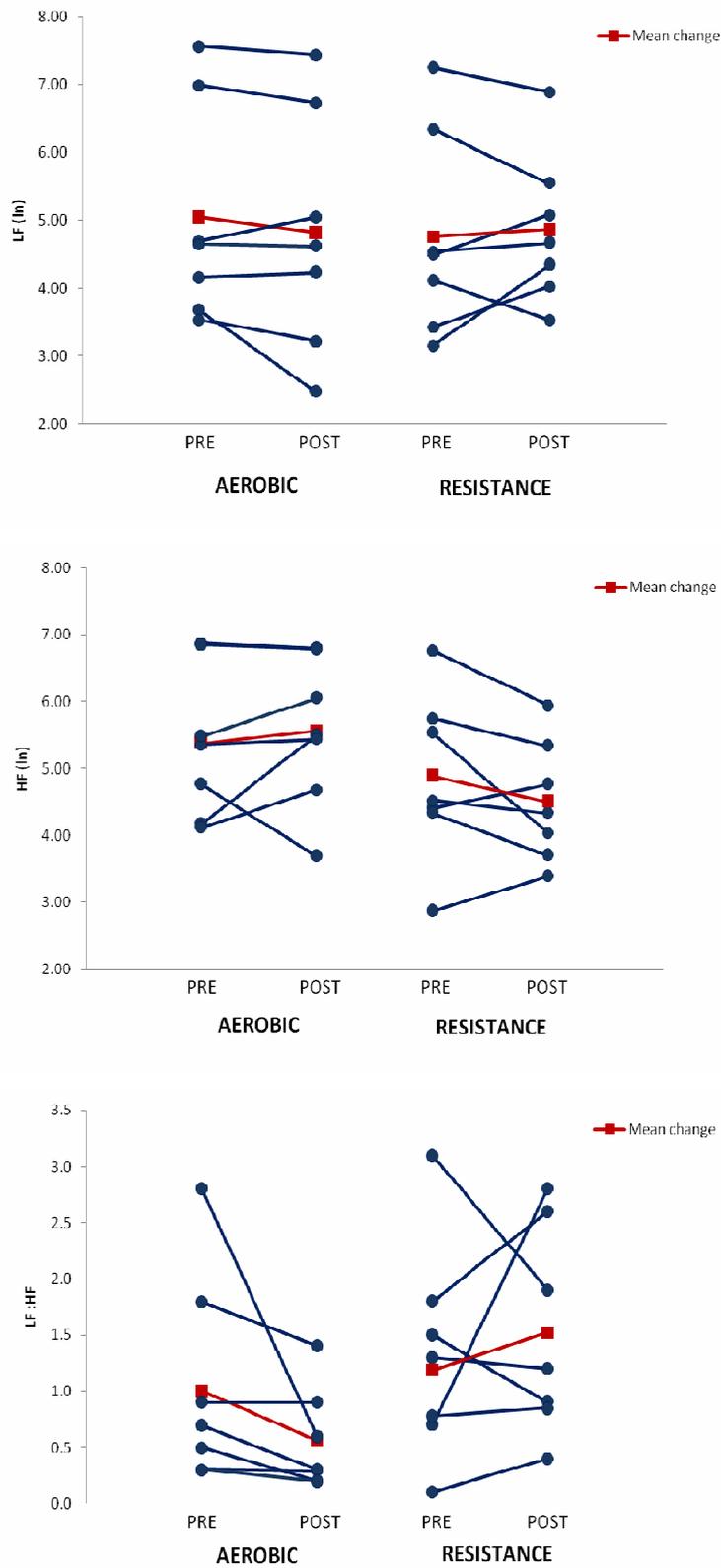
**Figure 8-3. Reactivity of autonomic modulations to paced breathing conditions before and after CR in the AR and RT groups.**

8.3.5. *Individual change in heart rate variability for aerobic and resistance cardiac rehabilitation groups.*

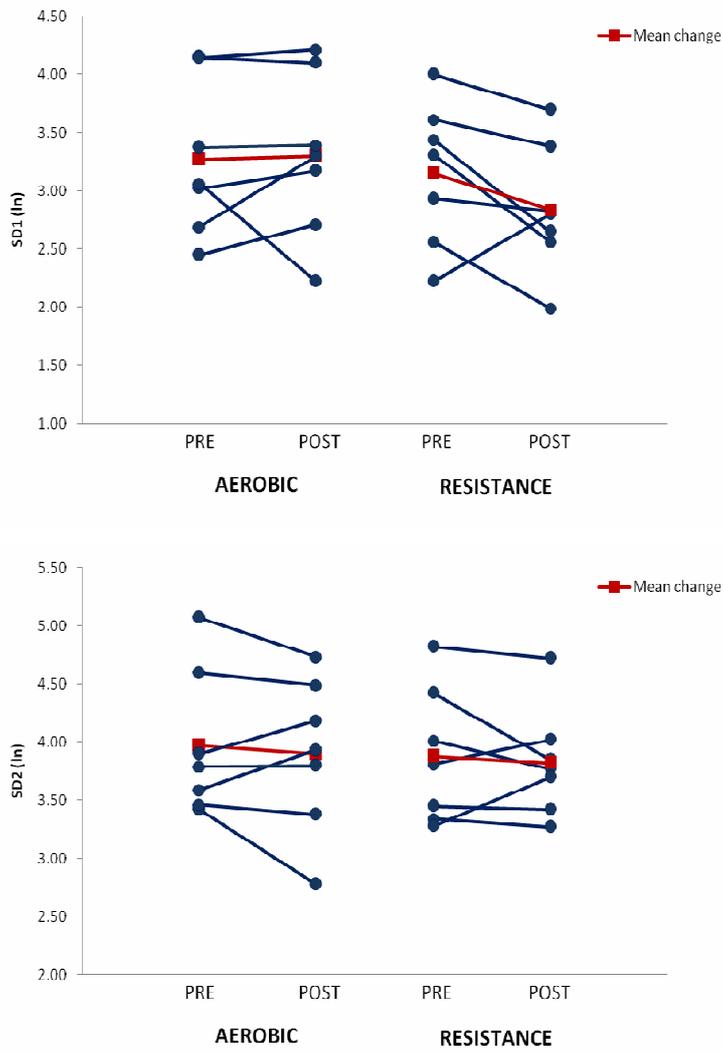
Figures 8-4, 8-5 and 8-6 respectively illustrate pre- and post-CR values of time domain, frequency domain and non-linear measures of HRV for individuals in the aerobic and resistance trained groups. Overall and for the majority of measures, mean changes are underpinned by a similar change in individual score indicating a systematic difference in the direction of change between AR and RT. Where large individual changes were observed, these were often negated by their equal size and directly opposite direction. For example, a large increase in SDNN score following AR training for one patient was matched by an equally large decrease in SDNN score for another (Figure 8-4, middle panel), thus negating their individual effects on the overall increase in SDNN observed in the remaining five patients. Similar findings were observed in one or both groups for mean RR, rMSSD, LF, HF, SD1 and SD2.



**Figure 8-4. Mean and individual responses of time domain measures of HRV to 12 weeks aerobic and resistance exercise training in mild-to-moderate chronic heart failure patients. Presented are mean RR (upper panel), SDNN (middle panel) and rMSSD (lower panel) in log units and obtained during paced breathing.**



**Figure 8-5. Mean and individual responses of frequency domain measures of HRV to 12 weeks aerobic and resistance exercise training in mild-to-moderate chronic heart failure patients. Presented are LF (upper panel) and HF power (middle panel) in log units and the LF:HF ratio (lower panel) derived from absolute units and obtained during paced breathing.**



**Figure 8-6. Mean and individual responses of non-linear measures of HRV to 12 weeks aerobic and resistance exercise training in mild-to-moderate chronic heart failure patients. Data presented are log units and were obtained during paced breathing.**

## 8.4. Discussion.

This is the first study to assess the differing effects of aerobic only and resistance only exercise on measures of short-term HRV in chronic heart failure (CHF) patients. The main findings of the study were:

- Meaningful but non-statistically significant differences between AR and RT groups were observed for change scores in a number of HRV measures following CR.
- There was a distinct difference between groups in the direction of change, with those in AR group demonstrating favourable changes for all measures of HRV and those in RT group demonstrating non-favourable changes in all but one measure.
- These findings were supported by data for individual changes in both groups.
- Resting measures of HRV were unable to predict change in the duration of GXT or peak oxygen uptake in either group; in the AR group, SDNN and DBP were almost significant predictors of changes in duration of GXT and oxygen uptake respectively.
- The resting LF:HF ratio was not significantly related to change in LF:HF in either group, however there was favourable change in the response of this measure to parasympathetic stimuli in the AR but not in the RT group following CR.

The outcomes listed above will be discussed and addressed with reference to previous data separately. Each finding and the methodology used to elicit it will be briefly reviewed and justified within each section.

### 8.4.1. *Baseline clinical and heart rate variability variables.*

Patient values for  $\dot{V}O_{2,peak}$  were similar between both groups but were not attenuated compared with those expected in age matched, healthy controls. These data both differ and concur with those from previous studies assessing 24 h (Coats *et al.*, 1992; Adamopoulos *et al.*, 1995) and short-term (Duru *et al.*, 2000;

Selig *et al.*, 2004) HRV in heart failure patients. Left ventricular dysfunction was confirmed by an attenuated ejection fraction but values were not as low as those reported in the majority of previous studies (Coats *et al.*, 1992; Adamopoulos *et al.*, 1995; Selig *et al.*, 2004). Normotensive values for blood pressure confirm the overall cardiovascular condition of patients in the present study to be greater of those in previous similar studies.

Compared with healthy adults (chapter five), the current patient cohort did not demonstrate a diminished short-term HRV at baseline and displayed a propensity toward vagal predominance at rest (e.g. a low LF:HF ratio), particularly in the AR group. Comparisons with previous data are compounded by the necessary use of log-transformed values in the present study. Attenuated baseline HRV in patients newly diagnosed with heart failure was observed for both time and normalised frequency domain measures by Duru *et al.* (2000). Selig *et al.* (2004) reported attenuated baseline values for time domain but not for frequency domain HRV measures in a cohort of CHF patients. Other studies assessing the HRV response to CR in CAD (Sandercock *et al.*, 2007b) and MI (Iellamo *et al.*, 2000) patients demonstrate greater attenuation of HRV at baseline. These findings indicate that the CHF patients studied here demonstrate a more normalized HRV at baseline compared with previously studied populations.

The impact of patient baseline characteristics on the findings of this study will be considered in each section of the discussion.

#### 8.4.2. *Changes in clinical variables in AR and RT groups.*

The efficacy of aerobic exercise in increasing  $\dot{V}O_{2peak}$  and exercise time in CHF patients has been demonstrated in numerous studies and reviewed extensively (Lloyd-Williams *et al.*, 2002; Smart and Marwick *et al.*, 2004; Ko and McKelvie, 2005; Pedersen and Saltin, 2006). There are less data pertaining to the efficacy of resistance training in CHF patients although that said, improved exercise oxygen uptake and time capacity has been routinely demonstrated (Pu *et al.*, 2001; Meyer, 2006; Feiereisen *et al.*, 2007). The present data agree with these findings and would suggest the exercise programmes performed in both AR and RT to be

of sufficient intensity and duration to elicit beneficial changes in the patients' capacity to perform exercise.

However, the fact that the current patients closely represented age matched healthy individuals in terms of baseline values for these measures, and the finding that RT increases  $\dot{V}O_{2\text{peak}}$  by less than 3% in healthy, sedentary populations (Tanaka and Swenson, 1998), suggests some other factors may have underlined the 10% improvement observed in both groups. These factors relate to motivation, musculoskeletal and test termination criteria and are discussed further in the limitations section (8.5).

#### 8.4.3. *Changes in heart rate variability in AR and RT groups.*

The general consensus from studies assessing the effects of exercise on both 24 h and short-term measures of HRV in cardiac patients is one of a beneficial outcome. These data relate to a multitude of cardiac conditions including IHD, chronic and/or acute MI, CABG, PTCA and all but two studies utilise aerobic exercise training. A thorough search for literature assessing HRV in CHF patients following exercise training identified three studies assessing 24 h measurements (Coats *et al.*, 1992; Adamopoulos *et al.*, 1995; Kiilavouri *et al.*, 1995) and only two assessing short-term measures of HRV measure (Duru *et al.*, 2000; Selig *et al.*, 2004). A closer look at these two studies shows mixed outcomes. Following eight weeks continuous aerobic exercise at an intensity of 70% HR reserve, Duru *et al.* demonstrated a significant and favourable increase in pNN50% in 12 recent MI and "new-onset" heart failure patients. There were no changes, however, in SDNN or any frequency domain measures at eight weeks.

The study of Selig *et al.* (2004) claims to report the effects of resistance exercise on autonomic nervous system activity as assessed by HRV. By performing resistance exercise with prolonged recovery intervals, 14 moderate CHF patients displayed a decreased LFnu and LF:HF and an increased HFnu after 12 weeks. Effect size calculations ( $d = 0.56 - 0.71$ ) reveal that changes were small to moderate. There were no changes in time domain measures of HRV. On scrutiny of the exercise programme followed, it appears a significant proportion of the activity performed was aerobic in nature. Whilst the programme consisted of

three solely resistance based exercises (knee extension/flexion, elbow flexion/extension and shoulder press), these were alternated with exercise involving leg cycling, stair climbing and arm cycling. The authors highlight minimal aerobic effects by the short duration (0.5 to 2 min) and relatively moderate intensity (data not provided) of these exercises. However, statements of a beneficial effect of resistance exercise on sympathovagal balance are undermined by these methodological concerns.

The present study aimed to avoid the issues presented by Selig *et al.* and others by ensuring the effects of resistance exercise were not influenced by aerobic activity. An additional aim was to assess the effects on HRV of completing a rehabilitation programme that closely replicated clinical practice and adhered to current UK guidelines for CR (SIGN, 2002; BACR, 2007). The present paper is unique in these aspects and found that when performed in this manner, patients using resistance exercise alone showed a trend for decreased values of HRV and a less favourable autonomic profile. It is important to note that for both groups effects were small ( $d < 0.6$ ) and could be considered clinically insignificant, although similar sized effects that demonstrated statistical significance (likely due to a larger  $n$  and/or lower between-subject variations) have been considered meaningful in previous CR/exercise training studies (Duru *et al.*, 2000; Selig *et al.*, 2004; Sandercock *et al.*, 2007b).

#### 8.4.4. *Reasons for observed effects.*

Longitudinal studies in healthy participants show mixed results, with some showing a positive change in HRV (Tulppo, 2003) and others showing no change despite improvements in peak oxygen uptake and resting bradycardia (Boutcher and Stein, 1995; Davy *et al.*, 1997). In contrast, data from chapter five of this thesis found an underlying role for higher values of HRV in individuals performing higher levels of physical activity. These data are supported by a recent meta-analysis which reports increases in RR interval and HF spectral power following exercise training (Sandercock *et al.*, 2005). Contrasting these data is made difficult by the mixed outcomes resulting from small sample sizes, varied data treatments and a lack of randomized control trials. One such study

recently reported no effect of low intensity physical training on the age related decline in spectral measures of HRV (Uusitalo *et al.*, 2004).

An equal period of training showed similar small effects ( $d = 0.1$  to  $0.3$ ) on HRV in peripheral artery disease (PAD) patients (Sandercock *et al.*, 2007a). Outcomes were believed to be due to lower absolute exercise intensities and/or the intermittent nature of activity performed. It is necessary here to consider differences between patient cohorts assessed in Sandercock *et al.* (2007a) and those of the present study. Patients in Sandercock *et al.* (2007a) suffered from PAD and demonstrated a low functional capacity common in these patients (Hiatt *et al.*, 1994). Patients were prescribed 30 minutes of presumably continuous treadmill walking at approximately 75% to 85% maximal HR (HR<sub>max</sub>). It turned out that patients could not complete 30 minutes continuous walking at this intensity due to the nature of their condition and could only perform the required exercise over a 1 h period. As a result, exercise was discontinuous/intermittent in nature and absolute intensities were lower (data not reported) than expected. These factors were postulated to be insufficient to promote central adaptations despite improved walk time; which may have resulted from improved peripheral adaptations (e.g. skeletal muscle mass, oxidative capacity) commonly observed following training in CHF patients (Hambrecht *et al.*, 1995; Pedersen and Saltin., 2006; Feiereisen *et al.*, 2007). Findings from one recent meta-analysis of all studies assessing the response to exercise training in heart failure patients up to 2004 revealed poorer increments in functional capacity following intermittent and/or resistance exercise protocols (Smart and Marwick, 2004), although results are not conclusive due to the small number of studies ( $n = 7$ ) utilizing incremental protocols. A second meta-analysis of nine randomised control studies assessing the effect of exercise on outcome in heart failure patients demonstrated a positive effect for predominantly aerobic training ( $n = 7$ ) on survival and/or hospitalisations (ExTraMATCH, 2004). It may be that the intermittent nature of the circuit training programmes used combined with the lower exercise intensities (~60 to 70% HR<sub>max</sub>) in part explain the small changes observed, although these were set at recommended levels (e.g. RPE 12 to 14; Fletcher *et al.*, 2001).

The findings from a second study carried out by members of the same group suggest that the type and degree of cardiovascular disease may play a greater role in physiological adaptations to CR. Following a CR programme involving aerobic exercise in the form of circuit training, Sandercock *et al.* (2007b) observed a significant and positive change in HRV in CAD patients. Patients also demonstrated improvements in exercise capacity and HR response during and following exercise despite the use of a shorter training period (8 weeks) and similar relative exercise intensities (70% HR<sub>max</sub> or ~60%  $\dot{V}O_{2\max}$ ). A greater percentage of patients in the CAD study (64%) were prescribed beta-blockers compared with those in the PAD study (14%). There is a well established link between improved HRV following administration of beta-blockers (Guzzetti *et al.*, 1988; Coumel *et al.*, 1991; Mortara *et al.*, 2000). Despite an unaltered HRV in the control group, a greater facilitative effect of beta-blockers on attenuation of HRV may have been afforded to CAD patients compared with patients in the PAD studies of Sandercock *et al.* (2007b and 2007a).

In the present study, the exercise programme (i.e. circuits) and use of beta-blockers matched that of the Sandercock *et al.*'s (2007b) CAD study, yet effects on HRV were smaller and more similar to those observed in their PAD study (Sandercock *et al.*, 2007a). The fact that the present and CAD study demonstrate a similar improvement in exercise capacity implies that factors other than exercise type/intensity *per se* and pharmacological treatment underline the discrepancies in HRV findings. One factor could relate to the patient cohorts themselves.

The present study involved patients diagnosed with mild to moderate (NYHA class I to II) CHF and stable pharmacological therapy. When comparing baseline physiological and HRV parameters, patients in the present study demonstrated values that were both higher and more closely matched to healthy norms for  $\dot{V}O_{2\text{peak}}$  (~25 ml·kg<sup>-1</sup>·min<sup>-1</sup>, data from Shvartz and Reibold, 1990) and measures of HRV (e.g. LF (ln) 5.01, data from chapter five). Moreover, current patients displayed a lower risk profile associated with a sympathovagal balance favouring parasympathetic cardiac modulations (LF:HF 1.0 and 1.2, aerobic and resistance

groups respectively). In the CAD study of Sandercock *et al.*, patients had lower aerobic capacity and demonstrated increased risk resulting from a sympathovagal balance favouring sympathetic modulations of cardiac ANS activity (e.g. LF:HF 2.3). It is plausible that the baseline condition of patients, based on values for HRV combined with the nature of cardiovascular disease (CAD), explains the improvements in HRV following aerobic based CR in Sandercock *et al.* (2007b).

Other studies involving CHF and other CV diseased patients have demonstrated a positive change in short-term supine HRV following CR and/or exercise training (Duru *et al.*, 2000; Selig *et al.*, 2004). Likewise, baseline values for absolute and ratio spectral measures were significantly lower and higher respectively than those reported here.

Differences in HRV between differing heart failure and healthy groups may reflect alterations in central efferent autonomic activity. An apparent absence of cerebral activations in heart failure patients was postulated by Rosen *et al.* (2004) as a possible mechanism underlying reduced HRV and baroreflex sensitivity in this patient group. In addition, a role for greater intermittent inputs from the cerebral cortex to the brainstem underlying a maintained variability was also postulated. This potentially offers an explanation as to the wide variations in values observed within similar patient populations and as such warrants further elucidation.

The intensity of exercise performed was set and routinely adjusted in accordance with current CR guidelines and recommendations (SIGN, 2002; Hunt *et al.*, 2005; Dickstein *et al.*, 2008). Because of the nature of disease in the present patient cohort, a cautionary approach was taken and exercise was lighter (RPE 11 - 12) than it was harder (RPE 13 - 14), particularly early in the intervention. Given the higher baseline HRV values that more closely matched those of healthy individuals, it is plausible that the prescribed exercise was of insufficient intensity and/or duration to induce significant changes in HRV in the present patient cohort. This finding also highlights a dissociation between augmentation of cardiorespiratory parameters and measures of autonomic modulation to exercise training based on current guidelines.

The response to exercise training has also been shown to differ according to disease aetiology, with non-ischaemic HF patients demonstrating better clinical outcomes for cardiovascular measures (Keteyian *et al.*, 1999). The majority of studies demonstrating an improved HRV have involved heart failure patients with ischaemic aetiology (Coats *et al.*, 1992; Adamopolous *et al.*, 1995; Duru *et al.*, 2000) as this represents approximately 70% of the aetiology of heart failure (Dickstein *et al.*, 2008). In our group of patients, a greater percentage (53%) of underlying aetiology was non-ischaemic in nature. This could explain the lack of significance and trend for differing group effects for measures of HRV despite observed improvements in cardiovascular parameters.

An often overlooked point by many studies showing no effect of exercise on resting autonomic modulations is the effect on its response to autonomic stimuli. A lack of effect on autonomic modulations at rest does not rule out the effectiveness of exercise to change the responsiveness of the ANS under induced sympathetic and/or parasympathetic conditions. To address this point, the present study assessed the responsiveness of ANS modulations to parasympathetic stimulation before and after CR. Observed moderate ( $d > 0.6$ ) to large ( $d > 1.2$ ) effects for differences in LF:HF over time and between groups demonstrated a significant improvement in the response of the ANS in the AR group. These findings warrant further discussion.

#### 8.4.5. *Changes in the reactivity of ANS modulations in AR and RT groups.*

There is much debate regarding the meaning and interpretation of the LF:HF. In healthy, sedentary adults there is general consensus that the lower the LF:HF ratio, the higher the relative vagal outflow. Conversely, a move toward a higher ratio shows increasing relative sympathetic predominance (such as during head up tilt (HUT)). At rest, vagal tone prevails and variations in heart period are largely dependent on vagal modulation (Chess *et al.* (1975; cited in Ori *et al.*, 1992); Pagani *et al.*, 1986). When supine and under paced breathing, healthy participants demonstrate a decrease in LF:HF compared to HUT resulting from a

decreased LF and increased HF spectral power (Pomeranz *et al.*, 1985). In the general population a higher LF:HF is indicative of increased cardiac risk (Tsuji *et al.*, 1996; Gerritsen *et al.*, 2001). As a result, exercise training programmes that have reduced LF:HF have been hailed as successful (Malfatto *et al.*, 2002).

An important paradox is that in some clinical populations, a low LF:HF ratio predicts increased risk of arrhythmia and sudden cardiac death (Bigger *et al.*, 1993; La Rovere *et al.*, 2003). The trend for a decreased LF:HF value in the present study could therefore be seen as a negative outcome of aerobic based CR. Likewise, a move towards a beneficial effect is suggested following CR based on resistance exercise.

Reasons for this paradox relate to problems with generalising findings from validation studies in healthy participants to clinical populations. In both populations, the value of the LF:HF ratio is the product of LF and HF power. In healthy populations, however, there is significant power in both these bands with values often running into the hundreds or even thousands of milliseconds. A balance between the two is indicative of healthy autonomic control and therefore, desirable. In cardiac diseased patients, oscillation in heart period is greatly reduced, probably resulting from chronic sympathetic predominance at the SA node. Values for LF and HF can often be in tens or even single figures, a finding demonstrated experimentally in CHF (van de Borne *et al.*, 1997; La Rovere *et al.*, 2003). In this situation a small variation in one band can create a misrepresentative or wholly erroneous value for LF:HF.

Patients with compromised autonomic function, a decrease in the LF:HF ratio may not necessarily be one indicative of improved cardiac control and could be counterproductive. In the present cohort, baseline HRV profiles suggested that autonomic function was not greatly impaired. Indeed, patients demonstrated a profile more akin to that of healthy individuals. The trend for a decrease in LF:HF ratio in the AR group was underlined by an increase in absolute values for HF power and a concomitant decrease in LF power. In the RT group, an opposite trend was observed with a small increase in LF power and a larger decrease in

HF. Combined with baseline ANS condition, these findings more likely support the idea of a decrease in LF:HF as a beneficial effect.

The discussion regarding the utility of LF:HF so far has focused on single measures obtained under a set condition (i.e. paced breathing). Assessing the response of the LF:HF ratio to changing stimuli may reveal its greater utility. The response of autonomic modulations before and after CR was measured as the difference in the LF:HF ratio under normal breathing (NB) compared to paced breathing (PB) conditions. The larger the difference in LF:HF between these two conditions, the larger the response to the stimulus. During PB, a healthy ANS response would typically comprise a decrease in the LF:HF. This is normally due to a vagally mediated increase in the HF component with a concomitant decrease or no change in LF power (Hirsch and Bishop, 1981; Ursino and Magosso, 2003). Patients who were prescribed aerobic CR showed an increase in this response; an opposing trend was observed following resistance training (Figure 8-3). This might suggest a better parasympathetic mediated response following aerobic but not resistance training. To ascertain if this was the case it is also necessary to consider responses of the absolute spectral components underlying the LF:HF ratio.

In the present study, stimulus of the ANS was provided by increased parasympathetic outflow induced by PB at 0.2 Hz. At this frequency, the HF peak is affected solely by vagal gains and is independent of sympathetic gains (Ursino and Magosso, 2003). Under such conditions power in the LF can either decrease as result of a parasympathetic mediated suppression of sympathetic outflow (Malpas, 2002) or remain unchanged (Ursino and Magosso, 2003). Prior to CR, the response of absolute LF and HF components matched expected changes in both groups. In the AR group, values for  $\ln$  LF  $\text{ms}^2$  under NB decreased during PB (5.73 versus 5.04), a difference of -0.69  $\ln$  units.  $\ln$  HF  $\text{ms}^2$  values showed an increase from normal to PB conditions (5.21 versus 5.38), a difference of +0.17  $\ln$  units. In the RT group, responses similar in magnitude and direction to those in the AR group were observed for LF (5.40 versus 4.76, NB versus PB; a difference of -0.64  $\ln$  units), and HF (4.74 versus 4.89, NB versus PB; a difference of +0.15  $\ln$  units).

Following cardiac rehabilitation, the response of the LF and HF components was altered differently in each group and suggested AR influenced more so the LF component compared with the HF component. In the AR group, an increase in the response of the LF component was accompanied by a higher value for this measure during NB ( $6.12 \ln \text{ms}^2$ ) and a lower value under PB ( $4.82 \ln \text{ms}^2$ ) conditions. A post-CR difference of -1.3 units shows an increase in the LF response of 0.61  $\ln$  units (i.e. -1.3 minus -0.69).  $\ln$  HF demonstrated only a small increase in response following AR training (0.09  $\ln$  units). This was due to an increase in the difference between values under NB ( $5.29 \ln \text{ms}^2$ ) compared with PB ( $5.57 \ln \text{ms}^2$ ) conditions to +0.28  $\ln$  units.

Opposite findings were observed following RT training.  $\ln$  LF under NB demonstrated a large decrease compared with pre-CR values (4.83 versus 5.40  $\ln \text{ms}^2$ , post- versus pre-CR). There was a small increase in the value for LF during PB following CR (4.87 versus 4.83  $\ln \text{ms}^2$ , post- versus pre-CR). This resulted in a decrease in the response of LF of 0.68  $\ln$  units (+0.04 minus -0.64) following training in the RT group. There was an actual improvement in the response (+0.33  $\ln$  units) of the HF component in this group resulting from an increase in the difference between values under NB ( $4.03 \ln \text{ms}^2$ ) and PB ( $4.51 \ln \text{ms}^2$ ).

These findings show that the improved response of the LF:HF ratio observed following AR training was actually mediated by a greater change in the LF and not the HF component. In addition, the decline in response of the LF:HF observed in the RT group was a result of a larger decrease in the response to PB of the LF component. In the later group, a greater response of the HF component was also observed. Perhaps most importantly, in the AR group the absolute measures of LF and HF showed a desired increase under NB conditions, and their response to parasympathetic stimuli was more representative of that expected in healthy autonomic function (i.e. a decrease in LF and an increase in HF under PB conditions). This was not the case for RT group, where decreases in the LF and HF components compared with pre-training values were observed under NB and PB conditions. By ignoring the absolute measures, incorrect conclusions can be drawn from assessing the response to specific stimuli with the LF:HF ratio. Caution should therefore be taken when using ratios of spectral

measures to assess the efficacy of interventions to alter cardiac autonomic modulations.

Further concern for the interpretation of LF:HF is raised by others (Taylor and Studinger, 2006). These authors stress that transforming variables to better correspond to an anticipated physiological response does not necessarily create a more valid measure. In the case of LF and HF, normalising the oscillations to one another can uncouple their amplitudes from the physiology. The authors refer to Montano *et al.* (1994) where normalised units were used to indicate significant oscillations remain despite a monotonic heart rate induced by cholinergic blockade. Under such conditions one would expect oscillations in heart period to be obsolete. These findings further confound the use of LF:HF to represent physiological phenomena.

Another factor that could explain the differences in response in the AR and RT relates to basal vagal status of each group and the level of parasympathetic stimulation. PB was used to provide parasympathetic stimuli. With increasing parasympathetic stimulation, the phasic changes with respiration are lost, resulting in a decrease in HRV. Moreover, there is suggestion of a saturation of the HF response to pharmacological vagal inducement that is related to the basal level of vagal tone (Goldberger *et al.*, 1999). Post-CR, compared to the RT group, patients in the AR group demonstrated a higher value for the HF component but demonstrated a smaller response to PB (0.28 versus 0.48 ln units, AR versus RT). Combined with a reduced HR, the higher HF may be interpreted as greater vagal tone in the AR group. A higher basal vagal tone may explain the reduced response of HRV to vagal stimuli in the AR group. Individual differences in the degree of stimulation may also have underlined group differences. However, it was not possible to quantify the degree of stimulation in each individual as this can only be provided by pharmacological methods such as phenylephrine infusion (Goldberger *et al.*, 1999).

8.4.6. *Biological mechanisms underlying responses to training.*

Some of the main systems affected by exercise training and the resulting outcomes are outlined in Table 8-6. Adaptations in central transport are actually not as common as one might expect, and in fact the positive benefit of training heart patients is often mediated by peripheral muscle adaptations (Pedersen and Saltin, 2006). In resistance training, improvements in exercise capacity (oxygen uptake) have been observed without an effect on central dynamics and also relate to improvements in peripheral factors including strength, endurance and type I fibre area of exercise muscle (Pu *et al.*, 2001). Considering these findings and the similarities observed for physiological measures, the reason why the autonomic response to training differed between the AR and RT groups is likely to relate to some other factor(s).

No definitive answer to the mechanisms underlying reduced sympathetic and/or increased drive following aerobic exercise has been elucidated but a central nervous system (CNS) effect mediated by baroreceptor/baroreflex alterations has been proposed (Negrao and Middlekauff 2007). A number of animal and human studies have demonstrated an improved baroreflex control following aerobic exercise training. In a rabbit model of pacing-induced heart failure, Liu *et al.* (2000) found that exercise training improved arterial baroreflex control and renal sympathetic nerve activity.

**Table 8-6. The response of various physiological systems and clinical outcomes following exercise training.**

Organ system/Tissue	Response to exercise training	Effect on mortality and morbidity
Improve central transport and regional blood flow	↑ in cardiac output; ↑ in peak VO <sub>2</sub> ; reverse chronotropic incompetence; ↑ regional blood flow	↑ peak VO <sub>2</sub> → ↑ survival; ↓ hospitalisation
Autonomic nervous system	↑ HRV; ↓ plasma NE (rest)	↑ HRV → ↓ arrhythmia → ↑ survival ↓ hospitalisation ↓ plasma NE → ↑ survival
Skeletal muscle	↑ aerobic enzymes; ↑ mitochondria size/density; ↑ capillary density; relative type I fibres	Change in muscle composition → ↑ QOL ↓ hospitalisation
Peripheral vasculature	↑ vascular reactivity	↑ coronary blood flow } ↑ survival ↓ ischaemia and MI } ↓ hospitalisation

NE, norepinephrine; HRV, heart rate variability; MI, myocardial infarct; QOL, quality of life. From Ko and Mckelvie (2005).

The same group report in a subsequent study that increases in baroreflex control in heart failure rabbits after training are mediated by an enhanced vagal outflow to the SA node (Liu *et al.*, 2002).

On the other hand, there is evidence that the sensitivity of resistance vessels (arterioles) to sympathetic efferent activity plays a major role in the origin of the LF peak (Ursino and Magosso, 2003). LF oscillations originate from oscillations in blood pressure, which are detected by the baroreflex system and conveyed to cardiac cycle modulations fluctuations (Moak *et al.*, 2008). Oscillations in resistance are in turn directly associated with pressure oscillations. If there is a depressed ability of the resistance vessels to respond to sympathetic stimuli, a resulting decline in the LF spectral component is the likely result (Ursino and Magosso, 2003). Likewise, an improvement in the response of resistance vessels would manifest as an increased LF component.

The findings of larger changes in raw values and the response of LF to PB could indicate an effect of exercise on both vagally and sympathetic/baroreceptor mediated modulations of ANS activity. A more beneficial change for LF and HF measures in the AR group could be underlined by an improved arterial baroreceptor control resulting from an increased vagal outflow and an increased capability of peripheral vessels to respond to sympathetic influences. Indeed, a larger decrease in systolic and diastolic blood pressure in this group may indicate an improved peripheral resistance.

The use of an additional measure to better quantify the effect on sympathetic outflow would have helped confirm these findings. One such approach could be the use of beat-to-beat changes in blood pressure and heart period to produce spontaneous baroreflex indexes that reflect the baroreceptor-heart rate reflex sensitivity (BRS). Data from animal studies suggest an important baroreflex role linking these variabilities (Frankel *et al.*, 1993). In humans, measures of BRS have recently been shown to provide strong and independent prognostic information in heart failure patients (La Rovere *et al.*, 2009). It appears inclusion of this measure could not only provide a more relevant indication of sympathetic outflow but may also provide useful information regarding changes to prognostic outcomes following CR, particularly in heart failure patients.

## **8.5. Limitations and recommendations.**

The lack of control group prevented the present study from being able to evaluate the effectiveness of CR *per se* on altering short-term HRV in CHF patients. A number of studies assessing short-term HRV in cardiac patient groups (e.g. post-MI, CAD and heart failure) report stable and unchanged measures when assessed in a non-exercise control group over a similar time period to that of the present study (Selig *et al.*, 2004; Sandercock *et al.*, 2007b). The findings of improved response of the LF:HF ratio in the AR group was underlined by a change in the response of the LF component and not the HF component as expected. An improved baroreflex mediated response to heart rate fluctuations may have occurred. The use of a quantitative measure of the baroreflex response (e.g. baroreflex sensitivity) could confirm these findings.

The present study was similar to the majority of previous studies in its assessment of adherence to the home-based programme. A limitation of many studies assessing home-based exercise is the reliance on patient compliance with the prescribed exercise and the accuracy of self-reporting. In this respect, a specific limitation to the present study may relate to differences in the nature of home-based exercise between groups. The AR group was requested to perform a minimum of 30 minutes brisk walking (eliciting an RPE of 11-13), five times per week. The RT group was required to perform two circuits involving four of the exercises performed in the supervised sessions on four separate days. The task required of the RT group was arguably more complex to that required of the AR group, particularly as many of the exercises were unfamiliar to the patients. Whilst individual tuition and information of each exercise was provided to those in the RT group, it is possible that patients may have had difficulty recalling specific exercises and/or the exact techniques involved. Also, the performance of only one supervised exercise session may have limited the adaptations to exercise training, particularly in the RT group.

Improvements in exercise capacity observed in both the AR and RT groups cannot solely be attributed to the exercise performed. Valid measurements of maximal aerobic capacity in healthy old people, but especially chronically ill

people, can sometimes be difficult because of lack of motivation, musculoskeletal limitations, peripheral arterial disease, or indications to stop the exercise by the test administrator(s) (e.g., ventricular ectopies), leading to premature cessation of the test. These factors become even more pertinent when considering many patients were performing baseline GXTs for the first time or following an extensive period from a previous GXT. A number of patients demonstrated limitations to treadmill exercise resulting from musculoskeletal problems with the knee (n = 1) and hip (n = 3) joint regions. A different mode of exercise testing (e.g. cycling) combined perhaps with the use of submaximal testing may have facilitated the validity of measurements in these patients (Bittner, 2003).

Finally, there is also strong argument, given the pathophysiology of heart failure, for exercise-training programmes to be designed to improve aerobic capacity, strength, range of motion, and flexibility of participants without producing harmful effects on the cardiovascular system. A programme that stresses one mode of exercise over another (e.g. aerobic over resistance) may not afford sufficient stress to improve all of these parameters. An obvious answer is the inclusion of several modes of exercise, in the form of a circuit based session, will most likely provide the best model that accommodates the main physiological systems of concern. These recommendations apply to supervised sessions and adoption of these for home-based exercise is likely to be impractical. Walking offers a form of activity that can be tolerated by a wide range of heart failure patients and remains a favoured mode for home-based exercise training in heart failure (ExTraMATCH, 2004; Ko and McKelvie, 2005; Hunt *et al.*, 2005, Dickstein *et al.*, 2008).

## **8.6. Conclusions.**

Neither the prescription of a 12 week aerobic only nor resistance only exercise programme based on current UK recommendations for cardiac rehabilitation in CHF patients significantly altered ANS modulations of resting cardiac activity. The relatively high baseline values for measures of HRV may have prevented a

greater degree of change in the current patient cohort. Aerobic only training did, however, result in a trend for favourable change in resting HRV measures and led an improved ANS reactivity underlined by a possible improved baroreflex control of cardiac modulations. A lack of control group prevents attribution of these findings solely to AR exercise training.

The present study highlights the importance in assessing not only the baseline level of heart rate fluctuations, but also their response to alternating conditions and activities. When assessing the efficacy of exercise training on the response of autonomic control using normalised measures, incorrect interpretations can occur when the response of absolute measures are ignored.

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## **CHAPTER 9. THE RELATIONSHIP BETWEEN RESTING HEART RATE VARIABILITY AND HEART RATE RESPONSES IN CHRONIC HEART FAILURE PATIENTS BEFORE AND AFTER 12 WEEKS CARDIAC REHABILITATION.**

### **Abstract.**

In chapter four, a strong negative association between resting heart rate variability (HRV) measurements and resting heart rate (HR) was indicative of a 'harmony' between autonomic cardiac control systems that exists under normal autonomic conditions. Moreover, a higher value for HF spectral power was able to predict patients likely to obtain a HR recovery (HRR) value indicative of lower risk following maximal exercise. There was an underlying role for higher values of HRV in low risk category participants when grouped according to risk for resting HR, change in rest to peak HR and HRR. Cardiac rehabilitation (CR) is becoming increasingly used in the management of chronic heart failure (CHF)

Eighteen, mild-to-moderate (mean New York Heart Association grade: 2.0) CHF patients undertook 12 weeks of CR including aerobic (AR, n = 9) or resistance (RT, n = 9) based exercise. Both programmes consistent of one weekly supervised and four home based sessions. Prior to and following the 12 week programme, patients underwent assessments of short-term resting heart rate variability (HRV) during normal and paced breathing. Cardio-respiratory and vascular responses to graded treadmill testing (GXT) were also assessed. The change in values for all measures was assessed within and between groups using repeated measures ANOVA and both paired and independent *t*-tests.

Altered associations between HR and short-term HRV are reversed following 12 weeks exercise based cardiac rehabilitation and patients demonstrate a partial normalisation of the HR-HRV relationship. A potential role for resting non-linear measures of HRV to predict the HR response to exercise following normalisation was also observed. Consideration of associations between both tonic (HR) and reflexive (HRV) indices should be given when determining the efficacy of exercise based CR on autonomic function. There is a need to identify the risk stratification role of these associations in CHF.

## 9.1. Introduction.

The concept of a relationship between heart rate (HR) and heart rate variability (HRV) indicating a harmonious behaviour between these indices of cardiac autonomic control was explored in chapter four. A strong negative association was observed between resting HR and several measures of HRV in a cohort of healthy adults and matched the findings of previous studies utilising 24 h measures (Coumel *et al.*, 1995). The findings indicated the associations between HR and HRV could be observed from short-term RR interval recordings (i.e. 5 minute).

The justification for assessing the association between HR and HRV is based on the idea that normal physiology supposes a harmony between the various indices. In particular, rather than reflecting a dependence of the HRV on HR, a close parallel of specific measures (e.g. LF:HF ratio) actually indicates a permanent modulation of the intrinsic HR mediated by vago-sympathetic interactions (Coumel *et al.*, 1991). In addition, a greater attention to the impairment of the HR-HRV correlations in diseased hearts may offer more information regarding autonomic function than that offered by looking at the decrease in individual indices (Coumel *et al.*, 1995). To this effect, Coumel *et al.* (1991) identified a loss in the correlation between HR and HRV in patients with left ventricular hypertrophy and heart failure that reflected the impaired state of the autonomic nervous system (ANS). There appeared to be a loss in one of the main characteristics of the HR-HRV relationships reflecting the physiological harmony of the ANS functions.

Chapter eight highlighted the effect different modes of exercise training had on resting measures of HRV. Results showed the expected improvements in functional and aerobic capacity following exercise training but adaptations to measures of HRV were non-significant. This was due to the low sample sizes involved as the magnitudes of effects for some measures were large. Assessing changes in the HR-HRV relationship may provide additional information to support these findings and could provide efficacy for exercise training to alter cardiac autonomic control and the harmony between its indices favourably.

A second aim of the empirical work carried out in chapter four was to identify whether resting measures of HRV were associated with the HR response to a graded exercise test (GXT). The existence of a strong association might enable the use of resting HRV as a screening tool to identify the need to carry out a physically, and in some cases psychologically, stressful GXT. The findings identified moderate associations between the recovery HR after exercise and vagal resting HRV. Resting vagal orientated measures of HRV predicted those individuals likely to demonstrate a low risk based on HR recovery (HRR) following exercise but was not able to predict those with a high risk HRR. In addition, participants demonstrating a higher risk based on known thresholds for HR measures systematically demonstrated significantly lower values for HRV.

In a clinical setting, patients maybe asked to undertake a GXT for a number of reasons including: to indicate the condition of the ANS, to identify risk and to assess the efficacy of treatments. Such assessments are often made based on changes to the HR response to exercise along with measures of functional capacity. In patients suffering from cardiovascular disease, there is an increased risk of acute events associated with the performance of maximal exercise testing due to the high stresses already placed upon the dysfunctional heart (Corrà and Piepoli, 2007). If such relationships as those seen in healthy participants can be observed in chronic heart failure (CHF) patients, HRV may be a potentially valuable tool with which to pre-screen and identify patients that may not benefit from a GXT. This would limit the risks involved in performing such exercise.

Chapter four showed that in healthy participants higher values of resting HRV predict a lower risk profile based on HRR measures. Many of the thresholds for the HR measures were originally identified in general populations that included patients with heart disease (Cole *et al.*, 1999; Jouven *et al.*, 2005; Leeper *et al.*, 2007). Jouven *et al.* (2005) found that that a resting HR  $> 75 \text{ b}\cdot\text{min}^{-1}$ , a  $\Delta\text{HR}$  at peak exercise  $< 89 \text{ b}\cdot\text{min}^{-1}$  and a HRR of  $< 25 \text{ b}\cdot\text{min}^{-1}$  were indicative of an increased risk for adverse cardiac events and/or mortality. Whilst some healthy participants demonstrated an increased risk, the risk is considerably smaller when compared with heart disease patients demonstrating a high risk HR response (Jouven *et al.*, 2005). There are no data as to the underlying role of HRV for

CHF patients demonstrating increased risk based on the resting and HR response to exercise and the effect of exercise training on this role.

The aims of this study were therefore;

- 1) To identify the harmony of cardiac autonomic indices in CHF patients as assessed by the HR-HRV relationship;
- 2) To identify associations between resting HRV and HR responses to exercise in CHF patients and determine the capacity of HRV to predict these responses;
- 3) To determine the underlying role of short-term measures of HRV in patients demonstrating an increased risk based on known HR thresholds;

The above aims will be sought in the same patient cohort that underwent the CR exercise intervention described in chapter eight. Correlation analysis was performed before and after CR in order to assess the impact of CR on associations but no consideration was given to the type of exercise programme performed. Comparisons would also be made to data from age matched healthy controls (see chapter four) in order to assess the normality of associations in CHF patients.

## **9.2. Methods.**

The methods outlined below follow those detailed in chapter eight. To avoid excess repetition, only the key elements are outlined here and readers are directed to section 8.2 of this thesis for complete details of methodologies. Where sections are the same as those in chapter eight, these have been *italicised*.

### *9.2.1. Patient sample.*

*Seventeen non-diabetic CHF patients gave full written informed consent to participate in the study. Heart failure was confirmed in all patients by the supervising cardiologist. The aetiology of disease included dilated cardiomyopathy (DCM, 53%), ischaemic heart disease (IHD, 40%) and*

*myocardial infarct (MI, 7%). New York Heart Association (NYHA) classification ranged from I to II across the patient cohort.*

#### *9.2.2. Instrumentation and data acquisition.*

*RR intervals and HR were recorded via a Polar S810 heart rate monitor (HRM) (Polar Electro OY, Kempele, Finland). The S810 was set to record beat-to-beat RR intervals with a sampling frequency of 1000 Hz providing an accuracy of 1ms for each RR period (Cottin et al., 2004). S810 recordings were transferred to a password protected PC via the Polar Precision Performance 4.03 software (Polar Electro OY, Kempele, Finland). Each downloaded RR interval file was exported as a .txt file to a separate folder for later HRV analysis using an advanced software package (HRV Analysis Software 1.1, University of Kuopio, Finland).*

*A 12-lead ECG recording was simultaneously made using the CardioPerfect ST 2001 module (Cardio Control, Delft, The Netherlands) of the MG system and blood pressure was obtained by manual sphygmomanometry.*

*Exercises in the aerobic training group were performed on treadmill, cycle and ski exercise based ergometers. A mixture of patients own body mass and ankle and wrist weights were used to provide resistance.*

#### *9.2.3. Protocol.*

##### *9.2.3.1. RR interval recordings.*

*Heart rate variability measures were derived from seven minutes of stationary ECG obtained supine and at rest using the S810. Following a familiarisation period, a five minute RR interval recording was made whilst controlling breathing at a rate of 12 breaths·min<sup>-1</sup> (0.2 Hz) via standardized instruction and metronome pacing. The S810 recordings were filtered for errors using the Polar software automated RR interval filtering algorithm set at medium filter power and minimum beat protection zone of 6 b·min<sup>-1</sup>. The interpolation of beats via this method has only minor effects on spectral measures of HRV measured from stationary tachograms (Jurca et al. 2004) in which <15% of beats are rejected.*

### 9.2.3.2. Heart rate variability analysis.

#### 9.2.3.2.1. Linear measures of heart rate variability.

*Linear measures of HRV were obtained from the filtered RR interval data according to recommended standards (Task Force 1996) using the HRV analysis software 1.1 as described earlier (chapters two and three). In the present chapter all HRV data were obtained from the HRV analysis software 1.1 after subjection to smoothness priors detrend and interpolation at 4 Hz. This was to account for non-stationary signals in the RR interval time series that often distorted LF and HF spectral measures. In the time domain, rMSSD was calculated. Fast Fourier transformation was applied to determine low frequency power (LF, 0.04 – 0.15 Hz) and high frequency power (HF, 0.15 – 0.40 Hz) in the frequency domain. The ratio between LF and HF power (LF:HF) was determined and used as a measures of sympathovagal balance (Pagani et al., 1986). Data were transformed, if necessary, to allow parametric analysis.*

#### 9.2.3.2.2. Non-linear measures of heart rate variability.

*In addition to the linear measures above non-linear measures were also obtained. RR interval time series often violate the assumptions of stationarity required for traditional linear HRV analysis methods (e.g. FFT) and present with non-linear characteristics (Tulppo et al., 1996; Kleiger et al., 2005; Contreras et al., 2007). This is particularly true in cardiovascular disease where several methods for analysing these non-linear aspects have been proposed (İşler et al., 2007; Maestri et al., 2007). The Poincaré plot, a graph of each RR interval plotted against the next interval, is a simple technique taken from non-linear dynamics to quantify the HRV data. By fitting an ellipse to the shape of plotted points, two standard deviations, referred to as SD1 and SD2, are obtained. These are related to the fast beat-to-beat and longer-term variability respectively. Moreover, these quantitative measures have been shown to independently predict all-cause and sudden cardiac death in CHF patients (Brouwer et al., 1996). The HRV analysis software 1.1 automatically derives SD1 and SD2 and these measures were included in this chapter.*

#### 9.2.3.3. Treadmill graded exercise test protocol.

*Following resting recordings, participants performed a GXT (modified Bruce protocol) on a motor-driven treadmill (Cardio Control, Delft, The Netherlands) to volitional exhaustion. A familiarisation session was provided to those patients unfamiliar with walking on a treadmill. During the GXT, heart rate was continuously recorded from the ECG and Polar S810 devices. The same tests were performed upon completion of the 12 week exercise training/control period.*

#### 9.2.3.4. GXT termination criteria.

*The GXT was stopped when patients could no longer maintain walking on the treadmill or observation of a sustained ST segment depression > 2mm, acute chest pain or achievement of  $\dot{V}O_{2\max}$ . Maximal oxygen consumption was defined as the highest  $\dot{V}O_2$  attained in a 30-sec period. Criteria to establish  $\dot{V}O_{2\max}$  were based on the ACSM (2001) guidelines. These were:*

- i. a plateau in  $\dot{V}O_2$  (increase of < 2 ml·kg<sup>-1</sup>·min<sup>-1</sup>) despite increasing work load;*
- ii. a final respiratory exchange ratio (RER) greater than 1.15;*
- iii. an RPE > 17.*

#### 9.2.3.5. Exercise training protocol.

*Patients were randomly allocated to one of two conditions: supervised and home based aerobic training (AR) or supervised and home based resistance training (RT). Supervised exercise sessions took place at the hospital once a week on the same day. During each session, patients in the AR group were required to complete a 40 minute circuit involving alternation between one minute of aerobic exercise and one minute of active recovery. Patients in the RT group were also required to complete a 40 minute circuit which involved alternating performance of one min of resistance based exercises separated by a one minute active recovery period. Intensity of exercise was assessed via RPE. All sessions started and ended with a 10 minute warm up and cool down period respectively.*

*For the home-based programme patients were asked to complete a selection of either AR or RT exercises according to group allocation. The AR group was required to perform a 30 minute walk four times a week for the duration of the study. The RT group was required to perform a shortened circuit of four of the six hospital based RT exercises, three times per week. Both groups were given an exercise diary with a copy of the RPE scale and the required exercises to perform. Exercise intensities, types and durations were based on current recommendations for CR in the United Kingdom (British Association of Cardiac Rehabilitation (BACR), 2007; Scottish Intercollegiate Guidelines Network (SIGN), 2002).*

#### 9.2.3.6. Exercise heart rate measures.

Measures of HR and RR interval were recorded continuously with the S810 during the seven min of rest and throughout the GXT. The S810 signal was synchronised with the start and end of the GXT by marking the S810 recording using the temporal 'event' (lap) marker. Only heart rate parameters showing strong relationships in healthy individuals as identified in chapter four were obtained; these included:

1. Resting HR – calculated as the mean HR during the 5 min controlled breathing rest period;
2. Change ( $\Delta$ ) in HR – calculated as the difference between HR at peak exercise and the resting HR when supine;
3. Heart rate recovery – calculated as the difference between peak HR and HR recorded one minute post completion of the GXT whilst in the seated position.

As with the healthy study in chapter four, subgroup analysis was performed. This was based on known increased risk factors including:

1. A resting HR above or below  $75 \text{ b}\cdot\text{min}^{-1}$
2.  $\Delta\text{HR}$  above or below  $89 \text{ b}\cdot\text{min}^{-1}$
3. HRR greater or less than  $25 \text{ b}\cdot\text{min}^{-1}$

This was performed for both aerobic and resistance trained groups.

Where sufficient numbers of participants fail to demonstrate values either side of these cut points, analysis was performed on participants grouped into study specific upper and lower tertiles for resting HR,  $\Delta$ HR and HRR.

#### 9.2.4. *Statistical Analysis.*

*All statistical analysis was carried out using SPSS version 13.0 (SPSS inc. Chicago, Illinois, USA). Normality of data sets was assessed using a Kolmogorov-Smirnov test. Where assumptions for parametric testing were not met data were subjected to logarithmic transformation (ln).*

##### 9.2.4.1. Baseline heart rate variability and exercise test responses.

The relationship between selected exercise test responses and resting measures of HRV was evaluated by Pearson's correlation analysis. For non-parametric data, relationships were analysed using Spearman's rank correlations. Associations between HR and/or HRV with age and/or gender were assessed first. Where significant associations were found, subsequent analyses for relationships between other dependant variables were assessed using partial correlation analysis with age and/or gender as appropriate covariates.

The effects of CR on the above associations was determined by comparing the magnitude of change in correlation coefficient pre- and post-CR. Magnitudes of correlations were defined according to Cohen (1988) whereby correlations  $\geq 0.5$  are considered large, 0.3 to 0.5 are considered moderate and 0.1 to 0.3 are considered small. Smallest worthwhile changes in correlation coefficient were considered as an change in effect size greater than 0.2.

Correlation coefficients for rMSSD, LF, HF and LF:HF ratio before and after CR were also compared with data obtained in age-matched healthy controls from chapter four. It was hoped that correlation coefficients would better match those of healthy adults when pre-CR values were compared with those post-CR. As observed in healthy individuals, a negative correlation between resting HR and absolute HRV measures and a positive association with HR and LF:HF was

considered an indication of a ‘harmony’ in cardiac autonomic control (Coumel *et al.*, 1995).

Exercise test responses showing significant or close-to-significant and at least moderate relationships with measures of HRV were entered into binary logistic regression analysis to assess the predictive power of baseline measures of HRV.

#### 9.2.4.2. Group comparisons based on heart rate risk values.

Analysis of between-group differences according to risk based on resting HR,  $\Delta$ HR and HRR cut-points were assessed using independent *t*-test, Wilcoxon’s rank-sum test and Chi square test as appropriate. A *P* value < 0.05 was considered statistically significant. The magnitudes of effects were also assessed and defined using standardised differences as follows: effects < 0.2 were considered trivial, 0.2 to 0.6 small, 0.6 to 1.2 moderate, 1.2 to 2.0 large, and > 2.0 as very large (Hopkins, 2000). Precision of estimates of outcome statistics is provided by 95% confidence intervals (CI).

### **9.3. Results.**

#### *9.3.1. Association between resting heart rate variability, resting heart rate and heart rate responses to treadmill testing.*

Due to skewed distributions, analysis of all HRV measures except mean RR and LF:HF was performed on log-transformed (ln) values. Analysis for age and/or gender as covariates revealed significant associations between gender and LF power (ln) ( $r = 0.52$ ,  $P < 0.05$ ) and LF:HF ( $r = 0.66$ ,  $P < 0.01$ ). Subsequent partial correlations were obtained for these measures with gender as a covariate.

The outcomes of correlation analysis presented in Table 9-1. Associations prior to CR are presented in normal type. Resting HR displayed a moderate and positive correlation with log-transformed values for LF and HF power and SD1 but none of these associations reached statistical significance. Measures of the HR response to exercise ( $\Delta$ HR and HRR) were not statistically associated with any resting measure of HRV and correlations were small ( $r < 0.3$ ).

**Table 9-1. Pearson correlation coefficients for measures of heart rate variability with exercise heart rate, metabolic and performance measures obtained in chronic heart failure patients pre and post cardiac rehabilitation.**

		Rest HR	ΔHR	HRR <sub>1 minute</sub>
Ln rMSSD	Pre CR	0.04 (-0.49 to 0.52)	-0.03 (-0.53 to 0.49)	-0.23 (-0.66 to 0.32)
	<b>Post CR</b>	<b>-0.10</b> <b>(-0.58 to 0.43)</b>	<b>0.42</b> <b>(-0.12 to 0.77)</b>	<b>0.13</b> <b>(-0.41 to 0.60)</b>
Ln LF	Pre CR	0.47 <sup>‡</sup> (-0.06 to 0.79)	0.27 <sup>‡</sup> (-0.28 to 0.69)	-0.19 <sup>‡</sup> (0.64 to 0.36)
	<b>Post CR</b>	<b>0.08</b> <b>(-0.45 to 0.57)</b>	<b>0.40</b> <b>(-0.76 to 0.14)</b>	<b>0.12</b> <b>(-0.42 to 0.60)</b>
Ln HF	Pre CR	0.32 (-0.23 to 0.72)	0.10 (-0.43 to 0.58)	-0.11 (-0.59 to 0.43)
	<b>Post CR</b>	<b>-0.16</b> <b>(-0.62 to 0.38)</b>	<b>0.46</b> <b>(-0.05 to 0.80)</b>	<b>0.18</b> <b>(-0.37 to 0.62)</b>
LF:HF	Pre CR	0.16 <sup>‡</sup> (-0.38 to 0.62)	0.19 <sup>‡</sup> (-0.36 to 0.64)	-0.20 <sup>‡</sup> (-0.65 to 0.35)
	<b>Post CR</b>	<b>0.49<sup>†</sup></b> <b>(-0.03 to 0.80)</b>	<b>0.15<sup>†</sup></b> <b>(-0.39 to 0.62)</b>	<b>-0.37<sup>†</sup></b> <b>(-0.74 to 0.18)</b>
Ln SD1	Pre CR	0.47 (-0.06 to 0.79)	-0.03 (-0.53 to 0.49)	-0.23 (-0.66 to 0.32)
	<b>Post CR</b>	<b>-0.10</b> <b>(-0.58 to 0.43)</b>	<b>0.42</b> <b>(-0.12 to 0.77)</b>	<b>0.13</b> <b>(-0.41 to 0.60)</b>
Ln SD2	Pre CR	-0.01 (-0.52 to 0.50)	0.17 (0.37 to 0.63)	-0.18 (-0.62 to 0.37)
	<b>Post CR</b>	<b>0.01</b> <b>(-0.50 to 0.52)</b>	<b>0.52<sup>*</sup></b> <b>(0.01 to 0.82)</b>	<b>0.17</b> <b>(0.37 to 0.63)</b>

†Controlled for age; ‡Controlled for gender; §Controlled for age and gender; \* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ ; HR, heart rate; HRR, heart rate recovery; rMSSD, root mean square of successive differences; LF, low frequency spectral power; HF, high frequency spectral power; nu, normalised units; LF:HF, the ratio of low to high frequency spectral power; SD1, standard deviation of points on the short-axis of Poincaré ellipse; SD2, standard deviation of the long-axis of the Poincaré ellipse; Ln, natural logarithm.

9.3.2. *Change in associations between heart rate variability and exercise test response following cardiac rehabilitation.*

The values for correlation coefficient outcomes following 12 weeks CR are presented in Table 9-1 (bold type face). A change greater than 0.2 was observed for associations between HRR and all measures of HRV, with the largest change in effect observed for SD1 and rMSSD. Associations demonstrating changes greater than 0.2 included resting HR with LF, LF:HF and SD1 and  $\Delta$ HR with rMSSD, HF, SD1 and SD2.

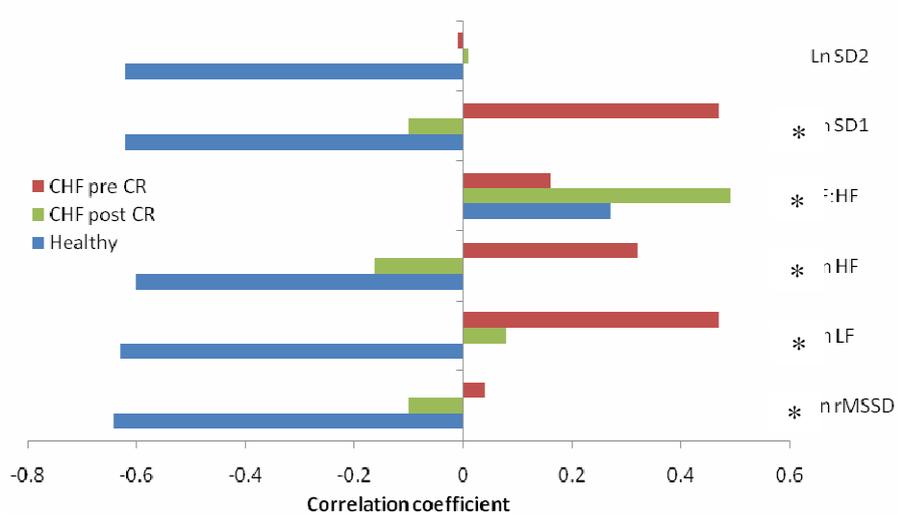
To provide the reader with an indication of the direction of change and whether this was beneficial, correlation coefficients for HRV measures pre- and post-CR are illustrated in Figure 9-1. Presented alongside these data are data for the same associations as obtained in a healthy age matched cohort. Where post-CR rehab correlations more closely match those of healthy participants this is considered a favourable effect and an indication of more normalised associations. An example will help to clarify the findings illustrated in Figure 9-1. Ln HF showed a correlation with resting HR of  $r = 0.32$  and  $r = -0.16$  pre- versus post-CR (Figure 9-1, panel a). This is deemed a favourable change because it demonstrates a shift toward a more normal association between these two measures ( $r = -0.63$  in healthy participants). Where favourable associations between measures of HRV and HR parameters occurred these were marked accordingly.

There was a favourable effect in the association between resting HR and nearly all measures of HRV (Figure 9-1, panel a). For all measures (except SD2), associations changed in a favourable direction. In CHF patients, associations between all measures became more similar to those observed in healthy individuals.

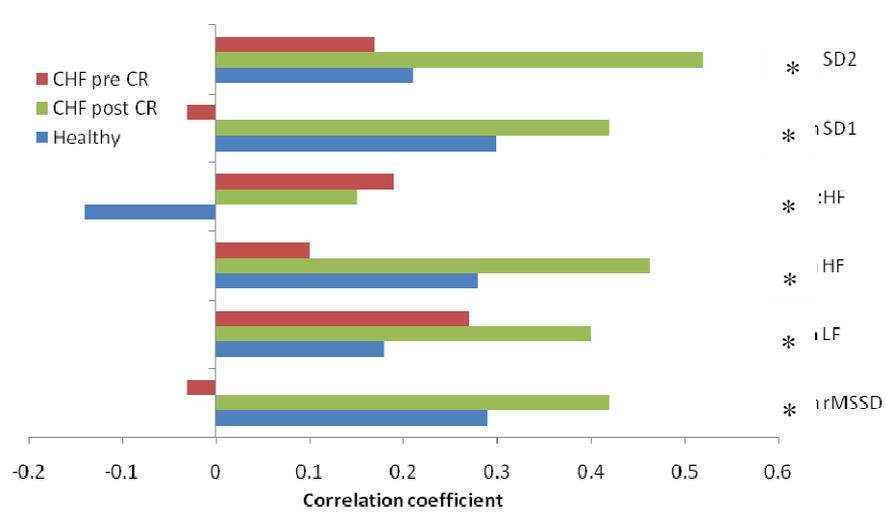
There were favourable changes in all associations between HRR and all HRV measurements (Figure 9-1, panel c). However no associations attained statistical significance before or after CR.

The change in association between  $\Delta$ HR and HRV was favourable for all measures (Figure 9-1, panel b). Following CR, associations between  $\Delta$ HR and several measures of HRV were not only in the same direction but were also stronger compared with those observed in healthy individuals. The measures showing such changes included (listed as post- and pre-CR respectively): rMSSD ( $r = 0.42$  versus  $0.29$ ), LF ( $r = 0.40$  versus  $0.18$ ), HF ( $r = 0.46$  versus  $0.20$ ), SD1 ( $r = 0.42$  versus  $0.30$ ). A statistically significant correlation was observed between  $\Delta$ HR and SD2 following CR ( $r = 0.52$ ,  $P < 0.05$ ).

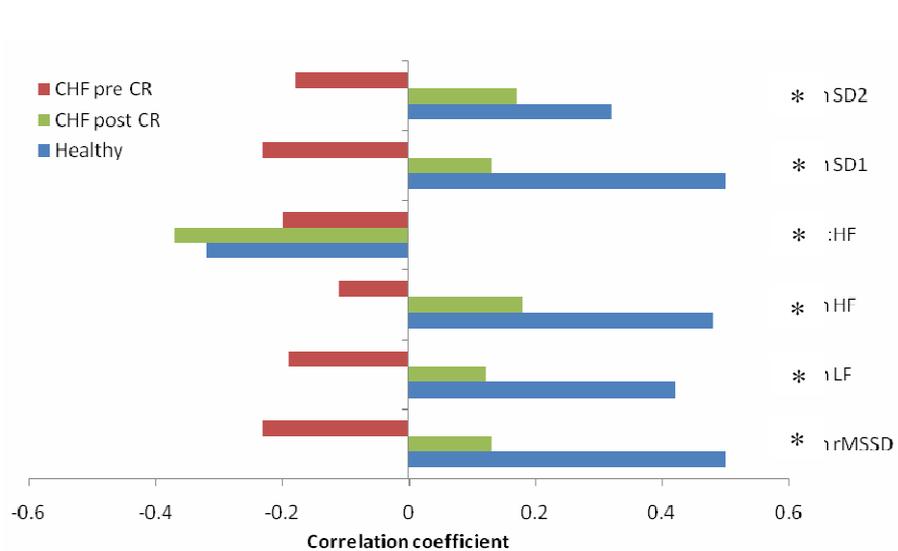
a) Resting HR



b)  $\Delta$ HR



c) HR recovery



**Figure 9-1. Correlation coefficients for measures of heart rate variability with resting heart rate (panel a), change in heart rate at peak exercise (panel b) and heart rate recovery at 1 minute (panel c) before and after cardiac rehabilitation. Correlations in chronic heart failure patients are compared with age matched healthy adults. \*Improved/harmonised relationship.**

9.3.3. *Measures of heart rate variability as predictors of heart rate response to exercise.*

Those measures demonstrating moderate to large associations were entered into regression analysis. There were no moderate associations between any baseline HRV and HR response measures prior to CR. Following CR,  $\Delta$ HR demonstrated a large association (i.e.  $r \geq 0.50$ ) with SD2 and moderate associations with HF power and SD1. To assess the capacity of baseline measures of HRV to predict the outcome values, these parameters were dichotomised according to values for a positive (risk) or negative (no risk) response and then entered in to binary logistic regression analysis. Table 9-2 presents the outcomes of this analysis.

Univariate analysis indicated that SD2, SD1 and HF ln values were unable to predict outcomes for  $\Delta$ HR risk significantly. Because only a small number of patients were assessed due to the use of dichotomised values this may have confounded the non-significant findings. Analysis of the sensitivity and specificity was therefore conducted in light of the non-significant prediction models. Analyses of individual models revealed a similar predictive capacity, with all three HRV measures able correctly to classify 80% of those demonstrating an increased risk (i.e. sensitivity) for  $\Delta$ HR and 60% of those with no risk (i.e. specificity). When combined, a model including SD1 and SD2 was able correctly to classify 80% of patients with either a high or low risk based on  $\Delta$ HR (Table 9-3).

**Table 9-2. Logistic regression predicting  $\Delta$ HR from SD2(ln), SD1(ln) and HF(ln).**

Predictor	<i>B</i>	Wald $\chi^2$	<i>P</i>	Odds ratio
SD2 (ln)	-1.76	1.31	0.183	0.17
SD1 (ln)	-1.15	1.23	0.267	0.32
HF (ln)	-0.96	1.95	0.162	0.38

SD1, standard deviation of points on the short-axis of Poincaré ellipse; SD2, standard deviation of points on the long-axis of the Poincaré ellipse; high frequency spectral power; Wald  $\chi^2$ , Wald Chi-Square statistic; ln, natural logarithm.

**Table 9-3. Sensitivity and specificity of SD1 and SD2 combined in predicting  $\Delta$ HR risk outcomes.**

Observed		Predicted		
		$\Delta$ HR		Percentage correct
		no risk	risk	
$\Delta$ HR	no risk	4	1	80.0
	risk	1	4	80.0
Overall Percentage				80.0

9.3.3. *Grouping patients according to prognostic heart rate values: underlying role of heart rate variability pre and post cardiac rehab.*

Differences in characteristics and dependent measures for participants when grouped according to risk cut-points for resting HR,  $\Delta$ HR and HRR are presented in Table 9-4. Patients were grouped according to tertiles for each measure due to insufficient numbers when patients were grouped according to set cut-points of 75, 89 and 25  $\text{b}\cdot\text{min}^{-1}$  for resting HR,  $\Delta$ HR and HRR respectively.

Pre-CR measures of HRV did not differ significantly between groups based on any of the prognostic HR measures and better HRV was not ascribed to a lower risk for any prognostic HR measure. Group differences were also non-significant post-CR. However, in groups based on  $\Delta$ HR and HRR risk, patients with a lower risk demonstrated a better HRV profile. To assess the meaningfulness of differences, effect size statistics (*d*) were calculated. When assessed in this manner, the largest effects were observed for differences in LF:HF (*d* = -0.96, *P* = 0.20) and SD1 (*d* = 1.00, *P* = 0.20) between patients grouped according the

HRR risk prior to CR and for HF power ( $d = 1.01$ ,  $P = 0.16$ ) and SD2 ( $d = 0.92$ ,  $P = 0.18$ ) for patients grouped according to  $\Delta$ HR risk post-CR.

**Table 9-4. Heart rate variability of chronic heart failure patients grouped according to prognostic cut-off points for pre- and post-cardiac rehabilitation resting, delta and recovery heart rate.**

Test measures	Rest HR tertiles				$\Delta$ HR tertiles				HRR tertiles			
	$\leq 57$ b·min <sup>-1</sup> (n = 4)	$\geq 69$ b·min <sup>-1</sup> (n = 6)	P value	Effect size	$\leq 61$ b·min <sup>-1</sup> (n = 5)	$\geq 78$ b·min <sup>-1</sup> (n = 4)	P value	Effect size	$\leq 14$ b·min <sup>-1</sup> (n = 4)	$\geq 26$ b·min <sup>-1</sup> (n = 6)	P value	Effect size
<b>Analysis pre-CR</b>												
mRR (ms)	1094	849	0.002	4.11	883	1021	0.11	1.22	949	1037	0.14	1.07
Ln rMSSD (ms)	3.78	3.67	0.85	0.12	3.68	3.57	0.80	-0.17	3.37	3.40	0.47	0.49
Ln LF (ms <sup>2</sup> )	5.08	5.63	0.59	-0.27	4.63	4.82	0.86	0.12	5.41	4.55	0.41	-0.55
Ln HF (ms <sup>2</sup> )	5.56	5.59	0.95	-0.02	5.08	5.46	0.62	0.35	5.10	5.34	0.78	0.16
LF:HF	-0.65	0.02	0.20	-0.96	-0.45	-0.65	0.71	0.23	0.12	-0.56	0.18	-0.96
Ln SD1 (ms)	3.50	2.94	0.20	1.00	3.33	3.23	0.80	0.17	3.39	3.05	0.46	-0.49
Ln SD2 (ms)	3.71	4.20	0.25	-0.87	3.84	3.89	0.89	0.09	4.10	3.74	0.40	-0.57
<b>Analysis post-CR</b>												
mRR (ms)	(n = 5)	(n = 5)			(n = 5)	(n = 5)			(n = 6)	(n = 5)		
mRR (ms)	1148	856	0.002	3.01	952	940	0.88	-0.10	972	947	0.74	-0.002
Ln rMSSD (ms)	3.62	3.67	0.94	-0.05	3.11	3.64	0.29	0.73	3.43	3.49	0.90	0.08
Ln LF (ms <sup>2</sup> )	5.12	5.79	0.64	-0.32	4.22	5.29	0.35	0.63	5.02	5.13	0.91	0.07
Ln HF (ms <sup>2</sup> )	5.60	5.52	0.94	0.05	4.38	5.53	0.16	1.01	4.84	5.31	0.57	0.37
LF:HF	-0.52	0.08	0.36	-0.64	-0.27	-0.35	0.90	0.09	0.01	-0.23	0.68	-0.26
Ln SD1 (ms)	3.28	3.30	0.94	-0.04	2.77	3.30	0.29	0.76	3.09	3.15	0.90	0.08
Ln SD2 (ms)	4.03	4.13	0.87	-0.10	3.53	4.11	0.18	0.92	3.86	3.96	0.79	0.17

HR, heart rate; HRR, heart rate recovery; m-RR, mean time between normal r-waves; rMSSD, root mean square of successive differences; LF, low frequency spectral power; HF, high frequency spectral power; nu, normalised units; LF:HF, the ratio of low to high frequency spectral power; SD1, standard deviation of points on the short-axis of Poincaré ellipse; SD2, standard deviation of points on the long-axis of the Poincaré ellipse; Ln, natural logarithm.

## 9.4. Discussion.

### 9.4.1. *Harmony between resting heart rate and short-term heart rate variability in chronic heart failure patients.*

In chapter eight, no statistical associations were observed for changes in HRV measures following 12 weeks CR and indicated no statistical effect of exercise on autonomic modulations. Consideration of the magnitude of differences revealed a role for exercise in providing clinically meaningful and potentially beneficial alterations in the HRV profile of mild-to-moderate heart failure patients.

The assessment of autonomic nervous system (ANS) functions should not, however, be considered on the basis of one index alone. In essence, HRV results from the modulation of the supposedly constant intrinsic heart rate (HR<sub>0</sub>) by the sympathovagal interaction. In clinical situations, measures of HR are used as a marker of the effect of sympathetic and parasympathetic activities due to the fact that HR<sub>0</sub> is unknown. It is often the case that measures of HRV and HR are considered separately but in reality ignoring one whilst assessing the other is not acceptable as these two variables are not independent (Coumel *et al.*, 1995).

Under normal resting conditions, a positive association between measures of HRV and mean RR interval has been observed over 24 h recording periods. Whilst correlations were relatively weak for spectral measures ( $r = 0.46$  and  $0.38$ , LF and HF  $\text{ms}^2$ ), significant associations were considered to reflect a 'physiological harmony' of the ANS functions (Coumel *et al.*, 1994, 1995). The authors considered that strong associations observed in healthy participants may reflect simple redundancy however their deterioration in diseased hearts suggested this was not the cause. The authors also concluded that abnormalities of the ANS functions may not be demonstrated by the analysis of HRV alone (Coumel *et al.*, 1994).

The data of Coumel *et al.* above can be interpreted as a negative association between HRV and HR due the reciprocal nature of the latter with RR interval. In chapter four a similar negative association was observed for commonly used

linear indices of HRV obtained from short-term recordings under controlled conditions.

In a clinical setting, a reduced HR-HRV association has been reported in heart failure patients when compared with healthy counterparts (Coumel *et al.*, 1991). It appears some of the characteristics of the HR-HRV relationships which reflect the physiological harmony of ANS functions are lost in these patients.

Prior to this study, it was unknown if the observations of Coumel *et al.* (1991) were true for the HR-HRV relationship from short-term recordings. The findings revealed a severe alteration of the relationship between HR and resting HRV measures in CHF patients prior to CR. The magnitude of associations was smaller and in an opposite direction from those observed in healthy age matched participants (Table 9-1 and Figure 9-2, panel a). These findings indicate an abnormal association between HRV and HR and confirm that the deterioration of the harmony between ANS function observed previously from 24 h assessments (Coumel *et al.*, 1991) is also present when measures are obtained from short-term recordings.

Although the findings indicate an abnormality in the HR-HRV relationship in HRV, the magnitude of these abnormal associations was none the less approaching large for some measures (e.g. LF and SD1). The reasons as to why a higher HR may reflect a higher value for HRV are likely to be related to the complex abnormalities of autonomic control in HF and the adaptation of the ANS functions to these. In the failing heart there is an augmentation of the sympathetic nervous system (SNS), most likely through baroreceptor perception of decreased ventricular performance. This is characterised by increased plasma catecholamines, a decrease in myocardial catecholamine stores and a reduced sensitivity to beta-adrenergic stimulation resulting from down-regulation of the receptors (Chidsey *et al.*, 1963; Bristow *et al.*, 1982; Mancina 1990). Along with these well documented adaptations to sympathetic control, there is also evidence of a reduction in vagal outflow in heart failure, presenting in these patients a diminished sympathetic inhibitory capacity (Eckberg, 1971; Routledge *et al.*, 2002). When such conditions are prolonged, as in CHF, these initial beneficial

adaptations actually result in adverse longer-term changes to the heart including ino-, hyper-, and chrono-tropic effects that eventually lead to a decreased stroke volume (Mann *et al.*, 1992; Communal *et al.*, 1999). An adaptation function of the ANS is to increase HR in an effort to maintain cardiac output (Coumel *et al.*, 1991). An important statement to make is that the abnormalities outlined here are part of a more complex neurohumoral activation involving several other mechanisms (i.e. the renin-angiotensin, antidiuretic hormone systems). The effect of abnormal function of these systems may play an underlying role in oscillations of HR control, especially at lower frequencies (Task Force, 1996; Moak *et al.*, 2008). As HR and HRV are dependent on the sympathetic and parasympathetic activity to the heart, the adaptations of these in heart failure may explain the abnormal associations observed.

Comparisons with the findings of Coumel *et al.* (1991) are made difficult by the use of different methods to derive HRV. Coumel *et al.* used non-spectral HRV analysis based on quantifying the number and amplitude of short- and long-term HR oscillations (SO and LO) which is an analogue of the power spectrum in the frequency domain. However, this provides measures that behave differently when compared with HR.

#### 9.4.2. *Changes to associations between resting heart rate and heart rate variability following cardiac rehabilitation.*

An additional aim of this study was to re-assess the associations between HR and HRV following a period of exercise CR. Prior to this study, the effect of exercise interventions on this association was unknown. In chapter eight, no significant effects following training were observed for measures of HRV alone. There was a trend for a beneficial effect, however, particular for measures mediated by vagal outflow. The sole use of HRV to identify the efficacy of exercise CR may have missed some important adaptations to cardiac ANS functions. These may be reflected better by changes to the associations between HR and HRV measures.

Following 12 weeks of CR there was a favourable change in correlation coefficients between HR and all measures of HRV so that all associations were

better related to those observed in healthy participants (Figure 9-1, panel a). The magnitude of effects were mixed, with associations for HR with rMSSD and SD2 demonstrating a small change (change in  $r < 0.3$ ) and the remaining measures demonstrating moderate (change in  $r > 0.3 < 0.5$  for HR with LF, HF and LF:HF) to large (change in  $r > 0.5$  for HR with SD1) changes. Perhaps the most important observation was that measures relating to parasympathetic outflow (i.e. rMSSD, HF and SD1) demonstrated not only the largest changes following CR (e.g. HF and SD1), but a negative association for these measures with resting HR, matching those seen in healthy controls, indicates some degree of normalisation of the HR-HRV relationship in these patients (Figure 9-1 panel a).

Data pertaining to the effects of exercise on measures of HRV are reviewed extensively in chapters seven and eight. Detailed discussion will not be repeated here except to mention the following. The consensus regarding the effects of exercise on both 24 h and short-term measures of HRV in cardiac patients is one of a beneficial outcome, particularly for vagally mediated HR modulations (Coats *et al.*, 1992; Adamopoulos *et al.*, 1995; Kiilavouri *et al.*, 1995; Duru *et al.*, 2000; Selig *et al.*, 2004; Dickstein *et al.*, 2008).

Whereas resting HRV is a marker of sympathetic and parasympathetic interactions, resting HR can be considered an indicator of overall autonomic tone (Buchheit *et al.*, 2007). Several studies in healthy participants have documented a resting bradycardia following exercise training that was (Melanson and Freedson, 2001; Tulppo 2003) or was not (Boutcher and Stein, 1995; Davy *et al.*, 1997) accompanied by an improved HRV. In heart failure, the opposite has been shown, whereby increases in HRV were (Adamopoulos *et al.*, 1995) and were not (Coats *et al.*, 1992) accompanied by a significant decrease in resting HR. In chapter eight a decrease of three beats per minute for resting HR was found not to be significant. A similar decrease was shown to be significant by Adamopoulos *et al.* (1995), the likely result of smaller inter-individual variations for this measure in their study. By considering the HR-HRV relationship, the present study demonstrates a positive effect of exercise on the physiological harmony between cardiac autonomic tone and its fluctuations, a finding that

would not have been observed from assessment of HR and its modulations in isolation.

9.4.3. *Associations between resting heart rate variability and the hearts response to exercise before and after cardiac rehabilitation.*

Assessment of the association between resting HRV measures and the HR response during and after exercise was made due to the fact that the latter measures were identified as strong prognostic measures in healthy (Cole *et al.*, 1999; Jouven *et al.*, 2005, Dewey *et al.*, 2007) and cardiovascular diseased patients (Falcone *et al.*, 2005, Evrengul *et al.*, 2006; Leeper *et al.*, 2007). In chapter four, a weak association between resting short-term HRV and the HR response ( $\Delta$ HR) was observed but vagal measures of HRV were significantly and moderately correlated with the HR recovery (HRR) following exercise. Whether this was the case in CHF patients was unknown. Also unknown was the effect of exercise interventions on the relationship of HRV and prognostic HR response measures.

The results for associations between HRV and both the  $\Delta$ HR and HRR before and after CR matched those for the resting HR-HRV relationships. Where a poorer or in fact opposite association with these two HR parameters was shown prior to CR, this was improved in a favourable direction for most measures of HRV (Figure 9-1, panel b and c respectively). For HRR this was particularly true, with associations between all measures of HRV matching in direction those of healthy controls and again indicating a partial normalisation of associations following CR.

A moderate increase in HRR was found not be significant in chapter eight. In the present chapter, however, the change in association between measures of HRV and HRR was meaningful, particularly for LF:HF. It is important to consider the underlying physiology relating to spectral measures and how this may differ in CHF. In normally healthy adults, the LF oscillations are mediated by both sympathetic and parasympathetic outflow (Akselrod *et al.*, 1981) and this is reflected by an LF:HF ratio greater than 1 (Task Force, 1996). Moreover, this is likely to hold true for the physiological range of autonomic drives in healthy

individuals. In cardiovascular disease, LF is likely to reflect the elevated sympathetic influences on the SA node (Coumel *et al.*, 1991) and a decline in value perhaps reflects a decline in this predominance. If accompanied by a reciprocal increase in HF this may indicate a vagal induced suppression of sympathetic outflow. The scenario described here was observed in chapter eight and a vagally mediated decrease in LF:HF could have been implied. Improvements in the relationship of LF:HF with HRR could be interpreted as reflecting an improved harmony between vagally mediated indices of tonic and reflex vagal tone following CR.

However, there is some concern with the utility of the LF:HF ratio, particularly when consideration is not given to the values of absolute measures underlining the ratio and the conditions in which these were obtained. In chapter eight, values for the LF:HF ratio obtained under paced breathing conditions were mediated by a strong change in the LF and not HF component, indicating larger effect on sympathetically/baroreflex and not vagally mediated ANS modulations as suggested by the LF:HF ratio. An interpretation that the improved relationship of this measure with HRR reflects improved harmony between vagally mediated indices of HR control is misleading.

In chapter four a weak association between resting HRV and  $\Delta$ HR was observed and indicated autonomic mechanisms underlying HRV at rest were not well related to the mechanisms underlying HR during exercise. This was supported by evidence of different autonomic modulatory activity during exercise (Sandercock and Brodie, 2006; Dewey *et al.*, 2007). In heart failure patients one would expect an even weaker association between resting HRV and  $\Delta$ HR due to additional effects of a dysfunctional resting autonomic cardiac control. However, this is more likely to be the case if patients demonstrate a severely depressed HRV. The present cohort of CHF patients did not demonstrate an expected depressed HRV (chapter eight). This may have been related to an overall better cardiovascular condition of patients compared to previous studies.

Following exercise an improved association between  $\Delta$ HR and HRV was observed. In the present study,  $\Delta$ HR was calculated as the peak exercise HR

minus resting HR. In chapter eight a small effect on these two measures following exercise was observed (range in  $d = -0.35$  to  $0.20$ ). A lack of response was related to an underestimation of appropriate training intensity. In a similar manner to the HR-HRV relationship, when analysing the association between  $\Delta$ HR and HRV a more efficacious role for the exercise employed is revealed. In fact post-CR, the associations were meaningfully increased to the point where they became significant for SD2. Other measures (SD1 and HF) came close to significance. This presented the idea that these measures may be able to predict the HR response to maximal exercise testing.

#### 9.4.4. *Resting heart rate variability as predictors of heart rate response to exercise.*

In healthy participants ln HF power successfully predicted a negative (low risk) HRR response following a GXT 97 times out of 100 (i.e. specificity of 97%). This measure was, however, only able to predict a high risk HRR correctly in 43% of cases. It is arguably more important to identify a relationship between the response to GXT and resting HRV in CHF patients, where maximal exercise presents a greater risk to adverse cardiac events (Fletcher *et al.*, 2001; Corrà and Piepoli, 2007) and also may become a source of psychological stress. Should strong associations exist, measures of HRV may be able to identify patients for whom knowledge of HR responses to exercise is unlikely to reveal any additional benefit.

Entering SD1, SD2 and ln HF into binary regression analysis revealed that none of these measures were able to predict a high or low risk  $\Delta$ HR significantly (Table 9-2). A lack of significance may be related to the small numbers when grouped for low ( $n = 5$ ) and high ( $n = 5$ ) risk according to dichotomised  $\Delta$ HR. The sensitivity and specificity of SD1, SD2 and HF was therefore calculated to identify the potential for these measures to identify risk response. The highest predictive capacity was observed when measures of SD1 and SD2 were combined, with 80% sensitivity and specificity and overall correct prediction in 80% of cases.

A lower  $\Delta$ HR during GXT predicted a four fold increase in risk of sudden death in healthy participants (Jouven *et al.*, 2005). Increased risk was related to an inability to increase maximal sympathetic drive. SD1 and SD2 are quantitative representations of the underlying patterns in heart rate time series and are synonymous with HF and LF in the frequency domain. These measures are therefore considered to provide an indication of parasympathetic and sympathetic/baroreceptor modulation of beat-to-beat HR (Stein *et al.*, 2005). The significant association between resting SD2 and  $\Delta$ HR post-CR could be related to an improved capacity to increase sympathetic activity to maximum extent.

An increase in peak HR, and concomitant decrease in resting HR, resulted in partial reversal of chronotropic incompetence following six months exercise training in a similar cohort of heart failure patients (Keteyian *et al.*, 1999). Increases in peak HR observed in the present study were small and non-significant. This may have been due to the smaller period of training compared with that of Keteyian *et al.* (1999). Combined with the decrease in resting HR, however, a similar reversal of chronotropic incompetence was observed in the present study (see chapter eight, section 8.2). The improved association with non-linear measures of sympathetic modulations not only supports the notion of an improved capacity to increase sympathetic activity but also strengthens the case for assessment of associations between HR responses and resting HRV and not just measures in isolation.

Although shown not to demonstrate statistical significance, the capacity of these two non-linear indices of HRV to predict low and high risk  $\Delta$ HR warrants confirmation in a larger cohort. The observation of an increased risk for all-cause (relative risk = 5.7) and sudden (relative risk = 6.8) cardiac death in NYHA class II to III heart failure patients with abnormal Poincaré plot (Brouwer *et al.*, 1996) and strong associations with mortality for an increase in their ratio (SD12, Stein *et al.*, 2005) supports this notion. These measures could be providing the same information as that provided by a poor  $\Delta$ HR response and therefore make redundant the need for its determination from a potentially harmful GXT in susceptible populations.

9.4.5. *Underlying role of heart rate variability for increased risk based on resting and exercise heart rate response.*

The finding in chapter four of higher values of resting HRV underlying a lower risk profile based on prognostic HR measures was related to healthy participants. Many of the thresholds for these HR measures were originally identified in populations that included patients with cardiovascular disease (Cole *et al.*, 1999; Jouven *et al.*, 2005; Leeper *et al.*, 2007). Whilst some healthy participants demonstrated an increased risk, the risk is considerably smaller compared with when heart failure patients demonstrate the same high risk HR responses. Prior to this study, there were no data as to the underlying role of HRV for heart failure patients demonstrating increased risk based on the resting and HR response to exercise. The effect of exercise training on this role was also unknown.

In CHF patients prior to a 12 week CR programme resting HRV did not differ between low and high risk groups based on dichotomised cut-points for resting HR,  $\Delta$ HR and HRR. Moreover, where differences were observed, these were not consistent for any one group (Table 9-4). Post-CR, there was a change in this finding, whereby those with greater risk for  $\Delta$ HR and HRR measures all demonstrated a non-significant but lower HRV. Parasympathetic mediated measures demonstrated the largest effects for HR responses most influenced by its activity (e.g. HRR). In CHF, a decreased HRV is an accepted indication of the decreased vagal outflow to the heart (Coumel *et al.*, 1995). In both animals and humans, vagal stimulation reduces susceptibility to ventricular fibrillation, particularly when sympathetic tone is high (DeFerrari *et al.*, 1992; Hull *et al.*, 1994). Intervention to increase cardiac vagal activity, particularly when sympathetic tone is heightened, may represent a method of reducing occurrence of sudden cardiac death (Routledge *et al.*, 2002). A move towards more favourable parasympathetic predominance of resting HR modulations in CHF patients demonstrating lower risk for parasympathetic mediated HR responses may underline the associated reduced risk (Jouven *et al.*, 2005).

Caution should be exercised when extrapolating improvements in parasympathetic modulation activity to a reduced risk from sudden death. Evidence from animal studies demonstrated that protection from ventricular

fibrillation was not solely a function of increased cardiac vagal activity in dogs (Billman *et al.*, 2006). In humans, dissociation between vagally mediated HRV measures and a resting bradycardia (indicative of a heightened parasympathetic tone) following exercise training has been reported in healthy populations (Sandercock *et al.*, 2005). Prolonged exercise, on the other hand, may present conditions where resting bradycardia is underlined by increased vagal modulations (Sandercock *et al.*, 2005). Whether this can be extrapolated to CHF populations and have a beneficial effect on risk from arrhythmic and sudden cardiac death requires further study.

In chapter four, a lower power in the LF spectrum was observed in healthy participants demonstrating a higher risk for  $\Delta$ HR. A greater sympathovagal function was hypothesised to prevent or minimise a possible circulatory collapse that may occur in participants demonstrating impaired baroreflex sensitivity (Jouven *et al.*, 2005). In the present study, there was an increase in the difference between values for SD1 and SD2 in low versus high risk patients for  $\Delta$ HR. These non-linear measures represent sympathetic/baroreceptor and vagal modulations of HR. An exercise related improvement in sympathovagal measures may present a degree of autonomic function more reminiscent of healthy participants and may present these patients with a greater capacity to minimise circulatory collapse during exercise as hypothesised by Jouven *et al.*

## **9.5. Limitations/Recommendations.**

Many of the limitations to the methodology employed in the present study are discussed in chapter eight (section 8.5).

Perhaps the biggest limitation specific to this chapter is the use of data combined from two groups undergoing different CR programmes. Although in chapter eight no significant differences in the response to exercise were observed between groups, there were trends for opposing effects. This may have confounded the associations observed in the present study. Equally, moderate and almost large associations observed suggest assessing autonomic function in

this manner offers a more robust measure. Any additional studies to confirm the trends observed in chapter eight should also consider the effect of differing modes of exercise on the association between HR and HRV measures. Also, and as highlighted in chapter eight, such studies should include a non-exercising control group so that effects be better ascribed to exercise training.

Non-linear Poincaré measures were shown to demonstrate the strongest association with HR responses to exercise and also perhaps play a role in distinguishing between patients with a higher risk HR response profile. Malik (1995) indicates that a substantial number of RR intervals are required to determine a valid Poincaré plot and that in practice this implies RR interval recordings of 20 minutes or more. Moreover, error-free RR interval sequences are a required necessity. In the present study, error free series were provided by the automated RR filtering feature of the Polar S810 software but measures were obtained from 5 minute recordings. Measures of SD1 and SD2 may therefore not represent the true condition of autonomic modulatory activity. A longer recording period may afford better definitions and inference from these measures. This however has implications for clinical settings where longer recordings may be unrealistic in clinical practice.

Recently in healthy adults, a decline in LF:HF was associated with a decline in the number of patients with increased cardiovascular disease risk factors (Stein *et al.*, 2009). Whether this is the same for the association between the LF:HF ratio and prognostic measures of HR is unknown. Indeed, the role of associations between HR and short-term measures of HRV as predictive of increased risk and/or prognosis is yet to be determined.

## **9.6. Conclusions.**

These findings imply that prior to cardiac rehabilitation, the normal association between HR and short-term HRV is altered in CHF patients. Following 12 weeks exercise based cardiac rehabilitation, there is a reversal of this alteration and favourable changes in associations indicated partial normalisation of the HR-

HRV relationship. Associations between non-linear measures representing sympathovagal modulations and the peak HR response to maximal exercise were improved after CR and suggest a potential role for resting HRV to predict the HR response to exercise in patients with a more normal association between autonomic indices. When assessing the efficacy of exercise based CR on autonomic function, consideration of the associations between both tonic (HR) and reflexive (HRV) indices can provide useful information that may not be apparent from assessment of these autonomic markers alone. Whether an improvement in the association between these indices affords an improved outcome and reduced risk in CHF patients requires further study.

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## **CHAPTER 10. THE IMPACT OF BRIDGING TO RECOVERY USING IMPLANTABLE LEFT VENTRICULAR DEVICES ON HEART RATE VARIABILITY IN SEVERE HEART FAILURE PATIENTS.**

### **Abstract.**

Autonomic dysfunction is common in dilated cardiomyopathy (DCM), with chronic activation of the sympathetic nervous system and greatly reduced reactivity to both sympathetic and vagal stimuli. This is implicated in both worsening pump function and in arrhythmogenesis. Bridging patients to recovery with a combination of a left ventricular assist device (LVAD) and pharmacotherapy leads to reversal of structural and electrical remodelling. The extent to which autonomic function is normalized in these patients is not known. Heart rate variability (HRV) provides a non-invasive measure of autonomic modulation.

HRV was measured in 20 explanted LVAD patients ( $814 \pm 607$  days post-explantation, age  $36 \pm 10$  years, 15 men) 17 implanted LVAD patients ( $33 \pm 10$  years, 16 men), 23 NYHA III – IV classified chronic heart failure (CHF) patients ( $42 \pm 12$  years, 14 men) and from ten healthy, age and sex-matched controls (age  $37 \pm 12$ , 8 males) in three conditions: supine free breathing, standing and supine controlled breathing at  $12 \text{ breaths}\cdot\text{min}^{-1}$ . The standing condition represents orthostatic challenge, evoking sympathetic response in healthy subjects whereas controlled breathing increases vagal modulation. Differences between groups and conditions were assessed for the following measures: mean RR interval (mRR), high frequency spectral power (HF, a measure of vagal modulation), low frequency spectral power (LF, a sympathetic and baroreceptor mediated measure), normalised low frequency spectral power (LFnu, a measure of sympathetic modulation) and the ratio of low to high frequency spectral power (LF:HF, a measure of sympathovagal balance).

ANOVA showed significant ( $P < 0.05$ ) differences between supine, standing and controlled breathing conditions within each group. However, no significant differences were seen between explanted, implanted and control groups for any condition. Values were significantly lower for CHF patients in all conditions compared to controls. When visual representation of known HRV risk factors

were analysed, all showed normalisation in explanted patients and a partial normalisation in implanted patients. Patients explanted following myocardial recovery demonstrate a lower HRV risk profile.

## 10.1. Introduction.

In chapter seven findings of a restoration in heart function of severe chronic heart failure (CHF) patients inserted with a left ventricular assist device (LVAD) were presented and reviewed. Unloading of the myocardium was shown to reverse the remodelling that occurs in the failing heart as a means to maintain cardiac output.

Originally used as a 'bridge-to-transplantation', recent evidence has shown that patients implanted with an LVAD, combined with optimal pharmacology, demonstrated an improved functional status, quality of life and greater survival rates in severe CHF patients inserted with an LVAD (Birks *et al.*, 2007; Miller *et al.*, 2007). Recovery was sufficient enough to allow removal (explant) of the LVAD in 73% of one patient cohort, with no deaths observed in any LVAD patient and a 4 year freedom from recurrent heart failure of 89% (Birks *et al.*, 2007).

It was highlighted in chapter seven (section 7.1.5.4) that despite a large body of literature concerning the role of autonomic measures as risk factors in CHF, no published data exists concerning changes or normalisation of invasive (cardiac noradrenaline spillover) or indirect (heart rate variability) measures of autonomic balance in patients receiving LVAD combination therapy.

### 10.1.1. *Justification.*

Autonomic control and therefore, heart rate variability are greatly disrupted in severe heart failure patients. Many measures of HRV are strong independent multivariate risk factors for all cause mortality and sudden cardiac death (Guzzetti *et al.*, 2005; Sandercock and Brodie, 2006). Autonomic disturbances may be altered via pharmacotherapy, surgical interventions and in less severe cases, by exercise training. In severe heart failure, it appears that unloading of the left ventricle, combined with optimal pharmacotherapy may allow cardiac reverse modelling. Unloading of the left ventricle is achieved by the implanting of an external device used to assist the left ventricle during systole. There are, however, no data at present which assess the impact such an intervention may

have on autonomic control. Should such an intervention improve autonomic function, this may lead to a decrease in the risk of further cardiac events and/or sudden cardiac death.

#### *10.1.2. Aims.*

To assess the impact of ‘bridging-to-recovery’ by the use of an implantable left ventricular assisting device (LVAD) on heart rate variability measures in patients previously diagnosed with end stage heart failure.

#### *10.1.3. Hypothesis.*

H<sub>0</sub>. Autonomic control of the heart will be improved in chronic, severe heart failure patients treated with an LVAD as a result of cardiac reverse modelling.

H<sub>1</sub>. Autonomic control of the heart will not be improved in chronic, severe heart failure patients treated with an LVAD, regardless of cardiac reverse modelling.

### **10.2. Methods.**

#### *10.2.1. Patients.*

Heart rate variability was assessed in 23 explanted LVAD patients, 24 currently implanted patients, and 38 patients with severe CHF. Ten healthy, age and sex-matched controls were also assessed. A number of patients demonstrated unstable SA rhythms that prevented RR interval recordings; these included three explanted, seven implanted and fifteen CHF patients. HRV data were, therefore, obtained in 20, 17 and 23 patients from each of these groups respectively. Of the explanted patients, the LVAD model implanted previously was either a HeartMate 1 (n = 12), a HeartMate 2 (TCI HeartMate VE, ThermoCardiosystems/Thoratec Laboratories Corporation, Pleasanton, CA, n = 6) or a Jarvik 2000 (Jarvik Heart Inc. NY, USA, n = 2). All LVAD patients had only been implanted once but one had received additional right ventricular assistance from a Thoratec VAD (Thoratec Laboratories Corporation,

Pleasanton, CA.). In all but five explanted patients, the original diagnosis was idiopathic dilated cardiomyopathy (IDCM). Three of the explanted patients were originally diagnosed with peripartum cardiomyopathy and one was diagnosed with myocarditis. Of the currently implanted patients, the LVAD model implanted was either a HeartMate 1 (n = 3), HeartMate 2 (n = 8), Jarvik 2000 (n = 3) or Thoratec (n = 3). All but five implanted patients also had IDCM; the remainder suffered ischaemic heart disease (IHD, n = 3), myocarditis (n = 1) and peripartum cardiomyopathy (n = 1). In CHF patients, 10 were diagnosed with IDCM, four with peripartum cardiomyopathy, five with myocarditis and three were diagnosed with ischaemic heart disease. Further anthropometric, physiological and pharmacological data are displayed in Table 10-1.

The control group were matched for age and sex with the explanted LVAD patient group. All controls were either sedentary or moderately physically active. None had history of cardioneuroregulatory disorders and none were taking any prescribed medication, with the exception of oral contraceptives, at the time of testing. Due to the oligomenorrhoeic nature of the female CHF patients studied, no control for menstrual cycle was made in these patients or in female controls.

#### 10.2.2. *Instrumentation.*

Two lead ECGs were recorded using two commercially available HRV analysis systems which have been described in detail both elsewhere (Sandercock et al., 2004) and in chapters two and three of this thesis. The first system was the TF5 heart rate variability analysis system (Advanced Medical Diagnostics Ltd., Leeds, UK). The second was a Polar S810 heart rate monitor (Polar OY, Kempele, Finland). In the first system the commercial HRV software was used for the analysis via fast Fourier transformation. In the second instrument, data were transferred to PC for storage as a .txt file and analysed *post hoc* using the package, Software for Advanced Heart Rate Variability Analysis 1.1 (University of Kuopio, Finland). When obtained in this manner, HRV data were found to demonstrate the same level of reliability in CHF patients as that observed in healthy participants (see chapter six). These systems also fulfil the criteria set out regarding sampling rates, conversion rates and mathematical treatment of data

for the measurement of ECG data suitably accurate for HRV analysis (Task Force, 1996). The reason for the use of two systems was as a safety measure to ensure that no data were lost and that testing did not have to be repeated on any patients. This was of particular importance due to the small overall number of patients involved in the study and the fact that many were outpatients who attended the hospital LVAD clinic only sporadically.

### *10.2.3. Protocol.*

After fitting the patients with both HRV recording systems in accordance with the manufacturers' instructions, 5 min RR interval recordings were made in three conditions: supine free breathing, standing and supine controlled breathing at 12 breaths·min<sup>-1</sup>. The supine condition was used as a baseline measure of resting autonomic modulation. The standing condition was used to represent orthostatic challenge, known to evoke sympathetic responses in healthy subjects. The controlled breathing condition was used to stimulate vagal modulation of the SA node. The TF5 was used as the reference system to which S810 recordings were synchronised.

#### 10.2.3.1. Heart rate variability analysis.

All RR interval data were filtered using the automated algorithms available in the software of both systems. Additionally the manual ECG analysis and beat rejection-interpolation in the TF5 was used by a single, experienced researcher. The resultant time series of RR intervals from the Polar system was plotted as a tachogram and also manually edited for obvious aberrant beats and/or movement artefacts by the same researcher.

All HRV measures recommended for use during short-term data collection were calculated (Task Force, 1996). These measures were, in the frequency domain: high frequency spectral power (HF, 0.15 - 0.40 Hz), low frequency spectral power (LF 0.04 - 0.15 Hz) normalised low and high frequency spectral power (LFnu, HFnu), and the ratio of low to high frequency spectral power (LF:HF). In the time domain, mean RR interval, standard deviation or normal to normal

intervals (SDNN) and the root mean square of successive interval differences (rMSSD) were measured.

#### 10.2.4. *Data analysis.*

Two-way mixed (group by position) analysis of variance was used to determine whether differences between conditions (position) and between the controls, CHF, implanted and explanted patients (group) existed. Analysis was carried out on HRV measures representative of sympathetic and baroreceptor mediated modulation (LF), vagal modulation (HF), relative sympathetic predominance (LFnu) and sympathovagal balance (LF:HF) and RR interval to reduce the number of repeated comparisons made. No correction for alpha was made. A value of ( $P < 0.05$ ) was considered significant.

Further, non-statistical comparisons were made by comparing mean ( $\pm$  SD) levels of significant risk factors reported previously (Malfatto *et al.* 2002; La Rovere *et al.* 2003) with values obtained for CHF patients, explanted patients, implanted patients and for comparison, control subjects. This visual analysis was designed to describe and evaluate the changes observed at different points during 'bridging-to-recovery' in comparison with heart failure patients and healthy individuals.

## 10.2 Results.

Table 10-1 provides the descriptive characteristics of the implanted, explanted and CHF patient groups. The implant and explant patients were similar in terms age and most anthropometric measures, disease aetiology, NYHA class and echocardiographic measures. The CHF group were slightly older, had a higher NYHA class and a greater number of patients with IHD cardiomyopathy and myocarditis as underlying aetiology of disease. Some differences in pharmacotherapy existed between groups, particularly in the frequency of clenbuterol use between groups.

**Table 10-1. Descriptive characteristics of chronic heart failure, implanted and explanted LVAD patients.**

	CHF	Implanted	Explanted
N =	23	17	20
Males/Females	13/9	16/1	15/5
Age (years)	42.3 ± 12.1	32.8 ± 10.2	36.3 ± 10.0
Time from explant/implant/diagnosis (days)	1291 ± 1577	184 ± 136	814 ± 607
Mass (kg)	82.1 ± 19.5	78.7 ± 19.4	87.4 ± 23.9
Stature (cm)	168.6 ± 11.4	180.4 ± 8.5	176.9 ± 12.2
BMI (m <sup>2</sup> .kg)	29.0 ± 7.7	24.0 ± 4.8	27.6 ± 5.3
BSA (m <sup>2</sup> )	1.93 ± 0.48	1.98 ± 0.55	2.18 ± 0.70
NYHA class	3.3 ± 0.7	1.8 ± 0.7	1.1 ± 0.3
Pre-op EF (%)	n/a	18.8 ± 11.4	17.3 ± 8.1
LVEF at time of test (%)	39.5 ± 14.2	47.8 ± 9.4	63.3 ± 12.3
Aetiology (number):			
IDCM	10	12	15
IHD	5	3	1
MYO	3	1	1
PP	4	1	3
Clenbuterol treatment (%)	0	25	100
Clenbuterol at time of test (%)	0	6	0
Digitalis (%)	27	38	100
β-blockers (%)	64	87	87
ACE-inhibitors (%)	27	62	100
ARB (%)	58	62	87
Spirolactolone (%)	41	50	62
Other (%)	60	87	38

BMI, body mass index; BSA, body surface area; LVEF, left ventricular ejection fraction; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; IDCM, idiopathic dilated cardiomyopathy; ICM, ischaemic heart disease; MYO, myocarditis; PP, peripartum cardiomyopathy; All pharmacological data refer to whether patients were prescribed the drug type at time of HRV measurement except clenbuterol treatment which refers to whether the patient had ever received clenbuterol.

*10.3.1. Comparison of heart failure and implanted and explanted LVAD patients with healthy controls.*

Table 10-2 shows the changes in RR interval, the vagal measure of HF power (in log units, ln), the sympathetic measure of LFnu and LF:HF, a measure of

sympathovagal balance under three conditions in all four subject groups. These were: lying supine (baseline), standing (sympathetic activation) and controlled breathing (vagal activation).

Repeated measures ANOVA showed significant ( $P < 0.05$ ) differences between all three conditions within groups. No significant differences were observed for RR interval, LF(ln), HF(ln) and LFnu between implanted, explanted and control groups. Values in the CHF group were significantly lower compared with the explanted group for LF(ln) ( $P < 0.01$ ) and HF(ln) ( $P < 0.05$ ) and also the control group for LF (ln) ( $P < 0.001$ ), HF(ln) ( $P < 0.05$ ) and LFnu ( $P < 0.01$ ). Due to heterogeneous variances and non-normal distributions which could not be modified successfully by transformation, LF:HF was analysed using repeated non-parametric Kruskal-Wallis tests ( $n = 4$ ) between values in each condition. This analysis revealed significantly lower LF:HF in the CHF group compared with the implanted ( $P < 0.01$ ) and control ( $P < 0.05$ ) groups.

**Table 10-2. Values for mean RR interval, vagal modulation, relative sympathetic modulation and sympathovagal balance under three conditions in controls, implanted and explanted LVAD patients.**

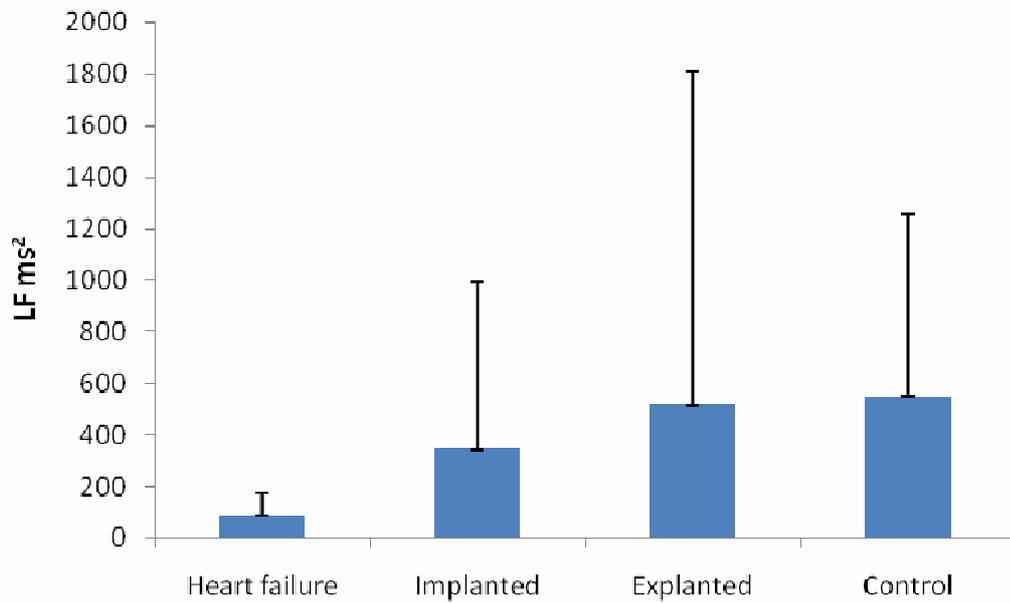
	CHF	Implanted	Explanted	Control
Measures obtained supine				
RR(ms)	911 ± 319	804 ± 132	878 ± 111	958 ± 123
LF (ln)	4.19 ± 1.72	4.99 ± 1.36	5.60 ± 1.49	6.26 ± 1.63
HF(ln)	4.08 ± 2.13	4.19 ± 1.42	5.40 ± 0.92	5.48 ± 1.28
LF(nu)	52 ± 23	68 ± 15	63 ± 25	66 ± 17
LF:HF	1.9 ± 1.9	3.2 ± 3.2	2.6 ± 3.5	3.3 ± 3.8
Measures obtained standing				
RR(ms)	759 ± 144	694 ± 82	763 ± 78	795 ± 81
LF (ln)	3.85 ± 1.13	4.78 ± 1.36	4.69 ± 1.20	6.04 ± 1.21
HF(ln)	3.54 ± 1.86	3.74 ± 1.47	3.66 ± 1.14	4.23 ± 1.39
LF(nu)	56 ± 25	74 ± 20	74 ± 17	85 ± 5
LF:HF	2.5 ± 2.7	5.3 ± 5.2	4.7 ± 5.1	7.3 ± 5.8
Measures obtained supine with controlled breathing				
RR(ms)	858 ± 210	770 ± 121	890 ± 97	978 ± 113
LF (ln)	3.57 ± 1.60	4.82 ± 1.17	5.36 ± 1.50	5.59 ± 1.58
HF(ln)	4.54 ± 2.39	4.58 ± 1.50	6.13 ± 1.36	5.57 ± 1.24
LF(nu)	32 ± 25	56 ± 21	42 ± 24	50 ± 23
LF:HF	0.9 ± 1.4	1.8 ± 1.4	1.3 ± 0.92	1.6 ± 1.5

All data Mean ± SD; CHF, chronic heart failure; LF, low frequency spectral power; HF, high frequency spectral power; RR, mean RR interval; ms, milliseconds; ln, natural logarithm; nu, normalised units;

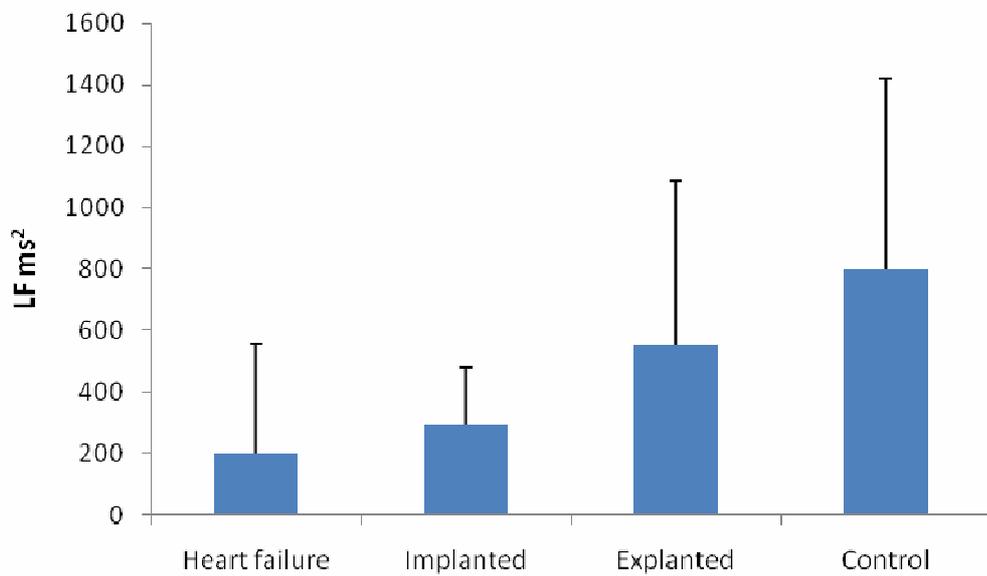
*10.3.2. Comparison of implanted and explanted LVAD patients with healthy controls and heart failure patients.*

Figure 10-1 provides a visual analysis of the power in the LF band recorded under controlled breathing conditions (significant multivariate risk factor) from CHF patients, implanted patients, explanted patients and age-sex matched controls recorded under free breathing conditions. Values for implanted and explanted LVAD patients are clearly much greater than those of CHF patients but not as high as those of the healthy controls. Figure 10-2 shows power in the LF band recorded supine, without controlled breathing. There is a similar pattern to that demonstrated in Figure 10-1. Values for LF are greater in explants and

implanted patients than CHF patients. Again these values remain attenuated when compared with those of healthy controls.

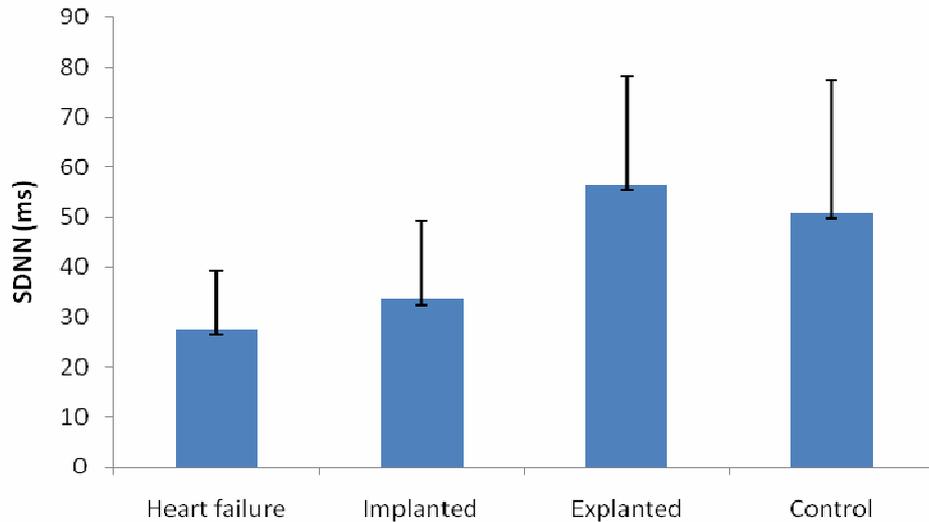


**Figure 10-1. Between-group differences in low frequency spectral power measured supine with controlled breathing.**

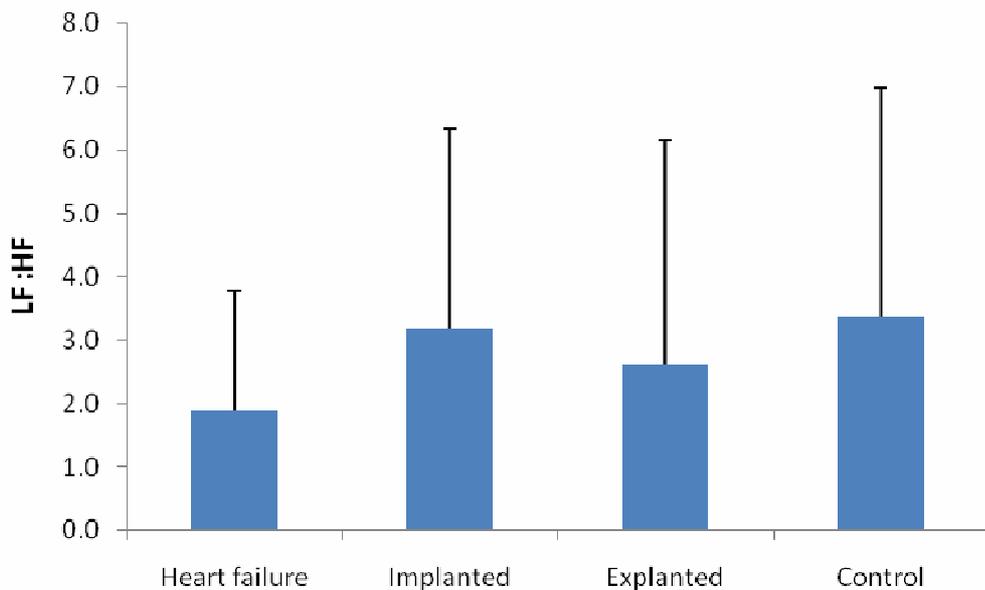


**Figure 10-2. Between-group differences in low frequency spectral power measured supine under conditions of free respiration.**

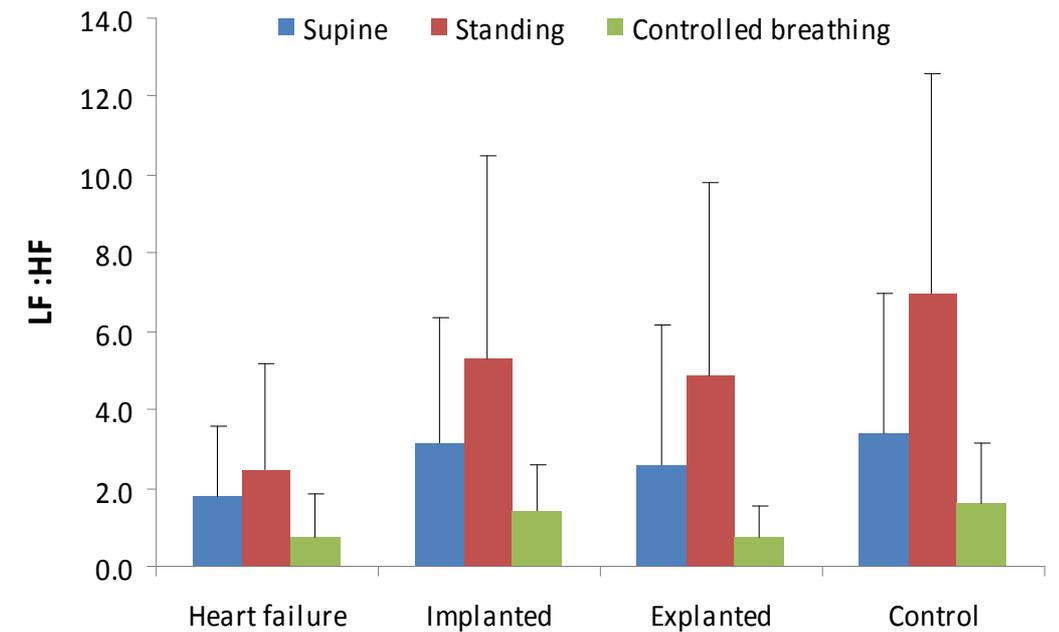
Figure 10-3 provides visual representation of SDNN (significant univariate risk factor in CHF) recorded with the subject supine under free breathing conditions. Mean SDNN for explanted patients is slightly greater than that of healthy controls and shows similar distribution. The mean SDNN for implanted patients was slightly attenuated compared with controls and explants but was higher than that of CHF patients.



**Figure 10-3. Between-group differences in the standard deviation of normal to normal intervals measured supine under conditions of free respiration.**



**Figure 10-4. Between-group differences in the low frequency to high frequency spectral power ratio measured supine under conditions of free respiration.**



**Figure 10-5. Between-group differences in change in LF:HF (arbitrary units) measured supine, standing and with controlled breathing in CHF patients, implanted and explanted LVAD patients and healthy controls.**

Figure 10-4 shows the mean values for LF:HF ratio measured supine under free breathing conditions. Values for implanted LVAD patients and controls are very similar. Explanted patients had lower values for LF:HF ratio than implants and controls. LF:HF in explants was not, however, as low as in CHF patients.

Figure 10-5 shows the response to sympathetic (standing) and vagal (controlled breathing) activation for all four groups. Direction and magnitude of change in implanted, explanted and control groups are similar throughout the three conditions. All measures of LF:HF demonstrated a much lower response in the CHF patients compared with the implanted and explanted patients.

#### **10.4. Discussion.**

The primary aim of this chapter was to assess the impact of bridging-to-recovery in a population of patients previously diagnosed with end stage heart failure. It is known that unloading the myocardium results in reversal of many haemodynamic and structural properties of the failed heart (Birks *et al.*, 2007)

but no study of non-invasive cardiac autonomic regulations has ever been made. The main finding of this chapter is that unloading of the myocardium using an implantable left ventricular assisting device (LVAD), combined with optimal pharmacotherapeutic intervention results in HRV profiles in explanted and implanted patients that do not differ significantly from those of healthy age-matched controls.

There are numerous published reports of derangements in autonomic function in heart failure patients. These derangements have been shown to manifest themselves as altered HRV profiles in this group. There is some disparity as to the exact appearance of the typical (or indeed atypical) HRV profile of a CHF patient. In the time domain, studies uniformly report lower values for global values (SDNN, HRV index), vagal markers (rMSSD, pNN50) and values indicative of slow oscillations in heart period (SDANN) (van de Borne *et al.*, 1997; Beckers *et al.*, 2002). Similarly, in the frequency domain, absolute measures (in  $\text{ms}^2$ ) of LF and HF are both greatly reduced compared with controls as are slower oscillations (VLF and ULF) (Bonaduce *et al.*, 1999; Lucreziotti *et al.*, 2000; Aronson *et al.*, 2004). In regard to relative measures it seems that very low levels of LF, which can be represented as low LF in normalised units (LFnu) or more commonly low LF:HF ratio, indicates an increased risk of sudden cardiac death (SCD) and death due to pump failure (Madsen *et al.*, 1997; La Rovere *et al.*, 2003; Guzzetti *et al.*, 2005). The importance of the latter findings will be discussed in context to the present study below.

Slow oscillations can only be measured over long (usually 24 h) ECG recording periods and are known to be strongly influenced by mean heart rate, overall level of and variation in physical activity (Bernardi *et al.*, 1996). Few data are available concerning the validity of LF and HF from ambulatory data, in fact there are no pharmacologically validated studies to suggest what the meaning of LF and HF values recorded over 24 h are in terms of autonomic modulation. It is commonly postulated that these values represent mean levels of mixed sympathovagal and vagal SA node modulation respectively. This is, however, generalised from findings using controlled, resting data collection under various

combination of vagal and sympathetic pharmacological blockade (Pagani *et al.*, 1986).

Using 24 h ECG recordings, many HRV measures have been identified as risk factors for all cause mortality and particularly sudden cardiac death. Many of these are long term measures of slow oscillations and therefore, could not be measured using the methodology employed here. However, low SDNN, LF power, and LF:HF ratios, which repeatedly show themselves to provide poor prognosis in CHF patients were measured here. The prognostic significance of these measures has been shown regardless of whether they were derived from ambulatory or resting ECG measurements (La Rovere *et al.*, 2003, Lahiri *et al.*, 2008). The robustness of these measures in predicting the number of negative outcomes regardless of data collection technique may indicate that they are potential therapeutic targets for treatment in CHF patients. Therefore, any intervention aimed at improving prognosis in this population should aim to reverse the derangement of these values, making them more approximate to values recorded in 'normal' healthy controls.

#### *10.4.1. Comparison of explanted LVAD patients with healthy controls and chronic heart failure patients.*

To increase the validity of any comparisons made, only short-term HRV measures previously shown to hold significant prognostic value in CHF were compared between groups. Specifically, these risk factors, are: LF (measured using controlled breathing), LF (measured supine), LF:HF ratio and SDNN (supine) (La Rovere *et al.*, 2003).

A low level of LF ( $\text{ms}^2$ ) under controlled breathing is the only HRV measure previously reported as an independent, multivariate risk factor in CHF (La Rovere *et al.* 2003). Figure 10-1 shows clearly, that levels of LF are much greater (~10 fold) in the explanted group compared with those of CHF patients. The LF in explanted patients also compares favourably to values ( $< 100 \text{ms}^2$ ) observed in the CHF patient cohorts of La Rovere *et al.* (2003) and Malfatto *et al.* (2002). Table 10-2 shows that explants and controls do not differ significantly

from one another in terms of LF recorded under controlled breathing. This is mainly however, due to the very wide distribution of scores in the controls. Despite the log-transformation of LF scores prior to statistical analysis to abide by the assumptions underlying parametric statistics, a wide kurtosis in the controls and relatively small subject numbers in both groups reduce the discriminant power of the test used. By not relying on statistical significance and instead, observing the mean values and distributions in Figure 10-1 the following pattern is obvious: that LF power in the explanted group is not completely normalised when compared with age and sex matched controls. It is however, much closer to those of the healthy control population than the mean value reported for the CHF patients here and for survivors and non-survivors in previous studies (Malfatto *et al.*, 2002; La Rovere *et al.*, 2003). It seems safe to assume that the large difference of the magnitude ( $d = 1.16$ ) seen between the CHF patients and the explanted patients here is a meaningful one.

When measured under normal resting conditions (free breathing), LF is also a significant univariate risk factor (La Rovere *et al.*, 2003). Similarly to the previous discussion, values for LF were not different between explants and controls and indeed Figure 10-2 shows the degree to which this values appears to have been 'normalised' in the explanted group. The mean value for LF is much closer to that of the control group than it is to those of the CHF patients.

This pattern of normalisation is continued in the values of other univariate risk factors. Values for SDNN are very similar between explants and controls which are in turn, more than twice those of CHF patients. SDNN is a global, time domain measure of HRV. As it gives information about only the gross variation around the mean heart rate (standard deviation) in the recording period the relative contribution of sympathetic and/or vagal modulation in creating this variability is not possible to determine. Nevertheless, the fact that low levels of SDNN are risk factors for a number of future adverse events in CHF and the fact that this relationship is maintained regardless of data collection technique (ambulatory or controlled) likely makes the 'normalisation' of this value a clinically significant finding.

In contrast to SDNN, it has been proposed that a great deal of information regarding interaction of both branches of the ANS on the SA node can be gained from the ratio of LF to HF spectral powers. The almost exclusively vagal genesis of oscillations within the HF band, combined with the mixed sympathetic and vagal activities which contribute to oscillations in the LF band have meant that assessment of the relative contribution of these measures make to total power can give information on what has come to be termed sympathovagal balance (Pagani *et al.*, 1991; Pagani *et al.*, 1986; Janssen *et al.*, 1993; Montano *et al.*, 1994; Introna *et al.*, 1995; Pagani *et al.*, 1995; Eckberg, 1997; Goldberger, 1999; Malfatto *et al.*, 2001; Uusitalo *et al.*, 1996).

In healthy subjects, mental and physiological stimuli known to increase sympathetic activity and/or induce vagal withdrawal such as head up tilt (Furlan, 1987; Iwase *et al.*, 1987; Jasson *et al.*, 1997; Laitinen *et al.*, 2004; Yoshiuchi *et al.*, 2004) or mental stress ( Pagani *et al.*, 1991; Pagani *et al.*, 1995) increase the LF:HF ratio. A higher (or relatively higher) LF:HF has therefore, been used to represent higher levels of sympathetic SA node modulation. As mentioned previously (see chapter seven), in CHF patients, who commonly show vagal withdrawal and sympathetic overactivity (Leimbach *et al.*, 1986; Kienzle *et al.*, 1992; Nolan *et al.*, 1992; Floras, 1993; Kingwell *et al.*, 1994; Mortara *et al.*, 1994; Guzzetti *et al.*, 1995; Burger and Aronson 2001;) LF:HF is actually very low, due to three contributing factors.

- 1 The large reductions in TP seen in all frequency bands.
- 2 The attenuation of oscillations in heart period within the LF band which have an almost purely nervous genesis.
- 3 The relative preservation of power in the HF band due to its combined neural (vagal), intrinsic (Bernardi *et al.*, 1990) and mechanical (respiratory) genesis (Chess *et al.*, 1975).

Values for LF:HF which are so different from the populations in which the measures use has been examined and validated (healthy subjects) make physiological interpretation of this measure difficult. Other factors, such as physiological meaning of absolute values (particularly the LF spectral component) and pharmacological determinants have been discussed previously

and serve only to further complicate this paradox. Regardless of the ‘meaning’ of low LF:HF, it has been identified as a risk factor both in studies using ambulatory data collection (Bonaduce *et al.*, 1999) and when derived from short-term, controlled ECG recordings (La Rovere *et al.*, 2003).

Figure 10-4 shows that the LF:HF ratio, recorded under resting conditions, was more similar between explants and controls compared with values reported for CHF patients. Values were also compared statistically between explants and controls. There were no differences in LF:HF levels recorded during in any of the three conditions. In fact there is good congruence between LF:HF values and changes in these values in the two groups (Table 10-2 and Figure 10-5). Values for LF:HF increased from baseline when the explanted patients stood (orthostatic sympathetic activation) and the values decreased during supine controlled breathing (vagal activation). The response of LF:HF was underpinned by a large decrease in HF during the standing condition and a concomitant increase in the same measure during controlled breathing conditions. The values for supine LF:HF and its reactivity to autonomic stimuli appear, therefore to have become normalised in the explanted patients. This appears to have been mediated by an increased basal vagal outflow and improvement in its reactivity.

Few short-term HRV data are available on CHF patients receiving  $\beta$ -blocker and ACE inhibitor therapy and not receiving digitalis. La Rovere *et al.* (2003) do not provide data to describe the pharmacotherapy received by their patients. However, the dates through which the data were collected suggest that some of the development population are unlikely to have been treated with  $\beta$ -blockers and ACE inhibitors. Data for the development population were collected later and it can be assumed that a mixture of therapies may have been received by these patients in line with recommendation for best practice at the time (Hunt *et al.*, 2001).

One study which provides data on the response of the LF:HF ratio to standing and controlled breathing in patients receiving the currently recommended pharmacotherapy (Malfatto *et al.*, 2002) found very different values to those reported previously. Values for LF:HF whilst supine ( $9.2 \pm 1.2$ ), standing ( $12.1 \pm$

1.5) and during controlled breathing conditions ( $5.1 \pm 0.7$ ) were considerably higher than those of the present CHF cohort. Comparing the explanted LVAD patients and healthy controls with these data shows that a similar pattern of behaviour for LF:HF in response to sympathetic and vagal activation manoeuvres. Similarly to healthy subjects, LF:HF increased in response to standing and decreased in response to controlled breathing in the CHF patients of Malfatto *et al.* (2002). However the levels of sympathovagal balance in these patients indicated greater sympathetic predominance under all conditions. Malfatto *et al.* (2002) concluded that the pharmacotherapy and rehabilitative exercise undertaken by their subjects had restored cardiac autonomic responsiveness but that high levels of sympathetic modulation remained evident. Figure 10-5 shows clearly that the therapy received by the explanted LVAD patients has greatly reduced this sympathetic predominance making the baseline levels and responses of LF:HF very similar to those of the healthy controls. The former is in fact quite different from that seen in the CHF patients of Malfatto *et al.* (2002).

The importance of improved HF power lies in the protective effect of parasympathetic tone on sudden cardiac death via an antiarrhythmic effect. Coherent findings from several studies have demonstrated increased ventricular refractoriness with parasympathetic stimulation and blockade (Prystowsky *et al.*, 1981; Litovsky and Antzelevitch, 1990). The similar, and even improved (e.g. under controlled breathing), values for HF(ln) compared with the control group indicates more favourable levels of cardiac parasympathetic modulation of cardiac activity and implies a reduced risk in the explanted group. This finding may also confirm an association between parasympathetic effects on the sinus node and parasympathetic effects in the ventricle that has undergone reverse remodelling (Lahiri *et al.*, 2008).

Patients with chronic IDCM commonly show marked sympathetic activation and reduced autonomic reactivity to sympathetic and vagal stimuli. Following myocardial recovery responses to autonomic stimuli are normalised, demonstrating that these changes are likely to be reversible. This has implications for the future risk of pump failure and arrhythmias in these patients.

One problem with this type of cross-sectional data is that it becomes impossible to determine which of the battery of interventions these patients have received is responsible for the marked recovery and normalisation of autonomic control evidenced here. Large variations in time from explantation to testing, the use of clenbuterol therapy, original diagnosis, sex and the variation in patients' age all make delineation of the exact mechanisms behind recovery difficult. One subject group which may be able to provide some information are the implanted patients. The implanted patients have still received a number of treatments (surgical and pharmacological), the number, nature and duration of these varies from patient to patient dependent on duration of implantation. However, by testing their autonomic control at an earlier stage than the explanted patients and prior to undertaking post-explantation treatments such as exercise therapy, these may provide information on the time course of recovery of the ANS. They can also provide information regarding the effect of LVAD implantation (or left ventricular unloading) *per se* on autonomic control in CHF patients.

#### 10.4.2. *Implanted patients.*

Statistical analyses between implants and the other three groups identified no significant differences in the chosen HRV measures between the control and explanted groups. In fact, the HRV profile of the implanted group was more similar to that of the explanted group and as such similar observations were made for implanted versus the CHF and control groups respectively. Likewise, plotting HRV measures as carried out for the explanted group, implanted patients demonstrated similar and clear emerging patterns.

Absolute spectral (LF,  $\text{ms}^2$ ) and time domain (SDNN) measures are less similar to those of controls when compared with explanted patients (Table 10-2, Figures 10-1, 10-2 and 10-3). These values are, however, improved compared with the values reported for CHF patients receiving pharmacological therapy alone. In terms of LF particularly, a clear progression from CHF, through implanted patients then explanted patients toward the normal values of controls can be seen. This pattern appears to be independent of the use of controlled or free breathing (Figures 10-1 and 10-2). When normalised units, which control for total spectral

power are analysed, differences become even less pronounced. Measures of relative sympathetic contribution to SA node modulation (LFnu) are broadly similar between implants, explants and control study groups when measured at rest, during sympathetic and vagal stimulation (Table 10-2). Additionally, measures of sympathovagal balance in implanted patients are closer to those of explants and controls than CHF patients assessed here (Figure 10-4) and those previously reported (Malfatto *et al.*, 2002). Finally, Figure 10-5 facilitates the description of changes in sympathovagal balance both within and between groups across the three conditions used here. The absolute levels of sympathovagal balance (LF:HF) and perhaps more importantly the changes in these values, purportedly indicative of alterations in relative sympathetic and vagal SA node modulation, are very similar in implanted patients, explanted patients and controls. They are also distinctly different to those of CHF patients receiving pharmacological therapy alone (Figure 10-5) and those who have completed a therapeutic exercise intervention (Malfatto *et al.*, 2002).

Studying patients within this intermediate phase of the total combined therapy received by the explanted patients demonstrates the clinically significant, positive effects that LVAD implantation has on autonomic function in bridged patients. It appears that by unloading the left ventricle, the cycle of sympathetic overactivity, the distinctive, possibly causative but definitely negative symptom of CHF may have been broken at least in part.

Additionally, all data here were recorded with the LVAD switched on. Flow rates and even flow types (pulsatile vs. continuous) varied between patients. As a whole, the implanted patients showed cardiac reactivity to both sympathetic and vagal stimulatory manoeuvres. The ability of HRV to measure sympathetic activation is somewhat limited; this is an undoubted limitation of the present study. Using normalised LF spectral power (LFnu) to examine sympathetic activation is problematic in that the power in the LF band ( $\text{ms}^2$ ) is partially mediated by the vagus. Additionally, observing heart rate increase in a response to a simple orthostatic challenge (such as standing) may also be problematic as any rise in heart rate may be due to withdrawal of vagal activity alone or combined to an unknown degree, with sympathetic activation. On this basis, it is

more correct to say that ANS interactions of heart rate response to standing were close to normal than to say that sympathetic activation was normalised. A better test of sympathetic activation may have been gained by observation of baroreflex activity by blood pressure and blood pressure variability (Mortara and Tavazzi, 1996) measurement or by invasive methods such as iodine-123 metaiodobenzylguanidine imaging (Yamada *et al.*, 2003).

Reactivity of the vagus, brought about by controlled breathing did show a normal pattern of change in sympathovagal balance (LF:HF). However, overall values for HF(ms<sup>2</sup>) were still lower in implanted patients compared with explants and controls. This infers that vagal modulation of the SA node has been only partially restored by the implantation of the LVAD combined with optimal pharmacotherapy.

#### **10.5. Limitations.**

The major limitation of this study is its cross sectional design. Due to the rarity and sporadic nature of LVAD implantation and therefore explantation, the duration of study required to collect longitudinal data would be several years. In recognition of this, the present study was conducted over a period of 15 months. During this period, HRV data across the three stages of treatment (i.e. pharmacotherapy, LVAD combined and finally explant and pharmacotherapy) were observed in the only single available patient. This may reflect an improved pharmacological strategy that allows better management of severe heart failure without the need for LVAD therapy and/or cardiac transplant. Alternatively, the time course of recovery with an LVAD is longer than anticipated.

A second limitation is the severity of CHF patients. More specifically, a control group of patients awaiting transplantation would be ideal, as these are the patients most likely to be 'bridged'. As it was, a number of patients in the present study did present with less severe CHF and presented with higher values for several measures of HRV. A more homogenous group would also be required for any longitudinal study assessing the time course of autonomic recovery.

In a number of patients HRV recordings were not possible. This happened most often in those patients fitted with an implantable cardioverter defibrillator (ICD). Electronic interference from this device, perhaps operating on a similar frequency to that of the ECG transmitter, may have caused the incoherent ECG observed for these patients. The fact that implantation of an ICD is now a recommended therapy in patients with an LVEF < 40% (Dickstein *et al.*, 2008) means a likely increase of this therapy in severe CHF populations. This has important implications for the current methods used to assess HRV.

A final limitation is, as mentioned, the lack of a preferred measure of sympathetic activation. However, poor prognosis in CHF is due to sympathetic overactivation and/or vagal withdrawal. It could be argued that measurements evidencing significant vagal modulation in CHF are useful in determining the efficacy of interventions in reducing sympathetic overactivation.

#### **10.6. Recommendations.**

A secondary analysis which could be carried out with greater patient numbers would be to examine the time course of recovery by grouping patients by LVAD implant duration and time since explantation. Additional subgroup analyses by disease aetiology and sex could also be carried out. It would also be of interest to collect immediately after explantation which could be consequently analysed by duration of implantation, a known risk factor in LVAD use.

It is recommended therefore that a longitudinal study tracking changes in HRV and possibly baroreflex gain or other sympathetic measurement be carried out. A prospective study may be prohibitively long. However, the fact that any high quality ECG recording made under resting conditions can be used to calculate HRV means that a retrospective study may be possible from existing data. At least such a study would be possible in the future with little additional work.

A potential problem for short-term HRV analysis in these patients is the standard use of ICDs. Alternatively such devices may offer an alternative means by which to derive information on cardiac autonomic control. Current devices allow continuous recordings of R and P wave intervals that enable HRV analysis based on atrial and ventricular basis (Schwab *et al.*, 2005). Such devices offer great potential for the assessment of cardiac modulatory activity in severe heart failure and LVAD populations, as well as predicting risk of life threatening arrhythmias and mortality risk via such measures as heart rate turbulence (Iwasa *et al.*, 2005; Stein *et al.*, 2008).

### **10.7. Conclusions.**

In severe heart failure patients under assessment for cardiac transplant, mechanical support with an LVAD combined with optimal pharmacological therapy results in significant and favourable changes in autonomic function. Moreover, in patients demonstrating a recovery following LVAD combined therapy, measures of HRV are more normalised compared to healthy controls. Patients explanted following myocardial recovery demonstrate a lower HRV risk profile.

## 10.8. References.

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## **CHAPTER 11. SUMMARY.**

The final chapter in this thesis provides a summary of the findings from each of the empirical chapters and overall outcomes from the thesis. For each chapter, the review is provided in bullet format modelled in the style of the British Medical Journal, with a number of statements as to the information already known prior to the completion of each particular chapter. This is followed up by a number of statements referring to knowledge added/gained from work carried out. Finally concluding paragraphs are given to integrate the overall findings from the thesis and provide directions for future study.

### **11.1. Review of empirical findings.**

#### Chapter 2 – The reliability of the Polar S810 heart rate monitor system and advanced analysis software to assess heart rate variability.

*What is already known on this topic:*

- Measures of heart rate variability (HRV) are inherently unreliable due to large inter- and intra-individual variations;
- The reliability of repeat measures using the Polar S810 RR interval recording heart rate monitor and accompanying software has yet to be assessed;
- The reliability of repeat HRV measurements using an alternative software package (HRV analysis software 1.1, Kuopio, Finland), has also not been assessed.

*What this study adds:*

- Measures of HRV from the Polar S810 are valid compared with criterion measures;
- The Polar S810 provides as reliable and reproducible measures of HRV as a criterion system;
- The reliability of measures of HRV from the HRV analysis software 1.1 differs according to the selected parameter settings.

Chapter 3 – Agreement between novel telemetric and laboratory based systems in the measurement of heart rate variability.

*What is already known on this topic:*

- The validity of the Polar S810 to record RR intervals had been confirmed in two previous studies using agreement analysis;
- There was no data as to the validity of measures of HRV obtained using the Polar S810 and Polar specific software as intended by the manufacture;
- Separate software (HRV analysis software 1.1) provides advanced HRV analysis features;
- The agreement of HRV obtained by the Polar S810 system and HRV analysis software is unknown.

*What this study adds:*

- RR interval data from the Polar S810 are in close agreement to that obtained by a criterion 12-lead ECG system (CardioPerfect – CP).
- Measures of HRV from the Polar S810 system and HRV analysis software demonstrate poor agreement to those obtained from the CP system and between one another;
- The Polar S810 system and HRV analysis software should not be used interchangeably with the CP to obtain measures of HRV;
- A need to establish a range for ‘normal’ HRV in healthy individuals was identified.

As part of the write-up of these two chapters for publication (Nunan *et al.*, 2008, 2009 – see Appendix III and IV) the following was found:

- The initial methodology used in chapter two did not assess the reliability of the Polar S810 but rather the reliability of repeat measures of HRV using the Polar.
- Re-assessment using appropriate methodology and statistical analyses revealed that measures from the Polar S810 were both valid and reliable compared with that of a criterion device;
- The use of appropriate statistical methods was highlighted by the fact that when assessed using limits of agreement analysis, measures of HRV from

the Polar did not agree with criterion measures and were considered invalid. When assessed using standard error of estimates, the Polar was found to provide valid and reliable data.

Chapter 4 – Short-term resting heart rate variability and prognostic exercise test responses: associations with heart rate, aerobic capacity and physical activity.

*What is already known on this topic:*

- Both HR response before, during and after exercise and resting HRV measures are significant predictors of adverse events in numerous patient populations;
- Studies using HR responses as indicators of ANS dysfunction fail to provide quantitative measures of ANS activity;
- As a non-invasive measure of ANS activity, HRV offers the potential to clarify findings for HR responses to exercise from previous studies;
- A strong association with exercise HR responses to exercise could imply the use of resting HRV to identify the need to perform stressful maximal exercise testing.

*What this study adds:*

- A strong negative association between resting HR and HRV indicated a ‘harmony’ between autonomic cardiac control indices;
- Weak associations with the HR response to exercise prevent its prediction from resting HRV. However, resting HRV is well related to post-exercise HRR and a higher vagally mediated spectral HRV predicts a better HRR response;
- An increased risk based on resting and exercise HR responses was independently underlined by lower HRV. Those performing lower levels of physical activity also demonstrate a lower HRV.

Chapter 5 – The range in normal short-term heart rate variability in healthy adults: a comparison to published norms and factors underlining disparate values.

*What is already known on this topic:*

- Norm values for measurements of HRV obtained from short-term (< 20 minute) RR interval recordings were provided by the 1996 Task Force.

However, values were obtained from a limited number of small scale studies;

- Increased interest in HRV over the past decade has made available numerous larger scale studies assessing short-term HRV in healthy adults and provides a data base to obtain a normal range;
- The popularity of HRV measurement has seen its introduction to private health care in the UK, yet normality of data from such settings has yet to be assessed;

*What this study adds:*

- From 376 papers returned from database searches, surprisingly few (44 or 12%) met study inclusion criteria.
- Literature values for short-term HRV were lower than those of the Task Force, showed a degree of homogeneity and demonstrated known gender and age related differences;
- Retrospective data obtained in a private hospital setting also demonstrated gender and age related differences. However, absolute values for spectral measures were incompatible with literature and Task Force values. A lack of transparency in the operating system of the device used for HRV measurements made findings difficult to explain;
- A need for large-scale population studies remains and a review of Task Force standards with focus on new technologies is required.

#### Chapter 6 – Measures of heart rate variability from the Polar S180 and HRV analysis software 1.1: a validity and reliability study in chronic heart failure.

*What is already known on this topic:*

- The stationarity of RR interval data often violates assumptions for linear spectral analysis and therefore requires the use of non-linear measures and/or the application of detrending methods;
- The HRV analysis software offers several detrending options and both the Polar S810 and HRV analysis software provide non-linear HRV measures;
- The reliability of linear and non-linear HRV obtained by the Polar S810 and the validity and reliability of linear, non-linear and detrended HRV

from the HRV analysis software in chronic heart failure (CHF) patients is unknown;

*What this study adds:*

- Measures of HRV from the Polar S810 demonstrated similar reliability compared with estimates in healthy participants;
- Correlation, standard error of estimate and limits of agreement analysis revealed good to excellent validity, trivial to small error and good agreement for mean RR, time domain and non-linear HRV measurements from the HRV analysis software without a detrend;
- Absolute and normalised frequency domain measures were underestimated by the HRV analysis software but uncertainty of error was smaller for absolute values.
- Application of smoothness priors detrend in the HRV analysis software removes adverse low frequency trends and the resultant data are as reliable as repeat HRV measurements from the Polar S810;
- Coefficient of variation analysis for measures of HRV obtained in CHF patients revealed large inter- and intra-individual variations that are comparable to data for healthy individuals.

Chapter 7 – Heart rate variability in heart failure: its role in diagnosis, prognosis and as a therapeutic target.

*The outcomes of this review were:*

- Patients with heart failure demonstrate severe autonomic derangements characterised by high levels of sympathetic activation and/or withdrawal of parasympathetic activity that manifest as low values for measures of HRV;
- Several HRV measurements have shown to be strong independent risk factors for adverse outcomes in CHF yet surprisingly few studies have utilised HRV in this patient population;
- As a therapeutic intervention exercise can favourably alter measures of HRV in myocardial infarct and CHF populations undergoing cardiac rehabilitation (CR), thus improving patients risk profile. There are few

studies assessing short-term measures of HRV following CR in CHF patients and none examining the effects of differing exercise modalities;

- In severe HF patients being assessed for transplantation, unloading of the myocardium via a left ventricular assist device (LVAD) can lead to recovery and improved survival. There are no data assessing HRV in patients receiving LVAD therapy.

Chapter 8 – Alterations in heart rate variability of mild-to-moderate heart failure patients following 12 weeks aerobic or resistance exercise training.

*What is already known on this topic:*

- The performance of exercise in CHF sufferers has changed from one of caution against its use to one of a possible role in the treatment of the disease;
- A beneficial role of CR on autonomic modulation has been shown by improved 24 h HRV in myocardial infarct and more recently by improved short-term HRV in those suffering from coronary artery disease;
- Recommended modes of exercise for CR range from aerobic (AR) to resistance (RT) based exercises;
- There are few studies assessing the benefit of CR on short-term HRV and other physiological parameters in CHF and none examine the differing effects of AR versus RT predominant exercise.

*What this study adds:*

- Magnitude of change for physiological and short-term HRV measures was generally larger in the AR compared with the RT group and only those in the AR group demonstrated favourable changes for all measures of HRV;
- Difference in the response of LF:HF indicated a beneficial parasympathetic mediated improvement in the AR but not the RT group. However, normalisation of LF and HF power resulted in a dissociation to the underlying physiology of absolute measures;
- No resting measures were able to predict change in the duration of graded exercise test or peak oxygen uptake in either group, although these were almost predicted by resting SDNN and DBP in the AR group;

- Cardiac rehabilitation based on current guidelines has no significant effect on resting HRV in heart failure patients with already preserved HRV.

Chapter 9 – The relationship between exercise heart rate responses and resting heart rate variability in chronic heart failure patients before and after 12 weeks cardiac rehabilitation.

*What is already known on this topic:*

- In chapter five, a strong negative association between resting HRV measurements and resting HR was indicative of a ‘harmony’ between autonomic cardiac control systems;
- A higher value for HF spectral power was able to predict patients likely to obtain a low risk HRR value but not those likely to obtain a high risk value;
- There was an underlying role for higher values of HRV in low risk category patients when grouped according to risk for resting HR, change in rest to peak HR and HR recovery;
- Cardiac rehabilitation (CR) is becoming increasingly used as a treatment and to encourage lifestyle changes in CHF.

*What this study adds:*

- There was a meaningful change in associations between a number of HRV measurements and resting HR and HR responses to exercise following CR.
- Changes in associations were in a favourable direction for the majority of measures and indicated normalisation of associations between HRV and HR following CR.
- No measures of resting HRV were found to predict HR response to exercise significantly, although non-linear measures demonstrated good sensitivity and specificity for predicting a higher risk  $\Delta$ HR response.
- Prior to CR a better HRV was not found to underline a lower risk profile in patients grouped according to prognostic HR thresholds prior to CR. However, patients demonstrating a lower risk for  $\Delta$ HR and HRR

following CR also demonstrated non-significant, but in some cases meaningful, higher values for all measures of HRV.

Chapter 10 – The impact of bridging to recovery using implantable left ventricular devices on heart rate variability in severe heart failure patients.

*What is already known on this topic:*

- Unloading of the myocardium via mechanical support from a left ventricular assist device (LVAD), and combined with optimal pharmacology, can lead to recovery and improved survival in severe CHF awaiting cardiac transplantation;
- There is a well documented autonomic dysfunction in severe CHF characterised by sympathetic overactivity and/or vagal withdrawal that manifests as severely depressed HRV;
- There are no data as to the autonomic function of patients undergoing (implanted) or recovered from (explanted) LVAD combination therapy.

*What this study adds:*

- The HRV profile of patients explanted after successful LVAD combination therapy does not differ from that of healthy counterparts, demonstrating a normalisation of risk factors in these patients;
- Patients currently implanted with an LVAD demonstrate partial normalisation of risk factors, with significantly improved HRV compared with CHF patients receiving pharmacological therapy alone;
- Assessment of autonomic function before, during and in recovery from LVAD therapy could identify the potential role for HRV in predicting outcomes and as a clinical tool in these patients.

The aim of this thesis was to assess the utility of short-term measures of HRV in real-life clinical situations away from the laboratory setting. In chapter seven, the importance of HRV was related to its prognostic power in a number of diseases including diabetes, myocardial infarction and heart failure (La Rovere *et al.*, 2003). In addition, evidence was found that points to a trainability of HRV measurements, whereby exercise interventions and other disease management

strategies can successfully modify known risk factors. This implies a role for HRV as a therapeutic target.

Validation of HRV measurements from new telemetric RR interval recording technologies and software was first sought from healthy participants' data in chapters two and three. Subsequent papers from these chapters revealed the importance of applying appropriate statistical procedures in methods analyses. The lessons learned from these experiences were applied when validation of the new technologies was sought in CHF patients (chapter six). Short-term measures of HRV were shown to be as equally reliable in CHF patients compared with healthy participants and the new systems provided valid measures in both populations.

In chapter eight, the application of techniques validated in healthy participants were applied to clinical settings. Twelve weeks of cardiac rehabilitation was unsuccessful in augmenting linear and non-linear short-term HRV measurements in mild-to-moderate CHF patients despite increases in cardiorespiratory parameters and improved exercise performance. Using data from chapter five reviewing values for recommended (Task Force 1996) short-term measures of HRV obtained in healthy participants, patients entering cardiac rehabilitation were found not to present with low levels of HRV. The findings indicated dissociation between adaptations to exercise of autonomic cardiac modulations and cardiorespiratory physiology when baseline HRV is preserved.

Sole consideration to measures of HRV alone may not have provided the best index of autonomic cardiac control or its response to cardiac rehabilitation. The association between HR and measures of HRV can be considered to reflect the degree of harmony between various cardiac autonomic indices (Coumel *et al.*, 1994). In chapter four, associations between measures of HRV and HR demonstrated the known normal autonomic harmony in healthy individuals. Measures of HRV were also shown to correlate well with the HR response to acute exercise, particularly its recovery following maximal graded exercise testing. Assessment of this association was then applied to heart failure populations in chapter nine. A decrease in the HR-HRV relationship compared

with healthy individuals indicated a loss in autonomic harmony. Large improvements in the associations between a number of HRV measurements and HR revealed a shift towards a more harmonious autonomic cardiac function and supported the efficacy of cardiac rehabilitation in CHF patients.

In chapter 10, the analysis of short-term HRV was again applied to clinical settings in the severest category of heart failure patients undergoing assessment for transplantation. Measures of HRV were obtained in patients being treated by a combination of pharmacological and mechanical ventricular support in an effort to assess its effects on cardiac autonomic function. Significant and favourable changes in measures of HRV were observed in patients demonstrating a recovery following LVAD combined therapy. Importantly, improved values for HF power indicated a decreased risk in this patient group. These findings may in part explain the improved survival and recurring heart failure rates in patients successfully recovered with an LVAD (Birks *et al.*, 2006).

## **11.2. Recommendations.**

The trend for a beneficial effect of aerobic based cardiac rehabilitation was supported by moderate improvements in short-term measures of HRV. These data agree with the majority of previous studies which have also reported either significant or moderate effect size changes in HRV calculated from either short-term or ambulatory ECG measurements. Confirmation of these findings is warranted in a larger randomised control trial, particularly as exercise may augment measures associated with a cardioprotective effect in CHF patients.

Recently the Task Force report was highlighted as the third most cited paper from the publication *Circulation* (Cerutti *et al.*, 2006); implying a wide application of its many measures in research and clinical settings. Suggestion of a new Task Force initiative on HRV with appropriate updating, critical review and suggestions for future directions that consider data obtained in the last 10 years was also given. Any new initiative should consider new technologies that demonstrate valid and reliable measures but do not adhere fully to current

technological recommendations. In addition, there are still no data for norm values and ranges for even the most commonly used measures of HRV. An attempt to provide such data in chapter five was limited due to the small number of population based studies from which norm values can be derived. There remains a need for a population based study to identify norms from short-term measures of HRV that incorporates both genders and the full adult age spectrum. Incidentally, such a study was recommended by the original Task Force 13 years ago.

A longitudinal study, tracking changes in various indices of autonomic function including HR and blood pressure variability, is required in patients treated with LVADs. Data in the present study could be used retrospectively to avoid such a prospective study from being prohibitively long. Consideration to outcome destination in these patients should also be given to evaluate the clinical utility of short-term HRV in these populations more effectively.

### **11.3. Conclusions.**

This thesis demonstrates the clinical utility of heart rate variability to evaluate specific treatment effects in chronic heart failure patients of varying severity. The value of HRV lies in the strong prognostic power of a number of its measures in CHF and other patient populations. Advancements in technologies have provided researchers and clinicians greater access to HRV measurements that appear both reliable and valid. Such measures can be used to assess the efficacy of patient treatments. To this effect, favourable alterations in HRV measurements known to be risk factors in healthy and clinical populations may be afforded by chronic adaptations to prolonged aerobic type exercise in favour of resistance based exercise. An improvement in associations between measures of HRV and HR imply a normalisation of the harmony between autonomic cardiac control indices and further the efficacy of exercise treatments. The significant and favourable modification of HRV measurements which are known risk factors in patients recovered from LVAD therapy supports its efficacy and may relate to the

improved survival following this treatment. These data support the routine use of short-term HRV in CHF patients.

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## APPENDICES.

**APPENDIX I** - Correlation matrix for participant characteristics, physical activity, resting heart rate, exercise and post-exercise heart rate response, aerobic capacity, test duration measures of heart rate variability.

	Gender	Age	PA-R score	Rest HR	$\Delta HR_1$ minute	$\Delta HR_{1/3}$ exercise	HR increase	$\Delta HR$	HR reserve at peak	HRR <sub>1</sub> minute	HRR <sub>2</sub> minute	HRR <sub>3</sub> minute	$\dot{V}O_{2\text{peak}}$	Duration of GXT	mRR	rMSSD ln	LF ln	HF ln	LF:HF
Gender	1.00	-0.42*	0.15	0.07	-0.11	0.14	0.55**	0.54**	0.32	0.01	-0.19	-0.07	0.49**	0.46**	-0.05	-0.02	0.20	0.01	0.26)
Age		1.00	-0.14	-0.41*	0.22	-0.09	-0.48**	-0.64***	-0.09	-0.08	-0.12	-0.17	-0.60***	-0.50**	0.39*	-0.23	-0.23	-0.33	0.28
PA-R score			1.00	0.35*†	-0.23	0.10	0.08§	0.24	-0.12	0.20	0.26	0.22	0.37*§	0.38*§	0.40*†	0.32	0.42*	0.38*	-0.04
Rest HR				1.00	0.01†	-0.20†	-0.31§	-0.57**§	0.34	-0.11†	-0.13†	-0.18†	-0.23§	-0.20§	-0.98****†	-0.72****†	-0.66****†	-0.67****†	0.22†
$\Delta HR_1$ minute					1.00	0.67***	0.50**§	0.16§	0.14	-0.27	0.15	0.20	-0.14§	-0.52**§	-0.03†	-0.08	-0.20	-0.12	-0.05
$\Delta HR_{1/3}$ exercise						1.00	0.55**§	0.36*§	0.25	-0.27	0.08	0.13	-0.03§	-0.22§	0.18†	0.16	0.10	0.18	-0.09
HR increase							1.00	0.66***§	0.47**	0.01§	0.41*§	0.47**§	0.22§	-0.22§	0.29§	0.18§	0.04§	0.20§	-0.31§
$\Delta HR$								1.00	0.50**	-0.09§	0.23§	0.33§	0.32§	0.04§	0.56**§	0.49**§	0.45**	0.49**§	-0.20§
HR reserve at peak									1.00	-0.22	-0.13	0.10	0.21	0.01	-0.32	-0.25	-0.13	-0.20	0.17
HRR <sub>1</sub> minute										1.00	0.72***	0.67***	0.36*§	0.06§	0.17†	0.29	0.25	0.35*	-0.23
HRR <sub>2</sub> minute											1.00	0.92***	0.36*§	-0.13§	0.16†	0.35*	0.19	0.44*	-0.41*
HRR <sub>3</sub> minute												1.00	0.35§	-0.13§	0.24†	0.37*	0.24	0.43*	-0.39*
$\dot{V}O_{2\text{peak}}$													1.00	0.55**§	0.30§	0.31§	0.40*§	0.30§	0.03§
Duration of GXT														1.00	0.24§	0.18	0.33§	0.18§	0.09§
mRR															1.00	0.69****†	0.66****†	0.63****†	-0.17†
rMSSD ln																1.00	0.83***	0.96***	-0.52**
LF ln																	1.00	0.76***	-0.04
HF ln																		1.00	-0.64***
LF:HF ln																			1.00

HR, heart rate; HRR, heart rate recovery; Mean RR, mean time between normal r-waves; rMSSD, root mean square of successive differences; LF, low frequency spectral power; HF, high frequency spectral power; LF:HF, the ratio of low to high frequency spectral power; ln, natural logarithm; PA-R, physical activity rating; GXT, graded exercise test. \*\*\*P<0.001, \*\*P<0.01, \*P<0.05; †Correlation controlled for age; §Correlation controlled for age and gender.

**APPENDIX II** - The physical activity rating questionnaire (PA-R) used in the present study to assess physical activity level. Derived from Jackson *et al.* (1990).

***NASA code for Physical Activity***

Use the number (0 to 7) that best describes your general activity level for the previous month.

Do not participate regularly in recreation sport or heavy physical activity

- 0 Avoid walking or exertion, for example, always use elevator, drive whenever possible instead of walking
- 1 Walk for pleasure, routinely use stairs, occasionally exercise sufficiently to cause heavy breathing or precipitation

Participate regularly in recreation or work requiring modest physical activity, such as golf, horseback riding, calisthenics, gymnastics, table tennis, bowling, weightlifting, yard work

- 2 10 to 60 minutes per week
- 3 Over 60 minutes per week

Participate regularly in heavy physical exercise such as running or jogging, swimming, cycling, rowing, skipping rope, running in place or engaging in vigorous aerobic activity exercise such as tennis, basketball, or handball

- 4 Run less than 1 mile (1.6 kilometres) per week or spend less than 30 minutes per week in comparable physical activity
- 5 Run 1 to 5 miles (1.6 to 8 kilometres) per week or spend 30 to 60 minutes per week in comparable physical activity
- 6 Run 5 to 10 miles (8 to 16 kilometres) per week or spend 1 hour to 3 hours per week in comparable physical activity
- 7 Run over 10 miles (16 kilometres) per week or spend over 3 hours per week in comparable physical activity.

**APPENDIX III** – Copy of paper involving data from chapter four published in the *European of Journal of Applied Physiology*.



















**APPENDIX IV** - Copy of paper involving chapter three and four study data published in the *Medicine and Science in Sports and Exercise*.

HEART RATE VARIABILITY IN HEALTHY AND HEART FAILURE  
POPULATIONS: ASSOCIATIONS AND RESPONSES TO EXERCISE AND  
SPECIFIC INTERVENTIONS

A thesis submitted for the degree of Doctor of Philosophy  
by

David Nunan

Research Centre *for* Society and Health  
Buckinghamshire New University  
Brunel University.

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## **Abstract.**

Autonomic function is severely disrupted in heart failure. Depressed heart rate variability (HRV) in these patients is associated with an increased risk of cardiac events and death. Studies from 24 h HRV assessments demonstrate an improvement following exercise training as part of cardiac rehabilitation. At the most severe level, a need to transplant has been offset following structural recovery as a result of mechanical support to the failing heart yet the effect on autonomic dysfunction is unknown. The aim of this thesis was to examine the effects of cardiac rehabilitation (CR) and mechanical support on short-term measures of HRV in heart failure patients of varying disease severity.

The first few chapters and subsequent papers assessed the reliability and agreement of newly developed wireless technologies and measurement software in healthy participants. The findings revealed agreement was poor between systems but the new technologies demonstrated similarly fair reliability compared to each other and criterion measures.

A potential role for resting HRV underlying the physiology and prediction of higher risk heart rate (HR) responses to graded exercise testing was then explored. The consequent chapter found that resting vagally mediated HRV measures were able to predict a low risk but not a high risk HR recovery accurately. Lower HRV also underlined an increased risk profile based on known prognostic HR measures in healthy populations.

An observation was made for a lack of normative data with which comparisons could be made. A review of all papers publishing short-term HRV data in healthy adults revealed poor methodological standards in many of the studies, limiting the final outcomes. For all measures of HRV, data from the literature were lower than previously published norms but known age and gender differences remained. These data provide a new source for identification of so called normal and abnormal HRV.

Reviewing the literature concerning the diagnostic and prognostic use of HRV in heart failure identified gaps in the literature. There were no data available relating to the effect of differing exercise training modalities on autonomic function. A randomised trial of 12 weeks aerobic or resistance CR training was successful in increasing functional and aerobic capacities but did not significantly alter resting absolute HRV values. However, the harmony between HR and HRV was favourably altered and better matched that of healthy participants.

Prior to this thesis, there were no data relating to the autonomic profile of patients receiving mechanical support via left ventricular assist device (LVAD) therapy. The study of patients recovered and currently undergoing LVAD treatment revealed significantly higher HRV in the former and latter compared with heart failure patients receiving standard care. Patients recovered from LVAD therapy demonstrated a decreased risk for known HRV markers and a normalisation of autonomic modulations.

In conclusion, a depressed HRV remains a significant risk factor in heart failure patients. Exercise training may afford a beneficial effect in mild-to-moderate patients. In more severe patients, HRV risk factors are favourably altered by mechanical support and should be considered in the assessment of these patients.

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## LIST OF ABBREVIATIONS.

ACE	Angiotensin converting enzyme
ACSM	The American College of Sports Medicine
AHA	American Heart Association
AR	Aerobic (exercise group)
ARB	Angiotensin receptor blocker
BMI	Body mass index.
BP	Blood pressure
BPV	Blood pressure variability
BRS	Baroreflex sensitivity
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CHF	Chronic heart failure
CO	Cardiac output
CR	Cardiac rehabilitation
CV	Coefficient of variation
DBP	Diastolic blood pressure
DCM	Dilated cardiomyopathy
ECG	Electrocardiogram
EF(%)	Ejection fraction
GXT	Graded exercise test
HR	Heart rate
HRR	Heart rate recovery
HRV	Heart rate variability
HUT	Head up tilt

ICC	Intraclass correlation coefficient
IDCM	Idiopathic dilated cardiomyopathy
ISHLT	International society for heart and lung transplantation
LVAD	Left ventricular assisting device
LVD	Left ventricular dysfunction
MET	Metabolic equivalent
MI	Myocardial infarction
MSNA	Muscle sympathetic nerve activity
NA	Noradrenaline
NYHA	New York Heart Association
PAD	Peripheral artery (or arterial) disease
PTCA	Percutaneous transluminal coronary angioplasty.
PVCs	Premature ventricular contractions
RER	Respiratory exchange ratio
RPE	Ratings of perceived exertion
RSA	Respiratory sinus arrhythmia
RT	Resistance (exercise group)
SCD	Sudden cardiac death
VPC	Ventricular premature contractions

## GLOSSARY OF TERMS.

Atrial fibrillation	Irregular and insufficient contraction of the atrial muscle most often caused by atherosclerosis, chronic rheumatic heart disease and hypertensive heart disease
Ambulatory monitoring	Continual recording of the ECG or blood pressure using a recording device worn by the subject during normal daily activities for 24 hours
Baroreflex sensitivity	The reactivity of the arterial baroreflex to alter blood pressure - usually in response to orthostatic challenge
Body mass index	The ratio of weight (kg) to body size (calculated as stature in m <sup>2</sup> )
Borg Scale	6 – 19 point scale providing subject self reported ratings of perceived exertion.
Bridging to recovery	The use of an LVAD to allow the dilated myocardium of a CHF patient to recover.
Bridging to transplantation	The use of an LVAD to keep a patient alive until a suitable donor heart becomes available for transplantation
Cardiac output	The flow of blood from the heart in a given time period (l·min <sup>-1</sup> )
Cardiothoracic Ratio	The transverse cardiac diameter (the horizontal distance between the most rightward and leftward borders of the heart seen on a postero-anterior (PA) chest radiograph) divided by the transverse chest diameter
Cardioversion	A controlled direct-current electric shock given via a modified defibrillator placed on the chest wall designed to restore normal cardiac rhythm
Coronary artery bypass grafting	Operation to reroute blood flow from blood vessels of the heart using veins removed from other parts of the body
Ectopic beat	A heart muscle contraction that is outside the normal sequence of the cardiac cycle and stems from an impulse outside the usual focus of the sinoatrial node.
End diastolic diameter	Geometrical measure of the heart showing the diameter of the left ventricle at the end of diastole (mm)

End diastolic volume	The volume of blood in the ventricle at the end of diastole (ml)
End systolic diameter	Geometrical measure of the heart showing the diameter of the left ventricle at the end of systole (mm)
Ejection fraction	The fraction or % of blood (usually in the left ventricle) at the end of systole as a function of the volume during diastole
Heart rate turbulence	The return to equilibrium of heart rate after a ventricular premature contraction
Holter monitor	Recording device worn by subject to continually monitor ECG and/or blood pressure
Iodine-123 metaiodobenzylguanidine imaging	The infusion and monitoring of iodine-123 metaiodobenzylguanidine to observe the distribution of sympathetic nervous tissue
Left ventricular end systolic volume	Volume of blood remaining in the left ventricle at the end of systole
Neurohumoral	Relating to the transmitting, uptake and action of neurohormones in the body
Percutaneous transluminal coronary angioplasty.	Operation to increase blood flow in (coronary) blood vessels by increasing the internal diameter of the vessel. May involve stenting
Peripheral bypass surgery	Rerouting blood flow around damaged or occluded vessels using grafts from other healthy vessels
Premature ventricular contractions	Spontaneous depolarization of the ventricular myocytes prior to and without stimulation from the SA node resulting in ventricular contraction too early in the normal cardiac cycle – sometimes VPC
Remodelling	Change in size, shape and function of the heart after injury usually to the left ventricle
Reverse remodelling	An improvement in ventricular mechanics and function after a remote injury
Stenting	Insertion of a device into a previously occluded blood vessel to hold back plaque built up due to CAD
Stroke volume	The volume (ml) of blood leaving the left ventricle

during each cardiac cycle

Tachycardia

A rise in the heart rate above the normal range at rest  
60 to 100 beats per minute

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I dedicate this thesis to those hard working many who realise there is no big secret to it. To paraphrase a term that I have become very familiar with, it's a question of "just do it".

David Nunan.

**Author declaration.**

I take responsibility for all the material contained within this thesis and confirm that it is my own work.

*David Nunan*

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