THE RELATIONSHIP BETWEEN HRV(rMSSD) AND OTHER CARDIOVASCULAR RISKS IN HEALTHY PARTICIPANTS AND PATIENTS WITH CHRONIC HEART FAILURE USING NOVEL INSTRUMENTS

A Thesis submitted for the degree of Doctor of Philosophy

By

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Abstract

Heart rate variability (HRV) reflects the modulation of cardiac function by autonomic and other physiological regulatory systems. HRV is accepted as a reliable and reproducible technique for assessing autonomic activity. Impaired autonomic function (measured through a reduction in HRV) predicts mortality and is associated with several disease states. Excess adiposity is also associated with higher risk of cardiovascular diseases, type 2 diabetes, cancer and other health disorders. Body composition analysis involves the measurement of adipose tissue and other components such as muscle, bone and minerals in the human body. The relationship between excess adiposity and autonomic dysfunction has also been reported.

The present thesis is divided into three parts: (i) validation studies, (ii) control studies and (iii) heart failure studies. The first validation study compares HRV (rMSSD) measured simultaneously with a Polar s810i and Ithlete on an iPod touch, in both healthy and heart failure populations. The second study examines measurement options for body composition by comparing several bioelectrical impedance analysis devices in a healthy population.

Four studies were then undertaken with control subjects, assessing differences in gender, ethnicity and lifestyle factors using the devices validated in the previous chapters. Finally, Ithlete software was used with heart failure participants to gauge the feasibility of using the device daily and obtaining user feedback. Ithlete was then used in a cardiac rehabilitation programme to help participants get the most out of the programme, by guiding their exercise to rest ratio.

The relationships between HRV, HR and body composition have been explored in this research work and have contributed to the knowledge around how these relationships can be used in healthcare. The benefit of novel devices to measure these relationships in both clinical and healthy populations has also been demonstrated, with an emphasis on low cost devices with good reliability.

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LIST OF ABBREVIATIONS

6MWT:	Six-minute walk test
ACE:	Angiotensin converting enzyme
AHF:	Acute heart failure
ANS:	Autonomic nervous system
BF:	Body fat
BHF:	British Heart Foundation
BMI:	Body mass index
BMR:	Basal metabolic rate
BPM:	Beats per minute
CHD:	Coronary heart disease
CHF:	Chronic heart failure
CR:	Cardiac rehabilitation
CVD:	Cardiovascular disease
DBP:	Diastolic blood pressure
DCM:	Dilated cardiomyopathy
ECG:	Electrocardiogram
EF (%):	Ejection fraction
FFM:	Fat free mass
FM:	Fat mass
H:	Healthy
HF:	Heart Failure
HFr:	High frequency[1]
HR:	Heart rate
HRR:	Heart rate recovery
HRV:	Heart rate variability
ICC:	Interclass correlation coefficient
ICD:	Implantable cardioverter defibrillator
LF:	Low-frequency
Mean R-R:	The mean R-R interval between all normal beats
MET:	Metabolic equivalent

[1] In the literature high frequency is often abbreviated as HF, however for the purpose of this thesis it will be abbreviated as HFr so it is not confused with the abbreviation for heart failure

MI:	Myocardial infarction
MM:	Muscle mass
MSNA:	Muscle sympathetic nerve activity
NICE:	National Institute for Clinical Excellence
NHS:	National Health Service
NN50:	The number of adjacent R-R intervals that varied by more than 50 ms
NYHA:	New York Heart Association
pNN50:	The percentage of adjacent R-R intervals, varying by more than 50 ms
PNS:	Parasympathetic nervous system
rMSSD:	The root mean square of the successive difference
R-R:	One peak to the other (R to R) in a QRS complex from a standard ECG
RER:	Respiratory exchange ratio
RPE:	Rate of perceived exertion
RR:	Respiratory rate
RSA:	Respiratory sinus arrhythmia
SBP:	Systolic blood pressure
SCD:	Sudden cardiac death
SD:	Standard deviation
SDANN:	The standard deviation of the average NN intervals calculated over short periods
SDNN:	Standard deviation of all R-R intervals or normal heart periods
SNS:	Sympathetic nervous system
STPD:	Standard temperature pressure dry
TBW:	Total body water
V_E:	Minute Ventilation
VLF:	Very-low frequency
Vo_2:	Oxygen consumption
Vo_2 max:	Maximal oxygen consumption
Vo_2 peak:	Peak oxygen consumption

GLOSSARY OF TERMS

Anaerobic threshold: Exercise oxygen consumption that marks the transition between no change or little change in arterial lactate concentration and the sustained increase in concentration of lactate (also known as the lactate threshold). Postulated by some authors to be the oxygen consumption above which anaerobic energy production substantially supplements aerobic energy production.

Aperiodic: irregular; not periodic

Arrhythmogenic: producing or promoting arrhythmia

Atrial fibrillation: Irregular and insufficient contraction of the atrial muscle most often caused by atherosclerosis, chronic rheumatic heart disease and hypertensive heart disease

Attenuation: to make slender, fine or small; the opposite of amplification.

Autonomic function: regulatory involuntary function; the part of the nervous system concerned with regulation of activity of cardiac muscle, smooth muscle, and glands.

Baroreflex sensitivity: The reactivity of the arterial baroreflex to alter blood pressure- usually in response to orthostatic challenge

Basal level: Associated with the base of an organism or structure

Borg scale: A 6-19 point scale which is used for individual to rate their perceived level of exertion during exercise.

Bradycardia: resting heart rate of under 60 beats per minute

Bruce protocol: Treadmill exercise test which is conducted in three minute stages. Each three minutes the workload is increased by a combination of increasing the speed and the grade of the treadmill.

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

Fat-free mass: The mass (weight) of the body that is not fat, including muscles, bone, skin and organs

Heart failure: A condition that can result from any structural and functional cardiac disorder that impairs the ability of the heart to fill with blood or pump a sufficient amount of blood through the body.

High-frequency power: the frequency domain band in the range from 0.15 to 0.4 Hz; this band reflects parasympathetic (vagal) tone and fluctuations caused by spontaneous respiration known as respiratory sinus arrhythmia.

Lean body mass: The sum of the bodyôs fat-free mass and essential fat.

Likert scale: A rating scale measuring the strength of agreement towards a set of clear statements.

Low-frequency power: The frequency domain band in the range from 0.04 to 0.15; this band can reflect both sympathetic and parasympathetic tone.

Meta-analysis: Methods focused on contrasting and combining results from different studies.

Myocardium: Muscle tissue of the heart

Oscillation: regular fluctuation in value, position, or state about a mean value

Oxygen consumption: The amount of oxygen utilized by the bodyôs metabolic processes in a given time, expressed in millilitres or litres per minute, STPD

Oxygen uptake: The amount of oxygen extracted from the inspired air in a given period of time, expressed in millilitres or litres per minute. This can be differed from oxygen consumption under conditions in which oxygen is flowing into or being utilized from the bodyôs stores. In the steady-state, oxygen uptake equals oxygen consumption.

Modified Bruce Protocol: A treadmill exercise test containing two preliminary three- minute stages of 2.7 km per hour at 0% incline and 2.7 km per hour at 5% incline. It is then followed by the standard Bruce protocol.

Myopathy: A muscular disease in which the muscle fibres do not function for any one or many reasons.

Parasympathetic nervous system: branch of the autonomic nervous system associated with promoting calm and return to regular function

Pathophysiological: explains the physiological processes or mechanisms whereby such condition develops and progresses.

Peak oxygen consumption: The highest oxygen consumption achieved during a maximum work rate test.

Psychosocial: relates to oneôs psychological development in, and interaction with, a social environment.

QRS complex: name for the combination of three of the graphical defelctions seen on a typical electrocardiogram

Respiratory exchange ratio: The ratio of carbon dioxide output to oxygen uptake per unit of time.

R-R interval: The interval from the peak of one QRS complex to the peak of the next as shown on an electrocardiogram

Sympathetic nervous system: branch of the autonomic nervous system associated with arousal and energy generation

Tachycardia: Heart rate that exceeds the normal range (usually over 100 beats per minute)

Vagal: Activity of the vagus nerve (associated with parasympathetic function)

Variable: A variable is a quantity whose value may vary over the course of an experiment (including simulations), across samples, or during the operation of a system. Variables are generally distinct from parameters, although what is a variable in one context may be a parameter in another.

EXTERNAL PUBLICATIONS FROM THIS THESIS

Submitted manuscripts

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Conference proceedings

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AUTHOR DECLARATION

This thesis is a presentation of my own original research work. Wherever contributions from others are involved, every effort was made to indicate this clearly, with due reference to the literature.

This work was completed at Bucks New University, under the guidance of Professor David A. Brodie and Dr. Gavin R.H. Sandercock.

Dionne N.Y Matthew

CHAPTER 1: INTRODUCTION TO THE THESIS

1.1 Introduction

The significance of the impact of lifestyle factors such as diet and exercise on disease risk has become more apparent. Over time, government initiatives have been put in place to encourage healthier lifestyles (Attree 2006; Kelly & Stanner 2003; Kraak et al. 2009; Vallgarda 2001). Measurement techniques with proven prognostic value may help this initiative by providing early warning signs for risk of disease. Measurements such as BMI are already in use, but more specific measurements such as body composition and cardio-respiratory measures may provide greater distinction. Body composition involves measurement of adipose tissue and other components such as muscle, bone and minerals in the human body. The relationship between excess adiposity and disease risk has been reported in several studies (Abbasi et al. 2002; Burton & Foster 1985; Must et al. 1999; Pi-Sunyer 1991). The diseases linked with increased adiposity include diabetes, cancers, lung and heart disease; these diseases are projected to cause 52 million global deaths annually by 2030 (World Health Organization 2010).

1.1.1 Heart failure

There are approximately 900,000 people known to be living with heart failure (HF) in the UK and a similar number are believed to be undiagnosed (National Clinical Guideline Centre 2010). The prevalence of HF is highly correlated with age, with the average age of diagnosis being 76 (Cowie et al. 1999). HF is one of the most common reasons for hospital admission (Cleland et al. 2005). The mortality of HF is less than 10% per year, with 30-40% of patients diagnosed with HF dying in the first year (Cowie et al. 2000).

First presentation or slow onset of symptoms is referred to as acute heart failure (AHF) while persistent, stable, or worsening symptoms are known as chronic heart failure (CHF) (Dickstein et al. 2008). HF can be complex and progressive, resulting in increased strain over time which can lead to hospital readmissions (Annema et al. 2009). Rates of readmission range between 25% and 50% within 6 months of the first hospitalization and are often seen as preventable in 23% to 31% of these cases (ibid).

Hospital admissions due to HF cause considerable public health expenditure (Brotons et al. 2009), costing the NHS an estimated £716 million per year (Petersen et al. 2002).

Early detection of critical changes in patientsô vital signs can help in identification of worsening HF and prevent rehospitalisation (Cleland et al. 2005). The use of communication technology to monitor patientsô clinical status is gaining attention as an important strategy to improve the care of patients with chronic disease (Chaudhry et al. 2007). Intervention techniques such as cardiac rehabilitation, daily monitoring of vital signs and weight monitoring can aid in preventing readmission by highlighting deterioration before it is severe enough for readmission.

1.1.2 Cardiac rehabilitation

Documented benefits of cardiac rehabilitation (CR) consist of improvement in exercise tolerance, improvement in symptoms, improvement in blood lipid levels, reduction in cigarette smoking, improvement in psychosocial well-being, reduction of stress and reductions in mortality (Wenger 2008). The benefits of exercise training were reported in a controlled cross-over trial where they observed a 20-25% increase in exercise tolerance, peak oxygen consumption and symptoms in patients with CHF (Coats et al. 1990). CR through exercise has been associated with a reduction in the debilitating symptoms caused by HF (ExTraMATCH Collaborative 2004). The intensity of CR and the physiological response to it requires careful monitoring. Heart rate variability (HRV) may be a viable alternative to present monitoring methods, such as heart rate, blood pressure and oxygen consumption.

HRV is accepted as a valid and reproducible technique for assessing autonomic activity (Nolan et al. 1998). Changes to HRV occur during exercise, and are caused by an increase in sympathetic activity and a decrease in parasympathetic activity (Gladwell et al. 2010; Perini & Veicsteinas 2003). An initial decrease in HRV has been demonstrated within minutes or hours following exercise in several studies (Mourot et al. 2004b; Parekh & Lee 2005; Terziotti et al. 2001). HRV measurements have been demonstrated as good tools for use in the prevention of overtraining, a state that occurs when the body has not had enough time to recover from exercise (Hedelin et al. 2000; Mourot et al.

2004a). By monitoring HRV levels daily, individuals can ensure they do not over-exercise. Since it has been recognized that HF patients are prone to impaired autonomic function (Nolan et al. 1998; Saul et al. 1988), the benefits of HRV measurement in patients with HF have been demonstrated (De Jong & Randall 2005; Sandercock & Brodie 2006).

1.1.3 Heart rate variability

HRV is a non-invasive measurement tool with great prognostic value. HRV has been defined as the amount of heart rate fluctuation found in the mean heart rate. HRV reflects the modulation of cardiac function by autonomic and other physiological regulatory systems (Akselrod et al. 1981). Since HRV has been demonstrated as an effective non-invasive measurement, its prognostic value has been utilized in the general population (Agelink et al. 2001; Amara & Wolfe 1998; Cowan et al. 1994; Yeragani et al. 1997; Zulfiqar et al. 2010) and diseased populations alike (De Jong & Randall 2005; Kataoka et al. 2004; Kudat et al. 2006; Nolan et al. 1998; Ponikowski et al. 1997; Sandercock & Brodie 2006; Schroeder et al. 2005; Tsuji et al. 1996; Tuininga et al. 1994). Impaired autonomic function, characterized by a decreased HRV is known to be predictive of death, especially in CHF (Marijon et al. 2010). In a prospective study of patients with CHF, a reduction in HRV was found to be the most powerful predictor of a risk of death due to progressive HF (Nolan et al. 1998).

The use of communication technology to monitor patientsô clinical status has gained attention as an important strategy to improve the care of patients with chronic disease (Chaudhry et al. 2007). Daily monitoring may provide patients with more access to care and can potentially give clinicians more information to help improve outcomes of chronic diseases (Dar et al. 2009). The present thesis uses a new daily monitoring device called Ithlete. Ithlete is an ECG receiver that attaches to a mobile device and takes one-minute measurements of HRV (rMSSD) and heart rate (HR), through the use of a standard heart rate monitor chest strap. As HRV can assess cardiac autonomic function, Ithlete measurements may provide a way to quantify the bodyôs autonomic response to exercise. Ithlete was developed as a tool for preventing overtraining in endurance athletes but may be a useful within clinical populations.

Therefore, the idea came about to apply HRV measurement by means of a simple, user friendly device, to guide exercise rehabilitation in patients with HF. The Ithlete device is a tool that can provide daily monitoring of HRV and HR, making these measurements available for both patients and clinicians. Ithlete could potentially help improve outcomes of chronic diseases by providing feedback on patientÕs responses to exercise/stress while also monitoring their risk for cardiac events. Daily HRV monitoring using Ithlete in patients with HF may have great potential as an easy to use, low cost medical device.

The proposed research study will deepen the understanding of HRV measurements in patients with HF using novel equipment that is easily accessible to the general population. Important questions will be answered about the ability of patients to monitor their own HRV on a daily basis. Therefore the main research aim of this thesis was to explore the potential use of home-based devices such as Ithlete and bioelectrical impedance analysis to supplement clinical care for patients with HF.

1.1.4 Body Composition

In the human body, body composition describes the percentages of fat, muscle and bone. The most common method used for measuring body composition at the population level is body mass index (BMI) (Department of Health 2011); however BMI is limited because it fails to discriminate between percent fat mass and lean mass (Romero-Corral et al. 2008). Due to these limitations, the use of other methods of body composition is becoming more mainstream. Body fat % can also be measured through a number of other methods, including skin-fold thickness, waist-circumference, waist-to-hip ratio, dual-energy x-ray absorptiometry (DEXA), and bioelectrical impedance analysis (BIA).

1.2 Aims and Objectives for this thesis

The aims for this thesis were:

1. To determine the feasibility of collecting daily measurements using a new personal HRV monitor (Ithlete) in healthy participants and patients with HF.
2. To define the normal range of rMSSD measurements in healthy participants and patients with HF using Ithlete software.
3. To test the reproducibility of rMSSD and HR measurements using the Ithlete software.
4. To look at how other correlates, such as exercise capacity, body composition or clinical symptoms, might affect HRV measurements.
5. To determine if Ithlete software can effectively aid CR programmes for patients with HF.

The objectives of this thesis were:

1. To assess the agreement between Ithlete software and the most popular field-based HRV measurement device (Polar s810i) in measurements of HRV (rMSSD) and HR, in both healthy participants and patients with HF.
2. To assess the ease of use of Ithlete software for measurement of rMSSD and HR in healthy participants and participants with HF, by evaluating compliance with day-to-day measurements in the home.
3. To determine the reproducibility of rMSSD measurements using a new personal HRV monitor (Ithlete) on a daily basis in healthy participants and patients with HF.
4. To explore the relationship between rMSSD and body composition measurements.
5. To examine interventions that take into account HF patientsô measurements of rMSSD, by utilizing Ithlete software to establish when the patient should train, how hard they can train, and when it is best to rest.

1.3 Outline

The majority of the empirical work undertaken for this thesis utilised a novel mobile application called Ithlete for measurement of HRV and HR. These measurements were validated against Polar heart rate software which has commonly been used for measurements of HRV and HR in both healthy (Earnest et al. 2004; Nunan et al. 2009; Vanderlei et al. 2008) and clinical populations (Conraads et al. 2004; Porto & Junqueira Jr 2009; Wisløff et al. 2007).

Chapter two is a review of the literature, which covers three main topics. First the review examines HRV and its value in clinical practice. Then HF is discussed and the importance of CR in treatment of the disease. Finally the review examines body composition, and how it can be measured. The empirical chapters (three-eleven) begin with two validation studies, the first compares HRV (rMSSD) and HR measured simultaneously with a Polar s810i and Ithlete on an iPod Touch. Chapter four examines measurement options for body composition by comparing several bioelectrical impedance analysis (BIA) devices of varying cost. The devices each measured weight, total body water and percentage body fat, with some devices measuring other items such as muscle mass or basal metabolic rate.

The next four chapters involve control subjects, first in chapter five the Ithlete application was used to explore the relationship between HRV and body composition measurements in healthy participants. The impact that these measurements could have on clinical populations was also discussed throughout that chapter. Chapter six used Ithlete software on an iPod touch for measurements of rMSSD and HR in healthy Caucasian and South Asian participants; this study investigated whether any ethnic or gender differences were demonstrated in various physiological measurements. Chapter seven assessed the relationship between HRV, body composition and aerobic capacity measurements in the same group of participants. Chapter eight assessed the use of HRV measurements to monitor exercise recovery in healthy participants. Participants completed HRV measurements daily, first thing in the morning, for a period of one-month, while also filling in a physical activity diary.

Chaptersô nine to eleven present empirical works undertaken in HF patients. In chapter nine, patients with HF completed daily HRV measurements first thing in the morning, for a period of one-month, while also filling in a physical activity diary. Chapter ten evaluated the adherence, user assessment and estimated a normal range for rMSSD in patients with HF. Chapter eleven discusses the implementation and evaluation of a CR programme using the Ithlete application for HRV measurements, as a guide for exercise intensity in patients with HF. Patients performed a six-minute walk test before and after the six-to-eight week CR programme, which involved home-based walking exercises with a pedometer to record the number of steps patients took each day.

Chapter twelve summarizes the findings of this thesis and provides recommendations for future research.

1.4 Thesis notes format

Within this thesis each chapter represents a separate piece of work linked by common themes (Figure 1-1). A common methodology was used in the work depicted in chapters six and seven; then chapters eight, nine, ten and eleven also share their methodology. Any repetition of material from one chapter to another is to give the individual chapters the look and feel of a full-length research paper. At the beginning of each chapter is a short executive summary. This is equivalent to an abstract, which could be used when the chapters are published. References conform to the format of Harvard referencing style and are found at the end of each chapter.

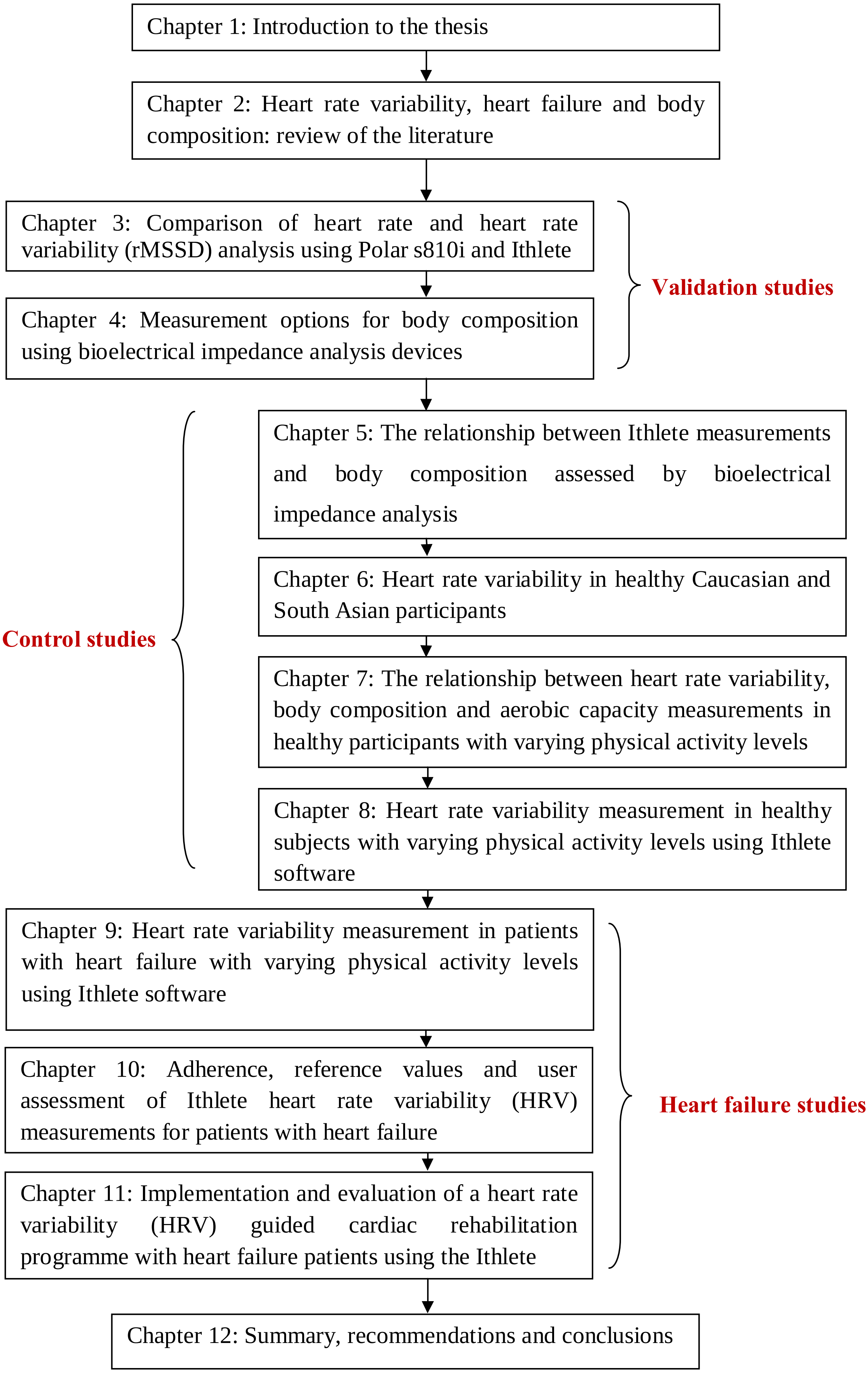

Figure 1-1 Flow of Thesis

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CHAPTER 2: HEART RATE VARIABILITY, HEART FAILURE AND BODY COMPOSITION: REVIEW OF THE LITERATURE

The amount of heart rate fluctuation known as heart rate variability (HRV) reflects the modulation of cardiac function by the autonomic and other physiological regulatory systems. HRV is accepted as a reliable technique for assessing autonomic function. Impaired autonomic function (measured through a reduction in HRV) is known to predict mortality from cardiovascular disease.

HF is a complex and progressive diagnosis which results in increased strain to the heart over time, which can lead to complications and associated hospital admissions. HF in various forms is highly correlated with age. Hospital admissions resulting from HF costs the NHS over £700 million per year, and is one of the most common causes for hospital readmission.

Cardiac rehabilitation has been credited with improvement in exercise tolerance, improvement in symptoms, reduction in cigarette smoking, reduction of stress and improvement in psychosocial well-being. A benefit from cardiac rehabilitation programmes of a 20-25% increase in exercise tolerance and symptoms has been cited in patients with chronic heart failure. Cardiac rehabilitation through exercise has been associated with reducing the debilitating symptoms caused by heart failure and providing patients with increased quality of life.

Obesity has become a global epidemic. Monitoring body composition can help identify those at greater risk of cardiovascular disease. It is recommended that nutritional status be measured on a regular basis in both hospitalised patients and those nutritionally at risk to reduce complications.

Identifying increased disease risk has become more important as diseases such as diabetes, cancer, heart and lung disease are on the rise; by 2030 it is projected that these diseases will cause more than fifty million global deaths annually (World Health Organization 2010b). Tools to monitor these risks are in growing demand and the accessibility of such devices for the general public may have an impact on the occurrence in the population. The aim of the present review is to discuss heart rate variability, heart failure, exercise in the form of cardiac rehabilitation and body composition measurements. This review will provide an introduction to methods of HRV analysis, the established prognostic value of HRV in both healthy and clinical populations, some limitations in the measurement of HRV, and discuss the effect of exercise on HRV. This review will also focus on one clinical population in particular, heart failure; and will examine the interactions that may occur between HRV, body composition and heart failure. These interactions will then be explored to see how they can help in the treatment of heart failure.

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2.1 Heart Rate Variability

2.1.1 Physiology of cardiovascular autonomic regulation

The human body is a complex system that has several subsystems interacting within it to keep it operational. One of those subsystems is the autonomic nervous system (ANS) which is part of the peripheral nervous system. It acts as the control system for visceral functions and works largely below the level of consciousness. The ANS can affect digestion, heart rate, respiration rate, salivations, perspiration, urination, sexual arousal and more. There are two branches of the ANS: the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS); the SNS generally coincides with arousal and energy generation while the PNS promotes calm and return to regular function (Brown et al. 2006). These two branches of the ANS control the rate at which the heart beats, working together to maintain homeostasis (Brown et al. 2006). At rest, the rhythmic beating of the heart was originally thought to be quite regular. However this view has changed to recognize that under healthy conditions the rhythm of a healthy heart is actually not at a steady rhythm. Heart rate variability (HRV) is a measurement of those beat-to-beat naturally occurring changes (Akselrod et al. 1981). There is a complex interaction between the sympathetic and parasympathetic branches which can be assessed using the non-invasive technique of HRV. This is achieved through analysis of the beat-to-beat oscillations of the R-R interval under various steady state conditions (Pagani et al. 1986).

2.1.2 Heart rate variability: definition and background

HRV was defined by Akselrod et al. (1981) as the amount of heart rate fluctuation found in the mean heart rate and reflects the modulation of cardiac function by autonomic and other physiological regulatory systems. Although various physiological regulatory systems are constantly at work throughout the body, the affect of respiration on heart rate variation in particular is an important factor to consider (Berntson et al. 1993). RSA (respiratory sinus arrhythmia) is a rhythmical fluctuation in heartbeat intervals (ibid). Changes in the length of these intervals occur in a phased relationship with inspiration and expiration (shortening during inspiration and lengthening during expiration). Current perspectives on RSA originated with Anrep et al. (1936) furthered by Daly (1985) and Feldman & Ellenberger (1988), which presented a clearer picture of determinants and underlying mechanisms of RSA (Berntson et al. 1993). HRV is a technique that measures the beat-to-beat variability in heart rate most often through an electrocardiogram (ECG). The cardiac cycle (heart beat) is represented in a typical ECG tracing by the QRS complex. From that QRS complex HRV is derived from one peak of the wave to the other (R to R) within the ECG. R-R intervals reflect the influence of changes in autonomic activity on cardiac function (Akselrod et al. 1981).

Homeostasis is maintained at the basal level through autonomic activity by balancing input from both branches of the ANS. HRV is mainly vagal, indicating parasympathetic influence which lowers heart rate. Some HRV measures are completely under vagal influence while others may represent sympathetic baroreflex activity. At rest vagal tone dominates over sympathetic tone; under normal physiological conditions abrupt activation of the PNS inhibits tonic SNS activation both at rest and during exercise (Levy & Zieske 1969; Yang & Levy 1984). Clinical application of HRV is somewhat limited due to a lack of standardization; this is due to practical problems such as noisy data, artefacts and ectopic beats (Kamath & Fallen 1995; Malik 1995). A task force set up in 1996 attempted to standardize and unify methodology (Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology 1996). This important paper is herein referred to as Task Force

(1996). There has since been other publications reporting normal HRV values (Agelink et al. 2001; Nunan et al. 2010); despite these efforts, there is still no consensus.

High variability in heart rate is an indication of good adaptability, which implies that an individual has well functioning autonomic control mechanisms. Cardiovascular autonomic regulation is associated with aerobic fitness; and enhanced autonomic nervous system function is associated with prolonged aerobic training. Aerobic training may protect the heart against harmful cardiac events, through a decrease in sympathetic outflow and an increase in cardiac modulation of heart rate (Billman 2002).

2.1.3 Introduction to methods of analysis

Measurement of HRV is typically undertaken using electrocardiogram (ECG) equipment with a sampling rate that is usually 1,000 Hz, providing accuracy at ±1 ms between R-R intervals. There is a large range in the recommended duration of recording throughout the literature. The duration can be as short as 30 seconds or as long as a 48-hour continuous recording. The significance of many HRV measures is often more complicated than generally appreciated, which leads to the potential for incorrect conclusions or unfounded extrapolations (Task Force, 1996). This led to the European Society of Cardiology and the North American Society of Pacing and Electrophysiology creating a task force to develop appropriate standards. Task Force (1996) advised and recommended definitions of terms, standards of measurement, defined physiological and pathophysiological correlates, described clinical applications and identified areas for future research. The task force provides the basis for many subsequent HRV measurements.

Different modes of analysis can be used for HRV measurement. There are three main modes which are time domain analysis (statistical measures), geometric methods and frequency domain analysis (also known as spectral analysis). All of these are discussed in more detail below.

2.1.3.1 Time domain variables

Time domain measurements are determined by either the heart rate at any given point in time or between successive normal complexes (Task Force, 1996). Using a continuous ECG recording, each QRS complex is detected and either instantaneous heart rate or all intervals between adjacent QRS complexes are used to derive HRV measurements (ibid). Each QRS complex results from sinus node depolarisations called normal to normal (NN) intervals and time domain variables can be derived either directly from the peak of one QRS complex to the peak of the other (R-R) interval measurements or from the difference between R-R intervals (Maud & Foster 2006). Time domain variables calculated directly from the measurement of R-R intervals are displayed in Table 2.1. Several of the time-domain measurements correlate highly with one other; due to its better statistical properties, rMSSD is preferred compared to pNN50 and NN50 (Task Force, 1996).

Table 2.1 Description of each time domain measurement

Measure	Description
Mean R-R (ms or seconds)	The mean R-R interval between all normal beats
R-Rmax – R-Rmin (ms or seconds)	Difference between the maximum R-R interval and the minimum R-R interval in the window of measurement or during a single or few breaths (Fouad et al, 1984)
SDNN (ms or seconds)	Standard deviation of all R-R intervals or normal heart periods
SDNN index (ms or seconds)	The mean of the standard deviations of all normal R-R intervals, usually five minute segments of the entire recording period in long-term recording e.g. the mean of 288 NN standard deviations
SDANN (ms or seconds)	The standard deviation of the average NN intervals calculated over short periods, usually for five minute segments which is an estimate of the changes in heart rate due to cycles longer than five minutes e.g. the standard deviation of 288 NN means
NN50 (number)	The number of adjacent R-R intervals that varied by more than 50 ms
pNN50 (%)	The percentage of adjacent R-R intervals that varied by more than 50 ms
rMSSD (ms)	The root mean square of the successive difference between the coupling intervals of adjacent R-R intervals

2.1.3.2 Geometric methods

Geometric methods represent R-R intervals in geometric patterns such as the triangular index and the triangular interpolation of NN. In the triangular index measure, the lengths of the R--R intervals are used to form the x-axis of the plot and the number of each R-R interval length is used for the y-axis. The triangular interpolation measure provides the baseline width of the distribution, measured as a base of a triangle which approximates the NN interval distribution of HRV (Maud & Foster 2006). This method is used less frequently compared to the others and further information can be found in the above reference. The advantage of geometric methods is their relative insensitivity to the analytical quality of a series of NN intervals (Malik et al. 1993); however a large number of NN intervals (at least 20 minutes, preferable 24 hours) are necessary to construct the geometric pattern, thus eliminating the option of short-term measurement (Task Force, 1996).

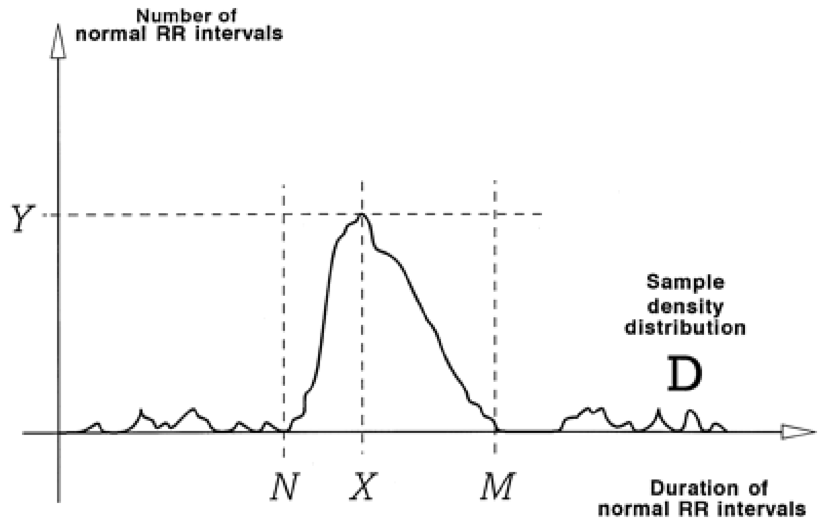

Figure 2-1 Geometric HRV measures on the NN interval histogram representing a 24 hour period (Task Force, 1996)

2.1.3.3 Frequency domain methods

Frequency domain analysis (spectral analysis) provides an understanding of the effects of sympathetic and parasympathetic nervous systems on HRV (Akselrod et al. 1981). Frequency domain measures are thought to have an advantage over time domain measurements because they offer more information about the relative contributions of sympathetic and parasympathetic function. How power (i.e. variance) is distributed as a function of frequency is demonstrated through power spectral density (PSD) (Task Force, 1996). There are three main activities recognized within the power spectrum described in Table 2.2.

Table 2.2 Description of each frequency domain measurement

Measure	Description
Very low-frequency (VLF)	Usually associated with less than 0.04 Hz and thought to represent fluctuations that occur very slowly and are possibly due to circadian rhythms and peripheral vasomotor and thermoregulatory influences (Appel et al. 1989)
Low-frequency (LF)	Usually associated with around 0.1 Hz and is partly dependent on sympathetic tone because of baroreceptor activity (Malliani et al. 1991)
High-frequency (HFr)	Synchronous with the respiration rate usually associated with a wide range of frequencies ranging from 0.2 Hz to 0.5 Hz depending on the breathing frequency and considered an indicator of vagal activity (Akselrod et al, 1981)

In physiological and environmental conditions where rapid dynamic changes in autonomic control may occur, investigators have used non-linear methods of measuring the complexity of heart dynamics (Goldberger 1996). Non-linear methods make the assumption that much of heartôs beating behaviour is aperiodic, but not totally random (Maud & Foster 2006).

Each method of HRV analysis has advantages and disadvantages to consider. HRV is mainly vagal (Karemaker & Lie 2000); some measures are totally vagal while others may represent sympathetic baroreflex activity. Factors that have an influence on HRV cause confounding effects, which limit the use of HRV in clinical populations (Huikuri et al. 1999). The next section will discuss some of those factors (both acute and chronic), which can influence HRV analysis.

2.1.4 Influences on HRV

There are various fundamental physiological acute and chronic factors that can have an effect on HRV. Acute factors include postural changes and time of day (Burger et al. 1999); various drug therapies such as beta-blockers (Chattipakorn et al. 2007); and caffeine has also been reported to improve autonomic function in both healthy participants and diabetic patients (Richardson et al. 2004). Chronic factors include the influence of age, aerobic fitness exercise, and overtraining; all of which have been reported in previous studies (De Meersman & Stein 2007; Hautala et al. 2009; Hedelin et al. 2000). Both factors will be discussed in more detail below.

2.1.4.1 Acute factors

Time of Day: Research into the affect of time of day on HRV is conflicting. In a study that analysed HRV measurements at three different times of day (morning, afternoon, evening) there was significant variation found and low reproducibility (Lord et al. 2001). When considering foetal HRV, Lange et al. (2005) found no effect of time of day. Another study however, on healthy male volunteers found that the reproducibility of some autonomic nervous tests varied throughout the day (Kowalewski & Urban 2004).

Postural changes: Vagal modulation in normal subjects did not reflect any changes due to different body positions (Avbelj et al. 2003). In a study of autonomic cardiovascular function in healthy young adults, autonomic activity was not significantly different in varying body positions (Watanabe et al., 2007). However HRV parameters within that study indicated sympathetic dominance during seated measurements (ibid). The short- and long-term reproducibility of autonomic measures in supine and standing positions found that HRV indices with the exception of the LF:HF ratio were independent of body position (Kowalewski & Urban 2004).

Exercise vs. Rest: The autonomic nervous system during exercise and physical training influences different mechanisms in the body. People that exercise regularly generally demonstrate an increased parasympathetic activity and lower heart rate when compared with sedentary people; this is especially noticeable at rest (Dixon et al. 1992). A high HRV at rest improves the capacity for adaptation to varying or unpredictable stimuli (Goldberger 1991). Athletes have a higher HRV at rest (this reflects a parasympathetic predominance) than sedentary people (Mourot et al. 2004). Different patterns of HRV measurements are found at rest and during aerobic exercise in both healthy subjects and acute myocardial infarction patients (de la Cruz Torres et al., 2008). Gender differences, hormonal regulation, thermoregulation and haemoglobin concentration have all been cited as potential influences on recovery and adaptation to exercise training and should be considered in the application of HRV training prescription (Kiviniemi et al. 2010b).

Overtraining or insufficient recovery period post exercise: An autonomic nervous system disturbance is suggested as a possible cause for symptoms such as reduced performance and pronounced fatigue (Hedelin et al. 2000). Overtraining is thought to have a negative impact on autonomic cardiovascular control (Hedelin et al. 2000). Female endurance athletes have displayed that increased training load and overtraining did not cause significant changes to cardiac autonomic modulation or intrinsic heart rate (Uusitalo 1998). Overtraining has a stronger effect on HRV in untrained women compared with their trained counterparts (Winsley et al., 2005). Abrupt changes in workload appear to signal changes in autonomic control compared with a progressively increasing load which triggers cardiovascular adaptation effects (Baumert et al. 2006).

Drugs (infusion studies/caffeine ingestion): An infusion study which assessed the role of free fatty acids (FFA) on the cardiac autonomic nervous system demonstrated that changes in plasma FFA levels may produce a parallel effect on cardiac sympathetic and parasympathetic balance in non-insulin dependent diabetic patients. Improved autonomic function was demonstrated with modest amounts of caffeine intake in both healthy and diabetic participants (Richardson et al. 2004). Caffeine intake in post myocardial infarction patients has been linked with an increase in parasympathetic autonomic function (Richardson et al. 2009). In a study of 30 male regular caffeine users, the effect of 100-200g of caffeine on HRV demonstrated no negative or positive effect from the drug (Rauh et al. 2006). Research on the effects of caffeine on HRV appears to be inconclusive.

Considering the influence of the acute factors on HRV, this thesis will attempt to streamline measurements. Participants will be encouraged to take their measurements in a seated position, first thing when they wake up to ensure it is a resting measurement. Participants will also be asked to take measurements before they have anything to eat or drink (including medication) to ensure measurements are taken under similar circumstances daily.

2.1.4.2 Chronic factors

Gender: Gender is an important determinant of HRV in healthy subjects (Antelmi et al. 2004). The majority of research looking at gender differences in adults cites women with a higher vagal influence than men (Antelmi et al. 2004; Gregoire et al. 1996; Liao et al. 1995). In contrast studies looking at gender differences in children have found girls to have a lower HRV compared to boys (Faulkner et al. 2003; Umetani et al. 1998). This signifies that the effect of gender may be modulated by age.

Age: There appears to be an inverse relationship between age and HRV: as age increases HRV decreases (Pomeranz et al. 1985). In the literature, this decline in HRV has been attributed to a decline in the efferent vagal cardiac tone and decreased B-adrenergic responsiveness (Mølgaard et al. 1991). HRV-parasympathetic function in particular has been connected to healthy longevity. A progressive decrease in HRV is associated with age and can be predictive of mortality in different clinical populations (Zulfiqar et al. 2010). The preservation of autonomic function was a key determinant of longevity; age related changes were discovered in four time domain measures of HRV (ibid).

Measurements of rMSSD and pNN50 rapidly decreased with aging, especially in the second to fifth decades of life. SDNN and SDANN measures also decreased with age, also highlighted in the second and fifth decades of life. The decrease in HRV-parasympathetic function with aging reversed in the eighth decade suggesting a critical threshold for long-term survival (Zulfiqar et al. 2010). Limitations to these finding however are important to consider as the study was cross-sectional. In order to make definitive analysis of age-related changes a prospective longitudinal study would be needed. The presence of other conditions that may have impacted the results were also not necessarily explored properly as no exercise testing, echocardiographic examination or other measures were used to help get a better assessment of overall health status. A constant decline of cardiac vagal modulation is associated with normal aging and is the result of a significant decrease in nocturnal parasympathetic activity (Bonnemeier et al. 2003).

Exercise: In a review of the effects of exercise on HRV, exercise training resulted in significant increases in R-R interval and high frequency spectral power following exercise (Sandercock et al. 2005a); this however, was influenced by study population age (ibid). Several other reviews have summarized the effects of exercise training on HRV (Aubert et al. 2003; Carter et al. 2003; Nunan et al. 2010b; Sandercock et al. 2005a). The largest increase in R-R interval was found in the youngest subjects and subgroup analysis demonstrated age, gender and previous physical activity level influenced R-R interval response. From the present review it is clear that HRV is an important tool to be utilized in several populations, but more research is needed to refine this technique.

Higher HRV values of rMSSD have been demonstrated in aerobically trained and anaerobically trained athletes when compared to their sedentary counterparts (Aubert et al. 2003). A lower resting heart rate in athletes was also demonstrated in several studies, after endurance training resulted in enhanced vagal tone in athletes (ibid). Endurance training results in decreased sympathetic activity and increased parasympathetic activity and increased HRV in the human heart at rest (Carter et al. 2003). In healthy individuals, Sandercock et al., (2005a) reported that exercise training causes increased cardiac vagal modulation accompanied by resting bradycardia. Before, during and after a graded exercise test, resting short-term HRV measurements have been recommended for assessing cardiac autonomic health (Nunan et al. 2010a).

A meta-analysis in 2005 demonstrated that exercise training lasting at least four weeks in duration resulted in significant increases in R-R interval and high frequency spectral power (Sandercock et al. 2005a). Hautala et al., (2009) confirmed that regular aerobic training is linked with increased cardiac vagal modulation of heart rate (HR) and autonomic nervous system function is an important determinant of a healthy individualôs response to aerobic training. In contrast, low variability in HR is an indication of abnormal and insufficient adaptability of the autonomic system; implying the presence of a physiological malfunction in the individual (Pumprla et al. 2002).

Prescription Drugs: In heart failure patients (NYHA class III and IV[2]) a significant improvement by 41% was observed in the HF component of those who used beta blockers (Aronson & Burger 2001). Tricyclic antidepressants have demonstrated reductions in HRV compared with selective serotonin inhibitor, paroxetine, which normalizes HRV (Gorman & Sloan 2000). Findings concerning oestrogen replacement therapy appear to be controversial with some citing moderate improvements to HRV (Gökçe et al. 2005; Rosa Brito-Zurita et al. 2003); and others citing no affect on HRV (Carnethon et al. 2003; Virtanen et al. 2000). Digoxin is known to increase HRV especially in measures thought to represent parasympathetic activity (Flapan et al. 1997).

Ethnicity: Ethnic differences in HRV have been reported in the literature with conflicting findings. In one study HRV measures were lower with larger sympathetic contribution to power in black adolescents (Faulkner et al. 2003). In other studies African American youth demonstrated a higher HRV when compared with European American youth (Urbina et al. 1998; Wang et al. 2005). A lower sympathetic drive was found in an age matched racial (black- white) comparison within an adult population (Guzzetti et al. 2000). The prognostic value of these ethnic differences in HRV are

[2] NYHA classes are explained in detail on page 33

unknown, researchers are beginning to look at how much physical activity and fitness contribute to these differences (Eyre et al. 2013).

2.1.5 The use of HRV for prognosis

For many years HRV was utilized as a measurement of cardiac autonomic modulation in scientific publications, despite clear concurrent validity or retest reliability ever fully being established. These qualities of validity and reliability should be identified for any clinical measurement (Task Force, 1996). Considering what factors may influence HRV is essential to consider when using its measurement as a prognostic tool. When considering specific populations, impaired autonomic function (measured through HRV) is known to predict death, especially in chronic heart failure patients (Marijon et al. 2010). Early detection of critical changes in patientsô vital signs such as HRV can help in the identification of worsening heart failure and prevent rehospitalisation and other outcomes (Cleland et al. 2005). The use of HRV in clinical populations is on the rise; however there are limitations of this method to consider.

It is unclear whether measures of decreased HRV and mortality are causative or if it acts as a marker that can reflect the severity of disease (Sueta 2003). Various medications act directly or indirectly on the autonomic nervous system which can affect the reliability of HRV measurements, especially when studying HRV in specific patient populations (Task Force, 1996). Previous studies have cited HRV to have low predictive value which can be improved with the addition of other ECG derived parameters measured at the same time (Chattipakorn et al. 2007).

An association between decreased HRV and mortality has been established throughout recent literature. Most studies however, did this after controlling for other known risk factors such as hypertension (Thayer et al. 2010). Reduced HRV may also lead to those other known risk factors, which could make those studies underestimate the role of vagal function in death and disease (Thayer et al. 2010). Isolated HRV measurements have inadequate prognostic accuracy with low sensitivity and low positive prognostic accuracy as a univariate predictor (Kleiger et al. 2005). As a result, therapeutic implications of HRV are in doubt. Combining HRV with other risk variables has however been demonstrated as beneficial in practice (Kleiger et al. 2005).

The prognostic value of HRV in patients with myocardial infarction was demonstrated in a study by (Zuanetti et al. 1996) where all indexes of low HRV identified patients with higher total mortality. Low HRV as an independent predictive value was also confirmed by adjusted analysis of measures such as SDNN, rMSSD, advanced age and previous myocardial infarction (ibid).

2.1.6 Reliability of HRV analysis

All measures routinely used in clinical practice and research need to be both valid and reliable to ensure that future utilization of these measures cause no unforeseen harm to participants. Validity and reliability are dependent on appropriate statistical analysis. A valid and reliable study implies that the research presented was based on true facts and was written ethically by the researcher (Wood & Ross-Kerr 2011). HRV was reported as a reliable and reproducible technique for assessing autonomic activity in the late 90s (Noland et al. 1998). Several reliability studies have been completed; however there is still little consensus on what normal HRV values should be. Reference ranges for the healthy population were provided by Nunan et al, (2010) with stipulation that consideration of underlying disparate values and methodological factors be taken into account.

Laboratory recordings of HRV are carried out using many different experimental conditions including sitting, standing, tilt tests, lower body negative pressure and more. Some experimental conditions are more reliable than others; for example spontaneous breathing is less reliable than paced breathing (Pinna et al. 2007). Specific values of LF power in normal units and LF/HFr were improved by paced breathing, leading to a dramatic reduction (>50%) in the estimated sample size needed (ibid). The authors suggest this is due to better stabilization of LF oscillations caused by virtual abolition of respiratory-related frequency components within the LF band. At a 70 ° tilt, HRV measurements decreased with a reciprocal increase in sympathetic activity when compared with tests done in the supine position and at 10 ° (Sharma et al. 2010).

To ensure HRV measurements are reliable, it is important to make reference to the literature to make certain there is similarity in data collection methods, data treatment and study population (Sandercock et al. 2005b). Appropriate reliability coefficients need to be established within each particular study for accurate sample size calculation and quantification of the likely variation from test to retest to prevent non-significant findings due to low statistical power (ibid). For HRV comparison experiments to fulfil statistical assumptions, measurement should not be too far apart in time or too close to avoid carryover (Pinna et al. 2007). Studies in the literature that look at reliability demonstrated reduced reliability in clinical populations when compared to healthy subjects (Sandercock et al. 2005b). Good reliability in the HRV measures within the clinical population should be established by ensuring the measurement has been validated in that population in previous literature (ibid).

2.1.7 HRV: Some limitations

Despite HRV being an important research tool for both clinical and basic scientists (Tulppo & Huikuri 2004) there are still limitations of published reliability studies which have been documented throughout the literature. These include: (i) inadequate protocol (e.g. replicating measurements were taken too far from each other); (ii) insufficient sample size; (iii) too short or too long recordings according to current guidelines; (iv) limited selection of studied HRV parameters; (v) inadequate assessment of reliability due to the use of inappropriate reliability indices or to misapplication/incomplete inclusion of appropriate indices; and (vi) lack of indications on the practical implications of computed reliability indices (e.g. for the assessment of individual responses or for sample size estimation) (Pinna et al. 2007).

HRV has not yet been used consistently as a routine clinical method for a number of reasons. There are methodological problems involved in recording and analysing ECG traces (Lu & Yang 2009). There are different factors that may contribute to daily HRV readings i.e. night-time sleep, psychological and physiological stressors (Kiviniemi et al. 2010a).

The potential influence of respiration on RSA and consequently HRV must be considered in measurement analysis. Respiratory measures should be accounted for in HRV analysis as different patterns can affect the outcome of analysis (Berntson et al. 1997). Control of breathing under experimental conditions may have moderate effects on relationships between respiration and HRV (Brown et al. 1993). If respiratory control requires considerable effort it may affect RSA and could be problematic for accuracy and reliability.

A single ECG measurement can produce a large number of HRV indices as described above. The best HRV measurement variable to use in disease prognosis is unclear (Kleiger et al. 2005). A variety of non-liner variables, conventional time domain, baroreflex sensitivity, heart rate turbulence, spectral measures and geometric measures have each been significantly linked with outcome, with no variable consistently superior over the other (Kleiger et al. 2005). Coupling HRV measurements with other clinical prognostic tools in specific populations is found in the literature. For example, ejection fraction, exercise testing, late potentials or ventricular arrhythmias combined with HRV may differentiate subgroups of patients with both very low and very high total cardiac and arrhythmic mortality after myocardial infarction (Kleiger et al. 2005). Patients with heart failure are the specific population that will be explored in the next section.

2.2 Heart Failure

The British Heart Foundation defines heart failure as the condition in which the heart cannot pump enough blood to meet the needs of the body. Heart failure (HF) is recognized as an increasing health concern in industrialized nations especially within aging populations (Stewart & Blue 2001). Determining the extent of the impact of HF in each nation is challenging because of two associated issues. The first issue is due to HF representing a complex pathological process that is manifested from a number of different disease states such as valve disease or pericardial problems. The second issue results from there being no large-scale, systematic investigation of the epidemiology of HF from both physiological and clinical perspectives, making accuracy of diagnosis difficult (Petersen et al. 2002). This inaccuracy could lead to misdiagnosis or leave asymptomatic patients without a legitimate diagnosis.

HF results from any structural or functional disorder that impairs the pumping ability of the heart. Problems within the heart, which have weakened the heartøs pumping action, lead to difficulties in other parts of the body receiving blood and therefore oxygen. Systolic HF and diastolic HF are the two main types. Systolic HF arises when the heart lacks sufficient force to eject enough blood into the circulation because its ability to contract deteriorates. Diastolic HF is a reduction in the heartøs ability to relax and fill with blood as a result of stiffening of the heart muscle. The most common cause of HF is systolic dysfunction which accounts for approximately 60-80% of patients compared with 20-40% from diastolic dysfunction. HF can be caused by different factors. Some common risk factors include high blood pressure, coronary artery disease, damaged heart valves, diabetes, and weakened heart muscle due to viral infections or toxins. For prevention of HF, maintaining a healthy weight, not smoking, eating a balanced diet and participating in physical activity regularly is recommended by the British Heart Foundation.

2.2.1 Prevalence

When considering the UK as a whole, the British Heart Foundationøs statistical database estimated a total prevalence of approximately 900,000 and a similar number as yet undiagnosed (National Clinical Guideline Centre, 2010). That estimation is based on the application of age-specific heart failure rates derived from several UK studies of population demographics. A large scale survey of patients being treated for HF determined prevalence rates to be 8-16 per 1000 in the general population; which rises to 40-60 cases per 1000 among those aged 70 and above (Clark et al. 1995). In 2002 around 650,000 people in the UK had definite HF while another 225,000 probably have HF (British Heart Foundation Health Promotion Research Group, 2002).

HF has a complex, progressive nature leading to adverse outcomes such as hospitalization. Readmission rates to hospital vary between 25% and 50% within 6 months of the first hospitalization for HF (Inglis et al. 2006). Hospital admissions due to HF cause considerable public health expenditure (Brotons et al. 2009), costing the NHS an estimated £716 million per year (Petersen et al. 2002). HF is one of the most common reasons for hospital admission and has a three-year mortality rate of approximately 60% (Cleland et al. 2005). Advances in treatment have improved outcomes in chronic heart failure (CHF) but high morbidity and mortality still persist and remain an increasing health problem (Investigators 2005). Potentially preventable factors such as non-adherence to drugs and diet, inadequate social support and failure to seek prompt medical attention when symptoms worsen result in an increased risk of readmission (ibid).

The prevalence of HF is highly correlated with age, with the average age of diagnosis being 76 (Cowie et al. 1999). The mortality of HF is 30-40% for patients in the first year of diagnosis but less than 10% per year after (Cowie et al. 2000). In the industrialized world, a predicted increase in the prevalence of HF is parallel with life expectancy. This is due to the successes of medical therapy for conditions such as hypertension which is known as one of the risk factors of HF (Senni et al. 1999).

Worldwide, HF affects many people and is expected to increase with the aging population and better rates of survival for patients after myocardial infarction (Annema et al. 2009). CHF is a syndrome that affects approximately seven million Europeans and five million North Americans each year (Inglis et al. 2006). Acute HF is the rapid onset of symptoms and signs secondary to normal cardiac function (Nieminen et al. 2005). This occurs when there is decompensation in chronic stable HF which usually happens in accordance with intercurrent illnesses such as pneumonia, uncontrolled hypertension etc. This is often life-threatening and requires urgent treatment (Nieminen et al. 2005). The most common cause of HF has been cited as coronary heart disease often in combination with hypertension but also on its own (Stewart & Blue 2001). There are also other common precursors including valvular dysfunction, cardiac arrhythmias, conduction disturbance, pericardial disease or infections (Stewart 2002).

2.2.2 Symptoms and classification

CHF usually involves symptoms such as breathlessness on exertion, fatigue, signs of fluid retention and/or other signs associated with the cardiac disorder (Scottish International Guidance Network 2007). Sometimes the cause of HF may be a congenital heart defect, infection of the heart valves or heart muscle itself, or can be unknown (ibid).

The New York Heart Association (NYHA) established functional stages of HF relating to everyday activities and patient quality of life. The best course of therapy is usually based on this assessment of which details are described in Table 2.3.

Table 2.3 New York Heart Association (NYHA) functional classifications

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

An early phenomenon in the clinical course of HF is sympathetic overactivation. This occurs when there is an increase in nerve activity which is clearly detectable in patients of all four NYHA classes. Consequences of sympathetic overactivation include increased oxygen and metabolic demands on the myocardium, reduced oxygen supply in the myocardium, augmented sodium and water retention, decreased myocardial arrhythmogenic threshold and a direct necrotic effect on the myocardium (Floras 1993). These consequences contribute to the exercise intolerance commonly found in HF patients (Grassi & Mancia 1999). The prevailing model associated with sympathetic overactivation assumes that it begins with ventricular systolic dysfunction, which increases the sympathetic outflow directed to all the vascular beds (Floras 2009). New knowledge however, such as the identification of a selective alteration in autonomic regulation with attenuation of HRV early in HF, amongst others, has prompted the proposal of a new contemporary model (ibid). The new contemporary model is an update on what mechanisms are responsible for sympathetic activation in HF. These mechanisms include 1) the impaired vagus nerve regulation of the arterial baroreceptor reflex; 2) muscle sympathetic nerve activity is blunted by conventional inhibitory ventricular baroreceptor reflex control; 3) elevated filling pressures may cause cardiac norepinephrine spillover by stimulating a cardiac-specific sympathoexcitatory reflex; 4) persistent pulmonary mechanoreceptor-mediated entrainment of sympathetic outflow; and 5) arterial baroreflex regulation of muscle sympathetic nerve activity modulates generalized sympathetic outflow and adjusts a centrally established set point for sympathetic outflow.

2.2.3 Pump failure vs. sudden cardiac death

Pump failure occurs when diminished cardiac output severely impairs the delivery of oxygen and nutrients to organs and tissues of the body. This is reflected by severe failure of the heartôs main chamber, the left ventricle. Sudden cardiac death is the result of a sequence of events produced by a lethal cardiac arrhythmia commonly ventricular tachycardia or fibrillation but could also be bradyarrhythmia or pulseless electrical activity (Tomaselli & Zipes 2004). In both cases the final pathway is the same, disruption to the electrical system causes the heart to stop beating, blood supply to the body is lost (particularly the brain) and the body dies. The prediction of sudden cardiac death appears more challenging because death in symptomatic CHF patients is often due to progressive pump failure (Brouwer et al. 1996). Sudden cardiac death does occur more often in less severe ambulatory CHF patients whose symptoms are less clear (Sandercock & Brodie 2006).

2.2.4 Predictors of morbidity and mortality in heart failure

HF has an unpredictable clinical path with a variety of individual factors relating to its outcome (Pocock et al. 2006). A number of models in HF have been reported as a means of refining and quantifying both individual and multiple factors together simultaneously for their predictive ability. In these models older age (starting at 60 years of age), diabetes and lower left ventricular ejection fraction (beginning <45%) are the three most powerful predictors (ibid). Other independent predictors include higher NYHA class, male sex, higher body mass index (BMI), lower diastolic blood pressure, previous hospitalization due to HF and decreased autonomic function. Common symptoms identified within HF are low exercise tolerance, arrhythmias, cardiothoracic ratio, disturbances in autonomic activity, and increased heart rate at rest. HRV is a measurement of autonomic function and its use as a predictor of mortality in HF patients is ongoing in research and will be discussed in the next section.

2.2.5 Heart rate variability in heart failure

In a prospective study of HRV and mortality in CHF, a reduction in the SDNN identified patients at higher risk of death (Noland et al. 1998). This study also found the reduction in SDNN to be a better predictor of death due to progressive HF than other conventional clinical measurements. A reduced cardiac parasympathetic activity indicated by a reduced HRV was found in 42 male patients with CHF (Nolan et al. 1992). This implies the importance of various HRV measurements in helping to diagnose or monitor high risks in the HF population.

Quality of life was assessed in two major studies in the USA which determined that HF impaired self-reported quality of life more than any other common chronic medical disorder (Stewart & Blue 2001). This suggests that the effect of HF on daily life is significant and needs to be addressed. HF can be complex and progressive, resulting in increased strain over time which can lead to hospital readmissions (Annema et al. 2009). Rates of readmission range between 25% and 50% within six months of the first hospitalization and are often seen as preventable in 23% to 31% of cases (Annema et al. 2009). Intervention techniques such cardiac rehabilitation, daily monitoring of vital signs and weight monitoring can aid in preventing readmission by spotting deterioration before it is severe enough for readmission.

The first study on HRV in HF was conducted by Saul et al. (1988) and sparked interest in the investigation of possible changes that occur in HRV in HF. The study explored correlations between HRV and current clinical status (Chattipakorn et al. 2007). The autonomic nervous system in HF is characterized by dysfunction in sympathetic activation, parasympathetic withdrawal and peripheral organ non-responsiveness (Grassi et al. 1995). As HRV provides a non-invasive, indirect measurement of autonomic control of the heart, it is an ideal measurement to use in patients with HF. A good functioning autonomic nervous system should yield a high HRV, which implies a healthy individual (Sueta 2003). In CHF patients, depressed HRV levels are regularly observed at all stages of systolic dysfunction (Fauchier et al. 1997). UK Heart was a significant prospective study conducted for more than a year on 433 patients with congestive heart failure (NYHA classôs I-III). It assessed the reduction of SDNN, creatinine, serum sodium, non-sustain ventricular tachycardia, cardiothoracic ratio and LV end diastolic diameter (Nolan et al. 1998). This study found that a reduced SDNN (<100ms) was the most powerful predictor of total mortality among a large number of clinical variables (Nolan et al. 1998).

Conventional HRV measurements are related to systolic left ventricular function (Nolan et al. 1992) and NYHA functional classification (Casolo et al. 1995). The severity of left ventricular dysfunction relates to decreased HRV and therefore is connected with a poor prognosis (Wijbenga et al. 1998). Compared with post myocardial infarction patients, evidence of HRV in HF has not been as extensively investigated (Chattipakorn et al. 2007). A continual progressive process of autonomic imbalance occurs in HF compared with myocardial infarction, where there is an impact of events followed by recovery of this imbalance (Chattipakorn et al. 2007). This makes finding the reference point to define the timing of HRV measurement in HF and comparison of different HF patients with similar clinical conditions difficult (Chattipakorn et al. 2007). A conclusive understanding of the pathophysiology of described alterations of HRV found in HF is lacking (Guzzetti et al. 2001). For HRV to be permitted for use as a clinical tool, more consistent data are required for understanding underlying mechanisms that induce the observed alterations in HRV in HF (Guzzetti et al. 2001).

Impaired HRV measures are commonly identified risk factors in CHF, where sudden cardiac death has been used as a clinical end point (Sandercock & Brodie 2006). The review paper by Sandercock and Brodie, (2006) found the best predictive HRV measures for all cause mortality were the global and/or slow oscillations in R-R intervals from both frequency and time domains. Sudden cardiac death was more difficult to predict because it occurs more often in lower NYHA class patients. Global HRV, along with NYHA class, patient age and Vo_2 max can predict pump failure, which suggests that it is closely related to disease severity. In sudden cardiac death however, the best risk factors are LF power, and LF/HFr power ratio which reflect the short term fluctuations and sympathovagal interaction (ibid). Sandercock & Brodie (2006) also found that the most powerful risk factor in three out of four subject groups from independent studies was power in the LF band from both long and short-term recordings. HRV can be improved with exercise training; this has already been demonstrated in older patients with HF (Murad et al. 2012). Exercise training in patients with HF can be facilitated through a treatment programme of cardiac rehabilitation. Cardiac rehabilitation is an important part of HF treatment along with pharmacological methods (Authors/Task Force Members et al. 2012).

2.3 Intervention: Cardiac Rehabilitation Programmes

Cardiac rehabilitation (CR) is a medically supervised programme designed to improve the health and wellbeing of people with heart problems. CR programmes usually encompass an overall approach to helping the patient adjust back to an active life style following heart problems. The programme usually consists of healthy lifestyle education including diet, exercise and stress reduction. Rehabilitation teams are made up of different professionals, which may include doctors, nurses, exercise specialists, dieticians, psychologists, physical and occupational therapists. CR clinical guidelines such as the Scottish Intercollegiate Guidelines Network, (2002) focus on rehabilitation of myocardial infarction and revascularization but also address angina and HF.

Patients with HF were originally cautioned against physical exercise until the late 1980s (Coats 2000). This was challenged and the benefit of exercise in patients with HF was demonstrated by Coats et al. (1990). An eight week training programme produced a 20-25% increase in peak oxygen consumption, exercise tolerance and reduced questionnaire-rated symptoms associated with their condition (Coats 1990). Participants in this study also found an increase in the ease and degree of performing daily activities (ibid). From the 1990s onwards the research in this area increased with larger and better designed studies in patients with HF, assessing the physiological benefits and increases in exercise capacity that are possible through CR (Coats 1999).

A CR programme is defined by the American Heart Association as a comprehensive exercise, education and behavioural modification designed for HF patients for improvement of physical and emotional well-being. CR has demonstrated improvement in physical health and a decrease in subsequent morbidity and mortality. This is achieved through exercise, education, behaviour change, counselling and support strategies (Taylor et al. 2010).

Increased morbidity from HF in developed countries is due to improved diagnosis and more successful treatment of acute illnesses including treatments such as CR (Neal 2004). Optimal physical activity levels of those participating in CR have not been established (Taylor et al. 2010). Reasons for this have been cited as difficulties in attending regular sessions and a reluctance to take part in group-based sessions. There are two types of CR, home-based and centre-based. Home-based rehabilitation is a structured programme carried out in the patientøs home with clear objectives for participants that include monitoring, follow-up visits, telephone calls etc. Centre-based CR is a supervised group based programme that can be based in various settings such as the hospital physiotherapy department, community sports centre or University gymnasium (Dalal et al. 2010).

2.3.1 UK cardiac rehabilitation guidelines

European and UK guidelines for CR are provided by a number of sources. These include The National Institute for Health and Clinical Excellence (NICE), The British Association for Cardiac Rehabilitation (BACR), The European Society of Cardiology (ESC) and the Scottish Intercollegiate Guidelines Network (SIGN). BACR and SIGN release guidelines for CR as a whole, while NICE and ESC release guidelines for specific disease states such as HF and myocardial infarction, and have the CR guidelines within that framework.

The BACR released standards and core components in 2007. The core components listed were as follows:

1. Lifestyle:
    I) Physical activity and exercise
    II) Diet and weight management
    III) Smoking cessation
2. Education
3. Risk factor management
4. Psychosocial
5. Cardio protective drug therapy and implantable devices
6. Long-term management strategy

Lifestyle should encompass risk stratification and baseline assessment to determine the appropriate exercise prescription, choice of venue (home/centre/community based) and appropriate staff and support structure for the patient. Dietary habits and anthropometric assessments should be used in diet and weight management. Counselling and pharmacological support should be given to each patient if smoking cessation is needed.

Misconceptions surrounding cardiac illness can be eradicated through education. Other risk factors should be highlighted for the patient and recognition of decreasing symptoms is paramount for patient health. Ensuring open communication with staff and counselling is appropriate to address problems such as sexual dysfunction, psychological issues or occupational factors. Close monitoring of risk factors such as blood pressure, lipid and glucose lowering are vital to ensure that patient health is not deteriorating. Psychological status should be monitored in patients to ensure anxiety and depression is not leading to a poor outcome. Psychological assessment through questionnaires and discussion should be used to monitor patient quality of life. Drug therapy such as ACE inhibitors, beta blockers and implantable devices are also important parts of patient therapy and should be taken into consideration throughout the rehabilitation process.

Long term management includes the patientø responsibility to pursue a healthy lifestyle while ensuring they have the appropriate support to do so. Assessment over time will ensure that patients have appropriate support and encouragement (British Association for Cardiac Rehabilitation 2007). NICE provides guidelines for CR in patients with HF through reviews of the literature. Clinical evidence statements provide information on standard care vs. exercise rehabilitation and changes in NYHA class recorded in the literature from various experimental groups.

The American Heart Association reported that CR programmes should consist of exercise training with multifaceted and multidisciplinary approaches to cardiovascular risk reduction (Balady et al. 2000). Every CR programme should include specific core components that aim to maximize the cardiovascular risk reduction by:

1. Encouraging healthy behaviours
2. Seeking ways to keep adherence to those behaviours
3. Reducing any effects that may lead to disability
4. Promoting an active lifestyle for patients with cardiovascular disease.

2.3.2 Core components

Core components of CR programmes include patient assessment, nutritional counselling, lipid management, hypertension management, smoking cessation, weight management, diabetes management, psychosocial management, physical activity counselling, and exercise training (Balady et al. 2000). Each section is explained briefly in table 2.4.

Table 2.4 Description of core components of cardiac rehabilitation programmes

Component	Evaluation	Interventions	Expected Outcomes
Patient Assessment	Medical history, Physical examination, Testing	Written record, feedback between patient and health care provider	Improved quality of life, goals and strategies established, written summary of patient outcomes
Nutritional Counselling	Estimates of daily caloric intake, assess eating habits and make targets for areas of nutritional intervention	Specific dietary modifications, diet plan, educate and counsel patient, incorporate behaviour change model and compliance strategies	Adherence to new diet, new understanding of good nutrition, plan in place to address eating behaviour
Lipid Management	Obtain fasting measures of lipid values, assess current treatment and compliance, add lipid lowering medication and assess at 6 weeks and 2 months	Provide nutritional counselling to help reduce triglycerides through exercise, alcohol moderation, drug therapy etc., provide intervention to increase HDL through exercise, smoking cessation etc.	Frequent assessment and modification of treatment, reduce LDL to <100 mg/dL, triglycerides to <200 mg/dL and HDL to >35 mg/dL
Hypertension Management	Measurement of resting BP on 2 occasions, assess treatment compliance	Provide lifestyle modifications such as exercise, sodium restriction, alcohol moderation, drug therapy	Get BP values to systolic of <130 mm Hg and diastolic of <85 mm Hg
Smoking Cessation	Assess psychological issues, classify patient as non-smoker, former smoker, current smoker, determine readiness to change	Provide education and counselling, encourage physician, staff, family support, provide relapse prevention	Select quit date, facilitate goal setting, complete abstinence from smoking and use of tobacco products

Weight Management	Measure weight, height, waist circumference and calculate BMI	Establish short-term and long-term weight loss goals, develop combined diet, exercise behavioural program, aim for energy deficit of 500-1000 kcal	Continued assessment, modification of interventions, monitor goal achievement, adherence to diet and exercise program to achieve weight loss goals
Diabetes Management	Identify diabetic patients through medical history, obtain fasting plasma glucose	Develop diet plan, monitor glucose levels, develop regimen of healthy diet plus exercise, insulin therapy etc.	Normalization of fasting blood glucose at 80-110 mg/dL
Psychosocial Management	Identify psychological distress through levels of depression and anxiety	Education, self-help strategies, refer to mental health professional if deemed appropriate	Develop plan for ongoing management, find evidence of emotional wellbeing, demonstration of self-responsibility
Physical Activity Counselling	Assess current physical activity levels, evaluate activities relevant to gender, age etc.	Provide advice, support and counselling, set goals to increase physical activity	Increased participation in domestic, occupational and recreational activities, improved psychosocial well-being
Exercise Training	Obtain exercise test before participation begins	Develop individualized exercise prescription, include warm-up, cool down and flexibility exercises	Patient understanding of safety issues during exercise, lowered cardiovascular risk and improvement in overall outcomes

Information in Table 2.4 is summarized from Balady et al. (2000).

A self-help manual called the Heart Manual is used in some UK home-based CR and other countries including Canada, Australia, Italy and New Zealand (Lewin 1998). The manual is a prescribed exercise rehabilitation method developed for cardiac event patients after hospital discharge using a cognitive-behavioural framework (Lewin 1998). The view of the amount of activity that a patient can undertake after a cardiac event has changed over time with research developments shifting the bases of HF treatment. Ground breaking work by Mæland, (1988) demonstrated the effect patientsô beliefs had on their health status. This psychological study highlighted that 67% of patients rated their health as high before the event, then down to 21% at discharge from the hospital, 31% at six weeks and just 42% at 3-5 years (Mæland & Havik 1988). The patients perceived health status predicted their psychological recovery process, along with how soon then would return to work or had to be readmitted to the hospital.

The Heart Manual involves some key features which make the programme a more holistic approach: a six-week programme which includes workbooks, audio and written materials to help monitor progress; elements of exercise, health education and psychological assessment; and finally a trained facilitator is used to help guide the patient and their family through the programme (Lewin 1998). The Heart Manual helps focus patient recovery and assists in answering questions and concerns. The structure allows for careful monitoring and patient feedback through the use of their facilitator and care management team. Despite this elaborate structure, uptake of the Heart Manual programme has been poorly supported (Taylor et al. 2007). Research into the use of the Heart Manual in other countries has begun in Canada, Australia, Italy and others (ibid).

2.3.3 Cardiac rehabilitation in heart failure

Exercise interventions can result in a number of positive outcomes for patients with HF. Documented benefits of CR consist of improvement in exercise tolerance, symptoms, blood lipid levels, and psychosocial well-being (Wenger 2008). Reductions in cigarette smoking, stress and mortality have also been demonstrated (ibid). Only two fatalities were reported for 1.5 million patient hours of supervised exercise, demonstrating the safety of CR (Wenger 2008). The benefits of exercise have been reported in various healthy and diseased populations emphasizing its importance to quality of life. The following section will discuss exercise intervention studies conducted within the HF population.

2.3.3.1 Exercise intervention publications

Historically exercise was not recommended for patients with HF, and this was the case until the late 1980s (Coats 2000). The first publication on exercise training in HF was in 1987 and compared an exercise group with a control group for 11 months (Lipchenko & Fomin 1987). The exercise included walking, cycling and exercise therapy; an increase in exercise capacity, reduced heart rate increment and a greater reduction in systemic peripheral resistance were demonstrated in the exercise group when compared with the control group. There are two major reviews that have assessed the effectiveness of CR in HF particularly, the Cochrane review by Davies et al, (2010) and ExTraMATCH Collaborative, (2004). The ExTraMATCH Collaborative, (2004), found a significant effect of exercise training on the reduction of mortality in HF patients; however re-analysis of that trial data found there was no statistically significant difference of exercise training for HF patients when compared with controls (Davies et al. 2010; Gotzsche 2005). This was due to ExTraMATCH only using trials that reported survival data and the inclusion of unpublished data (Davies et al. 2010).

Other factors to consider include medical therapy as that provides proven survival advantage (Shekelle et al. 2003). In the HF-ACTION trial 94% of patients were taking beta-blockers, angiotensin-receptor blockers or angiotensin-converting enzyme inhibitors while 45% had implantable cardioverter defibrillator (Whellan et al. 2007), all known to reduce the risk of mortality. Therefore assessment of CR programmes must also consider the affect of medical therapy when assessing outcomes. In 1990 the benefits of exercise training were reported in a controlled cross-over trial with a 20-25% increase in exercise tolerance, peak oxygen consumption and symptoms (Coats et al. 1990). CR through exercise has been associated with a reduction in the debilitating symptoms caused by HF (ExTraMATCH Collaborative 2004).

Exercise can affect symptoms such as breathlessness and fatigue, through the effects on both the cardiovascular and musculoskeletal systems (McKelvie et al. 2002). Symptoms found in CHF patients have been linked to peripheral manifestations (Coats 2000). Localized or systemic forms of exercise therapy could benefit these peripheral manifestations and therefore modify symptoms and benefit patients, possibly affecting disease progression and survival (Coats 2000).

Exercise training programmes produce positive outcomes such as delaying the onset of anaerobic metabolism, increasing vagal tone, reducing sympathetic drive and increasing aerobic capacity in patients with HF (Dracup et al. 2007). The majority of studies conducted in this area are randomised controlled trials that focus mostly on symptomatic benefits and substitute markers of prognosis such as HRV and peak oxygen consumption (ExTraMATCH Collaborative 2004). Exercise training improves survival time in patients with HF due to considerably improved left ventricular systolic function (ExTraMATCH Collaborative 2004). Exercise capacity assessed with or without metabolic measurements has proven a more powerful prognostic tool than other traditional risk factors such as smoking, hypertension and diabetes (Myers et al. 2002). Variability in heart rate suggests that exercise training may reduce adrenergic tone and increase vagal tone which can have a positive effect on the important neurohormonal and musculoskeletal abnormalities that occur in HF (ExTraMATCH Collaborative 2004).

Several explanations have been offered to suggest physiologically how exercise training benefits patients with HF. These include ventricular remodelling (Haykowsky et al. 2007), improved myocardial contractility and diastolic filling (Belardinelli et al. 1999). In ischaemic patients particularly, improvement is by stimulating new vessel formation and dilating coronary vessels from improved myocardial perfusion which alleviates endothelial dysfunction (ExTraMATCH Collaborative 2004). Patients with HF demonstrate neurohormonal and musculoskeletal abnormalities (Davies et al. 2010; ExTraMATCH Collaborative 2004); measurements of HRV have shown that exercise training may increase vagal tone and reduce adrenergic tone (Coats et al. 1992; European Heart Failure Training Group 1998; Hepburn et al. 2005; Libonati 2013; Wienbergen & Hambrecht 2012); therefore reducing the effect of those abnormalities.

With an aging population the prevalence of HF is increasing and will significantly affect costs in the public health system (Miche et al. 2009). Finding ways to combat and treat this growing epidemic are important to ensure the health system can work at its best for years to come. Various exercise programmes may have different benefits for patients with HF. An increase in physical performance in elderly patients has been documented, however no clear recommendations on endurance versus muscle strengthening programmes have been published (Miche et al. 2009). A clear correlation has been established between peak Vo_2 and performance in the six-minute walk test, providing easy measurement and evaluation of stress tolerance in CHF patients (Guyatt et al. 1985). An increase in physical performance has been demonstrated in older patients (age 74 ±3) where peak Vo_2 and muscle strength significantly increased after six months (Miche et al. 2009). Despite the benefits to CR, participation remains suboptimal (Dalal et al. 2010).

2.3.3.2 Barriers to cardiac rehabilitation

Gender differences have been documented in the literature. When considering womenӳ responses to CR, the effects are equivalent to those of menӳ in Vo_2 peak and cardiac mortality (Kavanagh et al. 2003). Elderly women are, however, less likely to be referred for CR and are less likely to attend compared to their male counterparts (Wenger 2008).

A lower functional capacity at the time of admittance to CR tends to attain greater benefit. It is important to recognize what barriers may be preventing patients from participation in CR programmes. In other countries such as the USA, there are financial and ethnic barriers with non-white women being less likely to gain referral to CR programmes (Wenger 2008). A number of potentially modifiable factors predict attendance for CR programmes (Cooper et al. 2002). Indirect influences included gender, job status and health concerns; direct influences included lower income/greater deprivation, age, lack of belief in ability to influence the disease outcome (Cooper et al. 2002).

Qualitative studies which have researched the barriers and enablers which impact CR uptake have cited flexible services, transport, individual views, level of awareness or understanding of services and intervention, religious and cultural issues, one-to-one care/group care, communication problems and the absence of services or long waiting lists (Lakhmana 2009). Drop-out rates in CR range from 20% in the first three months to 50% in six months; women, smokers and patients who suffered more than one myocardial infarction were more likely to drop-out (Jolly et al. 2003). The uptake rate for those deemed medically suitable was 83%. Around 27% of patients referred did not, however, attend sessions due to reasons cited as ótoo illô, óhaving further investigationsô or óphysically incapacitatedô (NACR 2009).

A review by Thompson & Clark (2009), which analysed why so many patients do not receive CR in the UK cited distance, transportation issues, lack of convenience, lack of referral by physicians, lack of funds, illness, lack of interest, denial of severity of illness, not believing it will work or is suitable for them and family or work obligations. Common themes appear throughout the literature and further investigation within the UK of barriers patients may face in their referral to rehabilitation, and how to combat them, could help to increase participation. It is also important to understand what will motivate patients to seek out CR and what factors may help maximize its benefits to their health. Excess weight and excess adipose tissue are risk factors for cardiovascular disease and could potentially be used to help motivate patients to exercise. Physical activity can result in decreased body fat, which can impact exercise performance and health. Body composition, a measurement of body fat, will be discussed in the following section to help assess what impact it may have on HRV and patients with HF.

2.4 Body Composition

Body composition is measured by models that divide body weight into two or more components. The most frequently used are two or four component models. Two component models (2-C) consist of fat mass and lean body mass; and assume a constant relative hydration value for lean body mass (73.8%). Assessment methods using this model include skinfold thickness, bioelectrical impedance analysis and hydrodensitometry. The 2-C models provide reasonable estimates of body fat percentage, however influences such as age, gender, ethnicity and physical activity levels affect the proportions of water, mineral and protein within lean body mass, causing discrepancies in the measurement (Baumgartner et al. 1991; Deurenberg et al. 1989; Wagner & Heyward 2001). Multi-component models [three component (3-C) and four component (4-C)] divide the body into fat, water and solids (protein and mineral). The 3-C assumes a constant for the protein-mineral ratio, while the 4-C model divides the body into fat, water, mineral and protein components. Assessment methods using this model include dual-energy x-ray absorptiometry (DEXA), and computed tomography (CT, CAT).

2.4.1 Obesity

The World Health Organization (WHO) defines overweight and obesity as excess amounts of body fat that presents a risk to health. Obesity has become a global epidemic, with over 1.4 billion adults diagnosed as overweight or obese in 2008 (World Health Organization 2010a). Globally obesity accounts for 44% of diabetes, 23% of ischaemic heart disease and 7-41% of certain cancers (ibid). In clinical practice, the purpose of body composition measurement is to evaluate clinical nutritional status through measuring fat mass (FM) and free fat mass (FFM) (Thibault et al. 2012). Obesity has been recognized as a risk factor for diabetes and cardiovascular disease, both of which are associated with autonomic dysfunction (Lindmark et al. 2005; Schroeder et al. 2005; Thayer et al. 2010). It has been hypothesized that insulin resistance and the development of obesity-associated diseases are mediated by autonomic dysfunction. The precise relationship however, between adiposity and insulin sensitivity is still unclear (Liao et al. 1996; Lindmark et al. 2005; Shibao et al. 2007; Thayer & Lane 2007). It is recommended that nutritional status be measured on a regular basis in both hospitalised patients and those nutritionally at risk to reduce complications that result from poor nutritional status (Kondrup et al. 2003).

Subtypes of obesity have been recognized to help characterize specific trends including metabolically healthy but obese and metabolically obese, normal weight (Karelis et al. 2004). Metabolically healthy but obese are individuals who have elevated body fat but maintain a normal metabolic profile (i.e. favourable cardiovascular risk profiles and normal to high insulin sensitivity); metabolically obese, normal weight are lean individuals with clustering of metabolic and cardiovascular risk factors including elevated fasting glucose, systematic inflammation and insulin resistance (ibid). Metabolically obese, normal weight women are reportedly at higher risk for cardiovascular mortality (Romero-Corral et al. 2008); anyone in this subtype of obesity are at increased risk of developing diseases associated with obesity (Shea et al. 2011). Those who are metabolically healthy obese are free from the metabolic disturbances associated with chronic disease, despite carrying excess fat mass (Bluher 2010; Primeau et al. 2011).

2.4.2 Fat mass and fat free mass

Fat mass constitutes all lipids from adipose and other tissues in the body. Adiposity is characterized by a high fat mass percentage caused by excessive storage of fat in adipose tissue (Deurenberg & Yap 1999). Fat mass functions as a thermal insulator, stores energy for periods of lower energy intake, produces hormones and protects certain organs against mechanical damage by surrounding them (ibid). Adipose tissue is essential for life; classifications of optimal amounts are determined by gender and age. Age-adjusted body fat % recommendations are displayed in Table 2.5 and 2.6.

Table 2.5 Body-fat percentage recommendations for males

Age	Under fat	Healthy Range	Overweight	Obese
20-40 years	Under 8 %	8-19 %	19-25 %	Over 25 %
41-60 years	Under 11 %	11-22 %	22-27%	Over 27 %
61-79 years	Under 13 %	13-25 %	25-30 %	Over 30 %

Source: Gallagher et al, (2000)

Table 2.6 Body-fat percentage recommendations for females

Age	Under fat	Healthy Range	Overweight	Obese
20-40 years	Under 21%	21-33 %	33-39 %	Over 39 %
41-60 years	Under 23%	23-35 %	35-40 %	Over 40 %
61-79 years	Under 24%	24-36 %	36-42 %	Over 42 %

Source: Gallagher et al, (2000)

Conversely, fat free mass consists of all lipid-free chemicals and tissues including water, muscle, bone, connective tissue and internal organs. Fat free mass and lean body mass are often used interchangeably, however there are slight differences between them. Lean body mass contains a small amount of essential lipids (Lohman 1992). In body composition analysis, water is separated into its own category as it comprises up to 63% of body mass (Armstrong et al. 1997), and therefore will be discussed in greater detail.

2.4.3 Water

Water is essential to life; humans cannot normally survive without water for more than a few days, whereas they can go without food for considerably longer (Benelam & Wyness 2010). Adequate hydration is necessary for the body to sustain normal physiological functioning such as the transportation of nutrients, waste removal and the regulation of body temperature. The human body consists of between 45% to 75% water by weight; lean tissue is made up of a higher percentage of water at 70% compared to just 20% of fat tissue (ibid). Water in the body is found in different compartments of inner and outer cells called the intracellular and extracellular cells. Intracellular cells account for 65% while 35% is found in extracellular cells (Sawka et al. 2005). There are two types of extracellular cells: interstitial fluid (the fluid present between cells) and plasma (the fluid in the blood that transports blood cells around the body) (ibid).

In 2010, a study of 80 adults living in the UK reported average consumption of 2402 ml/day for females and 2056 ml/day for males (Al-Jalali & Shirreffs 2010). This is comparably higher than the amounts reported in the National Diet and Nutrition Survey (NDNS), completed in 2000-2001. NDNS reported that total beverage consumption in males was 1988 ml per day and 1585 ml per day in females (Henderson et al. 2002). In both studies, UK males consumed below the recommended amount on average of 2500 ml/day; females were over the average in Al-Jalali & Shirreffs, (2010) but below the average of 2000 ml/day in the NDNS survey (2000-2001).

Water is an important component of the bodyős natural structure, used for circulatory function, biochemical reactions, metabolism, substrate transport across cellular membranes, temperature regulation, and numerous other physiological processes

(Armstrong 2007). Fluid-electrolyte turnover and total body water (TBW) change constantly due to water gained from food, fluids, and water loss from the lungs, skin and kidneys (ibid). Water is vital for survival, and there is great interest in the advantages of good hydration for people to function well and to look and feel good (Benelam & Wyness 2010). Hydration levels will have different effects on the healthy population, athletes and clinical populations and the interaction with the environment is also an important factor to consider.

Euhydration is the term used to describe normal body water content. This does not occur at a specific point but rather is represented by an average (Oppliger & Bartok 2002). Dehydration or hypohydration is the process of uncompensated water loss that results in total body water falling below the average basal value. This process occurs through sweat, respiratory vapour, urine or faeces (Armstrong 2007). Hyperhydration occurs when ingested fluid temporarily increases body water content over the average basal level (ibid). Levels of hydration change over time and this process is important for maintaining healthy body function. Clinical populations and athletes are special populations that need to consider their fluid status. Through various disease states or physical activity, both of these groups need to monitor their hydration levels to ensure optimal health and body function.

2.4.4 The effects of hydration levels on clinical patients

Chronic mild to moderate dehydration has been associated with several disease states including fatal coronary heart disease. The influence of hydration on cardiovascular reactivity during psychological stressors was examined and a positive relationship was found between TBW and the change in heart rate, diastolic blood pressure and total peripheral resistance during reactivity to posture change (Patterson 2002). The most common fluid and electrolyte imbalance in older people has been reported as dehydration. Among nursing home patients admitted to hospital for acute illness, 34% were dehydrated (Hodgkinson et al. 2001). Mortality rates among older people with dehydration have been reported as high as 46% (ibid). More research however is needed in this area, looking at understanding the underlying mechanisms and physiological implications of long-term hydration, while taking into consideration various health risks.

2.4.5 Body composition measurement techniques

Body composition can be measured using a variety of techniques which includes hydrodensitometry, air displacement plethysmography, hydrometry, dual-energy x-ray absorptiometry, skinfolds, bioelectrical impedance analysis and near-infrared interactance model. Each measure is defined in table 2.7.

Table 2.7 Definition of body composition measurement techniques

Measure	Definition
Body circumferences [waist circumference (WC) or waist to hip ratio (WHR)]	Prediction of body fat from measurements of the waist (WC) or the ration between the waist and hip (WHR).
Body mass index (BMI)	Weight to height index calculated by the equation (weight (kg)/ height (m)^2)
Hydrodensitometry (Underwater weighing)	Measurement of body density (estimate of total body volume from the water displaced by the body when fully submerged).
Air Displacement Plethysmography (ADP)	Calculated from air displacement to estimate body volume
Hydrometry	Measurement of total body water (TBW) by dilution of isotopic tracers (concentration of hydrogen or oxygen isotopes is measured in saliva, plasma or urine to estimate TBW)
Dual-Energy X-Ray Absorptiometry (DEXA)	Measures bone mineral density by x-ray of an individualộs bones by two x-ray beams with different energy levels
Skinfolds	Indirect measure of the thickness of subcutaneous adipose tissue by measuring two layers of the skin and the underlying subcutaneous fat at selected sites. These measures are then input into a prediction equation.
Bioelectrical Impedance Analysis	A current is applied at a given frequency (which may vary) and the higher conductivity of water compared to the other compartments is used to determine its volume
Near-Infrared Interactance Model	Estimation of body fat % from the reflectance of near-infrared light off the underlying tissue
Computerized Tomography (CT)	Medical imaging using computer processed x-rays to produce topographic images of specific areas of the body

Adapted from Heyward & Wagner, (2004) Applied Body Composition Assessment

2.4.5.1 Bioelectrical impedance analysis

Bioelectrical impedance analysis (BIA) is an easy technique to use in the determination of fat-free mass and TBW. BIA is a portable and relatively inexpensive, non-invasive measure (Kyle et al. 2004b). The results are reproducible and rapidly obtained and the use of BIA as a bedside method has increased (ibid). This suggests BIA is a beneficial tool for use with both healthy and clinical populations.

BIA is also one of the ways hydration can be measured by using equations that convert reactance and resistance to estimate TBW. The term impedance arises from the combination between reactance (arising from cell membranes) and resistance (arising from extra and intracellular fluid) (Kyle et al. 2004a). BIA measurement generally takes approximately five minutes to perform. An undetectable current is passed through the body to determine resistance and reactance (Wilmore & Costill 1999). Water and electrolyte distribution in the tissues determines the electrical conduction between the electrodes. Fat mass has a greater impedance, so it is more difficult for a current to flow through it when compared with free-fat mass. Free-fat mass consists of all the body water and conducting electrolytes making conductivity much greater within this tissue (ibid).

There are however several different methods of BIA. The following section briefly describes each method as reported by (Kyle et al. 2004a).

- *Single frequency BIA*: measurement at 50Hz via surface electrodes placed on the hand and foot. Total body water (TBW) is technically not measured through this method as it does a weighted sum of extra-cellular water and intracellular water resistivities. It does however estimate fat ï free mass and total body water but cannot determine differences in intracellular water.
- *Multi-frequency BIA*: involved impedances at multiple frequencies ranging from 0 to 500 kHz which evaluate free-fat mass, TBW, ICW and ECW. Poor reproducibility has been reported in frequencies above 200 Hz and below 5 Hz especially for reactance measurements.
- *Bioelectrical spectroscopy (BIS):* made up of mathematical models and mixed equations. Published values vary, which may be explained by the wide

biological variations already present in the normal population; leading to the lack in improvement of mixed theory analysis over empirical prediction.

- *Segmental-BIA:* this method was developed to overcome inconsistencies that arise from resistance and body mass of the trunk. This method uses a six-electrode technique on peripheral electrode sites with new equations for fat weight based on fat distribution
- *Localized bioelectrical impedance analysis:* this method focuses on well defined body segments which minimizes interference effects.
- *Bioelectrical impedance vector analysis (BIVA or vector BIA):* R and reactance (Xc) are standardized for height and plotted as point vectors in the R-Xc plane. The individual vector is then compared with references of 50%, 75% and 95% tolerance ellipses calculated in the healthy population of the same gender and race.

2.4.6 Body composition measurement limitations

Body composition is affected by age, gender, physical activity level and disease. Densitometry and electrical impedance are detailed methods, which are known to yield accurate results but are based on hypotheses established in normal weight adults and therefore are not necessarily transferable to other populations (Rolland-Cachera 1993). Skinfold thickness tests are affected by a number of factors, those that increase skin thickness such as exercise, oedema or dermatitis; and dehydration which reduces skin thickness (Wells & Fewtrell 2006). Skinfold measurement also needs a certain level of expertise by the technician (ibid). Limitations to hydrodensitometry include measurement of residual lung volume, variation in body mass, underwater weighing and water temperature (Lohman 1981). Air displacement plethysmography, computerized tomography, dual-energy x-ray absorptiometry and near infrared interactance models are expensive compared to other methods such as skinfold or BIA assessment (Wagner & Heyward 1999).

The need for sample-specific impedance prediction models for BIA (particularly for single frequency measurements) has led to criticism of the method; especially because of proven differences in the body geometry and chemical composition of fat-free mass between ethnic groups (Ellis et al. 1999). A comparison between BIA and BMI for accurate prediction of body composition variables in healthy adults found BIA a more useful method for use in epidemiologic health surveys because BIA explained more of the variance in estimated fat mass and fat-free mass (Lukaski 1990).

When considering TBW, 24-hour water deficit varies from person to person. In athletes the range is generally from 1.5 to 6.7 L, and in sedentary individuals it is generally from 1.1 to 3.1 L. This is primarily attributed to the size of the body and the activity. TBW balance is then only achieved if dietary and metabolic sources of water are sufficient (Board 2004). Next the volume and time of water consumption must be considered as it may alter measurement of hydration status. If a large quantity of pure water or hypotonic fluid (e.g. 1.2 L in five minutes) is ingested this would result in the water entering the blood and kidney function producing a large volume of dilute urine before the intracellular and extracellular fluid could equilibrate (Armstrong 2007).

When considering hydration measurement, other conditions or complicating factors must be controlled or accounted for (Shirreffs 2003). Measurements of hydration should measure fluid volume and concentration in real time, have excellent precision, accuracy and reliability, be non-invasive, interpreted in concert with other hydration indices, be portable, inexpensive, safe, and simple to use (Armstrong 2007). The choice of hydration measurement should ultimately be determined by the sensitivity, accuracy, technical and time requirements and expense of the measurement device (Shirreffs 2003).

2.4.7 Hydration and cardiovascular function

Hydration status and exercise heat stress influence HRV independently (Carter III et al. 2005). The strong return of parasympathetic activity is thought to be the main mechanism underlying cardio-deceleration after exercise and the degree to which autonomic control of heart rate during recovery from exercise may be affected by hydration status (Carter III et al. 2005). Dehydration is associated with increased cardiovascular strain and dehydration alone negatively influences parasympathetic control and therefore HRV (ibid).

Cardiovascular function can be severely affected by dehydration. These effects include a decrease in orthostatic tolerance and a relative tachycardia at rest and during exercise (Charkoudian et al. 2003). Mild post-exercise dehydration of approximately 1% of body weight or more can lead to an increase in resting heart rate and/or decreased tolerance to lower body negative pressure which indicates impaired cardiovascular control (ibid). These affects have mostly been demonstrated through healthy subjects therefore experimentation on specific disease populations could help expand this area of research.

NICE (National Clinical Guideline Centre 2010) state that fluid retention can occur with heart conditions for two main reasons:

1. Fluid leaks into the lungs and/or veins due to blood flow from the body to the heart backing up
2. Inadequate blood volume from the heart to the rest of the body resulting in the kidneys sensing a decrease in blood flow and compensating by retaining salt and water.

Accurate fluid volume assessment is essential as the impact of therapeutic intervention is critical and differential diagnoses can be long and complicated (Peacock & Soto 2010). Blood volume analysis in patients with a history of CHF shows that increased blood volume is associated with increased risk of death or urgent cardiac transplant (Androne et al. 2004). Maintaining adequate hydration is important for all populations, but can have serious consequences for those more vulnerable due to circumstances or illness. More research is needed to determine the optimum non-invasive method for maintaining good levels of hydration in clinical population.

2.4.8 Fat mass and cardiovascular function

Excessive fat mass has an impact on the structure of the heart and its function (Poirier et al. 2006b). Excessive abdominal fat is a global risk factor for cardiovascular diseases (Yusuf et al. 2004); levels of risk vary among different gender and ethnicities (Poirier et al. 2006a). Reduced vascular endothelial function (general functional capacity of endothelial cells to synthesize and release nitric oxide) is linked with increased adiposity, particularly visceral (Brook et al. 2001;

Hashimoto et al. 1998). Reduced arterial elasticity is also associated with increased adiposity (Christou et al. 2005). Increased adiposity is linked to hypertension (Hall 2003), with several clinical studies showing that a gain in fat mass predicts the development of hypertension (Hall 2000).

Worsened sympathetic and parasympathetic function is associated with higher abdominal-to-peripheral fat distributions (Christou et al. 2004). Disturbances in cardiac structure have been linked to excessive fat mass (Lauer et al. 1991). Obese individuals tend to have larger chamber size, greater wall thickness and greater left ventricular mass (Hammond et al. 1988; Messerli et al. 1983). Left ventricular hypertrophy is a strong predictor of cardiovascular morbidity and mortality (Levy et al. 1990). Greater resting stroke volume and resting cardiac output are a result of increased cardiac mass and chamber dimensions found in those who are obese (Alpert & Alexander 1998).

2.5 Conclusions:

As a measure of autonomic function, HRV is potentially useful in both clinical and healthy populations. This review has discussed the prognostic value of HRV in clinical populations such as HF. HF is a complex disease, which affects millions of people in the UK and around the world. CR as a medical intervention in HF is underused and ways to improve uptake and completion of programmes are essential. The use of HRV in CR will be explored in the present thesis, using a novel device called Ithlete to take daily measurements. As obesity increases globally, access to different body composition techniques is essential in helping individuals monitor their risk. Cost, usability and access are important for any body composition device. The present thesis will explore novel devices for body composition and assess the relationship that may exist between HRV measured with the Ithlete application and body composition measured through BIA.

Technological advances in microprocessors, wireless technology etc. allow the assessment of physical activity and energy expenditure using several different personalised body monitoring devices (Andre & Wolf 2007). These devices, including heart rate monitors, accelerometers, indirect calorimetry devices and pedometers are often flawed by being too expensive, inaccurate or difficult to use in a free-living environment (ibid). Nonetheless, it is recognized that accurate self monitoring can provide important feedback to the user (Dilley 1998; Schnoll & Zimmerman 2001; Wierenga, Browning & Mahn 1990), emphasizing the need to test and find accurate inexpensive devices.

Using a new HRV analysis device called Ithlete software for the IPod touch measurements of HRV in both a healthy population and patients with HF, will be assessed and the following research questions will be asked:

1. Is Ithlete a reliable HRV measurement?
2. Can daily measurements of HRV (rMSSD) be collected using a new device (Ithlete) in participants both healthy participants and patients with heart failure?
3. Is Ithlete an easy device to use daily?
4. What is the normal range of HRV (rMSSD) in healthy participants and participants with heart failure using Ithlete software?
5. Can Ithlete be used to help facilitate a cardiac rehabilitation programme post heart failure?

The use BIA to test body composition will be assessed and compared in the healthy and heart failure populations and the following questions will be asked:

6. Is BIA an appropriate measure for hydration status in healthy and/or heart failure patients?
7. What is the difference in accuracy between various BIA devices?
8. Is there a device that participants can use in their home daily to assess body composition?
9. Are similar relationships present between Ithlete measurements of rMSSD and HR and other clinical risk factors?

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CHAPTER 3: COMPARISON OF HEART RATE AND HEART RATE VARIABILITY (rMSSD) ANALYSIS USING POLAR s810i AND ITHLETE

The present study was conducted to compare the analysis of heart rate variability (HRV) root mean square of successive difference (rMSSD) in milliseconds (ms) and heart rate (HR) in beats per minute (bpm) obtained from the Polar s810i heart rate monitor (HRM) (Polar Electro Oy) with Ithlete software (HRV Fit Ltd, Hampshire, UK) for the iPod touch at rest. Four moderately active participants, two healthy (H) (29 ±2.8 years of age) and two heart failure (HF) patients (68.5 ± 7.8 years of age) performed seated measurements with each device simultaneously during which R-R intervals were recorded. Bias, limits of agreement (LoA), significant differences and interclass correlation coefficients (ICC) were calculated.

High ICCs and narrow limits of agreement in the present study demonstrate good agreement between Polar heart rate monitor (HRM) and Ithlete devices. In addition, no significant differences were found between rMSSD measurements at $p < 0.05$ for three out of the four participants however, a significant difference between HR measurements was found between devices for all participants. Pearson correlations for HR in H participants were $r = 0.81$ and $r = 0.92$ ($p < 0.001$). HR Pearson correlations for HF participants were $r = 0.92$ ($p < 0.001$) and $r = 0.30$ ($p < 0.05$). Pearson correlations in H participants for rMSSD were $r = 0.56$ and $r = 0.76$ ($p < 0.001$); and 0.87 and $r = 0.90$ ($p < 0.001$) for HF participants.

When participants were grouped together as H or HF participants, Bland & Altman analysis demonstrated a bias for HRV of 2.0 ms for healthy and -2.75 ms for HF participants. LoA of -15.6 ï 19.7 for healthy and -13.8 ï 8.3 for HF were demonstrated between Polar HRM and Ithlete. Despite the larger bias and LoA, there were a limited number of outliers for HRV and HR (4.7% of HRV in healthy participants lying outside the LoA and 2.7% for HF participants; for HR 5.9% of differences lay outside of the LoA for both healthy and HF participants). ICCs were >0.85 in three out of four participants, suggesting that Ithlete and Polar HRV (rMSSD) readings have good agreement.

Therefore the Ithlete measurement system provides a new perspective for investigation of rMSSD and can be considered a good alternative device for short-term rMSSD measurement in both healthy and heart failure individuals.

3.1 Introduction

3.1.1 Heart rate

Cardiovascular diseases (CVD) are increasing all over the world and have become the number one cause of death globally (World Health Organization 2011). Resting heart rate (HR) has been demonstrated as a strong predictor for morbidity and mortality in the general population (Kannel et al. 1987), and in chronic heart failure (CHF) (Lechat et al. 2001; Pocock et al. 2006). Risk factors which increase the chance of getting CVD include smoking, unhealthy diet, obesity and physical inactivity. In the UK it is recommended that adults do at least 150 minutes per week of moderate-intensity exercise. To monitor the intensity of exercise, reliable telemetry HR monitors can be used for immediate feedback and storage of HR data for further analysis at a later date (Gilman & Wells 1993; Macfarlane et al. 1989; Robinson et al. 1991).

3.1.2 Heart rate variability

Heart rate variability (HRV) was demonstrated as a reliable and reproducible technique for assessing autonomic activity in the late 90s (Noland et al. 1998). Different habitual levels of physical activity may cause changes in HRV (Nunan et al. 2009). Studies have demonstrated that CHF patients have decreased HRV, and this decrease can be used to predict cardiac events (Fauchier et al. 1997; Nolan et al. 1998; Task Force. 1996). A good functioning autonomic nervous system should yield a high HRV, which implies a healthy individual (Sueta 2003). In CHF patients, depressed HRV levels are regularly observed at all stages of systolic dysfunction (Fauchier et al. 1997).

Environmental conditions (i.e. temperature, humidity), mental stress and body position (i.e. standing vs. supine) strongly influence HRV (Ewing et al. 1991). There are various indices of HRV analysis (Task Force. 1996), which include time domain, frequency domain and non-linear methods; adequate reproducibility of HRV in both time and frequency domain analysis (also known as spectral analysis) have been reported in several studies (Kautzner et al. 1995; Lord et al. 2001; Marks & Lightfoot 1999; Pardo et al. 1996; Pinna et al. 2007). The range of HRV measurement parameters can be analysed by several commercial devices. A brief explanation of measurement parameters will be discussed in the following section.

3.1.2.1 Measurement indices of HRV

Time domain measurements are determined by the heart rate at any given point in time or between successive normal complexes (Task force, 1996). Geometric measurements represent R-R intervals in geometric patterns, such as the triangular index and the triangular interpolation of NN. In the triangular index measure, the lengths of the R-R intervals are used to form the x-axis of the plot, and the number of each R-R interval length is used for the y-axis. The triangular interpolation measure provides the baseline width of the distribution, measured as a base of a triangle which approximates the NN interval distribution of HRV (Task force, 1996). Frequency domain analysis (spectral analysis) provides understanding of the effects of sympathetic and parasympathetic systems on HRV (Akselrod et al. 1981). Each method of analysis has advantages and disadvantages to consider. The cost of data collection may be significantly higher for some methods of HRV analysis, and reliability is dependent on appropriate statistical analysis.

Time-domain measurements are commonly used and involve several different HRV measures; these include SDNN, SDANN, total power and ULF power, VLF power and LF power, rMSSD, pNN50 and HF power. A full review of these measures and their interrelation can be found elsewhere (Nunan et al. 2010). There are high correlations between time and frequency domain measures of vagal activity suggesting they can be used interchangeably (Bigger Jr et al. 1989). The root of the mean squared differences of successive heart periods (rMSSD) and the high frequency power of the normal R-R interval power spectrum have correlations as high as (>0.90) (ibid). The present study will focus on one measure in particular, rMSSD.

3.1.2.2 HRV measurement duration and position

In the literature there is a large range in the recommended duration of HRV recordings. The duration can be as short as 30 seconds or as long as a 48-hour continuous recording (Task Force, 1996). Bigger et al. (1993) compared HRV measurement epochs of 2-15 minutes with 24-hour ambulatory recordings in patients with HF. Measurements of 2-15 minutes predicted death nearly as well as the same measures computed over a 24-hour period. The prediction of 2-15 minute recordings improved significantly when matched individually with each of the three best predictors of mortality (NYHA class, left ventricular ejection fraction, and crackling noises heard on auscultation of the lung) (ibid). A one-minute bedside deep breathing test of HRV in post-myocardial infarction patients also demonstrated that short-term measurements of HRV were good predictors of all cause mortality and sudden death (Katz et al. 1999).

Sandercock et al. (2005) outlined advantages to short-term HRV measurements including speed of execution, and ease of analysis. Short-term HRV measurements can be edited manually in various software applications, as they contain a number of individual R-R intervals, can be recorded under controlled conditions, and can be supervised by a researcher to ensure standardisation. Short-term measurement reliability of multiple indices of HRV have been assessed in several studies (Aubert et al. 2001; Bigger et al. 1993; Choi et al. 2006; Koskinen et al. 2009; La Rovere et al. 2003; Nunan et al. 2009; Pinna et al. 2007; Tharion et al. 2009), all of which have found acceptable reliability. Between HRV measures, time-domain values demonstrate adequate homogeneity but spectral measures appear to be mainly heterogeneous (Sandercock 2007). Time domain (statistical) measures such as total power, ultra low frequency (ULF) power, very low frequency (VLF) power, low frequency (LF) power, rMSSD, and pNN50 are highly correlated with each other (Kleiger et al. 1991).

HRV has been demonstrated as an effective measurement for 24-hour ambulant measurements (Furlan et al. 1990; Task Force. 1996), short term measurements (Bigger et al. 1993; Lucreziotti et al. 2000; Pagani et al. 1986) and very short term measurements (Thong et al. 2003). Typically HRV analysis devices measure several

HRV indices. Spectral analysis requires recording periods of at least five minutes, and a signal which has stationarity (Task Force, 1996). These requirements may be more difficult to obtain outside of a laboratory, however a simpler measurement (rMSSD), can be measured over short R-R interval recordings. The rMSSD measure also does not require stationary signal like spectral measures. Therefore this thesis will utilize rMSSD.

3.1.2.3 rMSSD

rMSSD is a time domain measure of HRV which reflects parasympathetic activity without being dependent on heart trends (Stein et al. 1994). rMSSD is independent of mean HR and considered robust against gradual trends over time (Hilz & Dütsch 2006). rMSSD is sensitive to short term high frequency heart period fluctuations, and is often used in clinical cardiology (Porges & Byrne 1992). There is a good correlation between rMSSD and frequency domain measures of high-frequency HRV (HFr) which reflects respiratory sinus arrhythmia (RSA) (Task Force, 1996). rMSSD is influenced by a variety of factors which include rate and depth of respiration, physiology of sinoatrial node, physical conditioning and age (Berntson et al. 2005).

The rMSSD measure is reported to be less sensitive to variations in respiratory patterns and has been suggested as superior to spectral methods of HRV assessment due to its sensitivity to vagal cardiac control (Penttilä et al. 2001). In research assessing the reliability of ultra-short HRV measurements (10 s) rMSSD emerged with high correlations with the standard 5-minute short-term recording (Thong et al. 2003). Nussinovitch et al, (2011) also found rMSSD to be a reliable parameter for assessing HRV from ultra-short 1-minute or 10-second resting ECG recordings. For experimental work, Pinna et al, (2007) recommended that research designs using HRV parameters for outcomes should be based on the parameters with the lowest variation, of which rMSSD was listed as one.

The rMSSD measure has been suggested as superior to spectral methods due to its sensitivity as a measure of vagal cardiac control, and is less sensitive to variations in respiratory patterns (Penttilä et al. 2001). There is a high correlation between absolute values of rMSSD and HFr variability in the respiratory range (Berntson et al. 2005). This suggests that rMSSD is perhaps useful as a time-domain index of vagal control of the heart (Berntson et al. 2005). There is typically a low-frequency cut off of 0.12 to 0.15 Hz in spectral estimates of vagal control due to limited sympathetic contribution to heart period variability beyond that frequency (Berntson et al. 1993). rMSSD has been demonstrated as an effective measure for effectively capturing respiratory sinus arrhythmia and a reliable assessment of cardiac vagal outflow (Penttilä et al. 2001).

rMSSD values in HF patients have been recorded in the literature at 21.5 ± 12.3 in 529 HF patients with a mean age of 62.0 ± 9.6 (Nolan et al. 1998). Another study documented rMSSD at 20 ± 2 in 59 HF patients (Brouwer et al. 1995), while a study looking at sudden cardiac death in HF found rMSSD values at 22.9 ± 14.9 (n=135) in survivors and 21.1 ± 13.2 (n=55) in non-survivors (Galinier et al. 2000). Other factors affecting HRV measurement must be considered for testing conditions; especially the duration of measurement and body position during measurement. Body positions have been tested on several occasions suggesting optimal testing protocol in athletic populations (Dantas et al. 2010; Porto & Junqueira Jr 2009; Reland et al. 2005). For athletes with a low resting HR, standing HRV measures are better because changes in parasympathetic activity may be harder to detect in the supine position (Kiviniemi et al. 2007). This should not be an issue for the present studyĝs population, as participants are all moderately active with resting HRĝs above 60 beats per minute (bpm).

Average HRV values have been published in various studies in healthy (Nunan, Sandercock & Brodie 2010) and diseased (Brouwer et al. 1995; Nolan et al. 1998) populations. There are still no clear references or definitive figures for what appropriate HRV values should be within specific populations. Therefore, clinical use of HRV has not yet been solidified as common practice.

3.1.2.4 Reproducibility of HRV

The reproducibility of HRV has been highlighted throughout literature as an important area for further research (Leicht & Allen 2008; Sandercock et al. 2005; Task Force, 1996). For athletes, HRV testing in the upright (standing) position is recommended over supine measurement, due to their typically low resting HR and the increase of sympathetic drive (Dantas et al. 2010). Research has demonstrated good reliability for both supine and orthostatic testing (Chen et al. 1999; Radhakrishna et al. 2000; Siebert et al. 2004). Measurements cannot be compared in different positions i.e. supine vs. orthostatic. Reproducibility between devices is also necessary before they are used in a research capacity. Polar s810 models have been validated for HRV measurement against ECG, and Holter devices among some other HRMǿs (Gamelin et al. 2006; Porto & Junqueira Jr 2009; Weippert et al. 2010).

Measurement of HRV was originally undertaken using ECG equipment with a sampling rate of 1,000 Hz, providing accuracy at ±1 ms between R-R intervals. Reproducibility depends on the time interval between measurement, mental stress, local conditions (temperature, noise) and spontaneous or paced breathing (Pinna et al. 2007; Pitzalis et al. 1996; Sandercock et al. 2005). Reproducibility of HRV increases when breathing periodicity is controlled in short-term recordings (5-10 minutes) (Pitzalis et al. 1996). Elements of mood, alertness and mental activity affect intra-individual variability in HRV parameters because of intrinsic instability of HRV (Pinna et al. 2007). In clinical populations such as HF, this is very hard to control (Stein et al. 1995). However, it is not necessarily important how variable HRV is because it is so sensitive to change (Sandercock 2007). The significance lies in interpretation, both in terms of expected values at baseline, and the expected magnitude of change (ibid).

3.1.2.5 HRV exercise and overtraining

Changes to HRV occur during exercise, caused by an increase in sympathetic activity and a decrease in parasympathetic activity (Gladwell et al. 2010; Perini & Veicsteinas 2003). An initial decrease in HRV has been demonstrated within minutes or hours following exercise in several studies (Mourot et al. 2004b; Parekh & Lee 2005; Terziotti et al. 2001). Furthermore, it appears to take longer to restore vagal tone following a high intensity bout of exercise (80% Vo_2 peak) compared with moderate intensity exercise (50% Vo_2 peak) (Mourot et al. 2004b; Parekh & Lee 2005). Overtraining occurs when the volume and intensity of a personǿs exercise exceeds their capacity to recover. During the early stages of overtraining, there is a typical shift towards sympathetic activation (and/or vagal withdrawal) (Halson & Jeukendrup 2004). A quantitative measurement of this shift may be useful in athletic monitoring. Overtraining is thought to have a negative impact on autonomic cardiovascular control (Hedelin et al. 2000). When considering different fitness levels, overtraining has a stronger effect on HRV in untrained women compared with their trained counterparts (Winsley et al. 2005).

Since HRV has been demonstrated as a non-invasive measurement of autonomic control (Task Force, 1996), this suggests that sudden and larger changes in workload will have a greater impact on recovery and HRV. Monitoring training for quantifying workload has been used by athletes since the 1970ós, and has been assessed in several studies (Banister & Calvert 1980; Earnest et al. 2004; Foster et al. 2001; Kiviniemi et al. 2010; Manzi et al. 2009; Stagno et al. 2007). HRV measurements have been demonstrated as good tools for use in the prevention of overtraining (Foster 1998; Hedelin et al. 2000; Hynynen et al. 2006; Mourot et al. 2004a; Uusitalo et al. 2000). By monitoring HRV levels frequently, individuals can make sure they do not progressively dip during an exercise training programme.

3.1.2.6 HRV measurement devices

There are many ongoing discussions about the use of different measurements, and which are the most accurate or best measures for a specific population. There are now several different HRV analysis systems on the market which include Polar, Nevrokard, Leadtek, Nerve Express. Polar machines measure HRV using various features of their heart rate monitor ranges, including the OwnIndex, Ownzone, and EnergyPointer. Nevrokard offer professional software tools and devices that can measure advanced HRV, blood pressure variability etc. Leadtek provides an autonomic system measuring time and frequency domain parameters and Nerve Express also provides autonomic system assessment via different modalities. These devices however, have limitations. Because HRV is not displayed directly on the devices, it can only be derived after feeding measurements through a separate software tool. These devices also need measurement durations of at least 5-minutes.

Traditionally, HRV research was confined to ECG systems or Holter monitors which require trained personnel for operation, are expensive and time consuming (Nunan et al. 2009). The development of ECG telemetry on wireless HR monitoring systems allows for field-based assessment. The Polar s810i has been validated against various

ECG systems (Gamelin et al. 2006; Kingsley et al. 2005; Nunan et al. 2008; Vanderlei et al. 2008; Weippert et al. 2010) deeming HRV analysis from Polar s810 HR monitorôs reliable.

A new device, called Ithlete, was developed as a software application with a dongle that can be used with smartphones and the iPod touch (2nd generation or later). Ithlete is an ECG receiver that attaches to a mobile device and takes one-minute measurements of HRV (rMSSD) through the use of a standard HR monitor chest strap. As HRV can assess cardiac autonomic function, Ithlete measurements may provide a way to quantify the bodyôs autonomic response to exercise. Repeated inter-individual assessment of HRV can be used to optimise the work-to-rest ratio (Manzi et al. 2009). Ithlete was developed as a tool for preventing overtraining in endurance athletes. Ithlete software for iPod touch is yet to be validated. The device has great potential because of its short measurement time, low cost and accessibility of the device. Validation is necessary however, to ensure it is an appropriate device to use in both healthy and clinical populations.

3.1.3 Aims

The aim of the present study was therefore to validate HRV measurement on novel equipment called the Ithlete, specifically determining if Ithlete and Polar s810i are interchangeable for measurement of rMSSD and HR. The present study uses Polar as the ógold standardô, because it is the most popular field based assessment tool for HRV available. This study proposes to use just one measure, rMSSD, in one minute measurements to assess HRV. With high correlations between the time-domain measures, there is no need to measure all of them each time HRV analysis is undertaken. rMSSD has been demonstrated in the literature as a reliable measurement with high correlation to the others. For the purpose of this thesis, HRV (rMSSD) will be the main measurement assessed across the various chapters and therefore the most important measure being validated in this chapter.

It is hypothesized that a good relationship will be demonstrated between HRV rMSSD (ms) as obtained from the Ithlete and Polar heart rate monitor.

3.2 Methods

3.2.1 Participants

Four participants took validation measurements: two heart failure (HF) patients from a London based hospital, and two healthy (H) participants with no known cardiovascular disease. During HF clinics, a Consultant Cardiologist recruited two participants with HF in accordance with NHS Research Ethics Committee standards and expectations. Two healthy research students were recruited in accordance with Bucks New University ethics committee standards and expectations. Participants were given an information pack before agreeing to participate. This information pack included:

1. An information sheet with details of the requirements for each participant
2. An informed consent form
3. An HRV measurement information package

Participants were requested to read the information pack prior to meeting with the researcher. During the first meeting any questions or concerns were addressed. All procedures were approved by the local research ethics committee. Participants completed their consent form in front of the researcher, and the researcher countersigned the form.

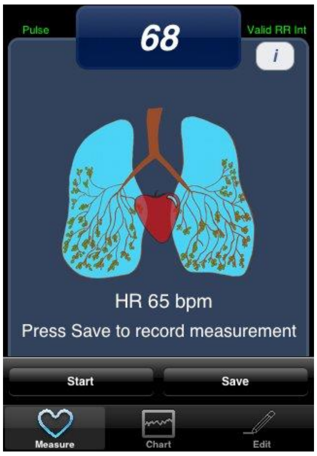
3.2.2 Experimental design

Following informed consent, participants with HF were asked to visit the clinic at their hospital to meet with the researcher for a demonstration. Two Bucks New University students met with the researcher in the University sport science laboratory. All four participants took part in a demonstration on how to use both the Polar s810i heart rate monitor (HRM) (Polar Electro Oy, Kempele, Finland) and the Ithlete software (HRV Fit Ltd, Hampshire, UK) on the iPod touch. They were required to complete two measurements in the presence of a researcher before taking the device home. Each participant then took both devices home and recorded R-R intervals simultaneously with a Polar s810i HRM, and the Ithlete software on the iPod touch. The researcher requested each participant record at least 50 HRV/HR measurements simultaneously with both devices.

3.2.2.1 Data acquisition

A standard analogue ECG chest strap was worn in the middle of the chest just under the sternum. Participants were instructed to undertake measurements in the seated position. Two indices (rMSSD in ms and HR in bpm) were recorded simultaneously via the Ithlete software (HRV Fit Ltd, Hampshire, UK) for the iPod touch (Ithlete 2009) and the Polar s810i HRM (Polar Electro Oy, Kempele, Finland). Real time heart and lung animation on the iPod touch facilitated paced breathing during one-minute Ithlete measurements, and the screen also indicated the reception of each heart beat from the analogue chest strap. Heart animation on the Polar HRM also signalled reception of each heart beat. First participants started the five minute measurement using the Polar s810i HRM, and within those five minutes were instructed to take a one-minute measurement using the Ithlete software. After each recording, measurements were saved to the respective device. The time was synchronized on both devices for each participant before measurement commenced. Measurements were matched by the time-stamp on each recording.

Figure 3-1 Ithlete software on an iPod touch vs. Polar s810i HRM



3.2.2.2 Data analysis

Ithlete readings via Ithlete software enables recordings to be emailed and saved into an excel spreadsheet. Polar HRM recordings were transferred wirelessly using a USB-infrared transmitter into Polar Precision Performance software. All recordings were transferred to a password protected PC. Polar R-R interval data were exported into Kubios Heart Rate Variability Analysis (Biosignal Analysis and Medical Imaging Group at the Department of Applied Physics, University of Kuopio,

Kuopio, Finland). After importing these R-R records into Excel 2007 (Microsoft Inc., USA) time series were graphically analyzed and manually edited to exclude aberrant beats.

3.2.3 Statistical analysis

Statistical analysis was carried out using PASW 19.0 (SPSS: An IBM Company. Somers, NY, USA). Data normality was tested by the Shapiro-Wilk test, and homogeneity of variance was verified by the Levene test. An independent-sample t-test was then undertaken to detect the presence of a systematic difference in HRV and HR values calculated by both systems. To compare the two devices on HRV/HR measurements, intra-class correlation coefficients (ICC) and their 95% confidence intervals (CI) were calculated. In addition, Bland-Altman plots with modified limits of agreement (LoA) were used according to Bland & Altman (2007) to evaluate the inter-method discrepancies and their stability across a wider value range.

Bland-Altman analysis involves a scatter plot, with the difference of the two measurements for each sample on the vertical axis and the average of the two measurements on the horizontal axis. Three horizontal reference lines represent the average difference between the measurements, along with lines to mark the upper and lower control limits of plus and minus 1.96 multiplied by sigma, respectively, where sigma is the standard deviation of the measurement differences. If the two methods are comparable, then differences should be small, and show no systematic variation with the mean of the two measurements ('Small' would be an amount that would be clinically insignificant for the factor being measured).

3.3 Results

The total number of recordings between all participants was 272. Twenty-three recordings had to be excluded due to large sequences of aberrant beats (error or noise) in the raw data. The two H participants, one male and one female, were aged 27 and 31 respectively. The HF participants were also one male and one female, aged 74 and 63 respectively. The HF participants were diagnosed NYHA class II (a disease characterized by a shift toward sympathetic over activity). All participants were moderately active, participating in exercise two-to-three times per week for no longer than 60 minutes per session. Average HR (bpm) and rMSSD (ms) values for each participant are displayed in table 3.1 below.

Table 3.1 Average values of heart rate variability (rMSSD) and heart rate (HR) for each healthy (H) and heart failure (HF) participant

	Polar HR (bpm)	**Ithlete HR (bpm)**	**Polar rMSSD (ms)**	**Ithlete rMSSD (ms)**
H participant 1	77.68 ± 8.14	74.47 ± 7.99	75.51 ± 13.07	78.29 ± 7.65
H participant 2	76.56 ± 6.53	74.28 ± 7.14	67.95 ± 7.20	68.56 ± 5.96
HF participant 1	83.24 ± 14.76	79.80 ± 12.83	55.16 ± 11.01	51.60 ± 10.51
HF participant 2	97.28 ± 15.52	91.99 ± 11.05	50.60 ± 12.98	48.81 ± 12.62

Repeated measures ANOVA revealed no significant differences in rMSSD measurements between Polar HRM and Ithlete in both H participants and one HF participant; the other HF participant had a significant difference. Details of the analysis can be found in table 3.2. Significant differences were found between devices in HR measurement. However, the standard error of the difference (SED) and mean difference (MD) were >2.5 bpm for HR and less than 2.5 ms for rMSSD.

Table 3.2 Paired sample t-test results for rMSSD (ms) and HR (bpm) in healthy (H) and heart failure (HF) participants

	p	**MD**	**Lower CI**	**Upper CI**
H participant 1 HR (bpm)	0.001	3.21	2.21	4.19
H participant 2 HR (bpm)	0.001	2.27	1.44	3.10
HF participant 1 HR (bpm)	0.001	3.44	1.73	5.14
HF participant 2 HR (bpm)	0.03	5.28	0.66	9.91
H participant 1 rMSSD (ms)	0.07	-2.77	-4.87	-0.68
H participant 2 rMSSD (ms)	0.55	-0.60	-1.99	0.79
HF participant 1 rMSSD (ms)	0.02	3.56	1.98	5.14
HF participant 2 rMSSD (ms)	0.06	5.61	0.17	3.39

Significantly high Pearson correlation coefficients were demonstrated between Ithlete and Polar HRM devices for both HR and rMSSD in both H and HF participants. Pearson correlations for HR in H participants were r = 0.81 and r = 0.92

(p < 0.001). HR Pearson correlations for HF participants were r = 0.92 (p < 0.001) and r = 0.30 (p < 0.05). Pearson correlations in H participants for rMSSD were r = 0.56 and r = 0.76 (p < 0.001); and 0.87 and r = 0.90 (p < 0.001) for HF participants.

Analysis of all participant data showed high interclass correlation and high lower 95% confidence intervals between Polar HRM and Ithlete for both HRV and HR in three out of four participants. Table 3.3 displays the ICC 95% CI for Polar HRM and Ithlete for the healthy and HF participants. The ICC 95% CI for HRV was >0.70 for three out of the four participants.

Table 3.3 Interclass correlation coefficient and 95% confidence interval for each participant group for HRV and HR

Participant Group	**ICC**	**95% CI**	
		Lower bound	Upper bound
H participant 1 HR (bpm)	0.93	0.71	0.97
H participant 2 HR (bpm)	0.86	0.65	0.93
HF participant 1 HR (bpm)	0.94	0.84	0.97
HF participant 2 HR (bpm)	0.42	0.01	0.67
H participant 1 rMSSD (ms)	0.85	0.74	0.92
H participant 2 rMSSD (ms)	0.67	0.51	0.78
HF participant 1 rMSSD (ms)	0.90	0.73	0.96
HF participant 2 rMSSD (ms)	0.94	0.90	0.97

Figures 3.1-3.4 are Bland & Altman plots of agreement for HR (bpm) and rMSSD (ms) recorded simultaneously via Polar and Ithlete systems. When considering Bland & Altman plots for each participant, there were narrow limits of agreement for HRV in both healthy and heart failure participants.

Figure 3-2 Bland-Altman plots of agreement and normally distributed differences for HR (bpm) for each healthy participant

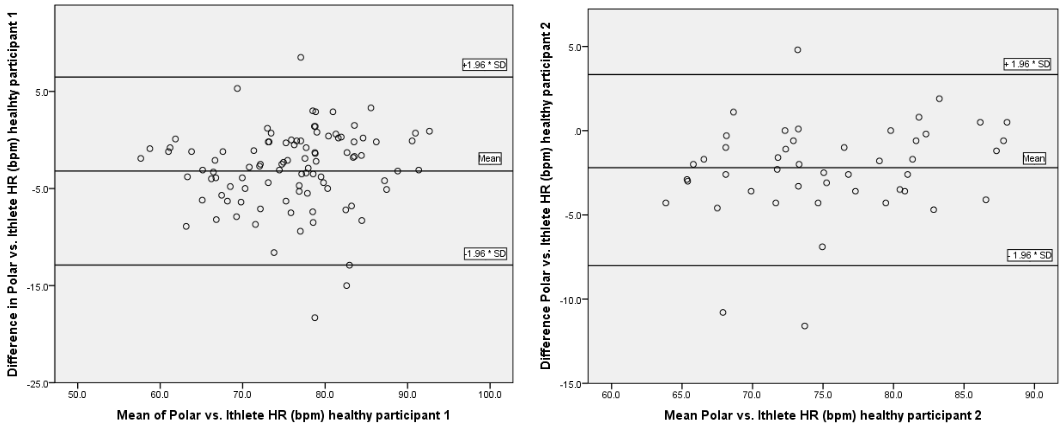


Figure 3-3 Bland-Altman plots of agreement and normally distributed differences for HR (bpm) for each heart failure participant

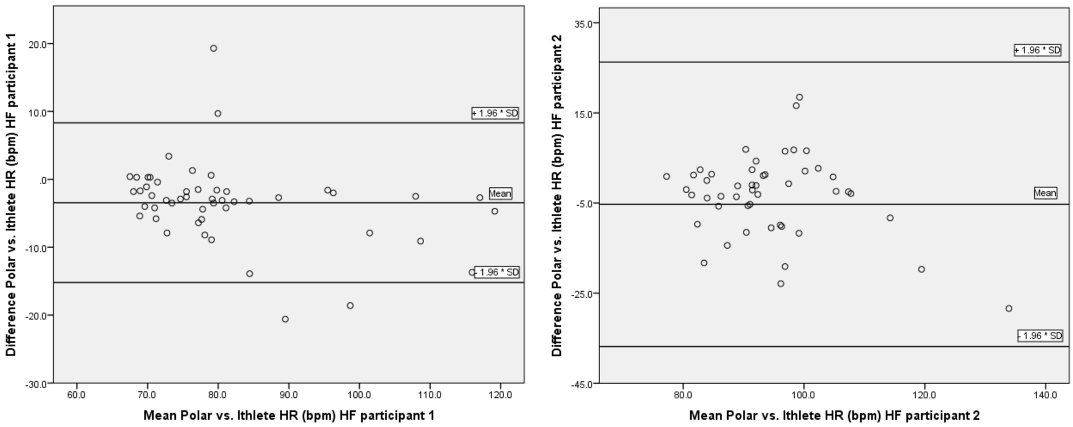


Figure 3-4 Bland-Altman plots of agreement and normally distributed differences for rMSSD (ms) for each healthy participant

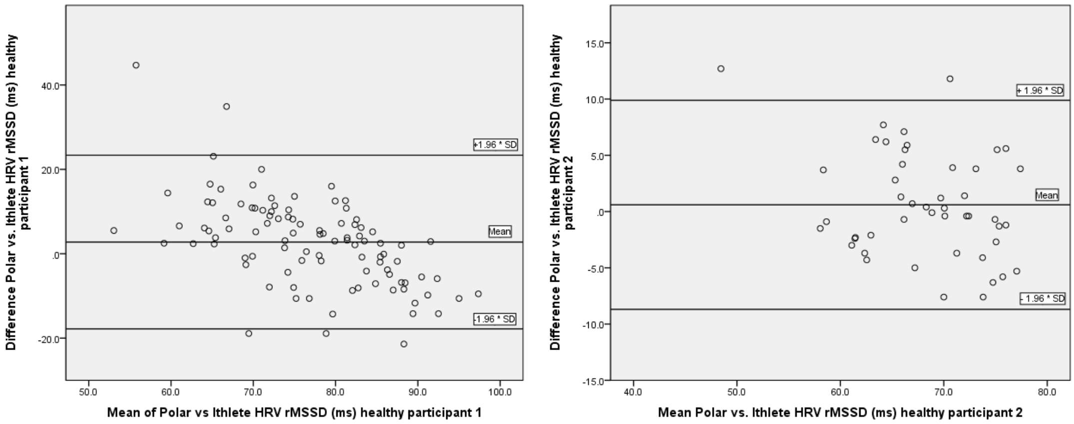
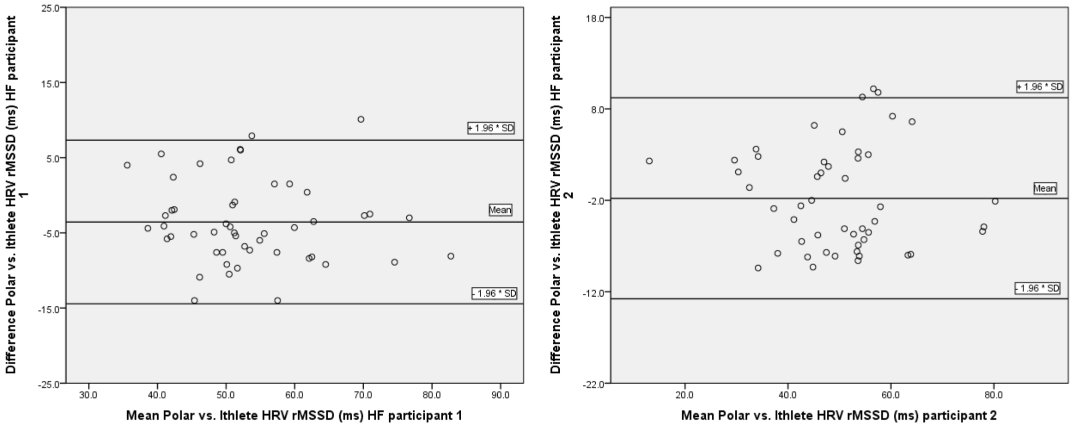


Figure 3-5 Bland-Altman plots of agreement and normally distributed differences for rMSSD (ms) for each heart failure participant



To allow for comparison with the literature, participants were grouped into H and HF participants. The ICCôs and Pearson correlations for each group were calculated and are displayed in Table 3.4. Figure 3.5 and 3.6 show Bland & Altman plots for participants grouped together as H and HF participants, first for HR and then for rMSSD.

Table 3.4 Interclass correlation coefficient, 95% confidence interval and Pearson correlation for each participant group for rMSSD and HR

Participant Group	ICC	95% CI		r
		Lower bound	Upper bound	
H HR (bpm)	0.76	0.66	0.83	0.81†
HF HR (bpm)	0.79	0.67	0.87	0.70†
H rMSSD (ms)	0.87	0.75	0.93	0.66†
HF rMSSD (ms)	0.93	0.86	0.96	0.89†

†Significant difference at p< 0.01

Figure 3-6 Bland-Altman plots of agreement and normally distributed differences for average HR (bpm) in both healthy and heart failure participants

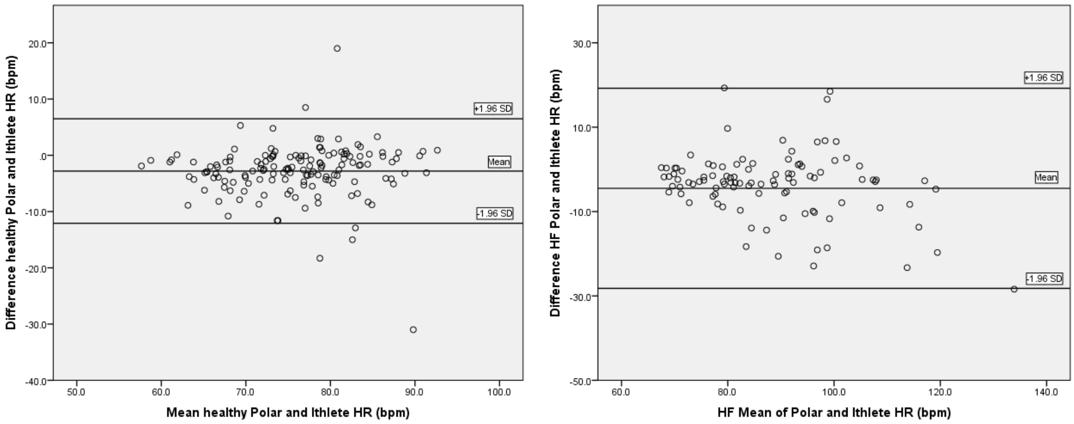
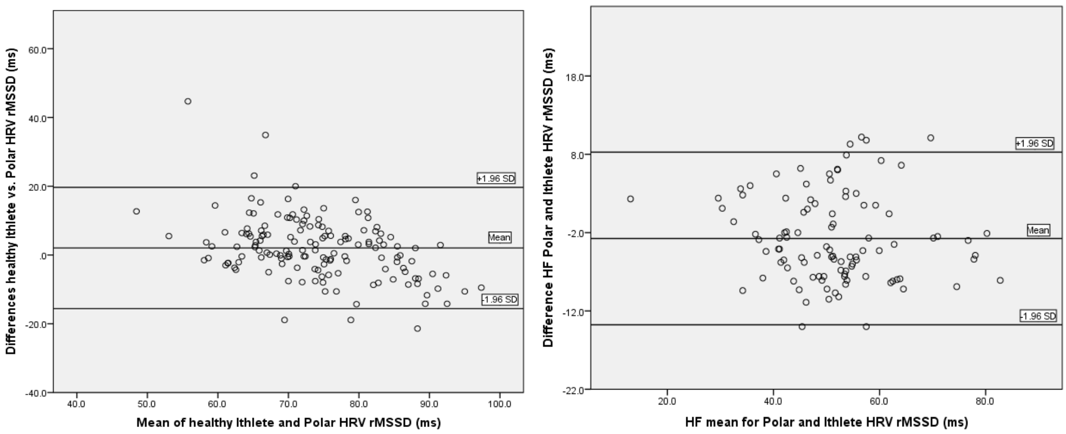


Figure 3.7 Bland-Altman plots of agreement and normally distributed differences for average rMSSD (ms) for both healthy and heart failure participants



3.4 Discussion

The purpose of this study was to compare rMSSD (ms) and HR (bpm) derived from Polar s810i HRM (Polar Electro Oy, Kempele, Finland) and Ithlete (HRV Fit Ltd, Hampshire, UK) in both healthy and heart failure participants. High ICCôs and narrow limits of agreement in the present study demonstrate good agreement between Polar HRM and Ithlete devices. In addition, no significant differences were found between rMSSD measurements at $p < 0.05$ for three out of the four participants however, a significant difference between HR measurements was found between devices for all participants.

HRV is an excellent tool for measurement of enhanced risk stratification, and may provide insight into physiological and pathological conditions (Task Force, 1996). In normal sedentary, athletic and clinical populations, HRV time and frequency domain measurements have been utilized for evaluating cardiac autonomic function and sympathovagal balance (Aubert et al. 2003; Dixon et al. 1992; Iellamo 2001; Kleiger et al. 2005; Pumprla et al. 2002). HRV has been recognised as an important and independent predictor of morbidity, mortality and risk of cardiovascular events (Task Force, Kleiger et al. 2005; Tsuji et al. 1996). For the purpose of this thesis, HRV (rMSSD) will be the main measurement assessed across the various chapters and therefore the most important measure being validated in this chapter.

rMSSD is an ideal tool for monitoring how the body responds to exercise training and other stressors because of its sensitivity to vagal cardiac control, and is less sensitive to variations in respiratory patterns (Penttilä et al. 2001). Autonomic activity becomes altered during exercise; HR increases as a result of increased sympathetic activity during exercise, and heart rate recovery is mediated by vagal reactivation following exercise (Myers et al. 2007). Monitoring HRV daily has been demonstrated as a valuable tool in making exercise training more effective and preventing overtraining (Manzi et al. 2009). Ithlete is an easy device for users to monitor their resting HRV and HR. With an easy user-interface, and immediate feedback displaying HRV and HR values, Ithlete also compares the latest dayôs HRV value with the moving average over the previous seven days. Comparing the difference in an individualôs HRV values over several days provides a unique, individual indication of how the body has recovered from exercise/stress over time.

For accurate measurement of HRV, it is important to consider factors that influence HRV (i.e. body position, time of day). Better reproducibility of both time and frequency domain parameters of HRV have been reported in the standing position (Dantas et al. 2010). In healthy subjects, better reliability of HRV has been demonstrated in the upright position during measurement (Dantas et al. 2010; Reland et al. 2005). HRV measures in the standing position, also appear to be more sensitive to variations in sympathetic activity (Dantas et al. 2010). External factors such as mood, stress, sleep and anxiety may have less influence on HRV in the orthostatic position because of the increase in the sympathetic drive (ibid).

The present study however, involves both clinical and healthy populations, and therefore the standing position was not always feasible for consistent measurement. After consulting with the Ithlete developer and a consultant cardiologist it was decided that seated measurement would be more appropriate than standing, to maintain continuity between H and HF participants. For this reason, participants were asked to do their measurements in the seated position, to ensure that both HF patients and H participants could stay upright comfortably for five minutes to take Polar HRM measurements and one minute Ithlete measurements.

Various studies have validated the use of different Polar HRM modelsô reproducibility and precision to measure HRV, when compared with Holter or ECG systems (Godsen et al. 1991; Leger & Thivierge 1992; Seaward et al. 1990); including the s810i used in the present study (Conraads et al. 2004; Gamelin et al. 2006; Nunan et al. 2009; Wisløff et al. 2007). When comparing Ithlete with Polar s810i, acceptable agreement was confirmed. Ithlete demonstrated high correlation coefficients (> 0.70) for both rMSSD and HR, in 75% of healthy and HF participants. Very little data are lost when using devices with Ithlete compared with Polar s810 HRM. HR and rMSSD average values are displayed directly on the screen of devices, immediately after measurement with Ithlete instead of having to input the data through external software on a PC. As both Polar and Ithlete use the same analogue chest strap for data acquisition, validation in the present study is more focused on software/data treatment as a source of variation. Therefore utilizing Polar HRM and Kubios software for comparison in the present study makes sense, as both have been demonstrated as effective in other studies (Åhs et al. 2009; Bricout et al. 2010; Tarvainen et al. 2009).

To facilitate comparison to other studies, participants were also grouped as H and HF participants for Bland & Altman analysis. The results from the present study have a larger bias and LoA for HRV, when compared with Kingsley et al. (2005) and Weippert et al, (2010). Kingley et al, (2005) demonstrated a bias of < 0.10ms and LoA of less than 10ms between Polar HRM and an ECG. Weippert et al, (2010) demonstrated a bias of <0.50ms and LoA of -15.1 ï 14.3 between Polar HRM and an ECG. The present study demonstrated a bias for HRV of 2.0 ms for healthy and -2.75 ms for HF participants with LoA of -15.6 ï 19.7 and -13.8 ï 8.3 respectively between Polar HRM and Ithlete. Despite the larger bias and LoA, there were a limited number of outliers for HRV and HR (4.7% of HRV in healthy participants lying outside the LoA and 2.7% for HF participants; for HR 5.9% of differences lay outside of the LoA for both healthy and HF participants). ICCôs were >0.85 in three out of four participants, suggesting that Ithlete and Polar HRV (rMSSD) readings have good agreement.

According to Lee et al. (2004), measurement devices for HRV can be considered interchangeable if the lower ICC 95% CI value exceeds 0.70. The present study found high interclass correlation and high lower 95% confidence intervals between Polar HRM and Ithlete for both HRV and HR in three out of four participants. This suggests that Ithlete and Polar measurements may not be interchangeable but are good enough because of the distinct advantages Ithlete provides. Short duration measurements are more susceptible to noise or erroneous beats (Vybiral et al. 1990). Therefore the presence of any erroneous beats could have a large impact in the results.

Ithlete measurements are short and convenient compared with other commercially available HRMs. Other HRMs are valid measurement devices for HRV (Nunan et al. 2009); however, there remains the need for users to lay supine for up to ten minutes to capture HRV. The measurements must then be stored to the device and transferred to a PC for data analysis. Through the use of a smartphone or iPod touch, Ithlete provides users with immediate data analysis on the device and provides a comparison to previous measurements. Therefore users can make sure the measurement is near enough, and if not, because Ithlete measurement duration is so short, repeat it. If that large difference remains, then the user can be confident it is due to their physiological response, and not device error.

As reported by Radespiel-Troger et al. (2003) and Gamelin et al. (2006), the present study found good correlations between HRV (rMSSD) and HR (bpm) in both H and HF participants from Polar HRM and Ithlete. Significant correlations were demonstrated for all participants in both rMSSD and HR measures. Overall, HRV measurements from the present study suggest good agreement between Ithlete and Polar HRM measurements.

3.5 Conclusions

HRV based on R-R interval analysis obtained by automated acquisition from Ithlete for iPod touch with a standard HRM chest strap, was reliable and feasible in both healthy and heart failure participants. Ithlete measurements are a simple and easy technique for HRV analysis. High ICCs in three out of four participants, for both rMSSD and HR suggest good agreement between devices. High Pearson correlation coefficients suggest Ithlete is a valid measure for rMSSD. Ithlete and Polar measurements may not be interchangeable but are good enough because of the distinct advantages Ithlete provides. Therefore the Ithlete measurement system can be considered a good alternative device for short-term rMSSD measurement in both healthy and heart failure populations. The Ithlete measurement system provides a new perspective for investigation of HRV in various populations in both sport science and clinical practice.

3.6 References:

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CHAPTER 4: MEASUREMENT OPTIONS FOR BODY COMPOSITION USING BIOELECTRICAL IMPEDANCE ANALYSIS DEVICES

Bioelectrical impedance analysis (BIA) is a widespread method used in both healthy and patient populations to measure body composition. Several initiatives, i.e. weight loss programmes and athletics have resulted in an increase in the demand for user-friendly devices. BIA devices are practical, convenient and potentially inexpensive. In the literature, BIA is shown to be valid in assessing body composition for adults when compared with the gold standard of underwater weighing. The purpose of this study was to compare six different BIA devices, ranging in price, to see if there is a sufficient level of agreement between them.

Sixty-one participants completed BIA measurements with all six devices; there was no statistically significant difference between BIA devices in the measurement of weight, body fat, basal metabolic rate and body mass index as determined by one-way analysis of variance (ANOVA). A significant difference was found in measurements of muscle mass between the BIA 101 and Homedics devices. Five devices had no significant difference in measurement of total body water (TBW) or body fat percentage between them.

The present study found good relative agreement in body composition measurements between five BIA devices, which suggests that it is acceptable to use any of the BIA devices from the present study at home and/or in a clinical setting.

4.1 Introduction

The energy stores in the body play a vital role in physiological function. Nutritional status, diet, exercise etc. have an impact on those energy stores. Measurement of these energy stores can be undertaken using body composition, which involve models that divide body weight into two or more components including fat, muscle, water, bone and mineral. Excess body fat puts individuals at higher risk for cardiovascular diseases, type 2 diabetes, cancer and other health disorders (Department of Health 2011). Adequate amounts of water are necessary for the body to sustain normal physiological functioning i.e. the transportation of nutrients, waste removal and the regulation of body temperature. In certain conditions, however, excessive water retention can be an indicator of pathophysiological conditions. Due to the necessity of body water balance, it is important to be able to measure this important variable.

In clinical practice, the purpose of body composition measurement is to evaluate clinical nutritional status though measuring fat mass (FM) and free fat mass (FFM) (Thibault et al. 2012). Numerous methods for body composition measurement exist; they include skin-fold thickness, waist-circumference, waist-stature ratio, dual-energy x-ray absorptiometry (DEXA), and bioelectrical impedance analysis (BIA). BIA was chosen for the present study because is it one of the most widely used techniques (Sun et al. 2005).

4.1.1 Bioelectrical impedance analysis

BIA is a method for estimating body composition. It operates by sending a small electrical current through the body and measuring impedance, which is the opposition to the current. As a consequence of homecare and weight loss therapy, there has been an increase in the demand for bioelectrical impedance analysis (BIA) consumer devices (Bosy-Westphal et al. 2008). In the literature, BIA is shown to be valid in assessing body composition for adults when compared with the gold standard of underwater weighing (Reilly et al. 1994; Segal et al. 1985). These consumer devices are relatively inexpensive and easy to use for indirect measurement of body composition.

There are a variety of BIA measurement techniques which include single frequency and multi-frequency systems. Single frequency systems infer total body water (TBW) from whole-body resistance to conductance of a current of 50 kHz. Multi-frequency devices measure at different frequencies ranging between 0 and 500 kHz. Single frequency BIA has been demonstrated as a valid and reliable means of measuring body composition in healthy populations with stable water and electrolyte balance (Pateyjohns et al. 2006).

BIA devices offer a variety of measurements which can include TBW, free fat mass (FFM), fat mass (FM), body mass index (BMI) and basal metabolic rate (BMR). The main principle involved in BIA is that an electrical current will flow more rapidly through tissues with higher water and electrolyte concentration than through tissue less hydrated (Nichols et al. 2006). Therefore resistance to the electric current directly relates to the amount of free fat mass (FFM). Fat mass (FM) can then be calculated by subtracting the amount of FFM from the total body mass. Fluid-electrolyte turnover and TBW change constantly due to water gained from food, fluids, and water loss from the lungs, skin and kidneys (Armstrong 2007). BIA analysis for the estimation of TBW is based on the electrophysical model where impedance is measured at a fixed frequency of 50 kHz and height is used as a substitute for conductor length. The use of BIA in a clinical setting is under debate. Within the NHS it is still not a recommended tool as a substitute for BMI according to NICE guidelines (National Institute for Health and Clinical Excellence 2006), however this has been questioned (Neville et al. 2006; Ode et al. 2007; Prentice & Jebb. 2001).

Sustaining normal physiological functions, like transportation of nutrients, regulation of body temperature or waste removal, require adequate hydration (Berdanier 2000). A decrease in orthostatic tolerance and a relative tachycardia at rest and during exercise, are a consequence of dehydration and its effect on cardiovascular function (Charkoudian et al. 2003). Dehydration has also been cited to cause a decrease in blood volume which then decreases stroke volume due to the increase in heart rate and decrease in filling time (Turkevich et al. 1988). Chronic mild to moderate dehydration is associated with several disease states including coronary heart disease (Rochette & Patterson 2005). Evidence of compromised performance in sport, due to increased physiological strain, occurred due to increased heart rate, decreased stroke volume, thermoregulatory strain and stress response, among other factors (Casa et al. 2010). Patterson (2002) examined the influence of hydration on cardiovascular reactivity during psychological stressors and found positive relationships between total body water and the change in heart rate, diastolic blood pressure and total peripheral resistance during reactivity to posture change. All these effects are significant and can cause serious complications if not remedied.

The present study aims to validate several low-cost BIA devices, for the purpose of using them in clinical populations such as heart failure. It would be a great advantage to have the ability to measure hydration status in different settings (i.e. hospital, GP surgery, on the field of play) to ensure people have optimal hydration whether they are athletes or patients. Measuring hydration status with just TBW however, has its limitations. TBW is a measure of the quantity of water in all tissues in the body and therefore is affected by hyperhydration, obesity and other cofactors (Tzamaloukas & Murata 1995; Tzamaloukas et al. 1998). Bioelectrical impedance vector analysis (BIVA) uses impedance measurements to create a pattern analysis which is plotted as a vector coordinated system (Bosy-Westphal et al. 2005). BIVA analysis is independent of hydration status, and therefore is a complimentary control measure for correct interpretation of BIA.

More research is needed in this area, to understand the underlying mechanisms and physiological implications of hydration status while taking into consideration various health risks. BIA is one of the ways hydration can be measured by using equations that convert reactance and resistance to estimate the TBW. However as stated above, this has its limitations. Body composition assessment for information on nutritional status through BIA is an undervalued technique in clinical practice (Walter-Kroker et al. 2011). There are many devices on the market that range in price from approximately fifteen pounds to over a thousand pounds, making it difficult to decide which devices to use.

4.1.2 Aims

The aim of the present study was to compare six different BIA devices, ranging in price, to determine if there was an acceptable level of agreement between them. The benefit of this would then be economical purchase of the required number of devices for experimental use. This would especially apply if the BIA device was to be used in the home, as access to a large number of devices would mean that more participants could use them concurrently.

4.2 Methods

4.2.1 Recruitment of participants

Staff and students of Buckinghamshire New University were invited by internal advertisement on notice boards and through emails. Each participant was recruited in accordance with University ethics committee standards and expectations. Participants responded via email or phone and were sent an information pack before agreeing to participate which included:

1. An information sheet with detail of the requirements for each participant during the laboratory visit
2. An informed consent form
3. A detailed demographic information sheet

Participants were requested to read the information pack prior to attending the laboratory and any questions or concerns were addressed. All participants were free from any serious medical conditions. All procedures were approved by the local research ethics committee.

4.2.2 Participants

Volunteers from 18 to 65 years of age were included. Any pregnant women or persons with a demand pacemaker or any other implanted automatically controlled electronic device were excluded. Participants completed a written consent form in front of a trained researcher who then countersigned the form.

4.2.3 Instrumentation and data acquisition

Six bioelectrical impedance analysis devices were used in each laboratory session for data acquisition. Two devices involved measurement in the supine position, four devices involved measurement in the standing position. At the beginning of each testing session, height was measured with a stadiometer (Leicester height measurement, Seca, UK). Weight was measured on a standard weight scale (HealthOMeter 142KL, Jarden Corporation, Bridgeview, IL) and waist circumference (WC) was taken with a tape measure (Myotape body tape measure, AccuFitness, Greenwood).

Previous research using the Tanita analyser has demonstrated good correlations between Tanita scales and the gold standard of dual energy x-ray absorptiometry (DEXA) (Frisard et al. 2005; Sung et al. 2001; Thomson et al. 2007). Hydrasite, is however a relatively new, non-invasive method for the classification of hydration in clinical outcomes. Hydrasite is based on the same resistance (R) and reactance (Xc) principles as the other devices, however it also uses bi-variate distribution (BIVA). This plots resistance and reactance over height using Xc/height against R/height for both men and women, yielding a phase angle with relevant confidence and tolerance limits or norms which can then be compared (Piccoli et al. 1995). This allows a more sensitive and specific classification of hydration state.

The BIA devices vary in which measurements they perform. The following is a list of all possible measurements:

- Weight (W)
- Total Body Water (TBW)
- Hydration level (HL)
- Body Fat % (BF)
- Muscle Mass (MM)
- Basal Metabolic Rate (BMR)
- Body Mass Index (BMI)
- Free Fat Mass (FFM)

Table 4.1 displays each BIA device and what measurements it performs.

Table 4.1 BIA devices and measurement capabilities

	W (kg)	BMI	BF (%)	TBW (%)	HL (%)	BMR (kcal)	MM (%)	FFM (%)
Tanita	✔	✔	✔	✔		✔		✔
Salter	✔		✔	✔				
Homedics	✔	✔	✔	✔		✔	✔	
Hanson	✔		✔	✔				
Hydrasite					✔			
BIA 101		✔	✔	✔		✔	✔	✔

4.2.4 Experimental design

4.2.4.1 Supine measurements

Participants were asked to lay down in a comfortable position with legs and arms slightly spread so as not to have contact with each other or with their trunk. Participants had to lie in a supine position for approximately five minutes pre-test to allow an even distribution of body fluids. Resistance and reactance measurements were then recorded via BIA 101 (Akern; Florence, Italy) and CardioEFG Hydrasite Technology device (Akern; Florence, Italy).

BIA 101

Four electrodes were placed on the same side of the body. One electrode on the bisecting line of the hand and wrist, one just below the fingers on the back of the hand, one on the bisecting line of the leg and the foot (on the front of the leg at ankle level), and another just below the toes on the top of the foot. Recording was executed allowing at least three reading cycles before inputting measurements into the Bodygram software (Akern; Florence, Italy). Bodygram software then computed body composition measurements including BMI, body fat %, fat free mass %, intracellular water, and extracellular water for each participant and stored it in the Bodygram software programme.

CardioEFG Hydrasite technology device

This device used two electrodes for measurement. One electrode was placed on the bisecting line of the hand and wrist, the other was placed on the bisecting line of the leg and ankle. TBW percentage was computed through resistance, reactance and phase angle measurements inputted into the Cardiogram software (Akern; Florence, Italy). Hydrasite performs estimates of hydration through measurement of TBW, extra cellular water (ECW) and intracellular water (ICW) together and supplies the percent content of water in the lean tissue. Therefore the other devices measure the quantity of water in the body, compared with Hydrasite which measures actual hydration state from the percent content of water in the lean tissue.

4.2.4.2 Standing measurements

Tanita Scale BC-418MA III

The weight of each participantôs clothes (usually 1-2 kg) was entered into each instrument- along with characteristics (standard or athletic, male or female). Then age and height (cm) were entered and the participant stood on the Tanita scale with their bare feet. Once in a stable condition, participants picked up the grips at the side in each hand and BIA took place.

For the remaining three devices (HoMedics 9116 Black Glass Platform Body Fat Analyser Scale, Hanson HFA Liner Body fat Analyser and Body Water Graduation, Salter 9106 WH3R Glass Body Analyser & Scale) participants stood on each scale with their bare feet for the measurement. Participant information such as age, height and fitness level (if necessary for that device) was entered into each machine before measurement took place. A stadiometer (Seca 213, United Kingdom) was used for height measurements.

4.2.5 Statistical analysis

All statistical analysis was analysed using PASW 19.0 (SPSS: An IBM Company. Somers, NY, USA). Values are reported in the text as mean ± standard deviation. Differences between individual values obtained from each BIA device were assessed using one-way analysis of variance (ANOVA). If ANOVA displayed a statistically significant main effect, differences among means were assessed with Tukeyôs honestly significant difference test. Regression analysis was used to determine the level of relative agreement between different BIA devices. A P-value of <0.05 was considered statistically significant. The CardioEFG Hydrasite Technology device (Akern; Florence, Italy) was not included in all statistical analysis tests because its measurement of hydration is not directly comparable to the other devices used in the present study.

Bland-Altman analysis was used to determine absolute limits of agreement between all BIA devices, with the Tanita scale serving as the criterion measure.

4.3 Results

Sixty-one people participated in the present study. Average participant characteristics are displayed in Table 4.2 below.

Table 4.2 Subject characteristics

Characteristic	Mean & Standard Deviation	Range
Age (years)	39.1 ± 13.1	19-65
Weight (kg)	71.8 ± 14.8	40-108
Height (cm)	168.4 ± 9.7	147-190
WC (cm)	87.6 ± 11.8	64-115

Table 4.3 Mean Body mass index (BMI), Body fat (%), Total body water (TBW), Basal metabolic rate (BMR) and Muscle mass (MM) measured by different BIA devices

	BMI (kg/m^2)	**Body Fat (%)**	**TBW (%)**	**BMR (kcal/day)**	**MM (%)**
Tanita	25.2 ± 4.6	27.8 ± 9.5	54.2 ± 9.0	1542 ± 309	__________
Salter	25.9 ± 4.6	28.0 ± 7.4	52.5 ± 5.3	__________	__________
Homedics	__________	27.5 ± 8.3	51.0 ± 8.3	1573 ± 233	35.6 ± 5.4†
Hanson	__________	29.9 ± 11.0	50.2 ± 6.7	__________	__________
Hydrasite	__________	__________	67.3 ± 6.9†	__________	__________
BIA 101	25.3 ± 4.5	28.5 ± 9.3	52.6 ± 6.9	1551 ± 190	47.6 ± 8.0†

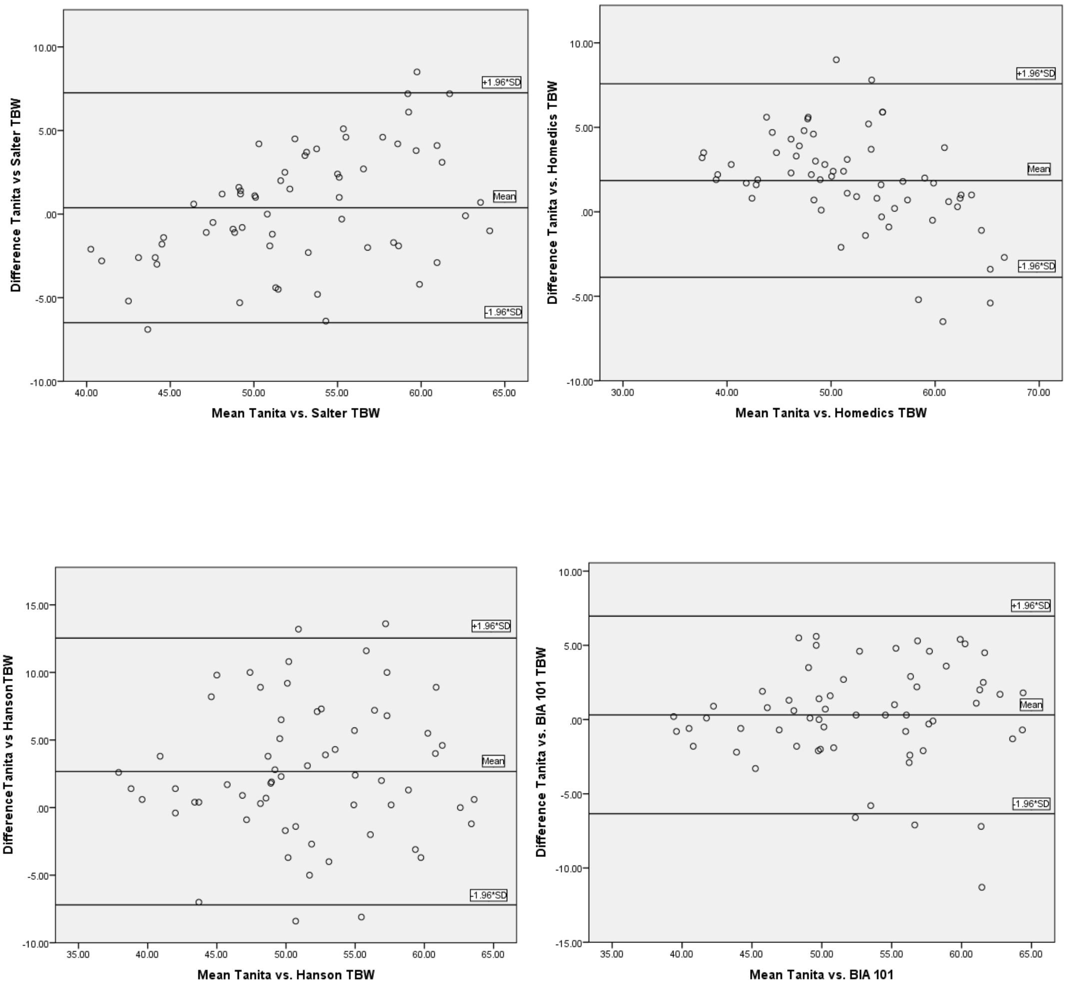
†Significant difference at p< 0.01

There was no statistically significant difference between BIA devices in measurement of weight (F (4,305) = 0.441, p = 0.779) or body fat (%) (F (4,304) = 0.709, p = 0.587). Neither were their differences in basal metabolic rate (F (2,182) = 0.251, p = 0.779), nor BMI (F (2,182) = 0.471, p = 0.625).

A significant difference was found between TBW and MM measurements using one-way ANOVA where (F (4,291) = 53.913, p <.001) and (F (1,121) = 95.360, p = .000) respectively.

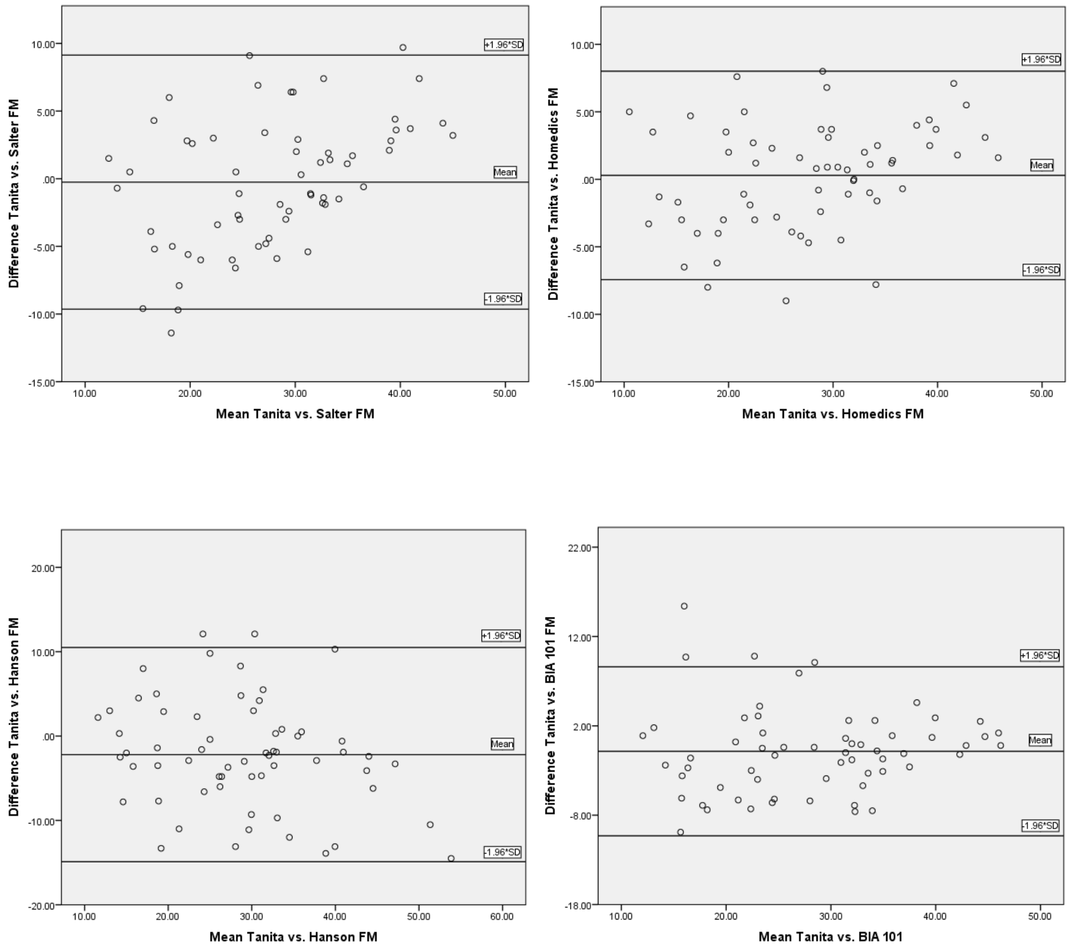
Analysis based on Bland and Altman, (2007) revealed good relative agreement with wide limits of agreement between the Tanita scale and four out of the five other BIA devices for TBW. Salter was r^2= 0.75 (7.24 to -6.47), Hanson was r^2= 0.52 (12.47 to -7.13), Homedics was r^2= 0.89 (7.57 to -3.87) and BIA101 was r^2= 0.77 (6.95 to -6.33). The only device that had poor agreement on this occasion was the Hydrasite which only yielded r^2= 0.018.

Figure 4-1 Bland-Altman plots comparing Tanita TBW (%) with TBW (%) from Salter (A), Homedics (B), Hanson (C), BIA 101 (D)



There was good relative agreement between Tanita and the other devices when considering body fat percentage with wide limits of agreement. For Salter r^2= 0.75 with limits of agreement (9.13 to -9.64) percentage points, Homedics was r^2= 0.83 (7.99 to -7.41), Hanson was r^2= 0.65 (10.51 to -14.89) and BIA101 was r^2= 0.75 (8.59 to -10.30).

Figure 4-2 Bland-Altman plots comparing Tanita BF% with BF% from Salter (A), Homedics (B), Hanson (C), BIA 101 (D)



4.4 Discussion

Body composition measurement is a useful tool for determining the ratio between body compartments such as body fat, free fat mass and total body water and measurements can be an indicator of disease. There are many commercially available devices representing a range in price (£15 to >£1000). The aim of the present study was to compare six different BIA devices, varying in price and complexity, to see if there was an acceptable level of agreement between them. The primary finding of this study was that four BIA devices assessed produced relative agreement with the reference instrument- the Tanita analyser. The remaining device produced measurements with unacceptably wide limits of agreement in absolute terms. For the purpose of this discussion each device will now be discussed in turn; in each case the systematic bias and random error (LoA) will be discussed and interpreted in terms of clinical acceptability.

All devices except for Hydrasite underestimated TBW when compared with the Tanita analyser, while BIA 101 and Homedics slightly overestimated BF. The average range of BF% found was between 27.5 and 29.9% which is within the acceptable range. The prediction error for BIA devices should be no more than 4% (Heyward 1991). Table 4.3 demonstrates that there were significant differences between devices in two measurements, TBW and MM. After excluding Hydrasite because of its different measurement output, there was no significant difference in TBW between the other five BIA devices.

The Tanita analyser and BIA 101 are the only devices within this study to already have been validated against the gold standard of underwater weighing. Comparing the Akern BIA 101 and underwater weighting Deurenberg et al, (1991) produced a good correlation between the two devices and equations predicted from this study are used throughout the literature indicating the significance of that work. That study, along with others, demonstrates the value of BIA evaluation of body composition (Erceg et al. 2010; Houtkooper et al. 1996; Khan et al. 2005; Kyle et al. 2004; Lukaski & Siders 2003; Pichard et al. 2000; Sun et al. 2003). Further research using BIA 101 has found it to be an accurate and reliable device when correlated with densitometry (Baumgartner et al. 1991) and dual-energy x-ray absorptiometry (Kanellakis et al. 2010).

The Tanita analyser demonstrated significant correlations between this device and underwater weighing in > 200 subjects, measurements obtained by the Tanita analyser correlated at (r= 0.89) with % fat determined by underwater weighing and at (r=0.89) with the same measure obtained by dual-energy x-ray absorptiometry (Nuñez et al. 1997). Ritchie et al, (2005) reported a correlation between measurement of body fat percentage obtained from the Tanita analyser and underwater weighing of r= 0.76 among men with cardiovascular disease. Based on this and other previous research it appears the Tanita foot-to-foot analyser is an appropriate measurement system for body composition among adults.

In the present study the Tanita analyser produced strong correlations with four other BIA devices. Despite strong correlation coefficients indicating good relative agreement, correlation alone is inadequate as a method to identify the degree of coincidence between the methods (Bland & Altman 1986). The correlations in this study were generally good, with the highest correlations demonstrated between Tanita and Homedics (r^2= 0.83 CI 7.99 to -7.41), Salter (r^2= 0.75 CI 9.13 to -9.64) and BIA 101 (r^2= 0.75 CI 8.59 to -10.30). The lowest correlation was demonstrated between Tanita and Hanson at r^2= 0.65 CI (10.51 to -14.89). These values are consistent with other studies (Bolanowski & Nilsson 2001; Lukaski & Siders 2003; Ravaglia et al. 1999; Shafer et al. 2009; Sun et al. 2003), which concluded that the method works but we wanted better so we also compared the cost of each device to determine if expense is in line with accuracy of measurement.

In the present study, the Homedics scale had both the highest relative agreement and the narrowest limits of agreement making it the most accurate when compared with the Tanita scale. As cited earlier in the discussion, the Tanita, when compared with the gold standard of underwater weighing was found to have similar relative agreement and limits of agreement. This would suggest that use of the Homedics scale in future research would be valid, and due to its low cost could be advantageous in a wide variety of settings.

Higher TBW and extracellular water measurements are reported in obese subjects compared with normal-weight subjects (Steijaert et al. 1997). BIA devices should take into account characterization (age, height, weight, BMI and ethnicity) of the sample population on which its equations are based (Bosy-Westphal et al. 2008). The user also must consider the impact inappropriate characterization would have on the accuracy of body fat prediction from the device; to ensure they are getting the best possible result. In each of the devices used in the present study, age, gender and in some cases physical activity level was entered into the machine before measurement. Population specific equations could confirm this method as the best for clinical practice. Commercially available values varied between machines; a Which? study (Which ?. 2006), observed that useful results can be obtained by using the same device consistently. Devices that can produce measurements within <4% error are deemed acceptable. This suggests that the importance lies with using the same machine, and not necessarily the calibre of the machine. Considering that high levels of agreement have been shown between several devices in the present study, it seems acceptable to focus on the change in measurements instead of the absolute figure that is given by the machine. This measurement when taken outside of the laboratory should be taken as a guide, especially considering that usage in the home setting will not necessarily be achieved using appropriate test conditions such as monitoring food and fluid intake before the test. Users should simply focus on using the machine at roughly the same time of day for repeat testing under as similar conditions as possible. The key is to look at the relative change from day-to-day to get an accurate picture. When thinking about the cost of the machine vs. its performance, the user must keep this is mind.

There are several publications citing the significance of dehydration in healthy people and recommended amounts of water intake. A number of adverse effects have been documented in the literature, including a decrease in orthostatic tolerance (Charkoudian et al. 2003). Other studies have found an increase in resting heart rate and decreased tolerance to lower body negative pressure (Davis & Fortney 1997); decreased orthostatic tolerance has also been linked to diuretic use (Frey et al. 1994) and prolonged bed rest (Kamiya et al. 1999). Dehydration is prevalent in both healthy populations and diseased populations, and is often related to a large number of hospital admissions and large expenditure (Ritz et al. 2008).

Progressively the propensity of body composition to cardiovascular disease, diabetes mellitus, cancer, osteoporosis and arthritis has been explored (Zeng et al. 2008). This makes accurate determination of body composition clinically useful in these populations to ensure therapy is optimised (ibid). Fluid balance is important in heart failure because inadequate fluid levels can result in cardiac or renal dysfunction. In particular dehydration and electrolyte imbalances can lead to cognitive impairment (Vogels et al. 2007). BIA can be used to monitor fluid balance in heart failure patients to ensure fluid imbalance is caught early enough to avoid organ dysfunction.

The cost of a BIA device will always be a substantial part of the decision making process for choosing a machine. With such a wide range in cost for devices it is not easy to decipher which machines are better than others and why. In this study six devices, all varying in cost, were used. Three of the devices assessed cost less than £20: HoMedics 9116 Black Glass Platform Body Fat Analyser Scale cost £15.98, Hanson HFA Liner Body fat Analyser and Body Water Graduation cost £19.40 and Salter 9106 WH3R Glass Body Analyser & Scale cost £19.99. The other three devices: Tanita Scale BC-418MA III, Akern BIA 101and Akern Hydrasite cost £1240, £899 and £6125 respectively. The cost was not related to the devices agreement with the reference device in this study.

The best agreement between the Tanita scale and another device was found with the HoMedics 9116 Black Glass Platform Body Fat Analyser Scale which cost £15.98. This suggests that consumers should not necessarily equate expense with accuracy. It is important to like the present study, test the devices with scrutiny in controlled settings to obtain definitive results on agreement between them. The level of agreement found in the present study is comparable with other studies comparing body composition measurement between different techniques and devices. The appropriate level of agreement depends on what is required from the device, hence the use of the Bland & Altman method. The purpose of the LoA is to provide generalizable values enabling researchers to determine whether two different assays agree to the point where they are interchangeable.

BIA offers a great opportunity for non-invasive assessment of human body composition in the clinical setting and other patient care options (Lukaski 1999). BIA is easy to use, non-invasive in nature, has a high degree of reproducibility at a relatively low cost (ibid). BIA absolute values of TBW are well correlated with the gold standard of isotope dilution and hydrostatic weighing (Kushner et al. 1992; Lukaski et al. 1986; Lukaski et al. 1985). When compared with other methods of body composition analysis such as skinfold thickness and dual-energy x-ray absorptiometry, BIA is easier machinery to use without the need for special technicians for operation.

When purchasing a BIA device, it is important to check what the device offers to see if it meets all needs. Some low cost devices do not offer as many measurements as other devices (i.e. basal metabolic rate, free fat mass). However they can still provide important information regarding body composition changes in fat mass or total body water. Studies investigating what value changes in body composition could have with specific diseased populations could provide more evidence for the benefits of BIA in practice.

The impact of hydration on disease has been documented in the literature investigating risk factors caused by environmental and lifestyle influences on different disease states (Manz 2007). Mild to severe levels of dehydration or euhydration may also account for different morbidity (ibid). Future research should look into daily measurements to test sensitivity of the devices. BIA is easy to use but is thought to generally lack the precision and accuracy necessary for hydration monitoring (Oppliger & Bartok 2002). Studies combining BIA sensitivity testing with longitudinal data on people with varying hydration levels could help to solidify the use of BIA in clinical and field settings and enhance what we already know about the importance of optimal hydration levels. BIA device measurements need to be within the limits of agreement to deem them accurate enough for use instead of the criterion measurement device in determining body composition. How far apart measurements from different BIA devices can be without causing difficulties is a question of judgement. A high correlation would be considered anything from 0.7 and upward and has been used in literature when comparing body composition measurement techniques (Bracco et al. 1996; Newton et al. 2005; Wattanapenpaiboon et al. 1998).

A limitation to this study is the lack of control over what participants ate or drank before participating in measurements, however this gives the experiment external validity as this is what ŏreal-worldô monitoring is like. The primary focus of this study however, was to compare measurements taken at the same time from different devices so this should not have had much impact.

4.5 Conclusions

Numerous measures can be used for body composition analysis in laboratory conditions including densitometry, dual energy x-ray absorptiometry, BIA and magnetic resonance imaging. Out of these devices BIA is a quick and simple method, which is non-invasive and takes reliable measurements with minimal intra- and inter-observer variability (Diaz et al. 1989). BIA also provides results immediately, is portable and reproducible within <1% error on repeated measurements (Segal et al. 1991), making it the most appealing of the devices listed above. This study found no significant difference between five BIA devices in measures of TBW and BF. The agreement between the various BIA devices was strong which suggests that either of the different BIA devices could be used both at home and in the clinical setting. BIA is a fairly inexpensive, non-invasive technique which has a good correlation with the gold standard of under water-weighing. The difference between devices was not significant, indicating that price may not be an important factor in deciding on a BIA device. This means that in large scale surveys, where cost becomes a major factor, it could be acceptable to use low cost devices to produce both cross-sectional and longitudinal values.

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CHAPTER 5: THE RELATIONSHIP BETWEEN ITHLETE MEASUREMENTS AND BODY COMPOSITION ASSESSED BY BIOELECTRICAL IMPEDANCE ANALYSIS

Heart rate variability (HRV) is the physiological phenomenon of variation in the time interval between heartbeats. There are several factors that influence HRV, including chronic factors such as gender, age, ethnicity, level of physical fitness and body composition, or acute factors such as postural changes, time of day, and drug therapy. The relationship between HRV, heart rate (HR) and fat mass (FM) has been documented in the literature where large amounts of body fat were associated with a depressed HRV and increased HR, both of which are associated with worse health status.

The aim of the present study was to try to expand the understanding of the relationship between HRV and body composition measurements. The present study proposes to use just one measure, rMSSD, in one minute measurements to assess HRV using novel equipment and software called Ithlete. With high correlations between HRV measures, there is no need to measure all time-domain indices each time HRV analysis is undertaken. The rMSSD measure has been demonstrated in the literature as a reliable measurement with high correlation to several other HRV measures. The aim of this study was to establish if there is any relationship between HRV and body composition measurements of weight, body fat percentage, total body water, basal metabolic rate and muscle mass using bioelectrical impedance analysis (BIA).

In the present study, significant differences between genders were observed for height, weight, body fat, muscle mass, basal metabolic rate, alcohol consumption, rMSSD, HR and total body water (TBW). Significant ethnic differences were only observed for age, HR and alcohol consumption. When comparing groups by body mass index (obese/overweight to healthy), significant differences were demonstrated in HR, BF, TBW and muscle mass. Smokers had significantly lower rMSSD and alcohol consumption. Different daily physical activity levels yielded significant differences in HR, BF, muscle mass and alcohol consumption. The present study furthered the knowledge of the relationships that exist between body composition variables and rMSSD/HR, with increased risk factors such as ethnicity, physical activity level and smoking status. BIA and Ithlete are both quick and simple methods, which are non-invasive and take reliable measurements. The use of these devices in clinical populations may benefit patient care and help provide valuable symptom monitoring in a clinical population, especially heart failure.

5.1 Introduction

Overweight or obese individuals are at a higher risk of cardiovascular diseases such as type 2 diabetes, cancer and other health disorders (Department of Health 2011). In the last 25 years, the prevalence of obesity has more than tripled with 62.8% of adults in the UK (aged 16 or over) classified as overweight or obese in 2010 (ibid). Body mass index (BMI) is the most common method used for measuring obesity at the population level (Department of Health 2011); the measure is however limited, because it fails to discriminate between percent fat mass and lean mass (Romero-Corral et al. 2008). Body fat % can also be measured through a number of other methods, including skin-fold thickness, waist-circumference, waist-to-hip ratio, dual-energy x-ray absorptiometry (DEXA), and bioelectrical impedance analysis (BIA). BIA was chosen for the present study because it is a potentially inexpensive, direct measure of body fat (BF). BIA is a widespread method used in healthy and clinical populations to measure body composition (Buchholz, Bartok & Schoeller 2004), and has similar advantages to other field techniques as it is safe, quick, and needs minimal operator training (Kushner 1992).

5.1.1 Bioelectrical impedance analysis

BIA estimates body composition by sending a small imperceptible electrical current through the body and measuring impedance (the opposition to current) (Pateyjohns et al. 2006). BIA devices typically measure total body water (TBW), free fat mass (FFM), fat mass (FM)/ BF %, body mass index (BMI) and basal metabolic rate (BMR). Electrical current will flow more rapidly through tissues with higher water and electrolyte concentrations (Nichols et al. 2006). Therefore, resistance to the electric current directly relates to the amount of FFM. FM can then be calculated by subtracting the amount of FFM from the total body mass.

5.1.2 Obesity

The increased prevalence of obesity in the population has occurred across both sexes and particularly among ethnic minorities in the UK (Department of Health 2011). Ethnic differences in anthropometric values such as BMI, waist-to-hip ratio and waist circumference have been reported (Brancati et al. 2000; Carroll et al. 2008; Flegal et al. 2010; Hedley et al. 2004). Estimates in adult obesity prevalence among various ethnicities vary based on the measurement criteria. Chinese men and women have the lowest reported obesity prevalence in the UK (Gatineau & Mathrani 2011), compared with White British individuals. Pakistaniôs, Bangladeshi and Black-Caribbeanôs have reported poorer health (Department of Health 2010). African-Americans tend to have higher rates of hypertension, atherosclerosis, obesity and insulin resistance when compared with Caucasians (Hoffman 2009).

When considering gender, men are classified as overweight when their BF % is between 19-30% (with age-adjusted range recommendations), and obese when BF % exceeds 25-30% (Gallagher et al. 2000). Women are classified as overweight when their BF % is between 33-38% (with age-adjusted range recommendations), and obese when BF % exceeds 39-42% (Gallagher et al. 2000). The pathophysiology of obesity has been linked with the autonomic nervous system (ANS) (Laederach-Hofmann, Mussgay & Ruddel 2000). Heart rate variability (HRV) is a non-invasive electrocardiographic measure that examines the sympathetic and vagal components of the ANS (von Borell et al. 2007). The ANS makes itself visible through HRV, indicating how the body is trying to preserve its equilibrium.

5.1.3 Heart rate variability and Ithlete

HRV is the physiological phenomenon of variation in the time interval between heartbeats. Measurement of HRV is non-invasive, and examines one aspect of autonomic nervous function. There are a number of fundamental physiological acute and chronic factors that can have an effect on HRV. Traditionally, HRV research was confined to ECG systems or Holter monitors, which require trained personnel for operation, are expensive and time consuming (Nunan et al. 2009). The development of ECG telemetry on wireless heart-rate monitoring systems allows field-based assessment. A new device called Ithlete was developed as a software application with a dongle, and can be used with Smartphones and the Ipod Touch.

Ithlete is an ECG receiver that attaches to a mobile device and takes one-minute measurements of HRV (rMSSD) through the use of a standard heart rate monitor chest strap.

5.1.4 Acute factors affecting HRV

Acute factors influencing HRV include postural changes and time of day (Burger et al. 1999). Conflicting results have been published about the affects of several acute factors. Various drug therapies including beta-blockers (Chattipakorn et al. 2007) have also been reported to affect autonomic function. Research has demonstrated that beta-blockers have a positive effect on HRV (Aronson & Burger 2001; Malfatto et al. 1998). Caffeine has also been demonstrated to have an effect in both healthy participants and diabetic patients (Richardson et al. 2004). Studies on the effects of caffeine on HRV analysis are inconclusive (Rauh et al. 2006). Research into the assessment of short- and long-term reproducibility of HRV in supine and standing positions found that HRV indices are mostly independent of body position (Kowalewski & Urban 2004). Conversely, there are also chronic factors affecting HRV which will be discussed next.

5.1.5 Chronic factors affecting HRV

Chronic factors which affect HRV include gender, age, level of physical fitness and body composition. The influences of age, aerobic fitness exercise, and overtraining on HRV have been reported in several studies (De Meersman & Stein 2007; Hautala, Kiviniemi & Tulppo 2009; Hedelin et al. 2000). Gender is an important determinant of HRV in healthy subjects (Antelmi et al. 2004). A progressive decrease in HRV is associated with age, and can be predictive of mortality in different clinical populations (Zulfiqar et al. 2010). People that exercise regularly will generally demonstrate an increased parasympathetic activity and lower heart rate when compared with sedentary people; this is especially noticeable at rest (Dixon et al. 1992).

When considering the effect of ethnicity on HRV, differences have been demonstrated in the literature. Ethnic differences in HRV have been studied predominantly in Afro-Caribbean vs. Caucasian populations, and studies have been inconclusive (Guzzetti et al. 2000). Two studies have reported a lower sympathetic drive in Afro-Caribbeanôs when compared with age-matched Caucasians (Guzzetti et al. 2000; Liao et al. 1995). Decreased sympathetic tone was also found in Afro-Caribbean adolescents compared with their Caucasian counterparts in a study that compared HRV with high and low blood pressure (Urbina et al. 1998). Conflicting results were then published in 2003, which found that Afro-Caribbean adolescents displayed a greater sympathetic contribution to total power when compared with age-matched Caucasian adolescents (Faulkner et al. 2003).

A comparison of Asian and Caucasian children found significantly elevated LF:HFr power in the Asian children which supports previous investigations of Afro-Caribbean vs. Caucasian differences (Reed et al. 2006). Independent studies of HRV in the Asian population demonstrated lower HRV in children born in Asia compared with Caucasian children living in North America (Kikuchi et al. 2003; Nagai et al. 2004).

The ANS has an influence on the function of the cardiovascular system and energy balance (Laederach-Hofmann et al. 2000). The relationship between HRV and adiposity is unclear, as results from previous research have been inconsistent. Zahorska et al, (1993) found that obese subjects had relatively poor HRV profiles, while only weak associations were found between HRV and adiposity by Peterson et al. (1988). Several studies, however, have linked an alteration in both sympathetic and parasympathetic activity to increased adiposity (Laederach-Hofmann et al. 2000; Peterson et al. 1988; Sztajzel et al. 2009). Decreased sympathetic responsiveness has also been associated with increased adiposity (Piccirillo et al. 1996; Piccirillo et al. 1998). There are several acute and chronic factors known to influence HRV. Such differences may be of importance due to the well-documented associations between HRV and health. These influences need to be considered when assessing the relationship between adiposity and HRV; they will now be briefly discussed.

5.1.6 Implications of reduced HRV

Reduced HRV indicates low levels of parasympathetic activity. Low levels of HRV are associated with several disease states, including diabetes and heart failure (Aronson et al. 2004; Kataoka et al. 2004). Reduced HRV is a powerful predictor of mortality after myocardial infarction (Kleiger et al. 1987) and risk of coronary heart disease (CHD) (Liao et al. 1997). HRV is lower in those with chronic heart failure (Sandercock & Brodie 2006), type 2 diabetes (Schroeder et al. 2005) and those who die (Zulfiqar et al. 2010). Reduced HRV is related to gender; HRV has been reported as much as 21% higher in males compared with females (Sookan & McKune 2012). HRV is known to reduce with age, with correlations such as r= -0.67 in males, and r=-0.45 in females (Yukishita et al. 2010). The correlation between HRV and obesity r=-0.39, demonstrated that with increased obesity, HRV decreases (Ramaekers et al. 1998). The established link between obesity and increased risk of cardiovascular disease, type II diabetes, hypertension, and certain cancers (Poirier et al. 2006), is similar to the risks associated with reduced HRV (CV disease, type II diabetes and insulin resistance) (Algra et al. 1993; Tsuji et al. 1994).

Reduced HRV has also been linked to several cognitive disorders such as depression (Thayer et al. 1998), generalized anxiety disorder (Thayer et al. 1996), and panic disorder (Friedman & Thayer 1998). However, the causal direction of these associations is still unclear (Su et al. 2010). Ingjaldsson et al, (2003) reported reduced HRV levels in alcoholic vs. non-alcoholic subjects and a positive association was seen between HRV and positive mood (ibid).

In healthy populations, reduced HRV is associated with a 32-45% increased risk of a first cardiovascular event (Hillebrand et al. 2013). In a study of 41 healthy participants, obesity indices including fat mass, percentage fat content, and waist-to-hip ratio were negatively associated with HRV at r=-0.33, r=-0.35 and r=--0.38 respectively (Kim et al. 2005). Weight reduction resulting in reduced adiposity is associated with improved ANS function (Arone et al. 1995; Ito et al. 2001; Karason et al. 1999).

5.1.7 Aims

The aim of the present study was therefore to examine if Ithlete measurements of HRV/HR demonstrate the same associations with cardiovascular risk factors as those already reported. Ithlete measurements will be compared with body composition measurements obtained by BIA (i.e. body fat %, muscle mass %, body mass index (BMI), total body water (TBW) and basal metabolic rate (BMR)). Lifestyle factors such as alcohol intake, physical activity (PA) level, and smoking will also be considered. Gender and ethnic comparisons will also be made to determine if patterns emerge in particular groups.

It is hypothesized that there will be a relationship demonstrated between HRV rMSSD (ms)/HR (bpm) measurement of HRV from Ithlete with BF % measured by BIA. In practical terms, low (optimal: within recommendations for age and gender) levels of adiposity should be associated with greater health, therefore higher HRV values.

5.2 Methods

5.2.1 Recruitment of participants

Staff and students of Buckinghamshire New University were invited to take part in the study through internal advertisement on notice boards and emails. Each participant was recruited in accordance with University ethics committee standards and expectations. Participants responded via email or phone and were sent an information pack before agreeing to participate. This information pack included:

1. An information sheet with details of the requirements for each participant and instructions for use of the equipment at home;
2. An informed consent form;
3. A detailed demographic information sheet.

Participants were requested to read the information pack, and during the first meeting any questions or concerns were addressed. All participants were free from any serious medical conditions. All procedures were approved by the local research ethics committee.

5.2.2 Participants

Seventy-eight participants were tested, of which 35 were male and 43 were female. Participant age ranged from 22 to 48 years. All participants were defined as healthy (free from any serious illness at the time of testing), and none of the participants was known to have any cardiovascular problems or to be taking any medication that would have influenced the experimental procedures.

The participants were asked to state their ethnicity and were then split into three ethnic categories, which included Caucasian (British, Irish or other White background), Afro-Caribbean (Black Caribbean, Black African or any other Black background), and Other, including South Asian (Indian, Pakistani, Bangladeshi or any other South Asian background), East Asian (Chinese, Japanese, Korean or any other East Asian background) and Turkish, Arab, or Mixed (Mixed White and Black, Mixed Black and Asian, mixed Asian and White, any other Mixed background).

There were three physical activity (PA) groups; group A: <30 minutes of exercise per day, group B: 30-60 minutes of exercise per day and group C: >60 minutes of exercise per day.

All the equipment used was calibrated according to the manufacturersô recommendations before each device was given out to participants.

5.2.3 Experimental design

Following appropriate ethical approval and informed consent, participants were trained by the researcher on how to use the devices at home. A demonstration was given by the researcher and then participants undertook a trial measurement themselves. Following the demonstration, participants completed a consent form and demographics form, kept by the researcher; an information sheet and measurement sheet were included in the package given to patients with the device.

5.2.3.1 Heart rate variability analysis

Heart rate variability measurements were taken using an iPod touch with the Ithlete application (Ithlete 2009). For the HRV measurement, a standard analogue ECG chest strap was worn in the middle of the chest just under the sternum. Using the Ithlete software for the iPod touch, participants measured HRV for one minute, three times in succession in a seated position. Participants were given one minute between each HRV recording.

Real time heart and lung animation on the iPod touch facilitated paced breathing during measurements, and the screen also indicated the reception of each heart beat from the analogue chest strap. After one minute of recording, measurements were saved to the device. HRV (rMSSD in ms) and HR (bpm) were recorded via the Ithlete software for the iPod touch (Ithlete 2009). The breathing frequency was set at 7.5 breaths per minute, designed to maximize RSA response (Brown et al. 1993).

When the one minute measurement was complete, the HR (bpm) and HRV (rMSSD in ms) were displayed on the screen and saved to the device. Ithlete recordings were transferred to a password protected PC via Ithlete software, which enabled recordings to be emailed and saved into an excel document.

5.2.3.2 Bioelectrical impedance analysis

The HoMedics 9116 Black Glass Platform Body Fat Analyser Scale was used by participants first thing in the morning when they woke up. The device was placed on a flat surface and participants stood on the scale with their bare feet for the measurement. Participantsô gender, age, and height were entered into the machine before measurement took place. Participants were asked to take the measurement 3 times in a row and record all the measurements.

5.2.4 Statistical analysis

All statistical analysis was undertaken using PASW 19.0 (SPSS: An IBM Company. Somers, NY, USA). Independent sample t-tests were performed to examine if differences occur in gender or smoking status. Analysis of variance (ANOVA) was performed to examine relationships between ethnic groups and physical activity levels. Pearson correlation analysis was used to evaluate the relationships between rMSSD, HR and various body composition analysis measurements, including body fat %, free fat mass % and total body water (TBW). Analysis of covariance (ANCOVA) was then performed to determine if age or gender were determining factors in differences between ethnic or physical activity groups. A P-value of Ò0.05 was considered statistically significant.

5.3 Results

Average participant characteristics by gender are displayed in Table 5.1. Ethnic differences were evaluated for all of the measurements; averages for each ethnic group are displayed in Table 5.2.

Table 5.1 Subject characteristics

Characteristic	Males (n = 35)	Females (n = 43)
rMSSD(ms)	73.3 ± 12.1	67.2 ± 13.1*
HR (bpm)	69.1 ± 12.9	75.9 ± 13.2*
Age (years)	33.9 ± 13.0	32.9 ± 10.5
Height (cm)	178.5 ± 8.5	165.5 ± 8.0†
Weight (kg)	77.7 ± 11.5	67.6 ± 11.6†
Body fat (%)	20.8 ± 6.9	30.5 ± 9.3†
Total body water (%)	53.6 ± 6.3	50.2 ± 6.7*
Muscle (%)	39.7 ± 3.8	35.3 ± 4.8†
Basal Metabolic Rate (kcal)	1796 ± 214	1469 ± 154†
Desk Job (%)	30.7	37.2
Smoker (%)	7.7	11.5
Alcohol (units/week)	8.1 ± 7.7	3.0 ± 4.6†

*Significant difference at $p<0.05$

† Significant difference at $p<0.01$

Table 5.2 Subject Characteristics by Ethnicity

Characteristic	Caucasian (n = 40)	Afro-Caribbean (n = 17)	Other (n = 20)
rMSSD(ms)	71.1 ± 13.7	65.2 ± 12.7	71.4 ± 11.3
HR (bpm)	69.2 ± 12.2*	79.4 ± 13.3*	75.3 ± 13.7
Age (years)	32.8 ± 10.9	34.1 ± 13.0*	32.0 ± 9.4*
Height (cm)	173.9 ± 10.5	173.1 ± 8.8	168.5 ± 11.0
Weight (kg)	73.9 ± 11.3	74.8 ± 13.3	67.0 ± 13.4
Body fat (%)	24.2 ± 7.2	29.6 ± 9.0	27.0 ± 12.8
Total body water (%)	52.1 ± 5.5	49.9 ± 6.9	52.5 ± 8.8
Muscle (%)	37.8 ± 3.8	35.6 ± 4.9	37.6 ± 6.6
Basal Metabolic Rate (kcal)	1692 ± 258	1571 ± 266	1776 ± 219
Desk Job (%)	39.7	13.0	15.6
Smoker (%)	7.8	3.9	7.8
Alcohol (units/week)	8.1 ± 7.6†	1.8 ± 4.2†	2.3 ± 3.7†

***Significant difference at p<0.05**

†Significant difference at p<0.01

Ÿ One participant did not disclose their ethnic group

Significant differences were demonstrated between the Caucasian and the Afro-Caribbean group in HR. Age was significantly different between the Afro-Caribbean group and the όOtherô ethnic group. A significant difference was also demonstrated in alcohol consumption between the Caucasian group and the other two ethnic groups. There was no significant difference in alcohol consumption between the Afro-Caribbean group and the όOtherô ethnic group. Average participant characteristics by physical activity level are displayed in Table 5.3.

Table 5.3 Subject characteristics by physical activity (PA) level

Characteristic	(A)<30 mins/day (n = 23)	(B)30-60 mins/day (n = 38)	(C)>60 mins/day (n = 17)
rMSSD at rest (ms)	65.4 ± 11.0*	73.3 ± 13.1*	68.3 ± 13.5
HR at rest (bpm)	81.0 ± 11.2	68.2 ± 13.3†	72.1 ±14.8*
Age (years)	32.2 ± 12.3	30.8 ± 7.6†	40.7 ± 15.1*
Height (cm)	170.7 ± 12.3	172.0 ± 9.9	174.1 ± 10.3
Weight (kg)	73.8 ± 12.1	70.8 ± 14.1	72.9 ± 9.2
Body fat (%)	30.6 ± 11.5†	23.1 ± 6.3†	26.8 ± 10.1
Total body water (%)	49.5 ± 6.9*	53.6 ± 5.9*	50.7 ± 7.5
Muscle (%)	35.5 ± 5.4	38.9 ± 3.6†	36.1 ± 5.6*
Basal Metabolic Rate (kcal)	1811 ± 1127	1640 ± 270	1601 ± 291
Desk Job (%)	19.2	35.9	12.8
Smoker (%)	6.4	9.0	3.8
Alcohol (units/week)	2.5 ± 5.2*	6.5 ± 6.3*	6.5 ± 8.4*

***Significant difference at p< 0.05**

†Significant difference at p< 0.01

Significant differences in rMSSD were demonstrated between groups A and B ($p < 0.05$). Significant differences in HR were demonstrated between groups A and B ($p < 0.01$), and groups A and C ($p < 0.05$). A significant difference between group A and B was shown in TBW and alcohol consumption at $p < 0.05$, and BF at $p < 0.01$. Significant differences between groups A and C were demonstrated for age and alcohol consumption at $p < 0.05$. Significant differences in muscle ($p< 0.05$) and age ($p < 0.01$) were demonstrated between groups B and C. The average participant characteristics divided into groups by smoking status are displayed in Table 5.4.

Table 5.4 Subject characteristics by smoking status

Characteristic	Non-Smoker (n = 63)	Smoker (n = 15)
rMSSD at rest (ms)	71.9 ± 11.2	61.8 ± 16.6†
HR at rest (bpm)	71.9 ± 12.3	76.7 ± 17.6
Age (years)	34.7 ± 12.4	27.7 ± 4.1
Height (cm)	173.3 ± 9.9	167.5 ± 11.8
Weight (kg)	73.1 ± 12.2	68.2 ± 13.3
Body fat (%)	26.6 ± 9.7	24.1 ± 8.3
Total body water (%)	51.2 ± 6.3	54.2 ± 8.0
Muscle (%)	36.8 ± 4.8	39.1 ± 5.0
Basal Metabolic Rate (kcal)	1708 ± 716	1571 ± 263
BMI	24.5 ± 3.6	23.8 ± 4.3
Desk Job (%)	17.9	50.0 *
Alcohol (units/week)	4.6 ± 6.2	8.5 ± 8.0*

***Significant difference at p< 0.05**

†Significant difference at p< 0.01

Table 5.5 Pearsonôs correlation for rMSSD/HR correlated with other measurement variables

	rMSSD		HR	
	Pearson correlation (r)	**p**	**Pearson correlation (r)**	**p**
rMSSD	_	_	-0.62	0.001†
Height	0.05	0.68	-0.01	0.95
Weight	0.07	0.54	0.02	0.84
Body Fat	-0.07	0.54	0.17	0.13
TBW	-0.03	0.79	-0.03	0.79
Muscle mass	0.03	0.77	-0.11	0.36
BMR	-0.01	0.92	0.001	0.98
Age	0.02	0.87	-0.26	0.02*
Alcohol units/week	0.07	0.52	-0.17	0.15
BMI	0.09	0.48	0.02	0.89
PA	0.11	0.33	-0.27	0.02*

***Significant difference at p< 0.05**

†Significant difference at p< 0.01

5.3.1 Partial correlations

Partial correlations were undertaken to explore the relationships between rMSSD, HR and lifestyle factors. Physical activity (PA) level, smoking, and alcohol consumption were assessed, while controlling for chronic factors (gender and age). There was a strong negative partial correlation between rMSSD and HR which remained when age and gender were controlled at r = -0.632 ($p < 0.001$). HR was still significantly negatively correlated with age at r = -0.26 ($p < 0.05$) when controlled for gender. HR was significantly negatively correlated with PA which remained when controlling for age (r = -0.22 $p < 0.05$) and gender (r = -0.24 $p < 0.05$) separately. However when gender and age were controlled for together, there was no longer a significant correlation between HR and PA at r = -0.19 p = 0.10. It is recognized that because of numbers, some low correlations will yield a significant probability. These low correlations will still leave a large proportion of unexplained variances.

5.3.2 Analysis of covariance

Analysis of covariance (ANCOVA) was performed to explore the relationships between categorical variables (ethnicity, gender and smoking), with characteristics where significant differences were found between groups. Chronic factors (age and gender) were controlled for to see if they had an impact on the significant differences demonstrated. Despite controlling for age, significant differences remained between genders in BF, BMR, TBW and muscle mass at $p < 0.01$. The significant difference between genders in rMSSD was no longer significant when controlled for age ($p = 0.11$).

Ethnic differences in HR remained significant at $p < 0.05$ when gender and age were controlled. Significant ethnic differences ($p < 0.01$) in alcohol consumption also remained when gender and age were controlled.

A significant difference in HR remained between PA groups when age and gender were controlled at $p < 0.01$. Significant differences in age between PA groups also remained when gender was controlled at $p < 0.01$. When controlled for age, significant differences remained between PA groups in BF, muscle and alcohol consumption at $p < 0.05$. When controlled for gender, there was no longer a significant difference between PA groups in BF, muscle and alcohol consumption. When controlled for age and gender together, there were also no longer significant differences between PA groups for BF, muscle and alcohol consumption.

Significant differences between smokers and non-smokers in rMSSD at $p < 0.01$ remained when controlled for age and gender. Significant differences in alcohol consumption ($p < 0.05$) between smokers and non-smokers remained when controlled for gender and age.

5.4 Discussion

The aim of the present study was to examine if Ithlete measurements of rMSSD (ms)/HR (bpm) demonstrated the same associations with cardiovascular risk factors as those already reported in the literature. Lifestyle factors such as alcohol intake, physical activity level, and smoking were also considered. Statistical analysis was undertaken to control for gender and age, to see if their influence caused the significant differences or correlations between groups. Ithlete measurements demonstrated relationships between physical activity levels, smoking and alcohol consumption; however in the present study, no relationships were shown between rMSSD/HR and body composition measurements. Resting HRV (rMSSD) analyses taken with the Ithlete software were easy and convenient; participants reported no problems using the device. HR and rMSSD were significantly negatively correlated at $p < 0.01$). This correlation remained when controlled for gender and age.

5.4.1 Gender

In the present study rMSSD was significantly higher in the male population. There was no significant difference in age between genders, so that did not play a role in this result. There were slightly more female participants (n=43) compared with males (n=35), but this also does not explain this result. Gender differences in HRV have been reported throughout the literature (Antelmi et al. 2004; Carter et al. 2003; Evans et al. 2001; Gregoire et al. 1996). Reported gender differences in HRV have been inconclusive, with some studies suggesting females have a higher resting HRV (Evans et al. 2001; Koskinen et al. 2009), and other studies suggesting males have a higher resting HRV (Bonnemeier et al. 2003; Umetani et al. 1998). In adult studies, there is a slight majority demonstrating that women possess a higher vagal influence than men (Antelmi et al. 2004; Gregoire et al. 1996; Liao et al. 1995). In contrast, studies looking at gender differences in children have found girls to have a lower HRV compared to boys (Faulkner et al. 2003; Umetani et al. 1998), signifying that the effect of gender may be modulated by age.

When controlled for age, there were no longer gender differences in rMSSD, suggesting that age had more impact on rMSSD than age in the present study. Measurements of rMSSD may have been higher in the male population within this study because changes in HRV may only be demonstrated in specific HRV measures. Umetani et al. (1998) reported differences in the specific time-domain indices where age related decreases in HRV occurred at different times. The SDNN index demonstrated a significantly steeper decline in HRV in females at >50 years when compared with their counterparts at >30 years. In comparison rMSSD and pNN50 demonstrated a decline in both genders at >30 years, but the rate of decline in females was slower (Umetani et al. 1998).

Typical resting measurements of HR should be between 60 and 100 bpm for the average sedentary adult. The mean for both male and female participants in this study were well within that range at 72.3 ± 13.4 and 67.2 ± 13.8 respectively. The mean rMSSD in the present study for male and female participants were similar to those systematically reviewed recently (Nunan et al. 2010). The relationship between HRV/HR and FM has been discussed throughout the literature. Few studies however, have looked at individual indices of body composition such as muscle mass, body fat percentage and total body water compared specifically with HRV and HR. When controlled for gender, HR and age were still significantly positively correlated. This confirms that resting HR increases with age in both males and females. HR and PA remained negatively correlated when controlled for gender and age separately, however when controlled for together the correlation was no longer significant. Physical activity is known to decrease resting HR (Katona et al. 1982; Smith et al. 1989; Wilmore et al. 1996). The results of the present study suggest that age and gender however, also affect these changes. PA level has an impact on body composition (Andreacci et al. 2008; Slentz Ca et al. 2004), and both these factors influence HRV measurements.

The present study found no correlations between HRV/HR and body composition measurements of muscle mass, BF, TBW or BMR. This is in contrast to other studies who have reported associations. Sztajzel et al, (2009) reported large amounts of body fat were associated with a depressed HRV and increased HR. Higher body weight was related to decreasing time domain parameters, including rMSSD and SDNN in adolescent obese subjects (Rabbia et al. 2003; Sztajzel et al. 2009). Decreased HRV indices have been associated with total body FM (Christou et al. 2004). Lower levels of rMSSD were associated with high levels of total body fat mass and fat free mass in obese children (Gutin et al. 2000). A relationship was reported between BMI and

HRV in women where a higher BMI had reduced parasympathetic control and elevated sympathovagal modulation (Pai et al. 2011). Partial correlations were assessed to control for gender and age, however significant correlations were still not found between HRV/HR and body composition variables.

Due to biological differences between males and females, significant gender differences observed in height and weight within the present study were as expected. Generally in England, males are reported on average to be taller and heavier than females (Department of Health 2010). Females had a higher average body fat percentage; lower average muscle mass and BMR which were also to be expected as previous research have also demonstrated these gender differences (Buchholz et al. 2001; Gallagher & Heymsfield 1998; Gallagher et al. 1997; Kim 2012). Alcohol consumption, as demonstrated in literature, was also significantly higher in males compared with females (Ely et al. 1999; Wilsnack et al. 2000). In the present study, gender differences remained between BF, BMR, TBW and muscle ($p < 0.01$) when controlled for age. Gender differences in rMSSD were no longer significant when controlled for age; suggesting that age has a significant influence on the difference found in the present studyôs population.

Desk jobs are associated with long periods of sedentary time which has been associated with increased risk of obesity, diabetes, heart disease, certain types of cancer, and death (Wilmot et al. 2012). In the present study no significant difference was found in occupation between men and women, which differs from Shauman (2006), who reported differences in the choice of occupation between women and men despite the same level and education. The present study only used two categories for occupation which may account for this; dividing into more specific occupational groups may show greater differences.

5.4.2 Ethnicity

In the present study, ethnic differences were only observed for age, HR, PA ($p<0.05$) and alcohol consumption ($p<0.01$). No significant differences were observed in rMSSD between ethnic groups. This is in contrast to the literature, as several studies have reported differences (Faulkner et al. 2003; Guzzetti et al. 2000; Liao et al. 1995; Urbina et al. 1998). Studies considering ethnic differences in Caucasian and

Afro-Caribbean populations found both decreased sympathetic activity in Afro-Caribbeanŝ (Guzzetti et al. 2000; Liao et al. 1995; Urbina et al. 1998), and greater sympathetic contribution in Afro-Caribbeanŝ (Faulkner et al. 2003). Similarly, studies examining HRV in Caucasian and Asian children are inconsistent. Kikuchi et al (2003) reported lower HRV in Asian children when compared with their Caucasian counterparts; but Reed et al (2006) found higher frequency domain indices in Asian children. The present study placed participants into three categories: Caucasian, Afro-Caribbean and other. There were notably more Caucasian participants (n=40) compared with the other two groups (Black n=17 and other n=20), which may have impacted results.

Bathula et al. (2008) reported higher HR in South Asian men when compared with their Caucasian counterparts. Higher average resting HR was also reported among South Asian children (Whincup et al. 2002). Lower resting HRŝ were reported in participants of European descent in an eight year follow-up study, examining the association between resting HR, cardiovascular, cancer and all-cause mortality (Kristal-Boneh et al. 2000). Results of resting HR from the present study follow the same pattern as the literature, with Caucasians demonstrating the lowest resting HR (69.2 ± 12.2 bpm), followed by Others (75.3 ± 13.7 bpm) and then Afro-Caribbeans (79.4 ± 13.3 bpm). Higher resting HR is associated with low physical fitness and increased risk of mortality (Kristal-Boneh et al. 2000). Ethnic minorities are at higher risk of heart disease. South Asians are known to have a higher prevalence of hypertension (Lane & Lip 2001) and are at increased risk of coronary heart disease (Balarajan 1991). Also, Afro-Caribbeans have a higher incidence of stroke (Saxena et al. 2004; Stewart et al. 1999). When controlling for gender and age, ethnic differences in HR still remained. This suggests that ethnic differences in HR can occur at various ages and in both men and women.

In the present study, significant ethnic differences were observed in alcohol consumption. Caucasian participants averaged more than three-times the amount of alcohol consumption per week than the other two ethnic groups. This is in line with the literature, as a review examining alcohol consumption in the UK found that most studies reported lower drinking levels in most ethnic minority groups when compared with their Caucasian counterparts (Hurcombe et al. 2010). The frequency and amount of drinking have both been reported higher in Caucasian populations compared with ethnic minority groups (Afro-Caribbean, South Asian, Chinese), with 36% of Caucasians reporting to drink at least three-times-per-week compared with 17% in Afro-Caribbeans (Cochrane 1999). Twenty-five percent of Caucasians regularly drink two or more times a week compared with just two percent in South Asians (Denscombe 1995). Nazroo (1997) assessed alcohol consumption once a week or more by ethnicity and gender, and reported Caucasians at 69% for males and 46% for females, compared with Afro-Caribbeans at 50% for males and 23% for females, South Asians at 25% for males and 4% for females, and Chinese at 32% for males and 11% for females. These findings are similar to those reported in the present study, where significant differences in alcohol consumption were found in both gender and ethnicity. When age and gender were controlled, significant ethnic differences in alcohol consumption remained; suggesting that alcohol consumption differs between gender and ethnic groups at various ages.

5.4.3 Physical activity levels

There were some surprising results when participants were split into PA levels. There was a significant difference in age, with those stating they were the most physically active also having the highest average age. This is in contrast with the literature where PA tends to decline with age (Droomers et al. 2001; Jackson et al. 2009; Sallis 2000). When controlled for gender, age was still significantly different at $p < 0.01$. Significant differences with respect to PA level were also found in HR, BF, muscle mass and alcohol consumption. There were three groups; group A: <30 minutes of exercise per day, group B: 30-60 minutes of exercise per day and group C: >60 minutes of exercise per day. Group B had the lowest resting HR and body fat percentage. Group C would be expected to have the lowest resting HR, because literature has shown an association between resting HR and fitness level (Aubert et al. 2001; Dixon et al. 1992; Loimaala et al. 2000; Pichot et al. 2000). Those who do more daily exercise would presumably be the most fit. When controlled for gender and age, HR was still significantly different at $p < 0.01$ between PA groups. This suggests that in both genders and regardless of age, HR is strongly influenced by regular PA.

Body fat percentage was lowest in group B but this could be due to group C having a higher average age, as body fat increases with age (Gallagher et al. 2000). The same relationship was demonstrated with muscle mass; with Group C demonstrating lower muscle mass than group B but this again may be attributed to age. When controlled for age, BF and muscle remained significantly different at $p < 0.05$. When controlled for gender however, they were no longer significantly different; suggesting that gender had a greater effect in the present study's population than age. When controlled for both gender and age together, BF and muscle were no longer significantly different. Alcohol consumption was significantly lower in group A compared with group B and C, but there does not appear to be any attributable reason for this, as no other factor associated with alcohol was significantly higher in group A. When controlled for age, alcohol remained significantly different ($p < 0.05$) between PA groups. When controlled for gender alcohol was no longer significant, again suggesting that gender has more impact within this population. When controlled for gender and age together, alcohol was also no longer significantly different between PA groups.

5.4.4 Smoking

Increased sympathetic nervous activity has been associated with cigarette smoking (Barutcu et al. 2005). Second-hand smoke has been associated with cardiac autonomic dysregulation (Felber Dietrich et al. 2007; Tsuji et al. 1996). Within the present study, significant differences between smokers and non-smokers were found in rMSSD and alcohol consumption. Smokers had significantly lower rMSSD. This is in accordance with the literature, which has reported lower HRV in those exposed to environmental tobacco smoke at home and at work (Dekker et al. 1997; Felber Dietrich et al. 2007; Pope et al. 2001). When controlled for gender and age significant differences in rMSSD between smokers and non-smokers remained. When controlled for alcohol consumption the difference in rMSSD between smokers also remained significant. This suggests that despite the known association between smoking and alcohol, rMSSD is still affected by just smoking.

In the present study, a difference in alcohol consumption was demonstrated between smokers and non-smokers. When controlled for age and gender, the difference remained significant at $p < 0.05$. Cigarette smoking has a history of being associated with alcohol abuse (de Vries et al. 2008; Keenan et al. 1990; Ma et al. 2000). Therefore higher alcohol consumption in the smoking population is in accordance with the literature. There is, however, a large difference in the amount of smoking compared with non-smoking participants within this study, which reduces the significance of these results.

None of the significant differences between genders observed in the present study were surprising or unexpected. The absence of a difference between genders in the amount of smokers, and those having desk jobs, is on the other hand intriguing. Historically, men smoke more than women. However, in European countries especially, there has been a sharp decrease in smoking prevalence amongst men (WHO 2005). In England, there are contradictory views about smoking cessation. Brose et al (2011) reported women as less successful than men in quitting smoking through an NHS smoking cessation service, while other research reported no clear evidence for overall sex differences in cessation of smoking (Jarvis 1984; Jarvis et al. 2012). A strong correlation has been found between the level of economic development and the prevalence of smoking among men and women (Hitchman & Fong 2011). All of this may be contributing to women smoking at nearly the same rate as men in Australia, Canada, USA and most of Western Europe (WHO 2008).

5.4.5 Limitations

Limitations to this study involve the method of obtaining participants. Self selection naturally occurred through the recruitment of participants. Those who are involved in this study were those that wanted to participate, and therefore are not necessarily representative of the population.

Participants took measurements at home first thing in the morning, without the presence of the researcher, and therefore the researcher cannot be absolutely sure that participants followed the instructions for optimal measurement completely. Participants were encouraged to not eat or drink before taking measurements and to ensure that their resting HRV/HR was taken first thing before moving around too much. If participants were inconsistent, this may have caused a small degree of error.

5.5 Conclusion

The present research study was unique in its use of a novel HRV measurement device (Ithlete). Gender differences were demonstrated in rMSSD, HR, alcohol consumption and body composition measurements; these differences remained in all except rMSSD when controlled for age. Ethnic differences were demonstrated in HR and alcohol consumption, and remained when controlled for gender and age. This suggests that ethnic differences in rMSSD are present in both genders and at various ages. Gender differences in rMSSD however, are modulated by age. In the present study, no significant correlations were demonstrated between rMSSD/HR obtained from Ithlete and body composition measurements. This is in contrast to the literature, suggesting that Ithlete measurements may not demonstrate the same correlations. More research is needed using the Ithlete device in a larger cohort to determine this definitively.

Future research should expand this research by increasing the participant base in both numbers and different ethnic groups. Ithlete is an easily accessible application for iPod touch (2^{nd} generation or later) or a smartphone, which can be used to measure HR and rMSSD. Future research should focus on utilizing Ithlete for measurement in special populations who are known to be at increased risk to further explore the relationships that exist between HRV/HR and other cardiovascular risks factors such as body composition. Knowledge of these relationships may lead to establishing increased risk factors, which in turn can lead to improvement in both diagnosis and care.

5.6 References

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CHAPTER 6: HEART RATE VARIABILITY IN HEALTHY CAUCASIAN AND SOUTH ASIAN PARTICIPANTS

Cardiovascular disease (CVD) is the leading cause of premature death in the UK. The health of the cardiovascular system is influenced by both modifiable and non-modifiable CVD risk factors. The link between ethnicity and health is well established. Ethnic minorities such as Black African/Caribbean or South Asians tend to have higher rates of risk factors for CVD (i.e. hypertension, atherosclerosis, obesity and insulin resistance) when compared with Caucasians. Higher rates of ischaemic heart disease and diabetes are found among the British South Asian community. Heart rate variability (HRV) is the phenomenon of the difference in time between heart beats, which is influenced by the autonomic nervous system (ANS). The ANS has an influence on the function of the cardiovascular system and energy balance. A reduced level of HRV has been demonstrated to be a significant predictor of a cardiac event, morbidity and mortality. There is no consensus on the effect of ethnicity on HRV, with studies demonstrating both higher and lower HRV in ethnic minorities.

The aims of the present study were two-fold; first to explore ethnic differences in HRV between healthy Caucasian and South Asian participants, while estimating the normal pattern for HRV in this population. The secondary aim was to determine the feasibility of HRV measurements, using a new personal heart rate variability monitor (Ithlete).

No significant difference was found in HRV or heart rate (HR) between South Asian and Caucasian participants. There were also no significant differences in HRV and HR when controlled for gender and age. No significant difference in resting HRV between South Asian and Caucasian or male and female participants when matched for age were found in the present study. This is despite indications that autonomic function is related to both cardiovascular diseases and diabetes. Ethnic differences demonstrated in this study were inconclusive; however future research in a larger cohort of participants could explain the natural differences that may cause increased cardiovascular risk.

6.1 Introduction

The link between ethnicity and health is well established and there are numerous ethnic differences in health risks including hypertension, diabetes and the risk of cardiovascular events. The human body is a complex system that has several subsystems interacting within it to keep the system operational. One of those subsystems is the cardiovascular system which involves the health of the heart and circulatory system. Problems with the cardiovascular system result in cardiovascular disease (CVD) which is currently the leading cause of death worldwide with an estimated 17.1 million people dying from CVD each year (World Health Organization 2011). Furthermore, CVD is the leading cause of death and premature death in the UK, with approximately 20% of men and almost 15% of women in the UK dying from complications related to CVD (British Heart Foundation 2008). CVD accounts for approximately 198,000 deaths per year in the UK, despite death rates falling due to improvements in treatment, secondary prevention, and a reduction in major risk factors (ibid). Coronary heart disease (CHD) and stroke are the most common forms of CVD, accounting for 48% of all deaths related to CVD. CHD alone costs the UK economy approximately £7 billion pounds per year (British Heart Foundation 2008). Several risk factors increase the likelihood of developing CVD, which are now discussed.

6.1.1 Risk factors

The health of the cardiovascular system is influenced by both modifiable and non-modifiable CVD risk factors. Modifiable or ólifestyleô risk factors include: a lack of exercise, diet, smoking, alcohol use and obesity. External or environmental factors are associated with increased CVD, most probably via differences in such risk factors. For instance, deprivation is positively correlated with deaths from circulatory diseases in England and Wales (British Heart Foundation 2008). The difference in CHD prevalence among different socioeconomic groups across the UK is attributed to modifiable factors including diet, smoking and alcohol (ibid). Mortality is 60% higher in smokers, and in 2001 27% of the population over 16 years of age smoked cigarettes (Doll et al. 2004). Poor diet increases the risk of CHD, particularly diets high in saturated fat, sodium and sugar (World Health Organization 2003). Physical inactivity is estimated to account for 20% of CHD in developed countries (ibid). Psychosocial well-being has also been linked with CHD; anxiety, depression, work stress, and lack of social support all increase the risk of CHD (Brezinka & Kittel 1996). While modifiable risk factors are important for public health, it should also be noted that they interact with a number of non-modifiable factors. Knowledge of these factors can help target health education and healthcare more effectively. Non-modifiable CVD risk factors include: family history, gender, age and ethnicity. A first-degree relative of someone with premature myocardial infarction (MI) is 50% more likely to have an MI themselves (Chow et al. 2007). The risk of CVD is also higher in some ethnic groups; specific examples will be discussed below.

6.1.2 Ethnic differences

There are ethnic differences in anthropometric values, including BMI, waist-to-hip ratio and waist circumference (Brancati et al. 2000; Carroll et al. 2008; Flegal et al. 2010; Hedley et al. 2004). Estimates of adult obesity prevalence among different ethnicities vary based on the measurement criteria. Chinese men and women appear to have the lowest obesity prevalence compared to other ethnicities (Gatineau & Mathrani 2011). African-Americans tend to have higher rates of hypertension, atherosclerosis, obesity and insulin resistance when compared with Caucasians (Hoffman 2009). In the UK, South Asians from India, Pakistan and Bangladesh have a higher prevalence of mortality from coronary heart disease (Balarajan 1995; Wild & Mckeigue 1997).

Ethnic differences in HRV have been studied predominantly in Black vs. White studies and have been so far inconclusive (Guzzetti et al. 2000). Ethnic differences in health vary from one condition to the next, as Black and minority ethnic groups tend to have higher rates of cardiovascular disease but lower rates of cancer (Bhopal 2007). Larger numbers of cardiovascular disease and stroke have been found in black and other ethnic minority groups (Lip et al. 2007). Black men born in the Caribbean are 50% more likely to die of stroke than the rest of the general population (Department of Health 2010). To break down ethnicity further, in England, surveys commonly show that Indian, East African, Asian and Blacks report the same health as White British participants; while Chinese report better health (Department of Health 2004). Statistically however, Pakistaniôs, Bangladeshi and Black-Caribbeanôs have poorer health than their White British counterparts (ibid).

6.1.2.2 White vs. South Asian

Higher body fat percentage, abdominal obesity and higher liver fat content have been reported in the Asian population when compared with their Caucasian counterparts of the same BMI (Lovegrove 2007). Increased body fat is an independent risk factor for diabetes, hypertension and cardiovascular disease (Wulan et al. 2010). There is a higher premature death rate in the South Asian population of the UK which is 46% higher in men and 51% higher in women (British Heart Foundation 2008). Men born in South Asia are 50% more likely to have angina or a heart attack compared with the general population in the UK (Department of Health 2010). The South Asian population is five-times more likely to suffer from diabetes mellitus when compared with the general population (Department of Health 1999), and have the highest prevalence of ischaemic heart disease (Department of Health 2004).

6.1.3 Heart rate variability

Heart rate variability (HRV) is a physiological phenomenon where the time interval between heart beats is measured through various techniques. Measurement of HRV is non-invasive, and examines one aspect of autonomic nervous function. The autonomic nervous system (ANS) controls visceral functions and functions predominantly below the consciousness level. The ANS affects heart rate, respiration, perspiration etc. The ANS makes itself visible through HRV indicating how the body is trying to preserve its equilibrium. rMSSD is an HRV measure of vagal tone which has been associated with health and disease. Thus HRV has the potential to monitor the autonomic response to exercise volume on a daily basis. HRV has been demonstrated as a reliable and reproducible technique for assessing autonomic activity (Noland et al. 1998). There are various parameters for HRV analysis (Task force, 1996) which include time domain, frequency domain and non-linear methods.

Good correlations (as high as 0.90) have been demonstrated between the time frequency measurement rMSSD and frequency domain measures of high-frequency HRV (HFr) (Task force, 1996). The present study will focus on one measure in particular, the root of the mean squared differences of successive heart periods (rMSSD). A full review of these measures and their interrelation can be found in Nunan et al (2010).

6.1.3.1 rMSSD

rMSSD is a time domain measure of HRV which reflects parasympathetic activity without being dependent on heart trends (Stein et al. 1994). rMSSD is independent of mean heart rate and considered robust against gradual trends over time (Hilz & Dütsch 2006). rMSSD is influenced by a variety of factors which include rate and depth of respiration, physiology of sinoatrial node, physical conditioning and age (Berntson et al. 2005). The prognostic value of HRV at rest has been demonstrated in healthy subjects (Ramirez-Villegas et al. 2011; Zulfiqar et al. 2010). The rMSSD measure has been suggested as superior to spectral methods due to its sensitivity to vagal cardiac control and its reduced sensitivity to variations in respiratory patterns (Penttilä et al. 2001).

6.1.3.2 HRV and ethnicity

When considering the effect of ethnicity on HRV, differences have been demonstrated in the literature. Blacks have a lower sympathetic drive when compared with age-matched whites (Guzzetti et al. 2000; Liao et al. 1995a). Decreased sympathetic tone was also found in black adolescents compared with their white counterparts in a study that compared HRV with high and low blood pressure (Urbina et al. 1998). Conflicting results were then published in 2003, which found that black adolescents displayed a greater sympathetic contribution to total power when compared with age-matched white adolescents (Faulkner et al. 2003).

A comparison of Asian and Caucasian children found significantly elevated ration of low frequency and high frequency power (LF:HFr) in the Asian children, which supports previous investigations of black-white differences (Reed et al. 2006). Independent studies of HRV in the Asian population propose that racial differences in time and frequency domain measures of HRV occur where Asian children living in Asia display a lower HRV than Caucasian children living in North America (Kikuchi et al. 2003; Nagai et al. 2004).

6.1.3.3 HRV measurement devices

HRV can be measured through a number of devices. Holter tapes are known as the standard measurement of ECG records for 24-hour ambulatory recordings (Task Force, 1996). Other devices have been tested for accuracy including the Polar s800 models and Suunto t6 with excellent agreement found with an ambulatory ECG system (Weippert et al. 2010). A novel short-term HRV measurement device called Ithlete was launched on the market in 2009. Ithlete is an ECG receiver that attaches to smartphones or iPod touch (2nd generation or later). The device is used with a regular analogue (5.4 kHz) heart rate monitor chest strap and takes a one-minute measurement of both HR and HRV. The Ithlete application uses a paced breathing frequency, and has lung and heart animation displayed on the screen during measurement. This new device has great potential because of its simplicity and low cost, and will be used in the present study.

6.1.4 Aims

This research study will focus on expanding the understanding of HRV measurements in two different ethnic groups. As discussed above there are various HRV measures that are used with high correlation between them. The present study proposes to use just one measure, rMSSD in one minute measurements to assess HRV. With high correlations between the measures, there is no need to measure all of them each time HRV analysis is undertaken. rMSSD has been demonstrated in the literature as a reliable measurement with high correlation to the others (Berntson et al. 2005; Task force, 1996).

The aims of the present study were two-fold: first to demonstrate any ethnic differences in rMSSD between healthy Caucasian and South Asian participants, while also trying to ascertain the normal range for rMSSD in this population. The secondary aim was to demonstrate ethnic differences in HRV measurements using a single measure of HRV (rMSSD) from a new, simple HRV device (Ithlete).

It is hypothesized that Ithlete software for measurement of rMSSD will demonstrate a reliable and normal pattern of rMSSD in South Asian and Caucasian populations.

6.2 Methods

6.2.1 Recruitment of participants

Staff and students of Buckinghamshire New University were invited to take part in the study through internal advertisement on notice boards and emails. Each participant was recruited in accordance with University ethics committee standards and expectations. Participants responded via email or phone and were sent an information pack before agreeing to participate. The information pack included:

1. An information sheet with detail of the requirements for each participant before and during the laboratory visit
2. An informed consent form
3. A physical activity readiness questionnaire (PAR-Q)
4. A detailed demographic information sheet

Participants were requested to read the information pack prior to attending the laboratory. Any questions or concerns were addressed during the initial meeting with the researcher. All participants were free from any serious medical conditions and contraindications to exercise as indicated by the PAR-Q. All procedures were approved by the local research ethics committee.

6.2.2 Participants

Caucasians were classified as Whiteҫs from European decent. South Asian participants were classified as those descending from India, Pakistan or Bangladesh (United Nations Statistics Division 2012). Fifty-nine participants were tested, of which 29 were Caucasian (13 male) and 30 were South Asian (15 male). Participant age ranged from 22 to 65 years. All participants were defined as healthy (free from any serious illness at the time of testing), and none of the participants was known to have any cardiovascular problems, or to be taking any medication that would have influenced the experimental procedures.

Participants completed a PAR-Q; those who answered ÷yesô to any of the conditions mentioned in the PAR-Q were excluded. Participants completed their consent form in front of the researcher, and the researcher countersigned the form.

6.2.3 Experimental design

Following appropriate ethical approval and informed consent, participants were asked to visit the cardiovascular research lab at Bucks New University, Uxbridge. Prior to the test, participants were asked to avoid caffeine, heavy physical activity, smoking, and alcohol intake for the 10 hours preceding their lab visit. Participants were also encouraged not to eat at least two hours prior to the test. All the equipment used was calibrated before each test according to the manufacturersô recommendations.

6.2.3.1 Heart rate variability analysis

Two measures (rMSSD in ms, and HR in bpm) were recorded via the Ithlete software for the iPod touch (Ithlete 2009). A standard analogue ECG chest strap was worn in the middle of the chest just under the sternum. Real time heart and lung animation on the iPod touch facilitated paced breathing during measurements, and the screen also indicated the reception of each heart beat from the analogue chest strap. Participants measured rMSSD for one- minute, three times in succession in a seated position. Participants were given one-minute between each rMSSD recording. After each one-minute recording, measurements were saved to the device.

The breathing frequency was set at 7.5 breaths per minute, designed to maximize RSA response (Brown et al. 1993). When the one minute measurement was complete the HR (bpm) and RMSSD in ms were displayed on the screen and saved to the device. Ithlete recordings were transferred to a password protected PC via Ithlete software, which enabled recordings to be emailed and saved into an excel document.

Examinations took place in the research lab, which was maintained at a comfortable temperature with limited distractions. Experimental procedures were described to participants in advance. All procedures carried out during the examination were considered non-invasive.

6.2.3.2 Bioelectrical impedance analysis

Body composition measurements involved participants lying in a supine position for testing allowing at least five minutes for even body fluid distribution before measurements were recorded. Two electrodes were placed on both the hand and foot of each participant, one on the bisecting line of the wrist/ankle and the other proximal to the fingers/toes. Once ready for measurement an undetectable current was passed through the distal electrodes on the hand and foot and the proximal electrodes on the wrist and ankle receive the current flow (Wilmore & Costill 1999). Water and electrolyte distribution in the tissues determines the electrical conduction between the electrodes. Fat mass has a greater impedance as it is more difficult for a current to flow through it when compared with free-fat mass. Free-fat mass consists of all the body water and conducting electrolytes making conductivity much greater within this tissue (ibid).

Using the BIA 101 and Bodygram software (Akern; Florence, Italy), small wires were connected for measurement and a recording was executed allowing at least three reading cycles before inputting measurements into the Bodygram software. Bodygram software then computed body composition measurements including BMI, body fat %, fat free mass %, intracellular water, extracellular water for each participant and stored in the Bodygram software program. BIA measurements take approximately five minutes to perform.

6.2.4 Statistical analysis

All statistical analysis was undertaken using PASW 19.0 (SPSS: An IBM Company. Somers, NY, USA). Differences between ethnicity and gender were assessed using analysis of covariance (ANCOVA). Owing to the established relationship with HRV, analysis was undertaken which controlled for gender and age. A p-value of < 0.05 was considered statistically significant.

6.3 Results

6.3.1 Participant characteristics

Anthropometric, HRV and HR characteristics for each group are represented in Table 6.1 displaying ethnicity (Asian and Caucasian) and gender (male and female). Student t-tests found a significant difference between the South Asian and Caucasian participants in age and weight (p Ò 0.05). A significant difference was also found between genders in weight. The other participant characteristics recorded were similar in both groups. Body composition characteristics for each group are represented in Table 6.2 displaying ethnicity (Asian and Caucasian) and gender (male and female). Student t-tests found a significant difference between the South Asian and Caucasian participants in BMI ($p < 0.05$), TBW and BMR ($p< 0.01$).

Table 6.1 Mean and SD for anthropometric characteristics, rMSSD and HR of the participants

Ethnicity	**Caucasian (n=29)**		**South Asian (n=30)**	
Gender	**Male (n= 13)**	**Female (n = 16)**	**Male (n = 15)**	**Female (n =15)**
rMSSD (ms)	67.4 ± 12.8	68.4 ± 8.2	69.2 ± 7.0	73.1 ± 6.8
HR (bpm)	79.4 ± 13.1	82.3 ± 11.1	83.9 ± 12.9	79.8 ± 7.3
Age (years)	38.4 ± 13.0†	34.6 ± 12.1*	24.9 ± 3.6†	26.6 ± 3.5*†
Height (cm)	173.4 ± 9.5†	163.9 ± 5.1†	171.5 ± 5.6†	161.7 ± 4.7†
Weight (kg)	80.0 ± 14.1†	67.3 ± 16.3†	70.0 ± 8.7†	57.2 ± 8.9*†
Waist Circumference (cm)	89.4 ± 10.9†	80.2 ± 13.9*	83.3 ± 6.8†	75.1 ± 10.5*†

***Significant difference at p< 0.05**
†Significant difference at p< 0.01

Significant differences in age were demonstrated between Caucasian and South Asian males ($p < 0.01$), and Caucasian males and South Asian females ($p < 0.01$). Significant differences in age were demonstrated between Caucasian females and South Asian females ($p < 0.05$), and Caucasian females and South Asian males ($p < 0.01$). There was no significant difference demonstrated between Caucasian males and females in age. In height, significant differences were demonstrated between Caucasian males and females ($p < 0.01$), Caucasian males and South Asian females ($p < 0.01$). No significant difference was demonstrated between Caucasian males and South Asian males. A significant difference in height was demonstrated between Caucasian females and South Asian males ($p < 0.01$), and between South Asian males and females ($p < 0.01$).

Significant differences in weight were demonstrated between Caucasian males and females, and Caucasian males and South Asian females at $p < 0.01$. A significant difference in weight was demonstrated between Caucasian and South Asian males at $p < 0.05$. Significant differences were also found between South Asian males and females ($p < 0.01$) and Caucasian and South Asian females ($p < 0.05$). Significant differences in WC were demonstrated between Caucasian males and females ($p < 0.05$), and Caucasian males and South Asian females ($p < 0.01$). A significant difference in WC was also demonstrated between South Asian males and females ($p < 0.01$).

Table 6.2 Mean (SD) body composition characteristics of the participants

Ethnicity	**Caucasian (n=29)**		**South Asian (n=30)**	
Gender	**Male (n= 13)**	**Female (n = 16)**	**Male (n = 15)**	**Female (n =15)**
BMI	26.3 ± 3.9†	24.9 ± 5.0	23.8 ± 3.2	22.0 ± 3.6†
Body fat (%)	23.8 ± 9.6	26.6 ± 11.9	27.4 ± 6.8	28.7 ± 9.2
Total body water (%)	44.6 ± 8.6†	35.3 ± 6.2*†	37.0 ± 5.0†	29.4 ± 2.6*†
Basal metabolic rate (kcal)	1784 ± 250†	1478 ± 174†	1570 ± 187†	1378 ± 111†
Free fat mass (%)	76.2 ± 9.6	73.4 ± 11.9	72.6 ± 6.8	71.3 ± 9.2
Muscle mass (%)	54.8 ± 11.9*	47.2 ± 10.2	49.5 ± 8.4	47.3 ± 9.1*
Exercise time (min)	13.6 ± 3.0	13.7 ± 2.1	14.3 ± 3.1	13.9 ± 1.4
V02max ($kg.ml.min^{-1}$)	29.2 ± 6.6*	27.5 ± 5.7	29.0 ± 6.0	24.8 ± 4.2*

***Significant difference at p< 0.05**
†Significant difference at p< 0.01

Significant differences in BMI were demonstrated between Caucasian males and South Asian females ($p < 0.01$). Significant differences in TBW were demonstrated between Caucasian males and all other groups at $p < 0.01$. Significant differences in TBW were also demonstrated between South Asian males and females ($p < 0.01$) and between Caucasian and South Asian females ($p < 0.05$). Significant differences in BMR were demonstrated between Caucasian males and all other groups at $p < 0.01$. A significant difference in BMR was also demonstrated between South Asian males and females at $p < 0.01$. Significant differences between Caucasian males and South Asian females were demonstrated in both MM and Vo_2 max at $p < 0.05$.

6.3.2 Analysis of variance (ANOVA) and analysis of covariance (ANCOVA)

ANOVA showed no significant differences between Caucasian and South Asian participants in measurements of HRV at $p = 0.19$ and HR at $p = 0.61$. For anthropometric characteristics there were significant ethnic differences in age, weight and waist circumference; a significant gender difference in height was also demonstrated. Significant ethnic differences were found for BMI ($p < 0.05$), TBW ($p < 0.01$) and BMR ($p < 0.01$).

ANCOVA revealed no significant ethnic difference ($p = 0.33$) for HRV or HR ($p = 0.08$), when controlled for age and gender. When presented graphically, approximately the same difference between parallel lines appeared between gender and ethnicity in covariate analysis of HRV and HR. When controlled for gender and age, significant ethnic differences remained at $p < 0.05$ for BMI, and $p < 0.01$ for TBW, WC, BMR, height, and weight. Significant differences emerged between South Asian and Caucasian participants in exercise time ($p < 0.01$) and relative V02max ($p < 0.01$) during ANCOVA analysis.

6.4 Discussion

6.4.1 Ethnic comparison

One factor noted in the evolution of CVD is autonomic dysfunction, but the few comparisons of autonomic system function made between ethnic groups are inconsistent. Ethnic differences in autonomic function are important, because research has shown that there is a relationship between HRV and diseases such as diabetes mellitus (Liao et al. 1995b; Schroeder et al. 2005), stroke (Robinson et al. 1999) and hypertension (Schroeder et al. 2003; Singh et al. 1998). In the UK, diabetes mellitus and CVD are more prevalent in ethnic minorities (South Asians, Black African/Caribbean) (Department of Health 2010). Within the present study, no significant differences were found in HRV or HR between South Asian and Caucasian participants. There were also no significant differences in HRV and HR when controlled for gender and age. Similar results were found with obese black and white youths with no significant difference in HRV (Gutin et al. 2000).

Ethnic differences in parasympathetic modulation have been reported in adults, with blacks having higher parasympathetic modulation than whites (Liao et al. 1995a). However, similar research undertaken with a smaller sample size in youths found different results (Franke et al. 2004; Urbina et al. 1998). A recent study in Pakistan looked at rMSSD (ms) in a healthy Pakistani population compared with healthy volunteers from a foreign population, and found increased rMSSD in the Pakistani population (Khan et al. 2010). Ethnic differences have been reported in diseases such as hypertension, diabetes and heart disease. Some ethnic groups are at an increased risk compared with others in different disease states, and it is important to promote prevention within these groups. Ethnic differences in cardiovascular risk profiles (Whincup et al. 2002) imply that ethnic differences in HRV could occur. When considering South Asians and cardiovascular disease specifically, genetic and environmental factors are likely to play a role (Bhatnagar et al. 1995; Williams 1995). Moreover, these factors also affect other ethnic groups (i.e. African, Chinese, Malay) (Lee et al. 2001; Marijon et al. 2007).

The average values obtained in the present study for rMSSD from Ithlete were similar to results in several other studies (Khan et al. 2010; Quintana et al. 1997; Ramaekers et al. 1998). Khan et al, (2010) compared healthy Pakistani subjects with a healthy foreign population and found higher rMSSD values in the Pakistani population. This is similar to the present study where South Asians also had a slightly higher rMSSD value, although this was not a significant difference. This suggests that Ithlete is a viable option for rMSSD measurement, and is an improvement in measurement technique considering its ease of use, short measurement duration and low cost.

Ethnic differences found in the literature regarding HRV are sparse and inconclusive (Choi et al. 2006), and tend to focus more on Caucasian and Afro Caribbean comparisons. When considering other cardiac measurement indicators such as hypertension, ethnic differences have been found between Caucasians and South Asians in the UK (Lane & Lip 2001). Most of the literature has demonstrated a higher prevalence of hypertension in South Asians and Afro Caribbeans (ibid). The present study found similar values of resting rMSSD with no significant difference between the two populations with a mean rMSSD of 71.1 ms in South Asians compared with 68.0 ms in Caucasians. Ethnic differences in HRV have been associated with a higher resting heart rate, and lower levels of both energy expenditure and physical activity (Eyre et al. 2013). The present study found no significant difference in resting rMSSD between South Asian and Caucasian, or male and female participants, when matched for age. It has been documented that ethnic minorities living in the UK have lower uptake rates of health service provision in coronary artery disease (Ford & Cooper 1995), and diabetes clinics (Hawthorne 1994). Higher rates of ischaemic heart disease and diabetes are found among the British South Asian community (Chandola 2001). This emphasizes the importance of defining ethnic differences in physiological measurements and promoting awareness of increased risk factors in these populations.

When considering ethnicity, there may be different degrees of body fatness in different populations (i.e. ethnicity) due to diverse body proportions which will have an impact on BMI (World Health Organization 2006). There has been increased attention placed upon the possible need for the development of different BMI cut-offs due to mounting evidence that the associations between percentage body fat, body fat distribution and BMI differ across populations (WHO expert consultation 2004). The National Institute for Clinical Excellence (NICE) released a new BMI and waist circumference guideline in the UK for black and minority ethnic groups in July 2013. This may help to increase the awareness within those communities to make them aware of when they become at higher risk of cardiovascular disease, hypertension and/or type-2 diabetes (ibid).

Analysis of variance revealed significant ethnic differences in age, weight and WC. The relationship between age and HRV has been documented in literature (Liao et al. 1995a; Pomeranz et al. 1985; Stein et al. 1997) and therefore ANCOVA analysis was used to control for age. Weight and WC differences were also expected, with other studies reporting ethnic differences in both variables (National Institute for Health and Clinical Excellence (NICE) 2006; Sisson et al. 2009; Staiano & Katzmarzyk 2012). Excess body fat is a contributing factor to common diseases including 58% of type 2 diabetes and 21% of heart disease (Department of Health 1999). The fat level at which this becomes higher risk differs between ethnic groups (ibid), resulting in the necessity for specific WC thresholds for various ethnic groups (Zhu et al. 2005).

Significant differences emerged between South Asian and Caucasian participants in exercise time ($p< 0.01$) and relative Vo_2 max ($p <0.01$) during ANCOVA analysis. Levels of physical activity and body composition have been associated with Vo_2 max (Dunn et al. 1999; King et al. 1995; Rump et al. 2002; Watanabe et al. 1994). Ethnic differences in body composition found in the present study may contribute to this, because of the established relationship cited in literature between body composition and Vo_2 max (Jackson et al. 1995; Jackson et al. 1990; Jackson et al. 1996). Furthermore, lower physical activity levels have been reported in the UK in the South Asian population, for both children (Eyre et al. 2013) and adults (Babakus & Thompson 2012; Fischbacher et al. 2004; Hayes et al. 2002), when compared with their White counterparts.

6.4.2 Gender comparison

A significant gender difference in height was also demonstrated; this was expected as on average, males in the UK tend to be taller than females (Office for National Statistics 2005). For body composition measurements, significant ethnic differences were found for BMI, TBW and BMR. These results are in accordance with literature where differences in body composition between ethnic groups have been demonstrated (Ama et al. 1986a; Ama et al. 1986b; Schutte et al. 1984). Strong associations between BMI and HRV have been reported in younger populations (Fagard et al. 1999; Felber Dietrich et al. 2006; Vallejo et al. 2005).

Gender comparisons are important to consider due to inherent physiological (i.e. hormonal) and anthropometric (i.e. body fat percentage) differences between genders which may impact on HRV. The impact of these factors has been assessed in several studies (Fagard et al. 1999; Matsukawa et al. 1998; Vallejo et al. 2005). Genetic influence may also account for up to 65% of the variance in HRV measurements (Kupper et al. 2004; Singh et al. 1999; Snieder et al. 1997). Women have been reported to have higher cardiac parasympathetic modulation compared to that of men (Evans et al. 2001). Gender differences have been controversial with studies suggesting females have a higher resting HRV (Cowan et al. 1994; Evans et al. 2001; Huikuri et al. 1996; Koskinen et al. 2009; Ryan et al. 1994), and other studies suggesting that males have a higher resting HRV (Bigger et al. 1995; Bonnemeier et al. 2003; Ingall et al. 1990; Saleem et al. 2012; Umetani et al. 1998).

The present study found no significant differences between male and female participants when controlled for age. This is in line with two other studies which reported no significant difference between genders in HRV indices denoting vagal activity (Moodithaya & Avadhany 2012; Ramaekers et al. 1998). Both gender and ethnic differences in resting HRV have been reported in the literature, however few studies indicate which ethnicity the gender differences were found in. Those that have assessed ethnicity and gender together, reported lower sympathetic activity in both young and older women in the Caucasian population (Hogarth et al. 2007; Narkiewicz et al. 2005), and healthy Pakistani subjects (Saleem et al. 2012).

6.4.3 Limitations

Limitations to this study involve the method of obtaining participants. Self selection naturally occurred through the recruitment of participants. Those who are involved in this study were those that wanted to participate, and therefore are not necessarily representative of the population. A percentage of the students within the present study were international South Asian students who were recent inhabitants of the UK within the last 6 months, making the comparison between ethnicities multifaceted. Studies in the literature of this nature have directly compared ethnicity based on populations inhabiting the same environment (Reed et al. 2006; Urbina et al. 1998). A comparison of the same ethnicity in different environments, i.e. South Asian participants born and raised in South Asia compared to those born and raised in the UK, might have demonstrated differences between both South Asians and also White British.

6.5 Recommendations

Future research should examine the differences that exist between different ethnicities in a large range of physiological characteristics. In future, a large longitudinal study could provide insight into the natural occurring differences between ethnicities, however the logistics and expense of such a study could be challenging. Better information about ethnic differences could help to promote awareness about common conditions found in certain ethnic groups, and perhaps in certain age ranges. This could lead to prevention strategies that may establish a healthier population and cost the NHS less money in the long term. The UK is home to many different ethnicities which could be researched. With a growing ethnic population (Department of Health 2010), it is important that considerations are made for those deemed to be at higher risk due to their genetic/ethnic background or other circumstances.

6.6 Conclusions

The present study provides unique ethnic comparisons, and argues for more research into the environment and physiology interaction that may naturally occur. No ethnic differences in rMSSD or HR measures between South Asian and Caucasian participants were found in the present study; however differences did emerge in several body composition measurements. Ethnic differences demonstrated in this study were inconclusive, however questions were raised regarding the difference between ethnic minorities born and raised in the UK versus those who immigrate in later life. Resting rMSSD analyses taken with the Ithlete software were easy and convenient; participants reported no problems using the device. The low cost, ease-of-use and great accessibility of Ithlete make it an excellent potential device for prospective research.

Future research in a larger cohort of participants with varying degrees of time spent living in the UK could explain the ethnic differences that occur. The notion that some ethnic groups are potentially at higher risk with certain characteristics, may have an effect on the way people live their lives, and consequently on their health. This insight into ethnic differences could lead to advances in prevention techniques. Better screening in the future for certain diseases that are found to be high risk in those specific populations, could reduce mortality and save the NHS money and resources long-term.

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CHAPTER 7: THE RELATIONSHIP BETWEEN HEART RATE VARIABILITY, BODY COMPOSITION AND AEROBIC CAPACITY IN HEALTHY PARTICIPANTS WITH VARYING PHYSICAL ACTIVITY LEVELS

Heart rate variability (HRV) is a non-invasive measure of autonomic function that has been demonstrated as a powerful predictor of mortality in the general population. Exercise capacity has also been associated with the risk of mortality. Body composition measurements are increasingly used along with body mass index (BMI) to assess increased risk of disease. Associations between these measurements have been demonstrated in the literature. The aim of the present study was to expand the understanding of heart rate variability measurements using a novel software application called Ithlete. This study will try to reproduce basic correlations seen between vagal HRV and other measures, including aerobic capacity and body composition, with the Ithlete device.

Fifty-nine healthy participants were tested, of which 28 were male and 31 were female. Participant ages ranged from 22 to 65 years. Participants completed a modified Bruce protocol incremental exercise test on a motorized treadmill. Body composition measurements were undertaken using a bioelectrical impedance analysis device and HRV and heart rate (HR) measurements were completed using the Ithlete for iPod touch. The present study found no significant gender differences in root mean square successive difference (rMSSD). Significant negative correlations at $p< 0.01$ were demonstrated between resting rMSSD measurements and HR, weight and BMI. rMSSD was also negatively correlated with waist circumference (WC) ($p <0.05$) and positively correlated with Vo_2 peak ($p <0.05$).

The rMSSD measure obtained from the Ithlete device showed the same relationships with descriptive characteristics that other vagal measures did in previous studies. This suggests that Ithlete is an acceptable alternative measurement device to others already on the market.

7.1 Introduction

The health of the population is an increasing concern. Public health campaigns have become a regular occurrence cautioning against health risks such as obesity, smoking, diet and lack of exercise. Such campaigns aim both to raise the awareness of the general population and encourage healthier lifestyles. Exercise capacity in itself has been expressed as the best predictor of mortality (Blair & Haskell 2006; Myers et al. 2002; Palatini et al. 2002; Pate et al. 1995). Exercise capacity is related to many health outcomes, one of which is heart rate variability (HRV) (Galetta et al. 2005; Levy et al. 1998; Perini et al. 2002). HRV is a non-invasive measure that has also been demonstrated as a powerful predictor of mortality in the general population (Rennie et al. 2003; Tsuji et al. 1996). Decreased HRV is an independent risk factor for morbidity and mortality and will therefore be discussed in more detail below.

7.1.1 Heart rate variability

Heart rate variability (HRV) is a non-invasive electrocardiographic measure that examines the sympathetic and vagal components of autonomic nervous function. The autonomic nervous system makes itself visible through HRV indicating how the body is trying to preserve its equilibrium. Thus HRV has the potential to monitor the autonomic response to exercise volume on a daily basis. HRV has emerged as a reliable and reproducible technique for assessing autonomic activity (Noland et al. 1998). Key determinants in healthy longevity depend on preservation of autonomic function, particularly HRV-parasympathetic function (Zulfiqar et al. 2010).

There are various parameters for HRV analysis (Task Force, 1996), which include time domain, frequency domain and non-linear methods. Time domain (statistical) measures such as the mean of the standard deviations of all normal R-R intervals (SDNN), the standard deviation of the average NN intervals calculated over short periods (SDANN), total power and ultra low frequency (ULF) power, very low frequency (VLF) power and low frequency (LF) power, root mean square of the successive difference (rMSSD), the percentage of adjacent R-R intervals that varied by more than 50 ms (pNN50) and high frequency (HFr) power are highly correlated with each other. HFr (by the Poincaré plot method) is a short-term index of HRV, which mainly reflects vagally mediated fluctuations of HR (Akselrod et al. 1981; Tulppo et al. 1996).

rMSSD is a time domain measure of HRV which reflects parasympathetic activity without being dependent on heart trends (Stein et al. 1994). High correlations have been found between time and frequency domain measures of vagal activity. This suggests that they can be used interchangeably (Bigger Jr et al. 1989). The rMSSD measure has been suggested as superior to spectral methods due to its sensitivity as a measure of vagal cardiac control and is less sensitive to variations in respiratory patterns (Penttilä et al. 2001). In this chapter rMSSD and HFr will be discussed analogous to one another because they demonstrate the same vagal physiological phenomenon. rMSSD and the HFr power of the normal R-R interval power spectrum have correlations as high as (>0.90) (ibid). In research assessing the reliability of ultra-short (i.e. 10 second) HRV measurements, rMSSD values emerged with high correlations, with the standard 5-minute short-term recording (Thong et al. 2003). Nussinovitch et al, (2011) also found rMSSD to be a reliable parameter for assessing HRV from ultra-short 1-minute or 10-second resting ECG recordings. For experimental work, Pinna et al, (2007) recommended that research designs using HRV parameters for outcomes should be based on the parameters with the lowest variation, of which rMSSD was listed as one. Due to the number of publications with favourable results using rMSSD, this study will focus on rMSSD in particular.

7.1.2 Clinical importance of HRV

Cardiovascular disease (CVD) is the leading cause of death and premature death in the UK (British Heart Foundation 2008). Increased cardiovascular risk is associated with a low HRV and high HR (Taylor 2010). HRV can be used to assess disease, autonomic imbalances, and mortality (Thayer et al. 2010). Increased cardiovascular deaths are associated with diabetes mellitus, which can cause cardiovascular autonomic neuropathy (Kudat et al. 2006). Cardiac autonomic neuropathy is a serious frequent complication of diabetes mellitus (Vinik et al. 2003). There is also an association between low HRV and the prevalence of diabetes (Gerritsen et al. 2001; Liao et al. 1995b; Tsuji et al. 1996).

When considering specific populations, impaired autonomic function (measured through HRV) is known to predict death, especially in chronic heart failure patients (Marijon et al. 2010). Early detection of critical changes in patientsô vital signs such as HRV can help in the identification of worsening heart failure and prevent rehospitalisation and other outcomes (Cleland et al. 2005). Reduced HRV is also associated with systemic hypertension (Singh et al. 1998). Continued health and longevity is dependent on the preservation of autonomic function over time (Zulfiqar et al. 2010). High HRV is a measure of good health, and a high level of physical fitness. Different habitual levels of physical activity may cause changes in HRV (Nunan et al. 2009). In the healthy population, HRV can be a valuable tool for monitoring the effects of stress on the body (Pieper et al. 2010; Thayer et al. 2012). Given the importance of HRV in clinical measures, the following will highlight the use of HRV in non clinical measures.

7.1.3 Non-clinical determinants of HRV

Chronic factors which affect HRV include gender, age, level of physical fitness, and body composition. Gender is an important determinant of HRV in healthy subjects (Antelmi et al. 2004). The majority of research looking at gender differences in adults shows that women possess higher vagal activity than men (Antelmi et al. 2004; Gregoire et al. 1996; Liao et al. 1995a). In contrast studies looking at gender differences in children show girls to have a lower HRV compared to boys (Faulkner et al. 2003; Umetani et al. 1998). This signifies that the effect of gender may be modulated by age.

There is an inverse relationship between age and HRV, as age increases HRV decreases (Koskinen et al. 2009; Nunan et al. 2010b). A progressive decrease in HRV is associated with age, and can predict mortality in different clinical populations (Zulfiqar et al. 2010). People that exercise regularly generally demonstrate an increased parasympathetic activity, and lower heart rate when compared with sedentary people; this is especially noticeable at rest (Dixon et al. 1992). A high HRV at rest improves the capacity for adaptation to varying or unpredictable stimuli (Goldberger 1991). Athletes have a higher HRV at rest (this reflects a parasympathetic predominance) than sedentary people (Aubert et al. 2003; Sandercock et al. 2005).

Acute factors such as time of day and postural changes can also have an effect on HRV (Pagani et al. 1986). Research into the effect of time of day on HRV is conflicting. In a study that analysed HRV measurements at three different times of day (morning, afternoon, evening) there was significant variation found and low reproducibility (Lord et al. 2001). Vagal modulation in normal subjects did not reflect any changes due to different body positions (Avbelj et al. 2003). In a study of autonomic cardiovascular function in healthy young adults, autonomic activity was not significantly different in varying body positions. However HRV parameters within this study indicated sympathetic dominance during sitting (Watanabe et al. 2007). Due to the number of factors that affect HRV, it is important to ensure they are considered when HRV is used as a research outcome.

7.1.4 Body composition: body fat and total body water

Excess body fat is associated with a number of health problems including cardiovascular disease, type II diabetes, and many cancers making it a major health issue worldwide (Haslam & James 2005; Kopelman 2000). Body composition outlines how much of body mass is made up of fat, fluid (mostly water), and muscle. Those with a body composition that contains more fat are more likely to have decreased HRV (Byrne et al. 1996). Healthy body fat ranges have been published for each gender in specific age ranges. The healthy body fat percentage range for 20-39 year old females is between 21-33% and 8-20% for males (Gallagher et al. 2000). For 40-59 year old females the healthy body fat percentage range is 23-34% and 11-22% for males of the same age (ibid).

The relationship between obesity and autonomic function has been explored by several researchers, with two contradictory opinions on how results should be interpreted. The first opinion assumes the obese have higher sympathetic tone verified by elevated catecholamine levels (Troisi et al. 1991). The other assumes that the obese have a lower sympathetic tone, as demonstrated by lower recorded low frequency (LF) component of HRV (Spraul et al. 1993). Despite these contradictory opinions, it is agreed that the autonomic nervous system contributes to regulation of energy expenditure and body fat content (Nagai et al. 2004). The extent to which however, is not known (ibid).

Water is essential to life; humans cannot survive without water for more than a few days whereas they can go without food considerably longer (Benelam & Wyness 2010). The human body consists of between 45% to 75% water by weight; lean tissue is made up of a higher percentage of water at 70% compared to just 20% of fat tissue (ibid). Water is an important component of the bodyǿs natural structure, used for circulatory function, biochemical reactions, metabolism, substrate transport across cellular membranes, temperature regulation, and numerous other physiological processes (Armstrong 2007). Fluid-electrolyte turnover and total body water change constantly due to water gained from food, fluids, and water loss from the lungs, skin and kidneys (ibid).

Bioelectrical impedance analysis (BIA) determines fat-free mass and total body water by using equations that convert reactance and resistance to estimate the total body water. The term impedance arises from the combination between reactance (arising from cell membranes) and resistance (arising from extra and intracellular fluid) (Kyle et al. 2004). The average TBW percentage ranges for a healthy adult female is 45-60% and 50-65% for a male (Maughan & Griffin 2001). Hydration status in humans effects cardiovascular function both at rest and during exercise (Charkoudian et al. 2003). Dehydration induces an increase in sympathetic outflow, which in turn may have an impact on sympatho-vagal balance and consequently HRV (Princi et al. 2005).

7.1.5 Exercise capacity

Exercise capacity has been demonstrated as a strong predictor of morbidity and mortality (Blair et al. 1996; Gulati et al. 2003; Kokkinos et al. 2008; Rognmo et al. 2004). The exercise test has become a valuable clinical tool due to it being relatively inexpensive, non-invasive and provides several clinically relevant diagnostic and prognostic pieces of information (Froelicher & Myers 2000; Gibbons et al. 1997). The influence of exercise on HRV has been demonstrated throughout literature (al-Ani et al. 1996; Gladwell et al. 2010; Hautala et al. 2001; Manzi et al. 2009; Ogoh et al. 2002; Raven et al. 2006). The relationship between exercise capacity, aerobic exercise and enhanced vagal modulation of the heart in healthy populations has been demonstrated (Billman 2002; Carter et al. 2003b; Hautala et al. 2009). This may be due to aerobic training protecting the heart against harmful cardiac events through a decrease in sympathetic outflow and an increase in cardiac modulation of heart rate (Billman 2002). Changes to HRV occur during exercise, caused by an increase in sympathetic activity and a decrease in parasympathetic activity (Gladwell et al. 2010; Perini & Veicsteinas 2003). Over time, exercise improves HRV in both healthy and clinical populations (Billman & Kukielka 2006; Kaikkonen et al. 2008; Levy et al. 1998; Mandigout et al. 2002).

7.1.6 Aims

The present study aims to expand the understanding of HRV measurements using novel equipment and software called Ithlete. This study proposes to use just one measure, rMSSD in one minute measurements to assess HRV. With high correlations between the measures, there is little need to measure all of them each time HRV analysis is undertaken. rMSSD has been demonstrated in the literature as a reliable measurement with high correlation to the others. The aim of this study was to reproduce basic correlations seen between vagal HRV and other measures including aerobic capacity and body composition, but with a new device (Ithlete). Establishing these relationships with the Ithlete device could provide a new monitoring tool for athletes, coaches and clinical populations. Because Ithlete is inexpensive compared with other medical devices, has a short measurement time and is user-friendly, it is an ideal tool for different populations to use outside the laboratory setting.

Given that the literature suggests that there is a close relationship between various HRV indices and measures such as aerobic capacity and body fat, it is hypothesized that there will be a significant relationship between aerobic capacity measured by Vo_2 peak, body composition measured by BIA and the rMSSD (ms) measurement of HRV from Ithlete. High rMSSD measurements will correspond to high aerobic capacity, lower body fat percentage and euhydration. Assessment by partial correlation will improve on the relationship established in the literature because chronic factors such as age and gender will be controlled for, taking away the effect of bias caused by these factors.

7.2 Methods

7.2.1 Recruitment of participants

Staff and students of Buckinghamshire New University were invited by internal advertisement on notice boards and through emails. Each participant was recruited in accordance with University ethics committee standards and expectations. Participants responded via email or phone and were sent an information pack before agreeing to participate which included:

1. An information sheet with detail of the requirements for each participant before and during the laboratory visit
2. An informed consent form
3. A physical activity readiness questionnaire (PAR-Q)
4. A detailed demographic information sheet

Participants were requested to read the information pack prior to attending the laboratory and any questions or concerns were addressed. All participants were free from any serious medical conditions and contraindications to exercise as indicated by the PAR-Q. All procedures were approved by the local research ethics committee.

7.2.2 Participants

Fifty-nine participants were tested, of which 28 were male and 31 were female. Participant ages ranged from 22 to 65 years of age. All participants were defined as healthy (free from any serious illness at the time of testing) and none of the participants was known to have any cardiovascular problems or be taking any medication that would have influenced the experimental procedures.

Participants completed physical activity readiness questionnaires (PAR-Q); those who answered óyesô to any of the conditions mentioned in the PAR-Q were excluded. Participants completed their consent form in front of the researcher and the researcher countersigned the form.

7.2.3 Experimental design

Following appropriate ethical approval and informed consent, participants were asked to visit the cardiovascular research lab at Bucks New University, Uxbridge. Prior to the test participants were asked to avoid caffeine, heavy physical activity, smoking, and alcohol intake for the 10 hours preceding their lab visit. Participants were also encouraged not to eat at least two hours prior to the test. All the equipment used was calibrated before each test according to the manufacturersô recommendations.

7.2.3.1 Heart rate variability analysis

Two measures (rMSSD in ms and HR in bpm) were recorded via the Ithlete software for the iPod touch (Ithlete 2009). A standard analogue ECG chest strap was worn in the middle of the chest just under the sternum. Real time heart and lung animation on the iPod touch facilitated paced breathing during measurements and the screen also indicated the reception of each heart beat from the analogue chest strap. Participants measured rMSSD for one- minute, three times in succession in a seated position. Participants were given one-minute between each rMSSD recording. After each one-minute recording, measurements were saved to the device.

The breathing frequency was set at 7.5 breaths per minute, designed to maximize RSA response (Brown et al. 1993). When the one minute measurement was complete the HR (bpm) and rMSSD in ms were displayed on the screen and saved to the device. Ithlete recordings were transferred to a password protected PC via Ithlete software which enables recordings to be emailed and saved into an excel document.

7.2.3.2 Bioelectrical impedance analysis

Body composition measurements involved participants lying in a supine position for testing allowing at least five minutes for even body fluid distribution before measurements were recorded. Two electrodes were placed on both the hand and foot of each participant, one on the bisecting line of the wrist/ankle and the other proximal to the fingers/toes. Once ready for measurement an undetectable current was passed through the distal electrodes on the hand and foot and the proximal electrodes on the wrist and ankle receive the current flow (Wilmore & Costill 1999). Water and electrolyte distribution in the tissues determines the electrical conduction between the electrodes. Fat mass has a greater impedance as it is more difficult for a current to flow through it when compared with free-fat mass. Free-fat mass consists of all the body water and conducting electrolytes making conductivity much greater within this tissue (ibid).

Using the BIA 101 and Bodygram software (Akern; Florence, Italy), small wires were connected for measurement and a recording was executed allowing at least three reading cycles before inputting measurements into the Bodygram software. Bodygram software then computed body composition measurements including BMI, body fat %, fat free mass %, intracellular water, extracellular water for each participant and stored in the Bodygram software program. BIA measurements take approximately five minutes to perform.

7.2.3.3 Cardio-respiratory capacity analysis

Participants were attached to a 12-lead ECG and facemask; five minutes of resting heart rate and gas measurements were then undertaken. After resting recordings, participants performed an incremental exercise test using the Bruce protocol on a motorized treadmill with online breath-by-breath analysis (Medical Graphics Cardio Control analysis system (MG) (Medical Graphics Corporation, St. Paul Minnesota, USA). The system was calibrated for each test using known reference and calibration gas concentrations.

Each stage of the incremental exercise test lasted three minutes, with the endpoint when participants reached 90% of their predicted maximum heart rate or voluntary cessation due to fatigue. Directly following the exercise test participants were seated and a five-minute recovery period was measured.

Examinations took place in the research lab maintained at a comfortable temperature with limited distractions. Experimental procedures were described to participants in advance. All procedures carried out during the examination were considered non-invasive.

7.2.4 Statistical analysis

All statistical analysis was undertaken using PASW 19.0 (SPSS: An IBM Company. Somers, NY, USA). Owing to their established relationships with HRV, aerobic fitness (Bruce protocol treadmill test) and gender were controlled for. Student t-tests were undertaken to measure differences. Pearson correlation analysis was used to evaluate the relationship between selected exercise test responses and HRV, HR and various body composition analysis measurements including BMI, body fat % and total body water (TBW). A P-value of Ò0.05 was considered statistically significant.

7.3 Results

7.3.1 Participant characteristics

Participant characteristics for each gender are displayed in Table 7.1. Student t-tests found a significant difference in weight. The other participant characteristics recorded were similar in both groups.

Table 7.1 Mean and SD for anthropometric and body composition characteristics of the participants

Characteristic	**Male (n = 28)**	**Female n = 31)**
Age (years)	30.6 ± 11.3	32.0 ± 9.8
Height (cm)	173.5 ± 7.2	162.8 ± 5.4†
Weight (kg)	74.9 ± 12.3	64.3 ± 15.8*
Waist Circumference (cm)	86.5 ± 9.5	78.7 ± 12.6*
Body Fat (%)	24.5 ± 7.5	29.2 ± 11.2
Body Mass Index (BMI) (kg/m^2)	24.9 ± 3.4	24.4 ± 6.1
Total body water (%)	41.6 ± 7.6	32.3 ± 5.3†

***Significant difference at $p < 0.05$**
†Significant difference at $p < 0.01$

7.3.2 HRV/HR, aerobic capacity and physical activity characteristics

HRV (rMSSD) and HR at rest are represented in Table 7.2 along with aerobic capacity characteristics (respiratory ratio (RR), respiratory exchange ratio (RER), maximal oxygen uptake (Vo_2 peak), unit of energy (METS) for each gender. Student independent t-tests revealed significant differences in Vo_2 peak and Borg scale between genders. Table 7.3 displays the average amount of physical activity completed per day for each gender.

Table 7.2 Mean and SD of rMSSD, HR and aerobic capacity characteristics of the participants

Characteristic	**Male (n = 28)**	**Female (n = 31)**
rMSSD (ms)	68.1 ± 10.2	70.8 ± 7.7
HR (bpm)	82.6 ± 12.7	79.3 ± 9.4
RR (breaths/min)	34.4 ± 6.7	33.6 ± 6.6
RER	1.1 ± 0.1	1.0 ± 0.1
Vo_2 peak ($ml·kg^{-1}·min^{-1}$)	29.5 ± 6.9	25.7 ± 4.9*
Borg Scale	15.3 ± 2.6	13.3 ± 3.8*
Exercise Time (min)	13.9 ± 3.1	13.7 ± 1.6
METS	8.2 ± 1.9	7.34 ± 1.4

***Significant difference at p< 0.05**

Table 7.3 Reported physical activity levels for male and female participants

Physical Activity Level	**Male (n=27)**	**Female (n=30)**
None	33.3 %	6.7 % †
< 30 minutes/day	37.1 %	33.3 %
30-60 minutes/day	14.8 %	46.7 %†
> 60 minutes/day	14.8 %	13.3 %

†Significant difference at p< 0.01

7.3.3 Analysis of covariance (ANCOVA)

There were no significant r gender differences observed for HRV, F (1, 52) = 1.342; heart rate, F (1, 49) = 0.78 or Vo_2 peak F (1, 49) = 1.045. When presented graphically roughly the same difference between parallel lines appeared between genders in covariate analysis of HRV, HR, and Vo_2 peak.

7.3.4 Correlations: Resting HRV/HR, aerobic capacity and physiological characteristics between genders

Correlations are displayed in table 7.4. Resting rMSSD measurements were correlated with Vo_2 peak at r= 0.302 and HR at r= -0.552 both at $p<0.05$. Body composition measurements of waist circumference, weight and BMI were also correlated with resting HRV at r= -0.297($p<0.05$), r=-0.363($p<0.01$) and r= -0.334 ($p<0.05$) respectively. Resting HR was correlated only with age at a level of r= -0.258 ($p<0.05$). Vo_2 peak correlated with age at r= -0.346 ($p<0.01$) and fat free mass at r= 0.449 ($p<0.01$).

7.3.5 Correlations: Anaerobic threshold and physiological characteristic between genders

Speed, RER, METS, RR and VE at anaerobic threshold were analysed through bivariate correlation analysis. Notable correlations were found between speed at anaerobic threshold and TBW (r= 0.300 p< 0.05), age (r= -0.351 p<0.01), and height (r= 0.277 p< 0.05). METS were correlated at anaerobic threshold with BF (r= -0.276 p< 0.05) and FFM (r= 0.276 p< 0.05); RR was correlated with resting HR (r= 0.298 p< 0.05). VE was correlated with BMI (r= 0.316 p< 0.05), TBW (r= 0.622 p< 0.01), height (r= 0.486 p< 0.01), weight (r= 0.532 p< 0.01), WC (r= 0.414 p< 0.01) and BMR (r= 0.540 p< 0.01).

7.3.6 Partial correlations: Resting HRV/HR, aerobic capacity and physiological characteristics

Partial correlations were used to explore the relationships between HRV, HR, aerobic capacity and physiological characteristics while controlling for participantôs gender and age. There was a strong negative partial correlation between HRV and HR at r= -0.60, (p< 0.01) with high levels of HRV being associated with low levels of HR. An inspection of the zero order correlation suggests that controlling for gender and age has little effect on the HRV/HR relationship. Partial correlations controlling for age and gender were also explored between HRV, aerobic capacity, waist circumference, weight and BMI. These partial correlations demonstrated negative correlations between HRV and waist circumference (r= -0.23, which was not significant), weight (r= -0.31, p< 0.05) and BMI (r=-0.32, p< 0.05).

Table 7.4 demonstrates correlations between physiological characteristics, aerobic capacity and body composition. Significant correlations for rMSSD and HR obtained from the Ithlete device with the other characteristics are highlighted in red because the present study is particularly interested in correlations between Ithlete measurements and other correlates.

It is recognized that because of numbers, some low correlations will yield a significant probability. Therefore significant but low correlations will still leave a large proportion of unexplained variance.

Table 7.4 Correlations between physiological characteristics, aerobic capacity and body composition measurements

	rMSSD	HR	Age	H	W	WC	BF	FFM	BMI	TBW	Vo2 peak	VE	ET	Borg	METS	RER	RR
rMSSD	--	-0.55À	-0.11	-0.07	-0.36À	-0.30*	-0.19	0.19	-0.33*	-0.20	0.30*	-0.12	0.23	-0.16	0.24	-0.19	-0.04
HR	--	--	-0.26*	0.07	0.39À	0.43À	-0.37À	0.02	-0.08	0.00	-0.22	-0.09	-0.18	0.00	-0.18	0.05	0.11
Age	--	--	--	-0.05	0.39À	0.43	0.17	-0.17	0.45À	0.25	-0.35À	0.00	-0.47À	0.14	-0.38À	0.31*	-0.33*
H	--	--	--	--	0.43À	0.31*	-0.37À	0.37À	-0.06	0.72À	0.31*	0.51À	-0.03	0.15	0.23	0.15	0.08
W	--	--	--	--	--	0.90À	0.36À	-0.36À	0.87À	0.73À	-0.17	0.55À	-0.26*	0.34*	-0.23	0.19	-0.09
WC	--	--	--	--	--	--	0.41À	-0.41À	0.81À	0.61À	-0.28*	0.40À	-0.37À	0.34*	-0.35À	0.14	-0.05
BF	--	--	--	--	--	--	--	-1.00À	0.60À	-0.35À	-0.50À	-0.06	0.24	-0.03	-0.45À	-0.03	-0.09
FFM	--	--	--	--	--	--	--	--	-0.60À	0.35À	-0.50À	0.06	0.24	0.03	0.45À	0.03	0.09
BMI	--	--	--	--	--	--	--	--	--	0.41À	-0.35À	0.36À	-0.26	0.39À	-0.37À	0.15	-0.16
TBW	--	--	--	--	--	--	--	--	--	--	0.18	0.54À	-0.09	0.37À	0.07	0.23	-0.09
Vo2 peak	--	--	--	--	--	--	--	--	--	--	--	0.61À	0.63À	0.13	0.99À	0.37À	0.18
VE	--	--	--	--	--	--	--	--	--	--	--	--	0.43À	0.37À	0.61À	0.64À	0.23
ET	--	--	--	--	--	--	--	--	--	--	--	--	--	0.15	0.71À	0.53À	0.19
Borg	--	--	--	--	--	--	--	--	--	--	--	--	--	--	0.14	0.30*	0.17
METS	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	0.46À	0.23
RER	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	0.16
RR	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--

***Significant at p< 0.05** **†Significant at p< 0.01**

Table 7.4 on the previous page is a correlation matrix displaying the correlations found between physiological characteristics and other variables including exercise capacity measurements including Exercise Time (ET), Body Mass Index (BMI), Borg Scale (Borg), Height (H), Respiratory Exchange Ratio (RER), Body Fat Percentage (BF), Respiratory Rate (RR), Total Body Water (TBW), Waist Circumference (WC), Free Fat Mass (FFM), Minute Ventilation (VE), Weight (W).

7.4 Discussion

The present research study sought to explore the relationships that exist between HRV (rMSSD), aerobic capacity and body composition while also reproducing basic correlations seen between vagal HR and other measures with a new HRV measurement tool (Ithlete). The present study found no significant gender differences in rMSSD. Significant negative correlations at $p < 0.01$ were demonstrated between resting rMSSD measurements and HR, weight and BMI. rMSSD was also negatively correlated with WC ($p < 0.05$) and positively correlated with Vo_2 peak ($p < 0.05$). Since rMSSD reflects parasympathetic activity without being dependent on heart trends (Stein et al. 1994), these correlations demonstrate the effect of parasympathetic tone on those variables. Resting rMSSD analyses taken with the Ithlete software were easy and convenient; participants reported no problems using the device.

7.4.1 rMSSD and heart rate

Gender differences in resting HRV have been reported in the literature. Gender differences have been controversial with studies suggesting females have a higher resting HRV (Evans et al. 2001; Koskinen et al. 2009), and other studies suggesting males have a higher resting HRV (Bonnemeier et al. 2003; Umetani et al. 1998). Within this study, females had a slightly higher resting HRV than males but this was not significantly different ($p<0.05$).

The present study found resting HR was negatively correlated with age ($p < 0.05$). Several studies have looked at the relationship between physical activity levels and HR (Aubert et al. 2003; Carter et al. 2003a; Nunan et al. 2010a; Sandercock et al. 2005), demonstrating the significance of this interaction. Autonomic activity becomes altered during exercise; HR increases as a result of increased sympathetic activity during exercise, and heart rate recovery is mediated by vagal reactivation following exercise (Myers et al. 2007). The interaction between the sympathetic and parasympathetic branches of the autonomic nervous system influences results in the autonomic state known as sympathovagal balance (Goldberger 1999). Sympathovagal tone assessed by HRV has been directly associated with BMI, body fat percentage and skeletal muscle in young healthy males and females (Duncker R. et al. 2011). This research study is unique due to its use of an innovative commercially available device called Ithlete which measures both HR and HRV. Ithlete is innovative because it takes one-minute measurements of rMSSD and HR, displaying the measurement directly on the screen instead of having to input raw data into external software.

The present study aimed to reproduce basic correlations seen between vagal HRV and other measures including aerobic capacity and body composition (specifically hydration) with the Ithlete device to see if a lower cost device can be used in healthy and clinical populations. Resting measurements of HR should be between 60 and 100 bpm (Kossmann 1953), the mean for both male and female participants in this study was well within that range. The mean rMSSD for male and female participants were found to be similar to other studies discussed in a systematic review completed in 2010 (Nunan et al. 2010). The relationship between rMSSD, HR and FM is well documented. Larger percentages of body fat were associated with reduced HRV and increased HR (Sztajzel et al. 2009). An increase in body weight was related to decreased time domain parameters including rMSSD and SDNN in adolescent obese subjects (Rabbia et al. 2003; Sztajzel et al. 2009). Decreased HRV indices have recently been associated with total body FM (Christou et al. 2004). Lower levels of rMSSD were associated with high levels of total body fat mass and fat free mass in obese children (Gutin et al. 2000). A relationship was found between BMI and HRV in women where a higher BMI had reduced parasympathetic control and elevated sympathovagal modulation (Pai et al. 2011), therefore lower HRV. HRV has also been associated with exercise capacity, where a higher exercise capacity corresponds to higher HRV (De Meersman 1993; Galetta et al. 2005; Melanson & Freedson 2001; Perini et al. 2002).

7.4.2 Body composition

BMI cut-offs have been criticised in recent years due to their inability to demonstrate a higher risk of adverse events in individuals classed as overweight (BMI 25-29 kg/m^2) when compared with normal weight counterparts (Lopez-Jimenez 2009; Romero-Corral et al. 2006). This is because BMI cannot differentiate between body fat from lean mass in various populations (ibid). A systematic review in 2010 suggests that when defining obesity based on the amount of body fat, the normal (healthy) cut-off level for BMI should actually fall between 25-30 kg/m^2 (Okorodudu et al. 2010).

Current guidelines in the UK state that a healthy BMI should be between 18.5-24.9 (National Institute for Health and Clinical Excellence (NICE) 2006). In this study the female average fell within this range at the upper limit while the male average fell just outside at 25 suggesting that half of the participants were in the overweight range of BMI. In the UK waist circumference is cited as an increased risk at ≥94 cm for males and ≥80cm for females (National Institute for Clinical Excellence 2007). In this study the average waist circumference was below both cut-offs at 86 ± 10 for males and 79 ± 13 for females, although the female average was only one point below the cut-off suggesting that about half of the female participants were above that cut-off. When BMI is less than 35, waist circumference is a valid measurement of abdominal fat mass and is suggested for use in indentifying disease risk (ibid). With this in mind, both males and females in this study could be considered at higher risk based on both BMI and WC measurements.

While there are some obvious drawbacks to the use of BMI including the inability to account for muscle, measures of body fat are better because BMI does not differentiate between adipose tissue and lean mass in intermediate BMI ranges (Frankenfield et al. 2001; Piers et al. 2000; Romero-Corral et al. 2007). The average body fat percentage for males and females in the present study were within the normal ranges when broken down into the age related body fat recommendations. The healthy body fat percentage range for 20-39 year old females is between 21-33% and 8-20% for males (Gallagher et al. 2000). For 40-59 year old females the healthy body fat percentage range is 23-34% and 11-22% for males of the same age (ibid). In the present study the body fat averages for 20-39 year olds was 24.2 ± 7.6 for males and 28.1 ± 10.1 for females. For 40-59 year olds the average for males was 24.6 ± 8.4 and females was 32.1 ± 14.0. This suggests that participants in this study had relatively healthy body fat percentages. Body composition measurement in the present study was derived from bioelectrical impedance analysis (BIA), where fat measurements are derived from prediction models to estimate total body water and free fat mass (Chumlea & Guo 1994; Guo et al. 1989).

Maughan & Griffin, (2001) report that the normal healthy range for TBW percentage for a healthy adult female should be between 45-60%, and 50-65% for a male. In the present study the average TBW for both male and female participants were below those averages. However there are many factors that could affect this. TBW levels change naturally throughout the day and will also fluctuate based on food and water consumption throughout the day. If a large quantity of pure water or hypotonic fluid (e.g. 1.2L in 5 minutes) is ingested this would result in the water entering the blood and kidney function producing a large volume of dilute urine before the intracellular and extracellular fluid could equilibrate (Armstrong 2007). In this case that would suggest that using urine indices would be invalid because the urine values would reflect the volume of liquid consumed instead of the change in TBW (Kovacs, Senden & Brouns 1998). Water and food consumption before the test were not controlled within the present study, therefore these daily fluctuations could have affected the results marginally.

7.4.3 Vo_2 peak

The average Vo_2 peak for a sedentary male is approximately 45 $ml \cdot kg^{-1} \cdot min^{-1}$ and 38 $ml \cdot kg^{-1} \cdot min^{-1}$ for sedentary females (Geddes 2007). The mean for both male (29.5 ± 6.9 $ml \cdot kg^{-1} \cdot min^{-1}$) and female (25.7 ± 4.9 $ml \cdot kg^{-1} \cdot min^{-1}$) in this study was much lower than that, suggesting that the fitness level of the participants within this study was not very high. When broken down into age specific groups, established guidelines for Vo_2 peak ($ml \cdot kg^{-1} \cdot min^{-1}$) for healthy non-athletic males and females are shown in table 7.5 (Wilmore & Costill 2005). Vo_2 peak for both males and females were all found to be lower in this study except for one group. Female participants (30-39) were the only group mean within the average non-athlete range. There could be many reasons for this which includes genetics, current state of health and current state of physical activity of the participants. Current state of physical activity is dependent mostly on lifestyle; most of the South Asian participants had recently arrived in England and did not report high levels of physical activity. The levels of physical activity reported from this cohort of participants were low, with 70.4% of males reporting their physical activity levels as < 30 min per day; 40% of females reported physical activity as < 30 minutes per day. Adults (18 ï 65 years of age) should undertake a minimum of 30 minutes of moderate-intensity aerobic (endurance) exercise five days a week or vigorous-intensity aerobic exercise for a minimum of 20 minutes three times per week (Haskell et al. 2007). These low levels of physical activity help to explain the lower Vo_2 peak values found in the present study, along with the use of the modified Bruce protocol for testing.

Table 7.5: Recommended Male and Female Vo_2 peak values **(**$ml{\cdot}kg^{-1}{\cdot}min^{-1}$**)**

Age	**Male**		**Female**	
	Non Athlete Average	This Study	Non Athlete Average	This Study
20-29	43-52	24.2 ± 10.3 (17)	33-42	29 ± 9.2 (19)
30-39	39-48	22.9 ± 2.2 (5)	30-38	23 ± 14 (5)
40-49	36-44	26.1 ± 5,2 (5)	26-35	33.7 ± 3.3 (2)
50-59	34-41	15.7 ± 11 (4)	24-33	22.2 ± 5.7 (3)

*Non-Athlete average accessed from (Wilmore & Costill 2005)
( ) Denotes the number of participants in each age group

Testing was carried out using the modified Bruce protocol, the test was stopped when participants reached 90% of their maximum heart rate (as predicted by 220-age) or if they could not keep up the pace on the treadmill. True Vo_2 max is dependent on maximal effort (Howley et al. 1995), however some participants did not appear to be at complete exhaustion but opted to end the test as they did not feel that they could continue. Different perceptions of exhaustion within this participant cohort suggests that a discrepancy existed which may not just be attributed to their physical performance. Other factors may have been their perceived level of their own athleticism, or their low self efficacy which many participants stated before the test. Some participants felt that they were not athletic and therefore would not be able to do well on the test. Some participants had also never used a treadmill, and consequently were apprehensive about completing the test.

The lower Vo_2 peak averages demonstrated in the present study may be due to the use of the modified Bruce protocol. Submaximal exercise tests are practical in a range of settings, require less time to execute and are usually safer than maximal exercise tests. Standard prediction equations are used for submaximal exercise testing to determine maximal oxygen uptake (Vo_2 max) (Noonan & Dean 2000); high reliability of predicted Vo_2 max when compared with measured Vo_2 max was reported at (r=0.96) for the general equation (ibid); suggesting submaximal tests are a useful measurement tool. Within the present study, participants may not have pushed themselves to their maximum as several volitionally stopped the test considerably below their maximum heart rate. Several participants had also never used a treadmill before and therefore found it hard to adjust to. The use of treadmills in submaximal testing provides benefits because treadmills are often used as a training modality and they are regularly found in fitness facilities and laboratories (Vehrs et al. 2007).

Gender differences were also considered in the present study, a significant difference between males (29.52 $ml \cdot kg^{-1} \cdot min^{-1}$) and females (25.68 $ml \cdot kg^{-1} \cdot min^{-1}$) for Vo_2 peak was demonstrated. Vo_2 peak decreases with age and decreases more in males than in females when matched for age (Buskirk & Hodgson 1987; Hossack & Bruce 1982). The present study also had males and females matched for age. Body composition measurements are also associated with Vo_2 peak in both males and females (Toth et al. 1994). Another gender difference observed in this study is the RER, a numeric index of carbohydrate and fat utilization. The present study found a lower RER on average in females (1.02 ± 0.07) compared with males (1.06 ± 0.11). Gender differences in RER have been reported by Tarnopolsky (1990) who found significantly lower RER values in females compared with males which indicated an increased reliance on fats as fuel (Vella & Kravitz 2002). Between gender differences in metabolism and storage of fat occur with women having an increase in the proportion of energy derived from fat during low to moderate intensity exercise when compared with men (Vella & Kravitz 2002). In the present study RER was lower in females compared with males but there was not a significant difference.

7.4.4 Cardiorespiratory correlations

Correlations between resting HRV measurements and Vo_2 max have been documented in the literature but are inconsistent (Grant et al. 2009). Either no correlation or significant correlations have been reported between the same HRV measurements and Vo_2 peak; however this could be attributed to differences between the participants investigated (ibid). This study did find a significant correlation between HRV and Vo_2 peak at r= 0.302 ($p<0.05$). However the sample size is slightly smaller compared with the literature, which reported the same findings and up to 91% of the variance is unaccounted for. There were significant correlations between anthropometric variables and exercise test measurements. Notably correlations found between age, height, weight, waist circumference and total body water with exercise test measurements strongly suggests the importance of each variable.

7.4.4.1 Partial correlations

Univariate correlations do not necessarily denote cause and effect and are problematic because they are limited to linear relationships between variables (Coppack 1990). Partial correlations have the advantage of facilitating correlation between two variables while removing the influence of another variable(s) (Stanovich 2007). In the present study a strong negative partial correlation was demonstrated between HRV and HR controlling for gender and age; other studies have also found high levels of HR associated with low levels of HRV (Ramaekers et al. 1998b; Tsuji et al. 1994). Controlling for gender and age is important because of the established interrelationships between these measurements (Agelink et al. 2001; Cowan et al. 1994; Stein et al. 1997; Umetani et al. 1998). Ramaekers et al, (1998b) also completed partial correlation analysis finding the same result as the present study; however these correlations rarely appear in the literature despite their importance. The effect age has on HRV has been extensively analysed and widely reported therefore it must be controlled for when analysing differences in HRV between groups. This finding is consistent with the literature, as sympathetic activation is known to result in an increase in HR and decrease in overall HRV (Berntson et al. 1997).

A negative correlation was demonstrated between 24-hour HR and rMSSD in healthy men and women between the ages of 18 and 71 (Ramaekers et al. 1998a), however when sub-analysed for age group this relationship was lost as participantsô age increased. Partial correlations controlling for age and gender were also explored between HRV, aerobic capacity, waist circumference, weight and BMI. These partial correlations demonstrated a negative relationship between HRV and three measurements: weight, waist circumference and BMI. This concurs with previous research showing that lower levels of HRV are commonly seen in people with higher weight (Hirsch et al. 1991; Sjoberg et al. 2011). Research on overweight and obese adults found a correlation between another HRV time-domain measure (low frequency power) and changes in WC (Sjoberg et al. 2011). BMI has been negatively associated with HRV in middle-aged and elderly subjects (Sajadieh et al. 2004), type 1 diabetes patients and the general population (Colhoun et al. 2001).

7.4.5 Limitations

Limitations to this study involve the method of obtaining participants. Self selection naturally occurred through the recruitment of participants. Those who are involved in this study were those that wanted to participate and therefore are not necessarily representative of the population. A percentage of the participants were international students who were recent inhabitants of the UK within the last 6 months; therefore their eating habits and physical activity may have been altered potentially affecting results.

7.5 Conclusion

The rMSSD measure from the Ithlete device shares the same relationships with aerobic capacity and body composition measures as other vagal measurements in the literature. The present study demonstrated negative relationships between rMSSD and HR, weight, WC and BMI. A positive relationship was demonstrated between rMSSD and Vo_2 peak. Further research is warranted for the use of Ithlete in clinical populations to determine if the same relationships occur.

7.6 References

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CHAPTER 8: HEART RATE VARIABILITY MEASUREMENT IN HEALTHY SUBJECTS WITH VARYING PHYSICAL ACTIVITY LEVELS USING ITHLETE SOFTWARE

Heart rate variability (HRV) is the phenomenon of the difference in time between heart beats, which is influenced by the autonomic nervous system. The root mean squared successive differences (rMSSD) of heart periods is a time-domain measure of HRV which is sensitive to vagal cardiac control, and is less sensitive to variations in respiratory patterns. High HRV is an indication of good adaptability, which implies a healthy individual with a good working autonomic nervous system. The influence of exercise on HRV has been demonstrated throughout the literature, and rMSSD or the high-frequency (HFr) range are the most widely used methods for quantifying parasympathetic activation after cessation of exercise. Following a major bout of prolonged high intensity exercise, a decrease occurs in cardiac vagal outflow. This decrease in cardiac vagal flow can be measured through HRV. A change in HRV demonstrates that the exercise intensity was enough to cause physiological adaptations; these adaptations can lead to improved cardio-respiratory health. Ithlete is an HRV measurement tool designed to monitor the bodyὂs autonomic response to exercise.

Twenty-four subjects successfully completed the study. Ithlete measurements were assessed 24 and 48-hours following exercise, and a decrease in HRV following exercise was found in 37.5%, and 58.3% of participants respectively. Those participants who did at least 30 minutes of exercise, three or more times a week had a lower resting average heart rate and a higher resting average HRV. In total, 86% of the participants completed Ithlete measurements for one-month. When assessing HRV 24-hours following exercise, 38.1% of participants were coded as dippers (those who demonstrated a decrease in HRV). Forty-eight hours following exercise, 58.3% of participants were coded as dippers. This suggests that changes in cardiac autonomic regulation may last for more than 24-hours. Ithlete appears to be an easy device to use for HRV assessment at rest in the healthy population. Ithlete provides easily interpreted, immediate feedback to the user which can be utilized to gauge how the body has responded to exercise. The range for rMSSD obtained from Ithlete in healthy participants was 65.1-87.7 ms.

8.1 Introduction

8.1.1 Description of HRV

Heart rate variability (HRV) is the phenomenon of the difference in time between heart beats, caused by the influence from the autonomic nervous system (ANS). The sympathetic and parasympathetic branches of the ANS influence the SA node which is the pacemaker of the heart. Several other influences have been proposed to affect the SA node, which include autonomic failure, changes in the autonomic nervous system throughout the day, and age-related or seasonal changes (Tulen et al. 1991).

Traditionally, measurement of HRV required a high-quality electrocardiogram (ECG) with a sampling rate above 250 Hz and an accurate algorithm to detect the QRS complex (Task Force, 1996). There is a large range in the recommended duration of recording throughout the literature. The duration can be as short as 30 seconds or as long as a 48-hour continuous recording. There are several modes of analysis that can be used for HRV measurement, including time domain, frequency domain, non-linear measurements. These modes were discussed in detail in the literature review (Chapter 2). High correlations have been demonstrated between time and frequency domain measures of vagal activity to suggest that they can be used interchangeably (Bigger Jr et al. 1989). rMSSD and the high frequency power of the normal R-R interval power spectrum have correlations with each other as high as (>0.90) (ibid). The present study will focus on one measure in particular, rMSSD.

8.1.1.1 rMSSD

The square root of the mean squared differences of successive heart periods (rMSSD) is a time-domain measure which is often included in analytical systems for measuring HRV (Berntson et al. 2005). rMSSD is a frequently used index in clinical cardiology (Task Force, 1996), and is known for its sensitivity to short-term, high frequency heart period fluctuations (Porges & Byrne 1992; Task Force, 1996). The rMSSD measure has been suggested as superior to spectral methods due to its sensitivity to vagal cardiac control, and it is less sensitive to variations in respiratory patterns (Penttilä et al. 2001). There is a high correlation between absolute values of rMSSD and HFr variability in the respiratory range (Berntson et al. 2005). This suggests that rMSSD is perhaps useful as a time-domain index of vagal control of the heart (Berntson et al. 2005).

8.1.1.2 What is a healthy HRV measurement?

High HRV is an indication of good adaptability, which implies a healthy individual with well functioning autonomic control mechanisms (Yerdelen et al. 2010). The typical resting heart rate (HR) for adults between the ages of eighteen to sixty is 60-100 beats/min. HRV does not have a similar well-known figure which constitutes a healthy range. HRV is thought to be a very individual measure, which can vary a great deal from person to person. The relationship between aerobic capacity, aerobic exercise, and enhanced vagal modulation of the heart in healthy populations has been demonstrated (Billman 2002; Carter et al. 2003b; Hautala et al. 2009). A reason for this might be that aerobic training protects the heart against harmful cardiac events, through a decrease in sympathetic outflow and an increase in cardiac modulation of HR (Billman 2002).

8.1.2 HRV and exercise

The influence of exercise on HRV has been demonstrated throughout literature (al-Ani et al. 1996; Gladwell et al. 2010; Hautala et al. 2001; Manzi et al. 2009; Ogoh et al. 2002; Raven et al. 2006). In a review of athletes and sedentary individuals, higher HRV values of rMSSD were found between both aerobically and anaerobically trained athletes (Aubert et al. 2003). A lower resting HR in endurance trained athletes was also demonstrated in several studies, suggesting enhanced vagal tone in athletes (ibid). Endurance training results in decreased sympathetic activity, increased parasympathetic activity and increased HRV at rest (Carter et al. 2003b). Higher HRV values are produced by a healthy well-rested body, but factors affecting HRV must also be considered.

Acute exercise responses and chronic adaptations to exercise have been considered (Ekblom et al. 1968; Nottin et al. 2002; Stratton et al. 1994), and are difficult to view in isolation (Thompson et al. 2001). The immediate responses that occur during exercise are known as acute responses, these include increased HR, increased temperature, increased respiratory rate and increased stroke volume. Chronic or long-term adaptations range from decreased resting HR, an increase in lung volume, cardiac hypertrophy, and changes in body composition.

Autonomic activity becomes altered during exercise; this is signified by an increase in sympathetic activity and a decrease in parasympathetic activity (Gladwell et al. 2010; Perini & Veicsteinas 2003). HR increases as a result of increased sympathetic activity during exercise, and heart rate recovery is mediated by vagal reactivation following exercise (Myers et al. 2007). The effects of gender (Huikuri et al. 1996; Kuo et al. 1999; Ryan et al. 1994) and age (Carter et al. 2003a; Lakatta 1993; Stein et al. 1997) on the ANS play a part in both acute and chronic adaptations to exercise; as do intensity and volume of exercise performed. Haskell et al, (2007) suggested that in order to see a health benefit, a minimum of 20-minutes of vigorous activity at least three times a week is necessary.

Examining HRV following exercise provides an indication of alterations to vagal ANS activity (Pagani et al. 1986). Post-exercise recovery in relation to HRV has been examined in previous studies with various intensities and durations (Javorka et al. 2002; Mourot et al. 2004b; Pober et al. 2004). An initial decrease in HRV has been demonstrated within minutes or hours following exercise in several studies (Mourot et al. 2004b; Parekh & Lee 2005; Terziotti et al. 2001). Furthermore, it appears to take longer to restore vagal tone following a high intensity bout of exercise (80% Vo_2 peak) compared with moderate intensity exercise (50% Vo_2 peak) (Mourot et al. 2004b; Parekh & Lee 2005). Following a major bout of prolonged high intensity exercise, a decrease occurs in cardiac vagal outflow, and was observed for several hours after the cessation of exercise (Hautala et al. 2001). On the second day, following prolonged high intensity exercise, an accentuated rebound phenomenon with enhanced vagal regulation was observed with large inter-individual variations of reduced vagal outflow at the time of recovery (ibid). The interaction between intensity, duration and HRV has become a tool in preventing staleness, overreaching or overtraining. These states are thought to develop as a result of excessive training loads, without adequate recovery in between. Several symptoms have been linked to overtraining, including changes in autonomic function (Mourot et al. 2004a).

8.1.3 Overtraining

Overtraining occurs when the volume and intensity (or TRIMP: to be explained in the next section) of a personôs exercise exceeds their capacity to recover. Symptoms can manifest as one or more behavioural, emotional and/or physical conditions. Overtraining most often manifests as pronounced fatigue, illness or reduced performance. An ANS disturbance is suggested as a possible cause for these symptoms (Hedelin et al. 2000). Overtraining is also thought to have a negative impact on autonomic cardiovascular control (Hedelin et al. 2000). When looking at the literature pertaining to athletes, a relationship between a drop in HRV and increased risk of illness was found in national level swimmers (Hellard et al. 2011). Cipryan et al. (2007) demonstrated a strong correlation between HRV and performance in male hockey players. Contrary to these studies, Uusitalo (1998) demonstrated that in female endurance athletes, an increased training load and overtraining did not cause significant changes to cardiac autonomic modulation or intrinsic HR.

When considering different fitness levels, overtraining has a stronger effect on HRV in untrained women, compared with their trained counterparts (Winsley et al. 2005). This suggests that those who are less fit will find it more difficult to overcome the symptoms of overtraining. Abrupt changes in workload also appear to signal changes in autonomic control, compared with a progressively increasing workload, which triggers cardiovascular adaptation effects (Baumert et al. 2006). This implies that sudden and larger changes in workload will have a greater impact on recovery and HRV. Therefore measurements of HRV are good tools to use in the prevention of overtraining because by monitoring HRV levels, individuals can make sure they do not progressively dip during an exercise training programme. While monitoring HRV, monitoring the dose-response relationship for exercise training load is also important. The dose-response relationship between physical activity and performance has been quantified using the TRIMP method in endurance and team sport athletes (Foster et al. 2005; Padilla et al. 2000; Padilla et al. 2008; Rodríguez-Marroyo et al. 2009; Stagno et al. 2007). This method shall be discussed in detail in the next section.

8.1.4 TRIMP

TRaining IMPulse (TRIMP) is defined as the training volume (total training duration) multiplied by the training intensity (average heart rate in beats per minute during exercise). TRIMP was developed by Dr. E. Bannister in the mid seventies to quantify training/exercise sessions. Quantifying training can be important for assessing how much impact training/exercise has on the body. The original TRIMP calculation was useful as a monitoring tool to assess progress and adherence to training; however the main drawback was that it did not distinguish between different levels of training. Exercise done at 60% of maximum HR (HRmax) is less demanding than exercise done at 85% HRmax, and therefore this needs to be accounted for. New calculations by Foster et al. (2001) devised five training zones (expressed as a % of HRmax) using heart rate zones to determine intensity. Athletes use this method to help define how hard to train at different periods of their season, and several studies analysing HRV have also used TRIMP (Earnest et al. 2004; Kiviniemi et al. 2010; Manzi et al. 2009).

The new equation including the training zones now accounted for variation in intensity. For the purpose of the present study however, this was still not suitable because the dependent variable being assessed is HRV. By using HR within the TRIMP equation in the present study, the independent and dependent variables would be too closely related. Therefore, within the present study, TRIMP was calculated with intensity multiplied by duration. For simplification, intensity was classified into three categories (low, moderate, high). Low-intensity aerobic activity was described as not working hard enough to raise your HR or break a sweat. Moderate-intensity aerobic activity was described as working hard enough to raise your HR and break a sweat, yet still being able to carry on a conversation. High-intensity aerobic activity was defined as breathing hard and fast, with a sharp increase in HR. Aerobic activity at this level, resulted in not being able to say more than a few words without needing to pause for a breath. When used effectively, TRIMP can provide athletes and coaches with a gauge to prevent them from overworking the body. Overworking the body can result in inadequate recovery, which if not dealt with effectively, leads to overtraining. Because measurement of HRV on a daily basis can also monitor recovery from exercise, the use of HRV together with TRIMP has the potential to enhance training programmes and consequently performance.

8.1.5 Measurement options for HRV

Ultra-short measurements of as little as 10 seconds have been reported as reliable in certain time-domain parameters (Nussinovitch et al. 2011). A new measurement tool called Ithlete has been launched on the market which takes short measurements (one-minute recordings), and is at a similar cost to Polar at approximately £200 per measurement kit. This is a much lower cost when compared with ECG systems. For the purpose of the present study, Ithlete was used because of its short measurement time, cost and accessibility of the device.

8.1.5.1 Ithlete

Ithlete was developed as a software package with a dongle that can be used with smartphones and the iPod touch. Ithlete takes one-minute measurements of HRV through the use of a standard HR monitor chest strap. Ithlete measurements should be taken first thing in the morning when the body is at rest. Measurements of HRV are used to help people monitor how their body is responding to exercise and stress. HRV is thought to decrease when the body is put under stress. As HRV can assess cardiac autonomic function, Ithlete measurements may provide a way to quantify the bodyôs autonomic response. Ithlete was developed as a tool for preventing overtraining in endurance athletes. For the purpose of this study however, Ithlete is used to quantify the bodyôs response to variation in exercise in a range of fitness levels. The creator of Ithlete modified its measurement output of rMSSD to make for an easily interpretable figure for non-expert users. The value displayed by the application is the natural log transformed rMSSD, multiplied by 20 (lnrMSSDx20). The ease and convenience of short-term rMSSD measurements from the Ithlete application should provide a good platform for maximum compliance from participants.

Several studies have analysed the effects of training on HRV using ECG readings which need to be converted from analogue to digital, and analysed through a software package (Aubert et al. 2003; Iellamo et al. 2002; Mourot et al. 2004a). Other studies have used Polar readings (Manzi et al. 2009; Nunan et al. 2009;

Vanderlei et al. 2008), which need to be inputted into software on a computer and converted into HRV measurements. The present study is the first to use Ithlete measurements in healthy participants to assess their response to exercise. Ithlete rMSSD readings are displayed directly on the measurement device screen (i.e. iPod touch or smartphone). Measurements are displayed immediately following a recording, instead of having to input raw data into a software package on a PC for analysis. Comparisons are made between previous measurements of rMSSD taken within the last month on that device. This provides each user with a unique pattern that corresponds to their own specific autonomic response to stressôsuch as exercise.

8.1.6 Aims

The aims of the present study were to: (i) assess the ability of Ithlete software to measure HRV daily for one month in healthy participants, (ii) assess the relationship between physical activity, smoking, and alcohol with HRV and HR, (iii) assess Ithlete measurements for 24 and 48-hours following exercise to see if a decrease (dip) in HRV occurs.

8.2 Methods

8.2.1 Recruitment of participants

Staff and students of Buckinghamshire New University were invited to take part in the study through internal advertisement on notice boards and emails. Each participant was recruited in accordance with University ethics committee standards and expectations. Participants responded in person, via email or phone and were sent an information pack before agreeing to participate. The information pack included:

1. An information sheet with details of the requirements for each participant;
2. An informed consent form;
3. HRV measurement information package;
4. Physical activity diary;
5. A detailed demographic information sheet.

Participants were requested to read the information pack, and during the first meeting any questions or concerns were addressed. All participants were free from any serious medical conditions. All procedures were approved by the local research ethics committee.

8.2.2 Participants

Twenty-eight participants were tested, of which 13 were male and 15 were female. Participant ages ranged from 25 to 64 years. All participants were defined as healthy (free from any serious illness at the time of testing), and none of the participants were known to have any cardiovascular problems, or to be taking any medication that would have influenced the experimental procedures.

Details of the study were explained when participants met with the researcher. The Ithlete software was demonstrated and the physical activity diary was also explained. Participants completed their consent form in front of the researcher, and the researcher countersigned the form.

8.2.3 Experimental design

Following appropriate ethical approval and informed consent, participants were asked to visit the cardiovascular research lab at Bucks New University, Uxbridge. Each participant was given a demonstration of how to use the Ithlete software on the iPod touch and required to complete two measurements in the presence of a researcher before taking the device home. Then each participant was required to take an HRV measurement daily, first thing when they woke up, for one month. Each day participants also recorded the following items in a physical activity diary:

1. What (if any) exercise was performed the day before;
2. Duration of that exercise;
3. Intensity of that exercise (Low/Moderate/High);
4. Daily scale of how they felt on a scale of 0-100% (100% being the best).

For the purpose of the present study, duration and intensity were used to calculate TRIMP. TRIMP was used to determine if subjects engaged in a sufficient amount of exercise on a given day to cause a change in HRV. The median-split method was used to determine if subjects exercised or not. If subjects did more than 50% of their mean daily exercise, this was then deemed an exercise/training session. This information will be used to assess the relationship between exercise and Ithlete rMSSD measurements. Additionally, participants were classified as dippers if their rMSSD reading was lower than the previous reading. Athleteœ systematically overload in order to improve their performance and therefore may cause dramatic decreases in rMSSD (equivalent to one or two standard deviations or more). The average individual however, will not systematically overload and therefore will not necessarily demonstrate dramatic decreases in rMSSD. Controls may have completed enough exercise to cause dramatic dips; however patients with heart failure often have low exercise tolerance and therefore are unlikely to demonstrate dramatic dips in rMSSD. Therefore in the present study, any dip in rMSSD was considered a training dip in order to keep consistency between controls and participants with heart failure in the following chapters.

8.2.3.1 Heart rate variability analysis

Heart rate variability measurements were taken using an iPod touch with the Ithlete application (Ithlete 2009). For HRV measurement, a standard analogue ECG chest strap was worn in the middle of the chest just under the sternum. Using the Ithlete software for the iPod touch, participants measured HRV in a seated position, for one minute when they woke up.

Real time heart and lung animation via the Ithlete application was displayed on the iPod touch. This facilitated paced breathing during measurements and indicated reception of each heart beat from the analogue chest strap. Participants followed a breathing frequency of 7.5 breaths per minute, designed to maximize RSA response (Brown et al. 1993). When the one minute measurement was complete, the HR (bpm) and HRV (rMSSD) were displayed on the screen and saved to the device. At the end of the one month recording period, Ithlete recordings were transferred to a password protected PC via the Ithlete software which enables recordings to be emailed and saved into an excel document.

8.2.4 Statistical analysis

All statistical analysis was undertaken using PASW 19.0 (SPSS: An IBM Company. Somers, NY, USA). Values are reported in the text as mean ± standard deviation. The median-split method was used with the HRV data to split each participantös values into two data sets (days when exercise was reported vs. days when no exercise was reported). Exercise was coded as 1 and corresponded to everything above and equal to the median. Anything below the median corresponded to no exercise reported and was subsequently coded 0. The median-split method was used to allow objective comparison between subjects, by making HRV values relative to each participant. The change in HRV from day-to-day was then calculated for each participant by subtracting the HRV value from the day before (HRV-day-2 minus HRV-day-1 etc.). Examining the change in HRV was also undertaken to allow objective comparison between subjects by disregarding absolute HRV values, as these can vary widely between subjects. Independent t-tests were then used to test differences in mean deviation of the change in HRV from day-to-day. Participant cases were weighted based on the number of recordings taken for each participant. From these data, participants were coded as dippers (those who showed a lower HRV following exercise) or non-dippers (no dip in HRV following exercise).

The general linear model was used to quantify the relationship between training and rMSSD. Univariate analysis was performed on the change in rMSSD 24-hours following exercise reported/not-reported and 48-hours following exercise reported/not-reported. Participants were grouped into those who had a dip in rMSSD the day following exercise (dippers) vs. those who did not have a dip in rMSSD the day following exercise (non-dippers). Participants were classified as dippers if their rMSSD reading was lower than the previous reading. Finally, binary logistic regression was used to predict the presence or absence of exercise. A p-value of <0.05 was considered statistically significant.

8.3 Results

Average participant characteristics are displayed in table 8.1. Of the twenty-eight participants, four did not complete the physical activity diary or Ithlete measurements correctly, and therefore their TRIMP data were excluded from analysis. Four participants reported minor issues with the equipment, but overall participants were all happy with the device and found it easy to use. Table 8.1 displays participant information including average HR, average rMSSD, average daily physical activity, and other demographic details.

Table 8.1 Participant total mean characteristics

	Male (n=17)	**Female (n=11)**
Age (years)	37 ± 13	33 ± 13
rMSSD (ms)	72.4 ± 7.4	69.3 ± 7.7
HR at rest (bpm)	67.5 ± 6.5	77.0 ± 7.0
Physical Activity (%) <30 minutes/day	41.2	58.8
Smokers (%)	17.6	19.0
Average alcohol units (n)	3.7 ± 2.3	3.5 ± 2.1

Table 8.2 displays average components for participants grouped by ethnicity (white or other), physical activity (less than 30 minutes per day, and 30 minutes or more per day), smoker or non-smoker and alcohol units (above or below the recommended intake per week of 21 units for men and 14 units for women).

Table 8.2 Mean rMSSD, HR, age by group

	Ethnicity		**Physical Activity**		**Smoker**		**Alcohol Units**	
	White (n=17)	Other (n=7)	<30 mins (n=7)	Ó30 mins (n=17)	Yes (n=7)	No (n=17)	Above (n=7)	Below (n=17)
rMSSD (ms)	70.6	74.1	66.5	73.9	72.9	71.0	69.6	72.1
HR (bpm)	72.1	68.8	78.9	67.4	65.4	73.3	69.6	71.8
Age (years)	35.2	28.9	34.7	32.9	30.0	34.8	32.1	34.0

Table 8.3 Change in rMSSD 24 and 48-hours after training

Subject #	Change in rMSSD 24-hours after exercise	Number of recordings	Average change 24-hours after exercise	Standard Deviation	Change in rMSSD 48-hours after exercise	Average change 48-hours after exercise	Standard Deviation
1	No	27	0.53	3.60	No	0.43	4.40
2	Yes	35	-0.65	6.40	No	0.56	6.86
3	Yes	28	-2.18	6.13	Yes	-0.32	6.68
4	No	21	0.41	9.17	Yes	-0.85	7.32
5	No	29	0.80	6.17	No	0.02	5.19
6	No	35	0.65	5.76	No	1.22	5.38
7	No	33	0.96	10.14	Yes	-0.51	11.18
8	No	33	0.70	8.00	No	1.79	7.04
9	Yes	36	-0.58	10.39	Yes	-0.15	10.68
10	Yes	28	-4.35	14.29	Yes	-2.98	13.30
11	No	28	3.86	11.79	No	2.10	10.66
12	No	24	7.61	18.97	No	7.25	16.65
13	No	38	0.42	4.88	Yes	-1.27	6.27
14	No	26	7.50	10.41	Yes	-0.25	7.76
15	No	19	9.25	15.10	No	1.67	19.96
16	No	31	0.26	30.45	No	5.19	20.04
17	No	34	-0.60	7.44	Yes	-0.73	9.33
18	No	29	0.20	9.34	Yes	-0.44	7.97
19	Yes	25	-3.85	20.15	Yes	-5.15	20.46
20	Yes	29	-1.59	9.14	No	1.14	9.36
21	No	23	2.44	8.08	No	0.57	9.86
22	Yes	26	-0.69	8.61	Yes	-2.65	10.38
23	No	34	0.79	7.21	No	1.10	7.85
24	Yes	33	-0.36	4.55	No	0.08	3.04

* Number of recordings refers to the amount of recordings which had corresponding measurements at 24 and 48 hours following reported exercise. Any recordings that did not have both follow-up recordings were excluded.

8.3.1 General linear model: Univariate analysis

Univariate analysis revealed that rMSSD 24-hours later was not significantly affected by exercise (p=0.12). The F value for rMSSD 24-hours after exercise was 2.44. rMSSD 48-hours after exercise was also not significantly affected (p= 0.30), with an F value of 1.68.

When participants did not exercise, the overall mean difference in rMSSD after 24-hours was -0.67 ± 9.67 (CI -1.729, 0.388) (N= 384). When participant did exercise, the overall mean difference in rMSSD 24-hours later was 0.578 ± 11.54 (CI -0.581, 1.737) (N= 320). The overall mean difference in rMSSD 48-hours after no reported exercise was 0.28 ± 0.56 (CI -0.814, 1.379) (N= 371), and when exercise was reported -0.57 ± 11.13 (CI -1.175, 0.628) (N= 309).

When participants were grouped into those who had a dip in HRV 24-hours following exercise (dippers) vs. those who did not have a dip in HRV 24-hours following exercise (non-dippers) the mean differences were -6.91 ± 8.47 for dippers and 6.51 ± 7.88 for non dippers. Forty-eight hours following exercise, participants were again grouped as dippers and non-dippers with a mean difference of -7.43 ± 9.24 for dippers and 6.98 ± 7.96 for non-dippers. A dip in HRV following exercise was expected; however, the magnitude of that dip is what indicates fatigue (i.e. if the dip in HRV is more that 1xSD, this would suggest the beginning of overreaching, and if this persisted, burnout would occur).

8.3.2 Binary logistic regression

Binary logistic regression was performed to access the impact of exercise on rMSSD. The first model was set to assess the effects of exercise on rMSSD, 24-hours following exercise, where the odds ratio was 1.056 (CI 0.784, 1.422) (p= 0.72). The second model looked at the effects of exercise on rMSSD, 48-hours following exercise, where the odds ratio was 1.219 (CI 0.901, 1.649) (p= 0.20). This suggests that a dip in rMSSD was more likely to occur 48-hours following exercise, when compared with only 24-hours.

8.4 Discussion

The present study assessed the use of daily Ithlete rMSSD measurements, to gauge how the body responded to exercise. Ithlete measurements were measured daily for at least 28-days by 86% of the participants. A decrease in rMSSD following exercise was assessed at 24 and 48-hours. A dip in rMSSD was demonstrated in 37.5% of participants 24-hours following exercise, and 58.3% 48-hours following exercise. Because HRV is a valuable indicator for monitoring the status of the ANS (Acharya et al. 2006), the prognostic value of HRV is a useful indicator of autonomic imbalance. An autonomic imbalance is thought to be a precursor to overtraining, caused by excessive exercise. Prognostic measurements of HRV are also useful in various disease states, such as depression (Birkhofer et al. 2006; Kemp et al. 2012), cardiovascular diseases (Carney et al. 2001; Gehi et al. 2005; Taylor 2010) and diabetes (Malpas & Maling 1990; Pagkalos et al. 2008; Schroeder et al. 2005)

The present study also assessed the relationship between rMSSD/HR and lifestyle factors (i.e. smoking, physical activity level). Smoking, low levels of physical activity and excessive alcohol consumption are known risk factors for cardiovascular disease (British Heart Foundation 2008; World Health Organization 2003). Some ethnic groups (Black, South Asian) are found to be at higher risk of acquiring diseases, such as diabetes and cardiovascular disease, when compared to the Caucasian population (Hoffman 2009; Lip et al. 2007; Wulan et al. 2010). Therefore the present study explored those relationships and the findings were compared with those already reported in the literature.

8.4.1 Ethnicity and lifestyle characteristics

When participants were grouped by ethnicity in the present study, (White vs. Other (Black, South Asian)), in the White population, the average rMSSD (ms) was found to be lower, while HR (bpm) was higher. These results are similar but somewhat conflicting with the two other healthy populations assessed within this thesis. In chapter five, rMSSD was very similar between the White and Other ethnic group, but higher in the South Asian population. In that same chapter, HR was significantly lower in the White group compared to the other groups. In chapter six, the White group had a lower rMSSD and HR. These results are therefore not surprising, as there are also conflicting results in the literature regarding ethnic differences in

HRV. Both a lower sympathetic drive (high HRV) has been reported in Black participants when compared with age-matched Whites (Guzzetti et al. 2000; Liao et al. 1995) and a higher sympathetic contribution to total power (lower HRV) when compared with age-matched White adolescents (Faulkner et al. 2003).

Smokers had a higher average rMSSD when compared with non-smokers and a lower average HR (bpm), which would be expected to be the other way around because smoking puts people at a higher risk of disease. The difference between the groups however was not significant, and for rMSSD especially, the margin between the two groups was very small. Both the number of smokers (n=7) vs. non-smokers (n=20) and age may have played a role in these results. The average age of non-smokers was higher by 5 years and age is known to have an effect on HRV (Liao et al. 1995; Reardon & Malik 1996; Ryan et al. 1994; Stein et al. 1997; Yeragani et al. 1997). However, the documented age differences in HRV tend to be compared either by decade (Bigger et al. 1995) or young vs. old (Bitsios et al. 1996; Stein et al. 1997). But in the present study, both averages would be classified within the same decade or age group, making the studies incomparable. When considering alcohol intake, participants who on average had less than the recommended intake per week had a higher average rMSSD but demonstrated a higher resting HR. A higher resting HRV and a lower resting HR are associated with better health. Those who average below the recommended weekly alcohol intake should exhibit those averages. Again the numbers in these groups were not even, which may have affected these results.

Participants were grouped into those who did at least 30 minutes of physical activity a day (n=17) vs. those who did less than 30 minutes of physical activity per day (n=7). Resting rMSSD was significantly higher ($p < 0.01$) in the group that did at least 30 minutes of exercise. Resting HR was also significantly lower ($p < 0.05$) in this group. These results are similar to those already found in other participants within the present thesis. This result was to be expected as the effect of exercise on HRV has been documented above and will be further explored in the next section.

8.4.2 Changes in HRV following exercise

To aid statistical analysis, the median split technique was used in the present study, because it facilitated a comparison between participants who reported exercise vs. non-exercise days. As each subjectôs physical fitness varied, the median split technique allowed for a quantifiable comparison between participants. The median-split technique resulted in two groups of equal size for each subject, making comparison between the two groups more statistically appropriate. The general linear model was used to allow for greater statistical analysis, exploring the interactions among both continuous and categorical variables. This model was used to decipher if there was a relationship between the independent variable (exercise training) with the dependent variable (a decrease in HRV), and if there was a relationship, to quantify that relationship.

Eighty-six percent of participants completed HRV measurements for at least 28 days and filled in their daily physical activity diary. Physical activity levels were important to consider as a relationship has been demonstrated between resting HRV and HR in several studies (Buchheit et al. 2004; Carter et al. 2003b; Furlan et al. 1993; Grossman et al. 2004; Melanson & Freedson 2001; Sandercock et al. 2005; Stein et al. 1999). The present study found that those who averaged at least 30-minutes of exercise per day at least three-times per week had a lower resting HR. This is in accordance with the literature, where those who are more physically active are found to have a lower resting HR (Goldsmith et al. 1992; Katona et al. 1982; Kingwell et al. 1996; Melanson & Freedson 2001), and higher HRV (De Meersman 1993; Dixon et al. 1992; Goldsmith et al. 1992; Jurca et al. 2004; Schuit et al. 1999).

When looking at rMSSD 24-hours after exercise was reported, 38% of participants were coded as dippers. Forty-eight hours following exercise 58% of participants were coded as dippers. This suggests that the change in rMSSD is best monitored 48-hours following training, as this is where the most significant changes were demonstrated. This is in contrast to what has been reported in the literature; however, the effect of a single bout of exercise on resting HRV has not been explored at great length. The benefits of a single bout of exercise that have been reported to include increased insulin sensitivity, lower blood pressure and decreased low density blood lipids (Ferguson et al. 1998; Mikines et al. 1989; Seals et al. 1997). The amount of time these benefits last has not been reported. Long-term improvements in resting HRV following chronic exercise training have however, been demonstrated (Iellamo et al. 2000; Melanson & Freedson 2001; Seals & Chase 1989).

The majority of studies that have explored the effect of the changes in HRV after a bout of sub-maximal exercise, only measured for relatively short periods of 15-180 minutes following exercise (Brenner et al. 1997; Gladwell et al. 2010; Oida et al. 1997; Terziotti et al. 2001). A limited number of studies have measured HRV for more than 24-hours, Furlan et al, (1993) observed increased sympathetic activity for more than 24-hours after heavy physical work. Pober et al, (2004) reported an increase in a couple of markers for vagal activity (pNN50 and HF normalised units) for up to 22-hours following exercise. Like the present study, Gladwell et al. (2010) demonstrated a decrease in rMSSD post-exercise, but this was only at 30-minutes. By 65-minutes post-exercise, they reported an increase in rMSSD over baseline of 13.9 ± 74.3%.

An initial decrease in HRV following a single bout of exercise has been demonstrated (James et al. 2002; Javorka et al. 2002). This might be explained by inhibitory affects from sympathetic blood hormones (Miyamoto et al. 2003), or the accumulation of waste products during exercise which activates metabolic receptors (O'Leary 1993). The combination of sympathetic activation and parasympathetic withdrawal are thought to be the cause of the rise in HR during exercise (Arai et al. 1989). Reactivation of the parasympathetic nervous system following exercise is then thought to cause a decrease in heart rate (Imai et al. 1994). Baroreflex action and insulin sensitivity have been suggested as the physiological reasons for the observed changes in HRV, because both have been linked to exercise and HR (Kirwan et al. 1991; Laitinen et al. 1999; Seals & Chase 1989). In healthy subjects this physiological response is culpable for changes observed in HRV, however in patients with heart failure, both baroreflex and insulin sensitivity are abnormal (La Rovere et al. 2009; Mortara et al. 1997). Therefore in these two populations, there may be something different happening physiologically to cause the decrease in HRV following exercise. In chapter ten, the results of the present study will be compared to results in patients with heart failure. If decreases in rMSSD are also found in patients with heart failure, future research should further explore the physiological causes for this decrease.

Changes to HRV during and following exercise may be as a result of changes in plasma volume, changes in sympathetic nerve outflow, increased baroreflex sensitivity, or changes in the levels of vasoactive substances in the circulation (Kirwan et al. 1991; Laitinen et al. 1999; Pober et al. 2004; Seals & Chase 1989). Evidence to explain what happens physiologically when changes in HRV occur during and following exercise have not yet been demonstrated sufficiently in the literature (Pober et al. 2004). More research is also needed for determining how long it takes for changes in HRV to return back to baseline. Hayashi et al. (1992) suggested that recovery of cardiac autonomic regulation following moderate to high intensity exercise occurs later than recovery of peripheral circulation or oxygen uptake. The present study contributes to the debate on when changes in HRV return back to baseline. More detailed follow-up in both healthy and clinical populations are necessary to determine how long these changes occur, and what may cause them.

In healthy adults there is an expected adaptational increase in maximal oxygen consumption in response to exercise training, which is also associated with longer term indexes of HRV. This presumed relationship is largely based on cross-sectional investigations, comparing athletes with sedentary individuals (Stein et al. 1999). Several studies have demonstrated modifications in HRV following an aerobic training programme (De Meersman 1993; Goldsmith et al. 1992; Schuit et al. 1999). Evidence suggests that HRV can be used for optimising individual training, and measurement of HRV overnight is a better tool for assessing accumulated fatigue when compared with resting HR alone (Earnest et al. 2004; Pichot et al. 2000). The present study had participants with varying levels of physical activity, none of which were participating in a specific training programme. After 48-hours, over 50% of participants still demonstrated a dip in rMSSD following exercise. This suggests that adaptations can still occur without being on a prolonged training programme. The present study did not assess if HRV improved over time in these participants because no exercise intervention was imposed on this group. This adaptation would not be expected in this population because they were not necessarily engaging in exercise on a regular basis.

8.4.3 Overtraining and HRV

The bodyôs ability to repair muscle, tissues and replenish energy stores is essential in the process of maximizing physiological adaptation. This is accomplished by ensuring that the body has enough time to recover adequately before the next bout of exercise. The balance between sleep, nutrition and other circumstances will also have a major impact on how well and how swiftly the body can recover. Reduced supine HRV has been reported in overtrained athletes when compared with trained athletes and untrained control subjects (Mourot et al. 2004a). Reduced parasympathetic HR control after wakening was observed in 12 overtrained athletes (Hynynen et al. 2006). Hedelin et al. (2000) found no significant changes in HRV in overtrained canoe athletes following a training camp, and Bosquet et al. (2003) reported no significant changes in HRV in nine endurance athletes both during, and two weeks following overtraining. In contrast to these studies, the present studyôs participants had various fitness levels (no participants reported heavy training regimes), and none were considered to be overtrained. Ithlete rMSSD measurements did demonstrate a dip in several participants. This dip did not last longer than seven consecutive days in any participant, suggesting that none were overtrained.

8.4.4 Limitations

In the present study, participants were asked to record their exercise activity daily on a physical activity diary. Participants had to choose a zone for the rate of intensity at low/moderate/high and this was a very subjective measure. It is hard to gauge how well they adhered to the described intensity zones within one work-out. However, they were asked to record the zone within which they thought they were within most throughout the workout. Conversely, the large range of activity levels within the participants in the present study, helped to counter that effect.

Median split is one of the techniques used to make continuous variables into categorical variables. This is done by finding the median of the continuous variable and placing any value below the median into the ôlowô group and every value equal to and higher into the ôhighô group. It must be acknowledged that the median split method has some disadvantages. Making continuous variables into categorical ones does reduce statistical power primarily because of the reduction in the inherent variability of the predictor variable. Aiken & West (1991) stated that regardless of how a median split is done, there is always a loss of power. Another issue resulting from the median split is that every value above the median and below the median are considered equal despite the fact that there may be a large variation between them. In the present study, several participants had very low activity levels. This therefore resulted in very small bouts of exercise being considered training, along with larger bouts of exercise. In these cases, this may have slightly skewed the results.

The median split technique was used within this study because it allowed for a comparison between subjects to dictate whether exercise occurred or not. Because each subjectsô physical fitness varied, the median split technique allowed for comparison between subjects by characterizing their own training regime into two groups, where exercise training was relative to each subject. This technique is not perfect, but was best for comparisons within this thesis.

8.5 Conclusions

Ithlete measurements of rMSSD and HR were undertaken on a consistent basis by 86% of participants for one-month. A dip in HRV was demonstrated in more than 50% of participants when exercise was reported 48-hours earlier. Ithlete appears to be an easy device to use for daily HRV assessment. It is also cost efficient when compared to other medical devices, and provides feedback to the user which can be easily interpreted without the use of inputting raw data into a software package. Future research should focus on the effects of exercise on HRV over various time periods with a large cohort of participants; especially monitoring HRV directly following exercise for up to 72-hours afterwards. This could be very beneficial in the assessment of the effect of exercise on the body over time, and the effect of intensity and duration.

8.6 References

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CHAPTER 9: HEART RATE VARIABILITY MEASUREMENT IN PATIENTS WITH HEART FAILURE WITH VARYING PHYSICAL ACTIVITY LEVELS USING ITHLETE SOFTWARE

Heart rate variability (HRV) is a non-invasive electrocardiographic measure that examines the sympathetic and vagal components of autonomic nervous function. There are various parameters for HRV analysis which include time domain, frequency domain and geometric methods. Conventional HRV analysis tends to produce all of these measures through measurement software; several of these measurements such as rMSSD and the high frequency power (HFr) of the normal R-R interval power spectrum are highly correlated with one another. With that in mind, the present study will focus on one of those measurements, the root of the mean squared differences of successive heart periods (rMSSD). There does not appear to be a need to compare several different measurements with such high correlations. The present study aimed to assess the ability of Ithlete software to measure HRV daily for one month in participants with heart failure (HF), while assessing if a decrease (dip) in rMSSD occurred following exercise.

One hundred and three participants with HF were recruited from three London hospital sites, and agreed to participate in the present study. Seventy participants were male and 33 were female; participant ages ranged from 24 to 87 years.

A dip in rMSSD, 24-hours following reported exercise was demonstrated in 46.5% of HF patients. Forty-eight hours after reported exercise, 65.1% demonstrated a dip in rMSSD. When patients did not report exercise, a dip in rMSSD was found in 55.8% of participants after 24-hours, and 53.5% 48-hours after. These results suggest that a dip in rMSSD may be more likely to occur at 48-hours after exercise was reported, however a dip was also observed in approximately 50% of participants when exercise was not reported. Approximately 50% of participants completed all the Ithlete measurements for at least 28 consecutive days. Participants reported good usability on a daily basis suggesting Ithlete to be an acceptable measurement device in this population. Effective daily use of the Ithlete HRV measurement device for gauging exercise response was demonstrated in patients with HF. Patients stated that using the device was simple, convenient and an effective use of time and recommended its use with other patients.

9.1 Introduction

9.1.1 Heart rate variability and heart failure

Heart failure (HF) can be defined as a condition in which a structural or functional abnormality impairs the pumping ability of the heart. Despite normal filling pressures, these abnormalities weaken the heartôs pumping action and lead to difficulties in the metabolizing tissues receiving enough blood, and therefore enough oxygen (Dickstein et al. 2008). Impaired autonomic function is recognized as a consequence of chronic heart failure (CHF) (Nolan et al. 1992). Heart rate variability (HRV) is a non-invasive electrocardiographic measure that examines the sympathetic and vagal components of autonomic nervous function. The autonomic nervous system makes itself visible through HRV, indicating how the body is trying to preserve its equilibrium. A good functioning autonomic nervous system should yield a high HRV, which implies a healthy individual (Sueta 2003). As HRV provides an indirect, non-invasive measurement of autonomic control of the heart, it is an ideal measurement to use in patients with heart failure.

The first study on HRV in HF was conducted by Saul et al, (1988) and sparked interest in the investigation of possible changes that occur in HRV in HF, seeking correlations between HRV and current clinical status (Chattipakorn et al. 2007). Other studies have demonstrated that as a result of CHF, patients have decreased HRV and this decrease can be used to predict cardiac events (Fauchier et al. 1997; Nolan et al. 1998; Task Force. 1996).

HRV has been demonstrated as an effective measurement for 24-hour ambulant measurements (Furlan et al. 1990; Task Force, 1996), short-term measurements (Bigger et al. 1993; Lucreziotti et al. 2000; Pagani et al. 1986) and very short term measurements (Thong et al. 2003). Bigger et al. (1993) compared HRV measurement epochs of 2-15 minutes with 24-hour ambulatory recordings in HF patients. This study found that measurements of 2-15 minutes predicted death nearly as well as the same measures computed over a 24-hour period. When matched individually with each of the three best predictors of mortality (NYHA class, left ventricular ejection fraction and crackling noises heard on auscultation of the lung) they significantly improved the prediction (ibid). A one-minute bedside deep breathing test of HRV in post-myocardial infarction patients also demonstrated that short-term measurements of HRV were good predictors of all cause mortality and sudden death (Katz et al. 1999).

The present study will use the root mean squared of successive differences of heart periods (rMSSD). rMSSD is a time domain measure of HRV which reflects parasympathetic activity without being dependent on heart trends (Stein et al. 1994). rMSSD has been suggested as superior to spectral methods due to its sensitivity to vagal cardiac control and is less sensitive to variations in respiratory patterns (Penttilä et al. 2001). rMSSD has been demonstrated as an effective measure for capturing respiratory sinus arrhythmia and a reliable assessment of cardiac vagal outflow (Penttilä et al. 2001).

In patients with HF, the autonomic nervous system is characterized by dysfunction in sympathetic activation, parasympathetic withdrawal and peripheral organ non-responsiveness (Grassi et al. 1995). CHF may result in depressed HRV levels, which are regularly observed at all stages of systolic dysfunction (Fauchier et al. 1997). A research project called UK Heart was a substantial prospective study which followed patients for more than a year, it was conducted with 433 congestive HF patients (NYHA classes I-III), with a mean ejection fraction of 0.41 ± 0.17 L. UK Heart found a reduction in several clinical variables including SDNN, creatinine, serum sodium, non-sustain ventricular tachycardia, cardiothoracic ratio and LV end diastolic diameter (Nolan et al. 1998). An SDNN of <100ms was the most powerful predictor of total mortality among a large number of clinical variables (Nolan et al. 1998).

Conventional HRV measurements are related to systolic left ventricular function (Nolan et al. 1992) and functional classification (Casolo et al. 1995). The severity of left ventricular dysfunction correlates with decreased HRV and, therefore, poor prognosis (Wijbenga et al. 1998). Reduced HRV is an established risk factor for sudden cardiac death in CHF patients (Sandercock & Brodie 2006). The best predictive HRV measures for all cause mortality are the global and/or slow oscillations in R-R intervals from both frequency and time domains (ibid). Given this relationship, it is important to identify interventions which are able to increase HRV in patients with CHF.

9.1.2 Exercise and heart failure

Patients with HF were originally cautioned against physical exercise until treatment changed in the late 1980s (Coats 2000). Coats et al, (1990) challenged this practice, and the benefit of exercise in patients with HF was demonstrated in an 8-week training programme. The programme produced a 20-25% increase in peak oxygen consumption, increased exercise tolerance and reduced questionnaire-rated symptoms associated with their condition (Coats et al. 1990). Participants in this study also found an increase in the ease and degree of performing daily activities (ibid). From the 90s onwards the research in this area increased with larger and better designed studies in patients with HF looking at the physiological benefits and increases in exercise capacity that are possible through cardiac rehabilitation (Coats 1999).

The American Heart Association defines a cardiac rehabilitation as a comprehensive exercise, education and behavioural modification programme designed for patients with heart disease to improve physical and emotional well-being. Cardiac rehabilitation has demonstrated improvement in physical health and a decrease in subsequent morbidity and mortality, achieved through exercise, education, behaviour change, counselling and support strategies (Taylor et al. 2010).

Exercise training programmes produce positive outcomes such as delaying the onset of anaerobic metabolism, increasing vagal tone, reducing sympathetic drive and increasing aerobic capacity in patients with HF (Dracup et al. 2007). The majority of studies conducted in this area are randomised controlled trials that focus mostly on symptomatic benefits and substitute markers of prognosis such as HRV and peak oxygen consumption (Belardinelli et al. 1999; Dubach et al. 1997; Giannuzzi et al. 1997; Hambrecht et al. 1995; Kiilavuori et al. 2000; McKelvie et al. 2002; Wielenga et al. 1999; Willenheimer et al. 1998). Exercise training considerably improves survival time in patients with HF due to improved left ventricular systolic function (ExTraMATCH Collaborative 2004). Exercise capacity assessed with or without metabolic measurements has proven a more powerful prognostic tool than other traditional risk factors such as smoking, hypertension and diabetes (Myers et al. 2002). Variability in heart rate suggests that exercise training may reduce adrenergic tone and increase vagal tone which can have a positive effect on the important neurohormonal and musculoskeletal abnormalities that occur in heart failure (ExTraMATCH Collaborative 2004).

TRaining IMPulse (TRIMP) is defined as the training volume (total training duration) multiplied by the training intensity (average heart rate in beats per minute during exercise). Exercise done at 60% of maximum HR (HRmax) is less demanding than exercise done at 85% HRmax, and therefore this needs to be accounted for. New calculations by Foster et al. (2001) devised five training zones (expressed as a % of HRmax) using heart rate zones to determine intensity. The new equation including the training zones now accounted for variation in intensity. For the purpose of the present study however, this was still not suitable because the dependent variable being assessed is HRV. By using HR within the TRIMP equation in the present study, the independent and dependent variables would be the same. Therefore, within the present study, TRIMP was calculated with intensity multiplied by duration.

Measurements of HRV are used to help people monitor how the body is responding to exercise and stress. HRV is thought to decrease when the body is put under stress. Increases in resting HRV following a exercise training in patients with HF have been documented in several studies (Kiilavuori et al. 1995; Kubinyi et al. 2003; Malfatto et al. 2002; Murad et al. 2012; Selig et al. 2004). However, an initial decrease in HRV in the minutes or hours following exercise is known to occur (Mourot et al. 2004b; Parekh & Lee 2005; Terziotti et al. 2001). As HRV is known to assess autonomic function, Ithlete measurements provide a way to quantify autonomic response. Ithlete was developed as a tool for preventing overtraining in endurance athletes. For the purpose of the present study however, Ithlete was used with heart failure patients with a range of fitness levels, to quantify the bodyôs response to variation in exercise.

9.1.3 Aims

Thus the aims of the present study were: (i) to assess the ability of Ithlete software to measure HRV daily for one month in participants with heart failure, (ii) to assess Ithlete measurements over 24 and 48-hours following reported exercise to see if a decrease (dip) in HRV occurs.

It is hypothesized that Ithlete software will be a feasible measurement device for capturing daily HRV in participants with HF. In accordance with the literature, a dip in HRV following exercise is expected to occur.

9.2 Methods

9.2.1 Recruitment of participants

The researcher attended clinics with either a Consultant Cardiologist or Heart Failure Nurse Specialist at three London hospital sites. Each participant was recruited in accordance with NHS Research Ethics Committee standards and expectations. Participants responded in clinic or by phone and were sent an information pack before agreeing to participate. The information pack included:

1. An information sheet with detail of the requirements for each participant before and during the laboratory visit;
2. An informed consent form;
3. HRV measurement information package;
4. A detailed demographic information sheet.

Participants were requested to read the information pack prior to attending the clinic to meet with the researcher and any questions or concerns were addressed. All procedures were approved by the local research ethics committee.

9.2.2 Participants

A total of n=103 participants responded within the clinics and agreed to participate in the study of which n=70 were male and n=33 were female. Participant ages ranged from 24 to 87 years. All participants were defined as suffering from heart failure with varying levels of impairment but all were deemed suitable by the medical team at the hospital they attended.

Inclusion criteria: The participants were recruited from three hospitals in the London area. The participants were heart failure patients within the New York Heart Association classifications of I, II & III aged at least 18 years of age. Heart failure treatment was under the control of the participant's consultant cardiologist.

Exclusion criteria: Participants were excluded if they had any of the following conditions: Consistent atrial fibrillation, unstable coronary artery disease with revascularization within the last 6 months or planned revascularization, planned heart valve surgery or planned transplantation, uncontrolled arterial hypertension, acute myocarditis, worsening clinical condition, inability to read the display of a handheld device or deemed unable to comply with home telemonitoring; inadequate understanding of English; any visual or cognitive impairment sufficient to interfere with the participant's ability to use the device (Cleland et al. 2005; Dar et al. 2009; Scherr et al. 2009).

Participants completed their consent form in front of the researcher and the researcher countersigned the form.

9.2.3 Experimental design

Following appropriate ethical approval from the NHS Southwest Research Ethics Committee and informed consent, participants were asked to visit the clinic at their hospital to meet with the researcher for a demonstration. Each participant was given a demonstration of how to use the Ithlete software on the iPod touch and required to complete two measurements in the presence of a researcher before taking the device home. Then each participant was required to take an HRV measurement once every morning when they woke up for 1 month in succession. Each day participants also recorded on a calendar:

1. What (if any) exercise was performed the day before;
2. Duration of that exercise;
3. Intensity of that exercise (Low/Moderate/High);
4. Daily scale of how they felt on a scale of 0-100% (100% being the best).

For the purpose of the present study, duration and intensity were used to calculate TRIMP. TRIMP was used to determine if subjects engaged in a sufficient amount of exercise on a given day to cause a change in HRV. The median-split method was used to determine if subjects exercised or not. If subjects did more than 50% of their usual daily exercise, this was then deemed an exercise/training session. This information will be used to assess the relationship between exercise and Ithlete rMSSD measurements. Additionally, participants were classified as dippers if their rMSSD reading was lower than the previous reading. Athleteõs systematically overload in order to improve their performance and therefore may cause dramatic decreases in rMSSD (equivalent to one or two standard deviations or more). The average individual however, will not systematically overload and therefore will not necessarily demonstrate dramatic decreases in rMSSD. Controls may have completed enough exercise to cause dramatic dips; however patients with heart failure often have low exercise tolerance and therefore are unlikely to demonstrate dramatic dips in rMSSD. Therefore in the present study, any dip in rMSSD was considered a training dip in order to keep consistency between controls and participants with heart failure.

9.2.3.1 Heart rate variability analysis

Heart rate variability measurements were taken using an iPod touch with the Ithlete application (Ithlete 2009). For HRV measurement, a standard analogue ECG chest strap was worn in the middle of the chest just under the sternum. Using the Ithlete software for the iPod touch, participants measured HRV in a seated position, for one minute when they woke up.

Real time heart and lung animation via the Ithlete application was displayed on the iPod touch. This facilitated paced breathing during measurements and indicated reception of each heart beat from the analogue chest strap. Participants followed a breathing frequency of 7.5 breaths per minute, designed to maximize RSA response (Brown et al. 1993). Ithlete software provides an indication of how the body has responded to exercise by displaying a colour behind the change in HRV as displayed below on an Iphone beside daily and weekly change. These indications are displayed in the table as an average number which corresponds to one of the four colour indications (1-1.5=Blue for normal recovery, 1.5-2.5=Green for good recovery, 2.5-3.5=Amber for not the best recovery, 3.5-4=Red for bad recovery). TRIMP is displayed as an average of intensity of exercise multiplied by the duration of exercise and Day Scale (how patients felt on a scale of 0-100, 100 being the best and 1 being the worst) is displayed as a percentage. More specifically, amber represents the first day when HRV is more than 1 x SD (standard deviation of natural log transformed rMSSD) below the moving average of the previous seven days (so excluding the most recent recorded value); red represents the second day when this condition is true (i.e. two successive days when the current value is more than 1x SD below the moving average blue line) and green represents a rise of more than 2 x SD compared to the previous day. Green is intended to indicate good recovery and signifies that the body is ready for harder exercise.

When the one minute measurement was complete, the HR (bpm) and HRV (rMSSD) were displayed on the screen and saved to the device. At the end of the one month recording period, Ithlete recordings were transferred to a password protected PC via the Ithlete software which enables recordings to be emailed and saved into an excel document.

9.2.4 Statistical analysis

All statistical analysis was undertaken using PASW 19.0 (SPSS: An IBM Company. Somers, NY, USA). Values are reported in the text as mean ± standard deviation. The median-split method was used with the HRV data to split each participant's values into two data sets (days when exercise was reported vs. days when no exercise was reported). Exercise was coded as 1 and corresponded to everything above and equal to the median, anything below the median corresponded to no reported exercise and was subsequently coded 0. The median-split method was used to allow comparison between subjects objectively by making HRV values relative to each participant. The change in HRV from day-to-day was then calculated for each participant by subtracting the HRV value from the day before (HRV-day-2 minus HRV-day-1 etc.). Independent t-tests were then used to generate mean and standard deviation of the change in HRV from day-to-day. Participant cases were then weighted based on the number of recordings taken for each participant. From these data, participants were coded as dippers (those who showed a lower HRV following training) or non-dippers (no dip in HRV following training).

The general linear model was then used to quantify the relationship between training and HRV. Univariate analysis was performed on the change in HRV 24-hours following exercise reported/exercise not reported and 48-hours following exercise reported/exercise not reported. Participants were then grouped into those who had a dip in HRV 24-hours following exercise (dippers) vs. those who did not have a dip in HRV 24-hours following exercise (non-dippers). Binary logistic regression was then used to predict the presence or absence of exercise. A P-value of <0.05 was considered statistically significant.

9.3 Results

In total forty-six participants completed measurements for a one-month period without missing two consecutive measurements. Participants have been placed into NYHA classes by the Consultant Cardiologist or Heart Failure Specialist Nurse; throughout section 9.3, results will either be displayed within those NYHA classifications, by gender or on an individual basis. In table 9.1 participants are divided into NYHA classes and average values for each class are displayed for age, rMSSD, heart rate and ejection fraction. Table 9.2 displays gender averages for rMSSD, HR, indication, TRIMP and day scale.

Table 9.1 Mean participant values for age, rMSSD, HR and EF by NYHA class.

	NYHA I N=11	**NYHA II N=17**	**NYHA III N=15**
Age (years)	64.6 ± 12.5	57.2 ± 19.1	63.3 ± 12.5
rMSSD (ms)	81.4 ± 10.2	75.9 ± 7.3	75.4 ± 12.3
HR at rest (bpm)	81.5 ± 10.2	82.2 ± 13.2	84.7 ± 6.1
Ejection Fraction (%)	41.5 ± 9.0	38.9 ± 11.3	31.3 ± 11.7
TRIMP	149.6 ± 56.7	135.38 ± 94.4	110.55 ± 82.6

Table 9.2 Mean rMSSD, HR, Indication, TRIMP and Day Scale for each participant by gender

Age	**Gender**	**rMSSD**	**HR**	**Indication**	**TRIMP**	**Day Scale**
63 ± 12	M	77.4 ± 10.5	82.4 ± 9.7	1.5 ± 0.9	116.2 ± 89.7	61.2 ± 12.8
59 ± 14.5	F	75.2 ± 7.2	86.9 ± 14.4	1.4 ± 0.8	111.5 ± 63.1	68.5 ± 17.2

For the above table, HRV, i.e. rMSSD is measured in milliseconds (ms), HR in beats per minute (bpm). Indication corresponds to the number allocated by Ithlete software to indicate how the body has responded to exercise (based on the difference between the rolling average of the previous seven days and the current measurement). TRIMP (corresponds to volume in minutes multiplied by an intensity number where low = 1, medium = 2 and high = 3) and day scale corresponds to the patients rating of how they feel on a scale from 1-100 (1 being the worst (very ill) to 100 being the best (feeling great)).

Table 9.3 Change in rMSSD 24 and 48-hours after training

Subject #	Change in rMSSD 24-hours after exercise	Number of recordings	Average change 24-hours after exercise	Standard Deviation	Change in rMSSD 48-hours after exercise	Average change 48-hours after exercise	Standard Deviation
1	No	52	2.94	10.22	Yes	-2.29	9.14
2	No	34	1.52	8.77	Yes	-2.11	12.70
3	No	27	1.69	8.31	Yes	-0.42	7.98
4	Yes	14	-0.36	5.56	Yes	-0.55	5.79
5	Yes	35	-0.79	9.54	No	0.05	9.29
6	Yes	18	-0.94	6.11	Yes	-2.50	5.82
7	Yes	17	-0.88	9.05	No	0.61	10.69
8	No	21	1.77	14.03	Yes	-2.25	18.25
9	Yes	24	-0.95	11.53	No	2.44	8.04
10	No	31	0.48	13.69	No	1.97	12.81
11	No	18	14.60	20.82	Yes	-13.63	14.26
12	Yes	32	-3.02	11.28	No	1.55	13.39
13	No	27	2.52	10.85	Yes	-2.63	15.14
14	No	30	0.25	7.23	Yes	-2.76	8.41
15	No	32	16.80	37.74	Yes	-5.63	69.52
16	No	21	0.30	8.11	Yes	-0.57	6.94
17	Yes	37	-0.44	11.05	No	1.14	12.79
18	No	25	0.77	13.86	Yes	-0.41	12.86
19	Yes	28	-1.91	9.13	Yes	-0.13	7.68
20	No	32	0.63	12.38	Yes	-0.12	11.47
21	Yes	19	-15.86	34.34	Yes	-1.18	5.75
22	No	25	3.65	6.38	Yes	-1.71	6.75
23	Yes	40	-2.08	22.74	Yes	-0.38	22.77
24	Yes	29	-14.46	42.22	No	6.94	34.72
25	No	15	5.83	5.52	Yes	-6.45	9.97
26	Yes	35	-0.42	22.36	Yes	-4.83	16.39
27	No	16	0.79	13.14	Yes	-1.54	19.70
28	No	27	2.54	15.09	No	0.18	11.71
29	Yes	42	-2.19	14.77	Yes	-1.08	16.97
30	Yes	32	-0.32	10.06	No	1.13	9.57
31	No	35	2.70	10.92	Yes	-4.53	12.07
32	No	35	0.394	8.64	No	0.31	9.88
33	Yes	37	-0.592	13.26	No	0.68	14.07
34	No	23	0.381	7.55	No	0.63	8.20
35	Yes	30	-3.61	12.32	Yes	-0.94	16.93
36	Yes	24	-1.96	17.11	Yes	-0.41	28.86
37	No	16	1.29	19.65	Yes	-3.03	22.71
38	No	26	2.45	40.84	No	3.91	41.13
39	No	23	0.66	19.52	No	1.86	19.77
40	Yes	31	-1.02	17.65	Yes	-3.32	17.30
41	Yes	26	-12.58	19.82	No	20.67	20.93
42	No	34	-0.59	10.46	Yes	-0.63	8.30
43	Yes	17	-1.36	5.59	Yes	-0.66	5.49
44	No	21	0.45	11.1	No	0.48	10.59
45	No	29	0.49	6.1	No	0.08	8.51
46	No	21	1.8	37.8	No	6.35	40.89

* Number of recordings refers to the amount of recordings which had corresponding measurements at 24 and 48 hours following reported exercise. Any recordings that did not have both follow-up recordings were excluded.

9.3.1 General linear model: Univariate analysis

Univariate analysis revealed that after 24-hours rMSSD was not significantly affected by exercise (p= 0.70). The F value for rMSSD 24-hours following exercise was 0.137. The rMSSD 48-hours after exercise was also not significantly affected (p= 0.06) with an F value of 1.978.

The overall mean change of rMSSD 24-hours after no reported exercise was -0.232 ± 0.845 (CI -1.889, 1.426) (n= 583) and 24-hours following reported exercise was -0.032 ± 0.813 (CI -1.628, 1.564) (n= 609). The overall mean change of HRV (rMSSD) 48-hours after no reported exercise was -0.492 ± 0.89 (CI -2.245, 1.262) (n=567) and 48-hours after reported exercise was -0.525 ± 0.492 (CI -2.255, 1.205) (n= 581). When participants were grouped into those who had a dip in HRV 24-hours following exercise (dippers) vs. those who did not have a dip in HRV 24-hours following exercise (non-dippers) the mean changes were -11.57 ± 13.51(rMSSD) for dippers and 10.12 ± 12.7 (rMSSD) for non-dippers. Forty-eight hours following exercise participants were again grouped as dippers and non-dippers with a mean change of -11.59 ± 13.52 (rMSSD) for dippers and 10.73 ± 12.94 (rMSSD) for non-dippers.

9.3.2 Binary logistic regression

Binary logistic regression was performed to assess the likelihood of exercise being associated with a decline in HRV. First, the effect of exercise on HRV (rMSSD) at 24 and 48-hours following reported exercise was assessed. At 24-hours after exercise the odds ratio was 1.007 (CI 0.802, 1.264) (p= 0.95). Forty-eight hours following exercise the odds ratio was 0.976 (CI 0.774, 1.230) (p= 0.84). This suggests that there was no greater likelihood of a decline in HRV (rMSSD) at 24 or 48-hours following exercise. Ratios so close to one indicate that there was no significant difference in HRV between days following exercise being reported vs. not reported.

9.3.3 Coefficient of variation

Table 9.4 below displays the coefficient of variation (CV) of HRV, HR, training impulse (TRIMP) and day scale (DS) by NYHA class. Table 9.5 displays the CV of HRV, HR, TRIMP and DS by gender, and Table 9.6 by exercise group (calculated by a median-split of TRIMP).

Table 9.4 CV for rMSSD and HR, TRIMP and DS for each NYHA class

NYHA Class	CV for rMSSD (ms)	CV for HR (bpm)	CV for TRIMP	CV for DS (%)
I	20.7†	7.4	94.4	22.5
II	17.5†	6.8	77.9	19.8
III	36.9†	6.6	88.1	47.6

Table 9.5 CV for rMSSD and HR, TRIMP and DS by gender

Gender	CV for rMSSD (ms)	CV for HR (bpm)	CV for TRIMP	CV for DS (%)
Male	26.6	6.8	89.0	30.0
Female	13.7	7.1	60.8	27.8

Table 9.6 CV for rMSSD and HR, TRIMP and DS for exercise group

Exercise Group	CV for rMSSD (ms)	CV for HR (bpm)	CV for TRIMP	CV for DS (%)
Regular exercise	23.7	6.4†	78.2	30.6
Not regular exercise	26.5	7.4†	93.5	28.8

ÀSignificant difference at $p < 0.01$

The CV rMSSD for all the HF participants was 25.1%. No significant differences were demonstrated between genders or exercise group for rMSSD, HR, TRIMP or DS. A significant difference was demonstrated between day scale groups HR at $p = 0.003$. A significant difference was also found between NYHA class II and III in the CV for rMSSD at $p = 0.01$.

9.4 Discussion

The present study aimed to assess the ability of Ithlete software to measure HRV daily for one month in participants with HF. This study also assessed the use of Ithlete HRV measurement daily to gauge how HF patients responded to exercise. Ithlete measurements were assessed 24 and 48-hours following exercise. Patients were encouraged to take measurements at rest, first thing in the morning before moving around too much or having any caffeine. In all, 103 HF patients agreed to participate in the present study. Of those, 45% completed all of the required measurements including the physical activity diary and Ithlete measurements for a one-month period without missing two consecutive measurements. A further 23% completed measurements with the device, but did not complete the required amount. Those that did not complete all the measurements cited reasons such as not enough time in the morning, difficulty saving the readings all the time, the device was too difficult to use, or they didnôt like using touch screen devices. Despite less than half completing all the required measurements, overall patients reported the device was simple and easy to use. Assessment of patientsô feelings toward the device will be explored further in chapter ten.

The overall coefficient of variation for rMSSD in HF patients within the present study was 25.1, with a larger variation found in male participants when compared with females. There were a significantly larger number of male participants, which almost certainly caused the greater variation in male vs. female participants. The greater the number of participants with differing values, it follows on that the greater the variation will become. A significant difference in rMSSD was found between NYHA classes II and III; this cannot be explained by numbers, because the groups had a similar number of participants. A larger variation was demonstrated in NYHA class III, which, is the group with the most severe symptoms. Impaired autonomic function in this group should be more severe, however the impact on HRV is not clear. Due to the inherent variation in dysfunction amongst participants, a large variation in rMSSD could be expected. Alternatively this group could also have demonstrated less variation in rMSSD, due to everyone having very poor function. Further investigation is needed to determine what affect specific symptoms may have on rMSSD. However more variation could occur because of different symptoms associated with HF, such as degrees of autonomic disturbance.

A dip in rMSSD was found in 46.5% of HF patientös 24-hours after reported exercise; 48-hours following exercise 65.1% demonstrated a dip in rMSSD. When patients didnöt report exercise, a dip in rMSSD was found in 55.8% of patients after 24-hours, and 53.5% after 48-hours. This suggests that the dip in rMSSD was not necessarily related to exercise in this patient group, and other stressors such as comorbidities may have played a role. Measurements of HRV in HF patients have previously been used as a measurement of cardiovascular status, implicating those at higher risk of mortality (Brouwer et al. 1996; Nolan et al. 1998). HRV measurements have also been associated with overtraining (Lehmann et al. 1993; Mourot et al. 2004a; Uusitalo 1998), which occurs when there is not a sufficient amount of rest/recovery time between exercise bouts. Monitoring HRV in patients with HF has several benefits, making Ithlete an attractive option as it can facilitate quick and easy measurements on a daily basis. Ithlete can be used to gauge a patientös risk of mortality as well as monitoring the effect of an exercise training programme by helping patients recognize when and how hard to exercise. These functions will be explored further in chapter eleven where Ithlete was used to help facilitate cardiac rehabilitation.

The benefits of exercise in patients with HF has been documented in the literature (Davies et al. 2010; ExTraMATCH Collaborative 2004; Selig et al. 2004; Wielenga et al. 1999; Willenheimer et al. 1998), however exercise prescription should be clinician directed. The first publication on exercise training in post myocardial infarction patients with HF was in 1987 and compared an exercise group with a control group for 11 months (Lipchenko & Fomin 1987). The exercises included walking, cycling and exercise therapy; an increase in exercise capacity, reduced HR increment and a greater reduction in systemic peripheral resistance were demonstrated in the exercise group when compared with the control group (ibid). The benefits of exercise training were demonstrated in a controlled cross-over trial with a 20-25% increase in exercise tolerance, peak oxygen consumption and symptoms (Coats et al. 1990). Cardiac rehabilitation through exercise has been associated with a reduction in the debilitating symptoms caused by HF (ExTraMATCH Collaborative 2004).

Participating in exercise can have a positive effect on HF symptoms such as breathlessness, fatigue, palpitations and quality of life through effects on both the cardiovascular and musculoskeletal systems (McKelvie et al. 2002). Following participation in an exercise programme, studies have demonstrated improvements in various symptoms including fatigue (Coats et al. 1992; Kavanagh et al. 1996; Oka et al. 2000; Shephard et al. 1998); breathlessness (Coats et al. 1992; Kavanagh et al. 1996; Tyni-Lenne et al. 1999); and quality of life (Belardinelli et al. 1999; Willenheimer et al. 1998). Localized or systemic forms of exercise therapy could modify symptoms and benefit patients, possibly affecting disease progression and survival (Coats 2000). Monitoring patients responses to exercise can help patients get the most out of their exercise programme; monitoring autonomic function is a good way to facilitate this.

Participants with HF were coded as dippers (those who showed a lower rMSSD following exercise) and non-dippers (no dip in rMSSD following exercise). Twenty participants were coded as dippers 24-hours following reported exercise. Forty-eight hours following reported exercise, 28 participants were coded as dippers. This suggests that the change in rMSSD is best monitored 48-hours following training, as this is where the most significant changes were found with over half of the participants showing a dip in rMSSD. The effect of a single bout of exercise on resting HRV has not been explored at great length; however improvements in resting HRV following chronic exercise training have been demonstrated (Iellamo et al. 2000; Melanson & Freedson 2001; Seals & Chase 1989). An initial decrease in HRV following a single bout of exercise has been reported in healthy subjects (James et al. 2002; Javorka et al. 2002). Gladwell et al, (2010) demonstrated a decrease in rMSSD post-exercise, but this was only at 30-minutes. However Pober et al, (2004) demonstrated autonomic changes in healthy young males persisted for at least 22 hours following the termination of exercise. The present study has identified that HF patients, like their healthy counterparts, may also display a dip in HRV on the days following exercise training. The dip in rMSSD was only demonstrated in approximately 50% of participants. These results are therefore inconclusive; the absence of a dip in some participants may be explained by a lack of enough exercise intensity, as these patients were not involved in a structured exercise programme. Future research in both healthy and HF populations should assess how long autonomic changes persist following exercise by measuring continuously for at least 48-hours to gauge when these changes occur and determine what intensity of exercise is necessary in order to elicit these changes.

Exercise training load is the cumulative amount of stress placed on an individual during an exercise bout. TRIMP was developed by Banister et al, (1980) to provide a quantifiable measurement of exercise training volume and intensity in a single term. Periodization is the organization of phases of training at specific periods by alternating training to its peak. A decrease in HRV has been associated with the intense phase of periodization, also known as overreaching (Kuipers 1998). Uusitalo et al, (1998) suggested that normal training compared with excessive training may cause different changes in HRV and a decreased HRV may be a sign of fatigue. That study found a decrease in HRV in the first four weeks of intense training (seven days a week at 70-90% of Vo_2 max) compared with a control group.

In elite rowers, changes in cardiovascular autonomic modulation involving a switch from vagal to sympathetic predominance has been observed when going from lower to higher intensities (Iellamo et al. 2002; Iellamo et al. 2004). Pichot et al (2002), demonstrated that HRV reflects recovery status in untrained athletes, male rowers from the Italian national team (Iellamo et al. 2004) and elite Olympic weightlifters (Chen et al. 2011). Exercise at moderate-to-high intensity is associated with a significant delay in post-exercise recovery of HRV when compared with low-to-moderate exercise (Buchheit et al. 2007; Kaikkonen et al. 2007; Kaikkonen et al. 2008). Participants within the present study were encouraged to keep to their regular routine during the 28 measurement days. Most participants reported low-moderate exercise patterns, and therefore may not have undertaken enough exercise to cause a significant decrease in rMSSD following exercise.

Vagal related indexes such as rMSSD or the power density in the high-frequency range (HFr) obtained by spectral analysis are the most widely used methods for quantifying parasympathetic activation following bouts of exercise (Task Force, 1996). After 20-minutes of short-term exercise Arai et al, (1989) proposed that recovery of autonomic regulation occurs a few minutes following exercise. Following a major bout of prolonged heavy exercise a decrease in cardiac vagal outflow was demonstrated for several hours (Hautala et al. 2001). On the second day following prolonged heavy exercise an accentuated rebound phenomenon with enhanced vagal regulation was observed with large inter-individual variations of reduced vagal outflow at the time of recovery (ibid). This was characterized by a quicker recovery of altered autonomic function in those with better cardio-respiratory fitness when compared with those of poorer fitness. This suggests that the fitness level, intensity and duration of exercise have an effect on the amount of decrease observed in HRV following exercise, and how long it takes to return to pre-exercise levels.

Odds ratios demonstrated in the present study suggested that 24-hours after exercise was reported, participants were 1.007 times more likely to have a dip in rMSSD. After 48-hours participants were 0.976 times more likely to have a dip in rMSSD following exercise. This suggests that within the present study, there was no difference in the likelihood of a dip from one day to the other. To my knowledge, no other research has looked at the dip in HRV following exercise in HF patients. An initial decrease in HRV has been demonstrated within minutes or hours following exercise in several studies (Mourot et al. 2004b; Parekh & Lee 2005; Terziotti et al. 2001). Furthermore, it appears to take longer to restore vagal tone following a high intensity bout of exercise (80% Vo_2 peak) compared with moderate intensity exercise (50% Vo_2 peak) (Mourot et al. 2004b; Parekh & Lee 2005). This may begin to explain the findings of the present study. HF patients may start off with a lower HRV initially due to their condition. Lower baseline HRV may affect their capacity to recover, as this suggests they have a low cardiorespiratory fitness. Cardiorespiratory fitness has been demonstrated as a factor affecting recovery of HRV to pre-exercise values. Another factor was HF patientsô physical activity was undertaken at what they considered low intensity suggesting they did not perform enough exercise to cause any autonomic modulation. If participants with HF had completed high intensity exercise, greater autonomic modulation would be expected.

A markedly reduced HRV is an established symptom of HF and predicts poor prognosis (Bilchick et al. 2002; Nolan et al. 1992). Participants from all three NYHA classes included in the present study had an average HRV within the normal range cited for healthy participants (Nunan et al. 2010). Cardiac autonomic dysfunction often occurs with HF patients, and is displayed through a reduced HRV (Task Force, 1996). Elderly patients with HF are thought to have even more impaired HRV due to age-related autonomic dysfunction (Reardon & Malik 1996) and associated co-morbidities such as diabetes, hypertension and inflammatory conditions (Task Force, 1996)

With an aging population the prevalence of HF is increasing and will significantly affect costs in the public health system (Miche et al. 2009). Finding ways to combat and treat this growing epidemic are important to ensuring the health system can work at its best for years to come. Various exercise programmes may have different benefits for patients with HF. An increase in physical performance in elderly patients has been documented, however no clear recommendations on endurance versus muscle strengthening programmes have been outlined (Miche et al. 2009). There is a clear correlation between Vo_2 peak and performance in the six-minute walk test providing easy measurement and evaluation of stress tolerance in CHF patients (Guyatt et al. 1985). An increase in physical performance has been demonstrated in older patients (age 74 ±3) where after six months, peak Vo_2 and muscle strength significantly increased (Miche et al. 2009). Despite the benefits to cardiac rehabilitation, participation remains suboptimal (Dalal et al. 2010). In chapter eleven the effect of exercise measured by HRV (Ithlete) will be explored through a moderate walking rehabilitation programme.

9.4.1 Limitations

Within the present study there was a wide age range within the participants. Some participants had concerns about using the touch screen on the iPod device and despite practicing with the researcher were still not comfortable when they took the measuring kit home. This may have accounted for errors in taking and saving measurements. Participants were also asked to record their exercise activity daily in a physical activity diary. Participants had to choose a zone for the rate of intensity at low/moderate/high and this was a very subjective measure. For some patients this concept was hard to grasp as they did not have much energy to carry out their daily activities. They cited that everything they did felt like it was at high intensity because it took so much effort to carry out and this could have an affect on comparisons between participants due to the subjectivity of the measurement.

Quantifying the level of exercise with percent Vo_2 max or maximum HR could have provided more accuracy; however you would then need participants to measure their HR during each bout of exercise. This would be quite tedious for participants as they would need to wear a heart rate monitor for potentially most of everyday. This was seen as too intrusive for the present research study, and therefore the intensity zones were used instead. It is difficult to gauge how well participants adhered to the described intensity zones within one exercise, therefore, they were asked to pick the zone within which they thought they were exercising within most during each exercise bout. There was however a large range of activity levels within the participants which helped to counter that effect.

9.5 Conclusions

Ithlete measurements of rMSSD and HR in HF patients were undertaken on a consistent basis for one-month for 46 patients. Of those 46 participants most reported that the device was easy to use and most did not have any trouble taking measurements on a daily basis. The remaining participants took no measurements or part measurements, where they either just did Ithlete recordings or only filled in the calendar. A dip in rMSSD following reported exercise was found in more than 60% of participants after 48-hours; 24-hours after reported exercise a dip was found in less than 50%. These results were somewhat inconclusive; however a lack of sufficient exercise intensity most likely played a role. Future research on the effects of exercise on HRV over various time periods with a large cohort of participants could be very beneficial in the assessment of the effect of exercise on the body over time. For patients with HF, this device can be explored for use in the clinical setting to provide patients and clinical staff with feedback on autonomic function. Ithlete appears to be an easy device to use for HRV assessment. Ithlete is also cost efficient when compared to other medical devices and provides feedback to the user which can be easily interpreted making it an ideal device for clinical research.

9.6 References

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CHAPTER 10: ADHERENCE, REFERENCE VALUES AND USER ASSESSMENT OF ITHLETE HEART RATE VARIABILITY (HRV) MEASURES FOR PATIENTS WITH HEART FAILURE

Short-term heart rate variability (HRV) measurements are the type most commonly used to non-invasively investigate cardiac autonomic function and provide as much information as long-term measurements. Impaired autonomic function, characterized by decreased HRV has been demonstrated in clinical populations when compared with healthy counterparts. Telemonitoring is a new diagnostic modality which records physiological data (i.e. HRV, blood pressure), and is used as a tool to monitor patients in their home. Telemonitoring is commonly used in the heart failure population for early detection of worsening heart failure (HF) symptoms and to help reduce rehospitalisation. The ease of use for a telemonitoring device is important to ensure that subjects can use the device consistently and supply reproducible results. Ithlete is a novel telemonitoring application for HRV measurement on a smartphone or Apple iPod touch.

The aims of the present study were to (i) assess the adherence of HF patients to daily measurement of HRV root mean of square successive difference (rMSSD) and heart rate (HR) in beats per minute (bpm) using Ithlete software (ii) establish reference values for patients with HF. User assessment through questionnaires was also completed to examine how patients felt about using the device daily. HRV values were also analyzed by looking at covariates such as comorbidities and medication to see what effect, if any, they had on adherence and HRV measurements.

Ninety percent of HF participants using Ithlete for daily measurement reported that they were able to use the device without any major issues. Ithlete measurements in HF patients were undertaken on a consistent basis for at least twenty-eight days for forty-six patients (44.6%). Males were no more likely than females to comply with the study protocol. Patients with comorbidities such as ischaemic heart disease or dilated cardiomyopathy were statistically no more or less likely to complete measurements. The average rMSSD for HF patients was marginally lower than those reported for healthy participants in chapter eight. The coefficient of variation for healthy participants was 10.9, compared with 25.1 for patients with HF; the difference between them is statistically significant at $p = 0.014$. The majority of patients reported Ithlete was easy to use, an efficient use of time and recommended its use for other patients. The touch screen was reported as easy to use and getting in and out of the measurement application was also easy. The Ithlete device is cost efficient when compared to other medical devices; providing immediate feedback to the user which is easy to interpret makes Ithlete an ideal telemonitoring device.

10.1 Introduction

10.1.1 HRV

The effective use of HRV to monitor how the body responds to exercise has been demonstrated (Kiviniemi et al. 2007; Kiviniemi et al. 2010). Measurement time has varied throughout the years; however research has demonstrated that short term measurements are found to be as valid as long term measurements (Nunan et al. 2009; Task Force. 1996). There are several devices on the market that can be used for short-term HRV measurements including Polar, Suunto, Biopac HRV, and most recently Ithlete. Of the devices, Ithlete is unique because it is compatible with smartphones, tablet PCs and the Apple iPod touch by attaching an ECG dongle into the headphones jack of those devices. Ithlete is a software application designed to measure heart rate variability (HRV) as root mean square of successive difference (rMSSD) (ms) and heart rate (HR) in beats per minute (bpm). Measurements take one minute and are advised to be taken first thing in the morning.

The rMSSD measure has been suggested as superior to spectral methods of HRV assessment due to its sensitivity to vagal cardiac control (Penttilä et al. 2001); and is less sensitive to variations in respiratory patterns (ibid). The mean rMSSD value for 529 heart failure (HF) patients was reported as 21.5 ± 12.3 with a mean age of 62.0 ± 9.6 (Nolan et al. 1998). Another study reported mean rMSSD as 20 ± 2 in 59 HF patients (Brouwer et al. 1995), while a study looking at sudden cardiac death in HF found rMSSD values at 22.9 ± 14.9 (n=135) in survivors and 21.1 ± 13.2 (n=55) non-survivors (Galinier et al. 2000).

Validity of a measurement is the extent to which the variable measures what it is intended to. Several studies have assessed the validity of HRV on several heart rate monitor devices against ECG and Holter devices (Gamelin et al. 2006; Porto &

Junqueira Jr 2009; Weippert et al. 2010). HRV was declared a reliable and reproducible technique for assessing autonomic activity by Nolan et al, (1998); but the reproducibility of HRV has been highlighted throughout literature as an important area for further research (Leicht & Allen 2008; Sandercock et al. 2005; Task Force. 1996). Reproducibility has been studied in both adults and children with intriguing results. In children, one study found the reproducibility of HRV was poor with a low coefficient of variation (Winsley et al. 2003); while other studies found significant differences in HRV when comparing children by age (Goto et al. 1997), and exercise (Mandigout et al. 2002). In adults however, good reproducibility of HRV has been demonstrated in several different measurement durations including 24-hours (Pinna et al. 2007), 48-hours (Amara & Wolfe 1998), 1-2 weeks (Schroeder et al. 2004), and 2-6 months (Kowalewski & Urban 2004). Traditionally, HRV research was confined to ECG systems or Holter monitors, which require trained personnel for operation, are expensive and time consuming (Nunan et al. 2009). The development of ECG telemetry on wireless heart-rate monitoring systems allows for field-based assessment. In patients with HF, improving the follow-up of patients care at home could reduce the amount of acute hospitalizations (Maggioni et al. 2010).

10.1.2 Telemonitoring

Telemonitoring is a new diagnostic modality which records physiological data (i.e. blood pressure, body weight, HR, HRV), and has been shown as beneficial for patients with HF (Clark et al. 2007; Clarke et al. 2011). Data is transmitted remotely using a computer, mobile phone or telephone line for review by a clinician or research staff (Giamouzis et al. 2012). Telemonitoring can also be regular structured telephone calls, with or without the transfer of physiological data, between patients and clinicians (McAlister et al. 2004). Telemonitoring in chronic heart failure (CHF) patients has been reviewed by several studies (Chaudhry et al. 2007b; Clark et al. 2007; Clarke et al. 2011; Giamouzis et al. 2012). Overall telemonitoring appears to be a favourable intervention in patients with CHF (Giamouzis et al. 2012); with all studies reporting improved quality of life for patients. There are however some conflicting results published; two large multicentre studies concluded that telemonitoring did not have a significant effect on death or rehospitalisation rates (Chaudhry et al. 2010; Koehler et al. 2011). Telemonitoring has also been linked with reduced costs when compared with usual care, ranging from 1.6% to 68% (Seto

2008). Three factors have been suggested as necessary criteria for telemonitoring to work. The first involves efficient transmission of physiological variables which would reflect early phases of decompensation (Mortara 2012). Second, data received should be translated into specific recommendations and third, patients must implement the recommended interventions (ibid). For successful telemonitoring, patient implementation can be coupled with their ability to continuously adhere to those recommendations over a specific period of time.

10.1.3 Adherence to telemonitoring in heart failure patients

Adherence is defined as the amount to which an individualôs behaviour complies with the healthcare providers recommendations i.e. medication, lifestyle changes etc. (World Health Organization 2003). Three categories to evaluate adherence to a prescribed therapeutic regimen were suggested for measuring the adherence to hypertensive medication (Cramer et al. 2008; World Health Organization 2003); and can be used on a wider scale for other therapeutic interventions such as exercise (Conraads et al. 2012). Patients who adhere to at least 80% of the prescribed regimen are the first category; patients who adhere to <20% of the prescribed regimen are the second category; and the third category consists of those patients in-between (ibid). Conflicting results have been published regarding adherence rates to telemonitoring in patients with HF. Low adherence rates were demonstrated in a large scale study of (n=1653) HF patients, where 14% never used the telemonitoring system and 55% used the system at least three times/week by the final week of the trial (Chaudhry et al. 2007a). Scherr et al, (2009) reported high adherence rates among HF patients in the telemonitoring group at 95%. In a more recent study on telemonitoring using mobile phones with HF patients, 89% of patients took measurements at least three times/week (Seto et al. 2012).

10.1.4 Establishing reference values for HRV

To ensure HRV measurements are reliable it is important to maintain consistency in data collection methods, data treatment and study population (Sandercock et al. 2005). Studies that look at reliability demonstrate reduced reliability in clinical populations when compared to healthy subjects (Sandercock et al. 2005). Good reliability in the HRV measures within the clinical population should be established by ensuring the measurement has been validated in that population in previous literature (Sandercock 2007a).

A measurement is considered reliable when there is a small degree of change in the measure at separate occasions, under the same conditions (Nunan et al. 2009). Despite the use of HRV by thousands of authors globally, there is no adequate consensus on concurrent retest reliability (Sandercock 2007b). Reliability and reference values of HRV have been assessed in several previous studies (Amara & Wolfe 1998; Guijt et al. 2007; McNarry & Lewis 2012; Nunan et al. 2010; Pinna et al. 2007; Sandercock et al. 2005; Schroeder et al. 2004; Sinnreich et al. 1998; Winsley et al. 2003); however there is still no consensus on what changes in HRV are of clinical significance (Pinna et al. 2007). There is also a need to establish what represents a normal value of HRV in different populations on which sample size estimates can be based on for future research (Sandercock 2007b). What has been demonstrated is that HRV indices (especially spectral measurements) appear to have a large inter-subject variation, and due to a variety of interventions, demonstrate very large effect sizes (ibid). This suggests that HRV indices are not very reliable but are very changeable, making them suitable for serial measurement particularly within individuals (Sandercock 2007b).

Short-term HRV measurements provide as much information as long-term measurements (Bigger et al. 1993). Short-term measurements of HRV are the type most commonly used when investigating cardiac autonomic function non-invasively (Pinna et al. 2007). When comparing different HRV measures, time-domain values demonstrate adequate homogeneity but spectral measures appear to be mainly heterogeneous (Sandercock 2007a). Random variation represented a small proportion of the between subject variability for most HRV parameters, and sample size determination for experimental work was recommend to be based on the parameters with the lowest variation, of which rMSSD was listed as one (Pinna et al. 2007). There is an expected level of variation as short-term parameters of HRV are subject to day-to-day random variations (ibid). Between subject variability is not caused entirely by random error, but instead represents the differences in each subjects true value (Pinna et al. 2007). Therefore making repeated measures on the same subject provides us with a within-subject coefficient of variation, and provides better reliability.

Respiratory sinus arrhythmia is the natural occurring variation in HR that takes place during the breathing cycle. The use of paced breathing within the Ithlete measurement tool is designed to assist participants by providing a breathing pattern for them to follow on screen which maximizes their RSA response. The relationship between HR and respiration has been studied for several years (Kobayashi 2009). Both the depth and frequency of respiration have an impact on RSA. Research has also focused on the relationship between HRV and paced breathing and found differing results. Kobayashi (2009) found that it provides limited improvement in the reproducibility of HRV and suggested that simply reminding participants to avoid irregular inspiration during measurement was enough. Synchronizing breathing rhythm is known as paced breathing and has been undertaken in research studies using a metronome. Changing someoneᾰs breathing pattern may not be optimal for measurement. Those who are not used to it may feel uncomfortable and therefore this may have a negative effect on measurement. Several studies have tried to identify the best breathing pattern for optimal heart rate variability measurements (Bernardi et al. 2000; Fang et al. 2008; Guzik et al. 2007; Hirsch & Bishop 1981; Kobayashi 2009; Kox et al. 2011; Maestri et al. 2010; Pinna et al. 2006) with conflicting results. Paced breathing may (Bernardi et al. 2000; Driscoll & Dicicco 2000; Pinna et al. 2007) or may not (Hirsch & Bishop 1981; Kobayashi 2009; Kox et al. 2011; Maestri et al. 2010) increase reproducibility of HRV measurements. It is therefore essential to strike a balance.

Evidently the best way to obtain totally reproducible methods is to control everything within a laboratory for several hours; however in most circumstances this is not practical. Finding innovative ways to perform short-term measurements in the comfort of the participantᾰs home using the same or similar circumstances such as measurements taken first thing in the morning before they have had anything to eat or drink and under the same breathing pattern can go a long way to ensuring reproducibility. For measurements to be completed regularly in the clinical population they need to be realistic and practical, trying to ensure as little inconvenience as possible to the participant. The Ithlete device fulfils these criteria, with daily result charting, short one-minute measurements, a fixed breathing pattern to maximize RSA and an easy to use interface.

10.1.5 Aims

The primary aims of the present study were to (i) assess the adherence of HF patients to daily measurement of HRV (rMSSD) and HR (bpm) using Ithlete software; (ii) to establish reference values for rMSSD in patients with HF using the Ithlete software. User assessment was also undertaken to examine how patients felt about using the device daily and what impact it had on their care if any. HRV values were also analyzed by looking at covariates such as comorbidities and medication to see what effect, if any, they had on adherence, rMSSD, and HR measurements. Consistent HRV Ithlete measurements and positive patient feedback would demonstrate the usability of Ithlete within clinical populations.

10.2 Methods

10.2.1 Recruitment of participants

The researcher attended clinics with either a Consultant Cardiologist or Heart Failure Nurse Specialist at three London hospital sites. Each participant was recruited in accordance with NHS Research Ethics Committee standards and expectations. Participants responded in the clinic or by phone and were sent an information pack before agreeing to participate. The information pack included:

1. An information sheet with detail of the requirements for each participant before and during the laboratory visit
2. An informed consent form
3. HRV measurement information package
4. A detailed demographic information sheet

Participants were requested to read the information pack prior to attending the clinic to meet with the researcher and any questions or concerns were addressed. All procedures were approved by the local research ethics committee.

10.2.2 Participants

One hundred and three participants responded within the clinics and agreed to participate in the study of which n=70 were male and n=33 were female. Participant ages ranged from 24 to 87 years with an average of 62.7 ± 17.9. All participants were defined as heart failure patients with varying levels of impairment but all were deemed suitable for the study by the medical team at the hospital they attended.

Inclusion Criteria: The participants were heart failure patients within the New York Heart Association classifications of I, II & III aged at least 18 years of age. Heart failure treatment was under the control of the participant's consultant cardiologist.

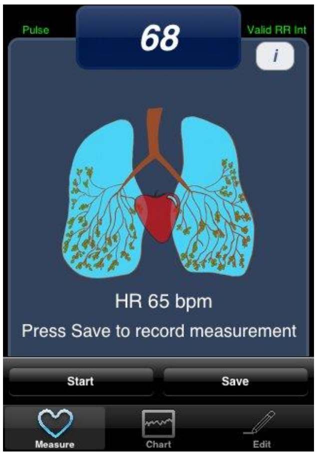
Exclusion Criteria: Participants were excluded if they had any of the following conditions: Consistent atrial fibrillation, unstable coronary artery disease with revascularization within the last 6 months or planned revascularization, planned heart valve surgery or planned transplantation, uncontrolled arterial hypertension, acute myocarditis, worsening clinical condition, inability to read the display of a handheld device or deemed unable to comply with home telemonitoring; inadequate understanding of English; any visual or cognitive impairment sufficient to interfere with the participant's ability to use the device (Cleland et al. 2005; Dar et al. 2009; Scherr et al. 2009). Participants completed their consent form in front of the researcher and the researcher countersigned the form.

10.2.3 Instrumentation and data acquisition

HRV (rMSSD in ms) and HR (bpm) were recorded via the Ithlete software for the iPod touch (Ithlete 2009). The breathing frequency was set at 7.5 breaths per minute, designed to maximize RSA response (Brown et al. 1993). Each measurement took 1-minute, when this was complete the HR (bpm) and HRV (rMSSD in ms) were displayed on the screen and saved to the device. Ithlete recordings were transferred to a password protected PC via Ithlete software which enables recordings to be emailed and saved into an excel document.

Patients were asked to record for one minute and the readings should be taken first thing in the morning. After using the device for at least 28 days (to provide within-subject coefficients of variation), participants were asked to fill in a questionnaire regarding their use of the device. Patients were given the option to fill out the questionnaire with the researcher posing the questions or by them filling it out themselves in the clinic room. A picture of the measurement screen is displayed below in figure 10-1.

Figure 10-1 Screen shot of Ithlete software on an iPod touch



10.2.4 Experimental design

Following appropriate ethical approval from the NHS Southwest Research Ethics Committee and informed consent, participants were asked to visit the clinic at their hospital to meet with the researcher for a demonstration. Each participant was given a demonstration of how to use the Ithlete software on the iPod touch and required to complete two measurements in the presence of a researcher before taking the device home. Then each participant was required to take an HRV measurement once every morning when they woke up for one month (at least 28 days). Each day participants were asked to fill in a physical activity calendar where they were asked to record the following:

1. What (if any) exercise was performed the day before
2. Duration of that exercise
3. Intensity of that exercise (Low/Moderate/High)
4. Daily scale of how you are feeling on a scale of 0-100% (100% being the best)

Low-intensity aerobic activity was described as not working hard enough to raise your heart rate or break a sweat. Moderate-intensity aerobic activity was described as working hard enough to raise your heart rate and break a sweat, yet still being able to carry on a conversation. High-intensity aerobic activity was described as breathing hard and fast, heart rate increasing substantially. At this intensity, participants would not be able to say more than a few words without pausing for a breath.

10.2.5 Heart rate variability analysis

Heart rate variability measurements were taken using an iPod touch with the Ithlete application (Ithlete 2009). For HRV measurement a standard analogue ECG chest strap was worn in the middle of the chest just under the sternum. Using the Ithlete software for the iPod touch, participants measured HRV for one minute each morning when they woke up.

Real time heart and lung animation on the iPod touch facilitated paced breathing during measurements and indicated reception of each heart beat from the analogue chest strap. Participants followed a breathing frequency of 7.5 breaths per minute, designed to maximize RSA response (Brown et al. 1993). When the one minute measurement was complete the HR (bpm) and HRV (rMSSD) were displayed on the screen and saved to the device.

10.2.6 Statistical analysis

All statistical analysis was completed using PASW 19.0 (SPSS: An IBM Company. Somers, NY, USA). Values are reported in the text as mean ± standard deviation. Chi-square analysis was completed to determine patient adherence to the study protocol. The coefficient of variation was calculated and used to determine variation in HRV/HR by gender and NYHA class and which medications should be covariates for binary logistic analysis. Univariate analysis was used to quantify the relationship between patient characteristics such as comorbidities and medications with their measurement results. Binary logistic regression was then performed on the change in HRV on the day immediately following training/non-training and two days following exercise/non-exercise with analysis controlling for comorbidities and different HF medications. A P-value of <0.05 was considered statistically significant.

10.3 Results

Forty-six out of 103 participants completed measurements successfully for at least one-month, of which eight were female and 38 were male (28% of the total female population within the study and 50.7% of the male population). The average age of participants who completed HRV Ithlete measurements and their physical activity calendar was 64 ± 13.8 for males and 59 ± 26.1 for females. Participantsô measurements were deemed unsuccessful if they had less than half of the recordings complete for the amount of time that they had the device, with no more than two days in a row of HRV measurements missing. The average age of those who did not complete measurements was 67.0 ± 13.7 for males and 73.4 ± 13.7 for females. For both genders, the average age was higher in those who did not complete measurements. This however was not a statistically significant difference (p= 0.286).

10.3.1 Questionnaires

Questionnaires were completed by patients when they returned the device back to the researcher after the first month of use. Results are seen in table 10.1.

Table 10.1 Questionnaire answers (n=87 of 103 patients)

Questions: Use of the Device	**Yes**	**No**	**Undecided**
1. Did you find the touch screen buttons easy to use?	85%	15%	-
2. Did you have any trouble turning the device on?	0%	100%	-
3. Did you have any trouble getting into the Ithlete application?	15%	85%	-
4. Did you have any trouble starting the measurement phase?	25%	75%	-
5. Did you have any trouble saving the measurements?	35%	65%	-
6. Were you able to flip between screens to see if your measurement saved?	70%	30%	-
Questions: Use of the Chest Strap	**Yes**	**No**	**Undecided**
1. Did the chest strap fit appropriately?	95%	5%	-
2. Did you have any problems connecting the strap?	85%	15%	-
3. Did you need to wet the sensors in order for it to register your heart rate?	90%	10%	-
Questions: Charging the Device	**Yes**	**No**	**Undecided**
1. Did you have any problems charging the device?	2.8%	97.2%	-
2. Approximately how often did you need to charge it?	3.8 ± 3.2 times/month		
Questions: Overall Use	**Yes**	**No**	**Undecided**
1. Did you enjoy using the device?	89.5%	5.2%	5.2%
2. Would you recommend use to other patients?	100%	-	-
3. Did you find the measurements too time consuming?	5.8%	94.2%	-
4. Is there anything about the device that you would recommend changing?	See comments below		

Patients expressed a few comments regarding the Ithlete device. Most enjoyed using the device and found the feedback helpful. Some issues cited were as follows:

- Better strap needed, contact was on and off so had to wet it several times in order to get a recording
- Ithlete dongle came loose at times (n=2)
- Saving measurements should be automatic (n=7)
- Sometimes no measurement came up after the minute was completed, or the device said irregular rhythm, please try again which could be quite frustrating

- Should just have one application on the main screen so as not to confuse users
- Not enough time to use it in the morning, would be better if measurements could be taken at any time of day (n=4)
- Moving between screens could be confusing
- Iôm old fashioned so using a touch screen is hard to get the hang of
- Touching the screen softly helps get the device working easier
- Not good for mornings because I have young children
- Good feedback to patients
- Should input exercises into the iPod touch as well as one programme
- Screen was hard to see first thing in the morning as Iôm old
- Easier strap, easier buttons on the device
- Device may be too hard to use for older people because you need to have steady hands
- Too complicated for an old man who lives alone

10.3.2 NYHA classifications and comorbidities

The percentage of HF participants with different comorbidities can be found in appendix III. Forty-six out of 103 participants completed the HRV Ithlete measurements and completed a calendar for one month. Table 10.2 displays the raw mean rMSSD, HR and TRIMP for each NYHA class, along with the mean age for each group and gender breakdown. As a whole, the mean age of those patients who completed measurements were 59.4 ± 18.5 compared with 66.3 ± 16.6 for those who did not complete measurements.

Table 10.2 Patient characteristics by NYHA classes including raw rMSSD and HR measurements

NYHA Class	Gender	Age	Mean HRV rMSSD (ms)	Mean HR (bpm)	Mean TRIMP
I	M- (8) F- (3)	64.6 ± 12.5	81.4 ± 10.2	81.5 ± 10.2	94.6 ± 56.7
II	M- (16) F- (4)	60.5 ± 12.1	72.4 ± 11.3	82.2 ± 13.2	135.38 ± 94.4
III	M- (15) F- (0)	63.3 ± 12.5	75.4 ± 12.3	84.7 ± 6.1	110.55 ± 82.6

Chi-square analysis results for patient adherence to Ithlete measurements for at least 28 days are displayed in Table 10.3. Table 10.4 displays the amount of patients assigned to the three suggested adherence categories discussed in the introduction. Of the patients that did complete measurements 39.5% have dilated cardiomyopathy, 37.2% have ischaemic heart disease, 23.3% have hypertension, and 9.3% have diabetes mellitus. Those comorbidities were controlled for with binary logistic regression analysis to examine if they had any significant association with HRV. For those patients who failed to complete measurements, 32.8% have cardiomyopathy, 38.8% have ischaemic heart disease, 21.0% have hypertension and 9.0% have diabetes mellitus. These percentages are very similar to those of the patients who completed measurements. A chi-square test demonstrated no significant differences between the two groups at X^2 (1, n=103) = 0.42, p= 0.52 for cardiomyopathy; X^2 (1, n=103) = 0.11, p= 0.74 for ischaemic heart disease, X^2 (1, n=103) = 0.10, p= 0.75 for hypertension and X^2 (1, n=103) = 2.36, p= 0.13 for diabetes. This demonstrates that nearly 50% of patients had ischaemic heart disease, cardiomyopathy or both and that having comorbidities made patients no more or less likely to complete measurements.

Table 10.3 Number of patients who adhered to the study protocol

Gender	Completed	Not completed
Male	41	34
Female	13	15

Table 10.4 Patient adherence groups for each gender

Gender	Completed > 80% of measurements (%)	Completed 20-80% of measurements (%)	Completed < 20% of measurements (%)
Male	64.1	26.6	9.3
Female	25.1	28.5	46.4

Chi square analysis revealed that males were no more likely than females to comply with the study protocol X^2 (1, n=103) = 0.56, p= 0.46. A one-way ANCOVA was then performed to evaluate the differences in raw rMSSD values between NYHA classes while controlling for age and gender. The homogeneity of regression assumption was tested first to evaluate the interaction between the covariates (age and gender) with NYHA class in the prediction of rMSSD. This interaction was not significant F (3, 35) p=0.607. The results of the one-way ANCOVA F (2, 38) = 1.49, p=0.24 showed that the differences in raw rMSSD values between NYHA classes were not statistically significant. There was no statistically significant difference between the amount of exercise (TRIMP) between NYHA classes as determined by one-way ANOVA (F (2, 43) = 0.932, p = 0.402).

10.3.3 Coefficient of variation

Table 10.5 displays the coefficient of variation (CV) of rMSSD, HR, TRIMP and DS for each gender. Table 10.6 displays the CV for rMSSD, HR, TRIMP and DS for each NYHA class. Leveneˆs F test determined significant differences in rMSSD between males and females, and NYHA classes II and III at p=0.01 and p=0.05 respectively. There were no female participants classified as NYHA class III, suggesting that gender did not have an impact on the difference between NYHA classes.

Table 10.5 Coefficient of variation for rMSSD, HR, TRIMP and day scale for each gender

Gender	rMSSD	HR	TRIMP	Day Scale
Males	26.6*	6.8	89.0	30.0
Females	13.7*	7.1	60.8	27.8

*Significant difference at F <0.05

Table 10.6 Coefficient of variation for rMSSD and HR for each NYHA class with mean TRIMP values

NYHA Class	CV for rMSSD	CV for HR	CV for TRIMP	CV of DS
I	20.7	7.4	94.4	22.5
II	17.5*	6.8	77.9	19.8
III	36.9*	6.6	88.1	47.6

*Significant difference at F <0.05

The CV for rMSSD classified in groups by various HF medications and any comorbidity present in at least 10% of the current studyŝ patient population can be found in appendix II. No significant differences were demonstrated between patients on any medication versus those who were not. There were also no significant differences demonstrated in rMSSD between those with dilated cardiomyopathy, hypertension, ischaemic heart disease or diabetes mellitus versus those who did not.

10.3.4 General linear model: Univariate analysis and Analysis of covariance (ANCOVA)

Univariate analysis revealed that after 24-hours rMSSD in patients with HF were not significantly affected by training (p=0.70). The F value for rMSSD on the day after training was 0.137. The rMSSD 48-hours after training was also not significantly affected (p= 0.06) with an F value of 1.978. ANCOVA controlled first for NYHA class (p= 0.70), then for age (p= 0.98) and then finally for gender (p= 0.92) demonstrated no significant differences in rMSSD following training. ANCOVA controlling for all three variables also demonstrated no significant difference (p= 0.98) in rMSSD following training.

10.4 Discussion

The aim of the present study was to assess the adherence of HF patients to daily measurement of HRV (rMSSD) and HR using Ithlete software, while also establishing reference values. Patients answered questionnaires, which assessed how patients felt about using the device daily and what impact they felt it had on their care. Covariates such as comorbidities and HF medications were controlled for in analysis of covariance to see what effect, if any, they had on adherence, rMSSD, and HR measurements.

10.4.1 HF patient's adherence to the study protocol

In the present study, 45% of 103 participants complied with the study protocol by taking daily Ithlete measurements for one month. When separated into the three suggested adherence groups, 40 patients completed over 80% of measurements (38.8% of total participants). Twenty-five percent of the female patients recruited completed over 80% of the measurements, compared with 44% of male patients recruited. Chi square analysis revealed that males were no more likely than females to comply with the study protocol X^2 (1, n=103) = 0.56, p= 0.46. The reported general adherence of HF patients to medication ranges from 10% (Monane et al. 1994) to 98.6% (van der Wal et al. 2006). This is compared with only 35% compliance with regular weighing (at least three times a week or daily) (van der Wal et al. 2006) and low compliance reported by several other studies (Artinian et al. 2003; De Geest et al. 2003; Ni et al. 1999; Strömberg et al. 2003). Compliance to exercise has also been reported as low in several studies (Artinian et al. 2003; Evangelista et al. 2003; Ni et al. 1999; van der Wal et al. 2006), suggesting that patients adhere well to some aspects of their care better than others.

Previous studies with similar telemonitoring, involving the use of an electronic machine at home recorded higher results; 95% adherence of 120 patients doing daily measurements of blood pressure, heart rate and body weight (Scherr et al. 2009), 461 patients completed 81% of vital signs transmissions and 95% of cardiorespiratory readings (Mortara et al. 2009), and 70% of 50 telemonitoring patients completed at least 80% of required recordings (Seto et al. 2012). Therefore for the present study, a higher compliance was expected. Poor completion results were discussed with the medical teams at each hospital; possible reasons suggested included the lack of automatic save for the first portion of the study, diminishing resources through the NHS budget for supporting patients with HF (specifically the lack of an established cardiac rehabilitation programme at the main hospital site), language barriers (large population of foreign participants) and lack of patient contact. In other telemonitoring studies, patients send information directly to the clinicians who monitor their measurements concurrently. Within the present study measurements were only collected once a month, possibly affecting results. Data collection at shorter intervals may have motivated more patients to keep up with the measurements. Alternatively, patients did not have to send data in regularly (weekly) via the internet, sparing them the need to learn how to transmit data. The researcher initially thought this would be easier for the patient, however some patients reported that they would have liked sending the information and thought it would be more encouraging for them to take measurements daily knowing it would be transmitted each week. Other telemonitoring studies demonstrate conflicting results when comparing age, gender and ethnicity, with no difference in use of daily monitoring between those groups (Dar et al. 2009). In the present study significantly more males participated, statistical analysis was completed to control for gender and age and will be discussed in the following paragraph; ethnicity data were not collected in this cohort of participants.

Reasons cited by patients for not complying with the study protocol predominantly related to time or incorrect use of the device (especially not saving measurements correctly). After the first 11 months of the study, the developer introduced an automatic save feature which prompted users to save at the end of each measurement. This was as a direct result of the feedback that the researcher received from questionnaires as this appeared to be the main barrier cited by patients who had not achieved correct measurements. Despite clear verbal and written instructions, many users were under the impression that they had saved the measurement but when the device came back there were no recordings or only a select few despite patients stating that they had taken measurements each day.

More males were recruited than females, and so consequently more males completed measurements. This is not unusual because there is a higher prevalence of heart failure in males (Mehta & Cowie 2006; Stromberg & Martensson 2003); at two London hospitals, the Heart Failure Specialist Nurses clinics are thought to be composed of more male patients than females (approximately 80/20%), which accounts for why more males were recruited. Chi-square analysis revealed that males were no more likely than females to comply with the study protocol. Overall males did however appear to be more open to participating in the research study when approached. The research team speculated this was due to a number of reasons. Male patients tended to be older and already retired, therefore potentially had more free time, they also took to the device quicker during demonstration and seemed generally more interested in trying out an iPod touch. After discussing this with the Consultant Cardiologist and Heart Failure Specialist Nurse, they both thought this was related to the rapport with the clinician or the patientôs previous experiences of research in healthcare.

10.4.2 User assessment of usability

There were significantly less female participants in the study. Many female patients who were asked to participate in the study did not agree to take part compared with men when asked. Some women cited that they were too busy with their family or work to do measurements every morning (mainly women who had children to take care of in the morning before other obligations like work). Patients were reassured that the requirement was only approximately 2-5 minutes each morning. Some would then see the device demonstration but still would not commit to participating. Others said that they were not comfortable using the technology and did not want to try it. Of the men that did not want to participate they were also either apprehensive about the time commitment or did not think they could handle the technology. Despite being reassured by both the researcher and the heart failure nurse, many chose not to even try taking the device home, because they did not think they could use it appropriately. Patients were offered a demonstration and given the opportunity to try using Ithlete on an Apple iPod touch themselves. However many did not try taking the device home. This process was frustrating and not an expected outcome. In future further emphasis on the benefits of daily measurement and the impact it could have on clinical care by both the researcher and the clinician may help to convince patients to try out the device before making judgments. Perhaps explaining the prognostic value of HRV in HF might help convince patients of its importance and potential to help them improve their disease state.

Just under half of the patients (44.7%) did not fill in the physical activity diary (PAD) completely, citing reasons such as it was too time consuming or too tedious. Some took the device home, took measurements but returned it without the PAD. In these cases patients were asked why they did not fill in the PAD and some of the responses stated that filling in their physical activity daily took too much time; or they often forgot to fill it in for a few days and then were unable to recall what physical activity they had completed. Some patients brought the PAD back incomplete but had filled in certain days that they remembered. These diaries were still used if the participants took at least 10 days of readings with corresponding physical activity information. Some patients mentioned that they had trouble choosing which activity to put down each day.

Participants were asked to write down one exercise a day, whatever they thought was the most strenuous on the body. Participants were asked to fill in the PAD daily (recording the information for the day before each morning when taking an Ithlete measurement). On the PAD for each day there was a space to record the highest intensity exercise, duration of the exercise and day scale. Intensity was classified as low/moderate/high and day scale was how the patient felt generally throughout the day on a scale of 0-100. To try to improve PAD compliance and reduce subjectivity, patients discussed an average week of activities with the researcher and assigned intensity numbers to those activities to help facilitate their understanding of the different levels.

The number of patients who completed the PAD was also less than expected, but this may be due to the use of a paper exercise diary, instead of inputting their exercise into the device. Fukuoka et al, (2011) assessed compliance with a mobile-phone based PAD with pedometer use and found that 88.3% of participants completed diary entries. Poor accuracy of recall and poor real-time compliance of patients with diaries mean there is a potential lack of confidence in validity (Stone et al. 2003). Within the present study 55.3% of patients completed their PAD. However this did not comply with the number of Ithlete measurements taken. This is a similar finding to Stone et al, (2002) where compliance with paper diaries were examined with an electronic diary. Reported entries into the paper diary suggested 90% adherence compared with actual compliance which was recorded by the electronic diary at only 11%. A centre-based cardiac rehabilitation (CR) programme would prove advantageous as clinicians could observe and monitor first-hand patient exercise adherence, intensity of exercise and duration. CR programmes typically run for approximately eight weeks, following that patients are encouraged to keep exercising with little guidance on what to do next. Using Ithlete long-term could help patients monitor their own exercise and recovery while providing feedback on their recovery from exercise. Following a CR programme where Ithlete was utilised, patients could track their progress and feed it back to clinicians. This could also help encourage patients to keep active by providing accountability to the clinical team. In the absence of a centre-based CR programme, Ithlete could be utilised for home-based programmes by providing feedback to both the patient and clinician on how the patient is responding to the programme. With the decreasing amount of NHS resources in real terms however, programmes such as this are unlikely and therefore alternative ways must be found and utilized. The problem is that preventative work like this is hard to justify economically when budgets need to be cut because you cannot quantify the savings, only predict what the potential savings could be.

Standardizing measurement conditions as much as possible are imperative for ensuring usability and reproducible measurements. With Ithlete measurements specifically, participants were asked to take measurements first thing when they woke up daily, in a seated position. Ninety percent of HF participants using Ithlete for daily measurement reported that they were able to use the device without any major issues. Participants reported that the device was easy to use and not too time consuming. The touch screen was reported as easy to use and getting in and out of the measurement application was also easy. Patients were encouraged to take a second measurement if the HRV or HR looks drastically different to their normal readings. The device reports when more than one measurement is taken in one day, which allowed the researcher to remove some outliers if patients took more than one measurement.

Overall 89.5% of patients reported that they enjoyed using the device, 100% of patients said they would recommend the device to other patients and 94% stated that the measurements were not too time-consuming. This is despite just over half of these patients not taking complete correct measurements (this includes not taking any measurements, not taking enough measurements or not completing the physical activity diary). Overall that is a very positive outlook and bodes well for the use of Ithlete in future clinical practice. The issue remains that there was a lower completion rate than expected regardless of the positive feedback received and ease of use patients reported. We are not entirely sure why this has occurred, but speculate it is partially due to the older population used within the present study. The device is gaining popularity with athletes looking to improve performance and inhibit overtraining; perhaps the patient population needed more information about the potential benefit to their health and lifestyle.

The device is both easy to use and cost effective when compared to other medical devices of the same nature. The cost of the Ithlete kit (iPod touch + charger, Ithlete dongle, ECG chest strap) is approximately £230. This is considerably cheaper than other measurement devices typically used within the HF population for home telemonitoring; e.g. Honeywell HomMed Sentry system has been used in various studies (Alaoui et al. 2003; Dar et al. 2009; Levine et al. 2006; Martínez et al. 2006; Riley & Cowie 2009), with an approximate cost of $899 (£550).

10.4.3 Reference values for HRV in heart failure

Measurement length does not affect vagal HRV measurements such as rMSSD in the supine position (Grant et al. 2011), which is why it is such a good measure. In research assessing the reliability of ultra-short HRV measurements (10 s) rMSSD emerged with high correlations with the standard 5-minute short-term recording (Thong et al. 2003). Nussinovitch et al, (2011) also found rMSSD to be a reliable parameter for assessing HRV from ultra-short 1-minute or 10-second resting ECG recordings. Therefore on principle, Ithlete one minute measurements can be considered a reliable parameter for assessing rMSSD. There is a big influence of age on short-term HRV measurements (Nunan et al. 2010). rMSSD values of heart rate variability would be expected to be lower in heart failure patients when compared with values cited in literature for the healthy population because HRV depends on the activity of the autonomic nervous system, particularly sympathetic activation and reduced vagal tone which are known to be characteristic in chronic heart failure patients (Sztajzel 2004). HRV can be used as a marker for predicting sudden cardiac death or progressive LV dysfunction in heart failure patients (Nolan et al. 1998).

Reference values for rMSSD of healthy subjects compared with certain diseased populations have been compared in the literature. Sztajzel et al, (2004) reported rMSSD values of 27 ± 12 ms for healthy subjects vs. 24 ± 12 ms for patients with a recent MI. Nolan et al, (1998) reported the average rMSSD values for patients with chronic heart failure within that study at 21.5 ± 12.3 ms. Ithlete rMSSD values are different from those in literature because the values displayed are the natural log transformed rMSSD multiplied by 20. In chapter nine of this thesis, mean rMSSD in healthy participants using Ithlete was 76.3 ± 6.2 ms. Within the present study the average rMSSD value for heart failure patients was 74.8 ± 10.4 ms. The mean rMSSD would expectedly be lower in patients with HF however the mean of 74.8 ms is above the averages cited in the literature for patients with HF. The difference between the two averages is not statistically significant. This may imply that participants in the present study were only in mild HF.

The CV for healthy participants was 10.9, compared with 25.1 for patients with HF; the difference between them is statistically significant at $p = 0.014$. A larger CV was expected in the healthy population to demonstrate large variation in their rMSSD, however that was not the case. A larger number of participants would increase the statistical power of these tests. There was a larger number of HF patients in the cohort (n= 46) compared with healthy participants (n= 24), which could have affected the amount of variation. The larger amount of variation in the patients with HF, also suggests that the HF participants in the present study were only potentially in mild HF.

When divided into NYHA classes and controlled for gender and age NYHA class I demonstrated a higher average rMSSD than NYHA classes II and III comparatively which would be expected because of the physical capabilities of each class. The averages for rMSSD were NYHA I 58.6 ms (95%CI (42.5-85.3) ms, NYHA II 44.5 (95%CI 29.74-49.57) ms, and NYHA III 43.4 (95%CI 30.24-55.33) ms. The difference between the groups however was not significant ($p=0.34$), likely due to the small number of participants. Symptomatically, NYHA class III are said to be comfortable at rest however have marked symptoms during physical activity including fatigue, palpitations and dyspnea, compared with NYHA class I with no symptoms at rest or during physical activity. The difference between class II and III was comparatively small; a bigger difference in average rMSSD between the two might have been expected. NYHA class II has slight limitation of physical activity compared with marked limitation for NYHA class III suggesting a marked difference should be demonstrated in cardiac autonomic function at rest.

Considering the relationship between HRV and risk of mortality in patients with HF (La Rovere et al. 2003; Nolan et al. 1998), bigger differences in HRV between NYHA classes would be expected, especially considering the link between HRV and physical activity (Lai et al. 2011; Murad et al. 2012; Routledge et al. 2010). Within the present study, NYHA class II had the highest TRIMP values (135.38 ± 94.4) suggesting that they did the most exercise on average, followed by NYHA class III (110.55 ± 82.6) and then NYHA class I (94.6 ± 56.7). NYHA class II also had the lowest CV for HRV indicating the smallest amount of dispersion in the variable compared with NYHA class I and then NYHA class III. This is contrary to the CV for HR where the lowest CV was in NYHA class III, then NYHA class I followed by NYHA class II. HRV and HR are known to be negatively correlated (Javorka et al. 2003; Migliaro et al. 2001), and therefore this difference is to be expected.

10.4.4 Differences in HRV according to medication and comorbidities

Drug treatment in heart failure has an effect on HRV. There are several classes of heart failure drugs which were controlled for in statistical analysis. These drugs were controlled for because of their potential effect on HRV. Beta blockers and anti-arrhythmic drugs are administrated to reduce HR, directly impacting HRV. ACE inhibitors, diuretics and aldosterone antagonists are administered to reduce blood pressure (to reduce the amount of force needed to eject blood from the heart) (National Institute for Health and Clinical Excellence 2010). This initially would not necessarily impact on HRV, however as the heart adjusts to the reduced pressure, heart rate may be altered over time. When not controlling for any heart failure medication, the odds ratio for a dip in HRV was 1.007 (95%CI 0.802 - 1.264) (p= 0.95). Beta blockers did not have a large effect on the odds ratio which went from 1.007 to 0.996. In patients with chronic heart failure beta blockers are reported to restore autonomic imbalance. ACE inhibitors affect HRV by increasing parasympathetic activity in patients with chronic heart failure (Tuininga et al. 1994). Some of these medications will affect HRV in HF patients as they are meant to directly act on HR to help the patient cope with their symptoms.

All HF patients were taking at least one type of medication, and several patients were on multiple medications. When examining coefficients of variation of rMSSD, beta blockers, ACE inhibitors, diuretics, and aldosterone antagonists demonstrated more variation among patients who were on those medications compared with those who were not. Beta blockers are known to act directly on HR while the others reduce blood pressure, thus less variation would be expected with the use of beta blockers but not necessarily the others. In the present study, the CV for patients on beta blockers was 13.1 compared with 12.1 for those not on beta blockers. This difference was not statistically significant. Angiotensin II receptors, nitrates, digoxin, diabetic medication and amiodarone showed more variability with patients who were not taking them; the differences were not significant. Considering the action of the drugs, it would be expected that there would be less variation on those who were taking amiodarone, nitrates, or digoxin because these drugs act directly on HR. In the present study, there were no significant differences demonstrated in the coefficient of variation between groups on those medications vs. those who were not. The CV for patients on amiodarone, nitrates and digoxin were lower compared with those patients not taking them.

The effect of beta blockers on HRV was assessed by Cook et al, (1991) who found significant increases in HF power, rMSSD and pNN50 with the use of atenolol and propranolol, however the effects may differ with certain beta blockers. The suggested influence of ACE inhibitors on HRV is an increase in parasympathetic activity through the reduction of angiotensin II levels which removes cardiac vagal inhibitory activity (Clemson et al. 1994). Digoxin is thought to increase vagal modulation of R-R intervals but not cause a significant change in the mean value of R-R intervals (Kaufman et al. 1993).

Significant differences were however found in the CV in regards to comorbidities. There was a significant difference in the CV between those with ischaemic heart disease, hypertension and diabetes compared with patients who did not have these conditions. Lower values of HRV in patients with diabetes (Kataoka et al. 2004; Kudat et al. 2006; Liao et al. 1995; Liao et al. 1998); ischaemic heart disease (Dekker et al. 2000; Liao et al. 1997; Tsuji et al. 1996) and hypertension (Gerritsen et al. 2001; Huikuri et al. 1996; Langewitz et al. 1994; Singh et al. 1998) have been demonstrated in the literature. In patients with coronary heart disease low values of HRV are strong predictors of mortality reflecting excessive sympathetic or inadequate parasympathetic modulation (Carney & Freedland 2009). In the present study no significant differences were demonstrated in HRV between patients on heart failure medication compared with those who were not; this may be due to the small population size within the study.

10.4.5 Limitations:

The recruitment process for patients was undertaken through the Consultant Cardiologist or the Heart Failure Nurse specialist at each hospital. Bias may have occurred in the selection of participants. The Consultant Cardiologist or Heart Failure Nurse would decide which patients to approach or not, so even if some patients met the criteria, some patients were not recruited because the consultant or nurse did not think they would be appropriate. This made recruitment slightly subjective. Some of the reasons cited were patient anxiety or stress associated with their condition, comorbidities that made them unsuitable even though they were within the inclusion criteria, attitude of the patient, or capabilities of the patient.

When sitting in on clinics, the researcher could only observe; it was up to the Nurse or Cardiologist to approach the patient about participation in the study. This may have created some bias as some suitable patients may not have been asked because of external factors. The clinician often made a judgement call based on what they thought the patient could handle, without necessarily asking the patient first. The clinicians stated that this was done because they did not want to upset the patient or cause them any unnecessary duress. Despite the validity of these external factors, all patients who met the inclusion criteria should have been approached and given the opportunity to accept or decline. Patient care is a priority within the NHS; appropriate ethical decisions must be made to ensure the well-being of the patient always comes first. This can be a complex process and balance is essential, and despite its impact on study recruitment it is necessary for best clinical practice.

Within this study there was a wide age range within the participants with very small numbers of participants at the younger end (20-35) and the older end (75+) which could skew the average HRV results; the prevalence of heart failure increases with age therefore the HRV average results within this study might be higher than those that would generally be observed in the overall heart failure population. Age was controlled for however, in the majority of the statistical tests.

Some participants had concerns about using the touch screen on the iPod device and despite practicing with the researcher were still not comfortable when they took it home. This may have accounted for errors in taking and saving measurements. Participants were also asked to record their exercise activity daily in calendars provided. Participants had to choose a zone for the rate of intensity at low/moderate/high and this was a very subjective measure. For some patients this concept was hard to grasp as they did not have much energy to carry out their daily activities. For some patients, walking for longer than five minutes was reported as high intensity compared with other patients who reported cycling or jogging for thirty minutes as high intensity. Some patients reported climbing the stairs as high intensity while others reported it as low. They cited that everything they did felt like it was at high intensity because it took so much effort to carry out and this could have an effect on comparisons between participants due to the subjectivity of the measurement. It is hard to gauge how well participants adhered to the described intensity zones within one exercise and this, again, could be highly subjective. They were asked to pick the zone within which they thought they were within most during the exercise. This is a common limitation within HF patients especially because the overall range of intensity is low due to functional capacity. Patients with heart failure with low functional capacity will have a low range of activities, leading to limited options for TRIMP resulting in poor statistical power. There was however a large range of activity levels within the participants which helped to counter that effect.

10.5 Conclusion

Ithlete measurements of HRV (rMSSD) and HR in patients with HF were completed on a consistent basis for one-month for forty-six patients (44.6% overall). Of those forty-six participants most reported that the device was easy to use and most did not have any trouble taking measurements on a daily basis. The remaining fifty-seven participants either took no measurements at all, took incomplete sets of measurements where they did Ithlete recordings (but not a sufficient amount) or only completed the physical activity diary. The use of and iPod touch for telemonitoring provides easy access to potential medical equipment however may have a slight age effect due to the use of a electronic touch-screen device. Some patients had reservations about using the device before even trying it, simply because it appeared too technical (i.e. the touch screen looked too difficult to use). Those patients who were familiar with the use of a Smartphone for example were much more comfortable with the idea, thus perhaps identifying an experience effect.

Generally patients were satisfied with measurement time and Ithlete usability. The majority would recommend the use of Ithlete to other patients. This was despite some of these patients not completing measurements correctly themselves. Overall that is a very positive outlook and lends well to the use of Ithlete in future clinical practice. The device is both easy to use and cost effective when compared to other medical devices of the same nature. Despite the lower than expected success rate for complying with the study protocol, future research should focus on using the device with larger populations, with varying age range. To improve outcomes, the device should be used in conjunction with an established cardiac rehabilitation programme to provide greater support and guidance for patients. There was more variation in rMSSD among patients who were on beta blockers, ACE inhibitors, diuretics, and aldosterone antagonists compared with those who were not. Statistically significant differences in the CV of rMSSD were demonstrated among patients with ischaemic heart disease, hypertension and diabetes compared with patients who did not have these conditions.

For patients with HF, this device can be explored for use in the clinical setting to aid cardiac rehabilitation and provide patients and clinical staff with feedback on autonomic function. Overall Ithlete appears to be an easy device to use for HRV assessment in this population due to its usability, immediate easy to interpret feedback for the user and cost efficiency when compared to other medical devices. Due to large interpersonal variation of HRV, emphasized importance should be placed on daily measurement over a period of at least one month to ensure enough data for comparison.

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CHAPTER 11: IMPLEMENTATION AND EVALUATION OF A HEART RATE VARIABILITY (HRV) GUIDED CARDIAC REHABILITATION PROGRAMME WITH HEART FAILURE PATIENTS USING THE ITHLETE

Heart failure occurs when the pumping ability of the heart is impaired. The prevalence of chronic heart failure (CHF) is increasing. CHF is usually characterized by breathlessness on exertion, persistent fatigue, and/or signs of fluid retention. The New York Heart Association (NYHA) established functional stages to clarify the extent of heart failure (HF) from no limit to physical activity to severe limitation. Patients with HF have depressed HRV levels and this is a commonly identified risk factor for sudden cardiac death. Cardiac rehabilitation (CR) is a medically supervised programme designed to improve the health and wellbeing of people with heart conditions such as HF. Its benefits include improvement in exercise tolerance, improvement in symptoms, improvement in psychosocial well-being and reduction of stress. HRV measurements daily have the potential to gauge how HF patients are responding to exercise and stress during a CR programme.

The purpose of the present study was to determine if a home-based CR programme using Ithlete as a biofeedback tool would be beneficial. This study also examined whether or not patients demonstrated a dip in HRV following exercise. A six-minute walk test (6MWT), HRV daily measurements from the Ithlete device and patient feedback via a questionnaire were used to assess the benefits.

The 6MWT demonstrated improvements in each NYHA class in the overall distance patients were able to cover in the test after the CR programme. A dip in HRV 24-hours following exercise was found in 78.9% of HF patients, and 68.4% demonstrated a dip 48-hours following exercise. This is in contrast to HF patients not involved in a CR programme, where a dip was demonstrated in 46.5% of participants at 24-hours after exercise and 65.1% 48-hours after exercise. This suggests that different physiological adaptations occurred as a result of the CR programme. Patients stated that Ithlete was an easy device to use, and enjoyed receiving regular feedback. Other benefits included regular feedback for the practitioner and the cost compared to other medical devices.

11.1 Introduction

11.1.1 Heart failure

The prevalence of heart failure (HF) is increasing due to improved secondary prevention, aging populations, and improved survival following coronary events. Acute symptoms of cardiac insufficiency include undue fatigue, palpitations and shortness of breath. Depending on the severity of HF, acute symptoms worsen when physical activity is undertaken. HF is a multisystem condition with complex aetiology. It is commonly characterised by chronic autonomic dysfunction which can affect heart rate, blood pressure, sweating etc. and is important because it may have a large impact on a personộs quality of life (Stubendorff et al. 2012; Van Gestel et al. 2011). Chronic autonomic dysfunction can be measured invasively by muscle sympathetic nerve activity (Furlan et al. 2000; Pagani et al. 1997), noradrenalin spillover (Coats et al. 1992; Kingwell et al. 1994) or non-invasively through measurements such of heart rate variability (HRV) (Bigger et al. 1988; Guzzetti et al. 1988; Lombardi et al. 1987; Sztajzel 2004; von Borell et al. 2007). The importance of autonomic dysfunction in heart failure is described below.

11.1.1.1 Autonomic dysfunction in heart failure

Parasympathetic dysfunction in HF is characterized by increased firing of the sympathetic afferent cardiac fibres when the heart dilates, leading to tonic and reflex inhibition of cardiac vagal efferent activity (Schwartz & De Ferrari 2011). A reduction in vagal activity is most likely caused by systolic dysfunction (impaired ventricular contraction). The mechanisms involved in reduced vagal activity in diastolic dysfunction (where the heart does not dilate) have not been fully explained (Kishi 2012). Sympathetic dysfunction in HF is characterized by reduced sensitivity of various sympathoinhibitory reflexes such as baroreflex and cardiopulmonary reflexes (Zucker et al. 2009). Activation of the sympathetic nervous system in HF has been linked with sympathoexcitation and abnormal cardiovascular reflex functions (Zucker et al. 2007). A reduction in parasympathetic activity (Casolo et al. 1989) and sympathetic activation (Kienzle et al. 1992), indicated through time domain and spectral HRV measurements, reflect the influence of the autonomic nervous system on cardiovascular function in patients with HF (De Jong & Randall 2005; Lauer 2009; Nolan et al. 1996; Phillips 2012).

11.1.2 Measurement of autonomic dysfunction using heart rate variability (HRV) in heart failure

The autonomic nervous system in HF is characterized by dysfunction in sympathetic activation, parasympathetic withdrawal and peripheral organ non-responsiveness (Grassi et al, 1995). As HRV provides a non-invasive indirect measure of autonomic control, it is an ideal measurement to use in patients with HF. Time domain HRV measurements of rMSSD and pNN50 are accepted measurements of vagus nerve activity (Task Force, 1996). Where sympathetic over-activity is prevalent, global R-R variability measures (SDNN, HRV-index) are reduced (Notarius & Floras 2001). The vagal measurement pNN50, has also been cited as a risk factor in CHF by Bonaduce et al, 1999; the other vagal measure, rMSSD however has not yet been identified as a risk factor. Sympathovagal measures of spectral power (high-frequency and low-frequency) are also not cited as non-significant predictors for all-cause mortality (Aronson et al. 2004; Brouwer et al. 1996; Mortara & Tavazzi 1996; Nolan et al. 1998).

Patients with CHF have depressed HRV levels which are regularly observed at all stages of systolic dysfunction (Fauchier et al. 1997). Reductions in HRV measures are commonly identified risk factors in CHF where sudden cardiac death has been used as a clinical end point (Sandercock & Brodie 2006). Reduced HRV is thought to occur as a result of a failure in the response of the sinoatrial node to autonomic regulation (or attenuation in that regulation) (Task Force, 1996). Reduced HRV measures predict all cause mortality in several diseases including renal disease (Hayano et al. 1999), haemodialysis patients (Fukuta et al. 2003), and particularly in congestive heart failure (Bilchick et al. 2002; Binder et al. 1992; Nolan et al. 1998; Ponikowski et al. 1997). Reduced HRV demonstrates impaired autonomic function and therefore is a useful measurement within these clinical populations. Exercise improves HRV in both healthy (de la Cruz Torres, López & Orellana 2008; Gladwell et al. 2010; Pober et al. 2004) and clinical populations (Kubinyi et al. 2003; Murad et al. 2012; Turker et al. 2013). Cardiac rehabilitation (CR) is a medically supervised programme designed to improve the health and wellbeing of people with heart problems, and usually involves an exercise programme. To improve HRV and alleviate common symptoms of HF, CR programmes have been utilized. Increases in HRV following a CR programme involving exercise training in patients with HF have been documented in several studies (Kiilavuori et al. 1995; Kubinyi et al. 2003; Malfatto et al. 2002; Murad et al. 2012; Selig et al. 2004). The next section will discuss CR and its implications for improving HRV.

11.1.3 Cardiac rehabilitation

The World Health Organization (WHO) defines cardiac rehabilitation as:
άthe sum of activities required to influence favourably the underlying cause of the disease, as well as the best possible, physical, mental and social conditions, so that they (people) may, by their own efforts preserve or resume when lost, as normal a place as possible in the community. Rehabilitation cannot be regarded as an isolated form or stage of therapy but must be integrated within secondary prevention services of which it forms only one facetô(World Health Organization 1993).

A CR programme usually encompasses an overall approach to helping the patient adjust back to an active lifestyle following heart problems. The programme usually consists of education that promotes a healthy lifestyle including diet, exercise and stress reduction. Rehabilitation teams are typically made up of different professionals and should include a cardiologist, nurse specialist, exercise specialist, dietician, psychologist, physiotherapist, occupational therapist and clerical administrator (BACPR 2012). The benefits of CR involving exercise have been reported, including reductions in cardiac mortality by 26-36% and total mortality by 13-26% (Heran et al. 2011). CR is typically offered to three main groups, those who have had a myocardial infarction (MI), percutaneous cardiac interventions (PCI) and coronary artery bypass graft (CABG). Many CR programmes exclude HF patients, however this number dropped from 20 to 15% from 2010 to 2011 (NACR 2012). Currently the most likely group to take part in CR are CABG patients (ibid). Despite the known benefits and recommendations, stated by the British Heart Foundation (BHF) and National Institute for Clinical Excellence (NICE), most patients do not receive exercise-based CR as an essential component of comprehensive cardiac care (Bethell et al. 2008). Overall referral, enrolment and completion of CR programmes are suboptimal across the UK; especially in women and the elderly (Beswick et al. 2004).

Patients with HF were originally cautioned against physical exercise until the late 1980s (Coats 2000). This was challenged and the benefit of exercise in patients with HF was demonstrated by Coats et al. (1990) where an eight-week training programme produced a 20-25% increase in peak oxygen consumption, exercise tolerance and reduced questionnaire-rated symptoms associated with their condition. Participants in that study also found an increase in the ease and degree of performing daily activities (ibid). From the 1990s onwards the research in this area increased with larger and better designed studies in patients with HF; particularly assessing the physiological benefits and increase in exercise capacity that is possible through CR (Coats 1999).

Programmes of CR comprising supervised exercise produces well-documented benefits including improved exercise tolerance, improvement in blood lipid levels, reduction in cigarette smoking, improvement in psychosocial well-being, reduction of stress and reductions in mortality (Wenger 2008). The safety of CR was estimated by investigators at 1 in 50,000 to 100,000 injuries during patients-hours of supervised exercise (Wenger 2008). Only two fatalities were reported for 1.5 million patient hours of supervised exercise (ibid). The overall benefits of exercise have been reported in various healthy and diseased populations, emphasizing its importance to improved quality of life.

Exercise training improves survival time in patients with HF by improving left ventricular systolic dysfunction (ExTraMATCH Collaborative 2004). Varying the type of exercise, may have different benefits for patients with HF. There are no clear recommendations for endurance versus muscle strengthening programmes in elderly patients (Miche et al. 2009).

Despite the known benefits of CR to health and quality of life, participation remains suboptimal (Dalal et al. 2010). Women are less likely to be referred for CR programmes; and those who are referred are less likely to attend compared with their male counterparts (Wenger 2008). This is notwithstanding womenõs responses to CR being equivalent to those of menõs in improvement of Vo_2 peak and as a good predictor of cardiac mortality (Kavanagh et al. 2003). Thompson & Clark, (2009) examined why so many patients do not receive CR in the UK, and cited several different issues. They included distance, transportation, lack of convenience, lack of referral by physicians, lack of funds, illness, lack of interest, denial of severity of illness, not believing it will work or that it is suitable for them, and family or work obligations being more important. For patients with HF particularly, the barriers are even greater as there are still 15% of CR programmes excluding HF patients (BACPR 2012). Examining the barriers patients may face in their referral to rehabilitation and how to combat them, could help to increase participation. This, along with health care teams gaining a better understanding of what will motivate patients to seek out CR, are important for the future.

There are two types of CR, home-based and centre-based. Home-based CR is a structured programme carried out in the patientôs home with clear objectives for participants that include monitoring, follow-up visits, and telephone calls (Dalal et al. 2010). Centre-based CR is a supervised group based programme that can be based in various settings such as the hospital physiotherapy department, community sports centre or University gymnasium (Dalal et al. 2010).

Optimal physical activity levels of those participating in CR have not been established (Taylor et al. 2010). Barriers to uptake of centre-based CR include difficulties in attending regular sessions, reluctance to take part in group-based sessions (ibid), the distance and ease of access (Dollard et al. 2004). To help overcome some of these barriers, home-based CR programmes such as the Heart Manual (Lewin et al. 1992) and the Angina plan (Lewin et al. 2002) were developed. Both programmes involved a specially trained facilitator and included the use of a workbook, diary and record sheets aimed to facilitate a walking exercise programme, focused on self recording. Standard attendance for centre-based CR programmes has been reported at less than 50% in two North American studies, which followed up with over 1000 patients (Grace et al. 2011; Martin et al. 2012). In England, in 2003-2004 only 29% of patients eligible for CR attended (Bethell et al. 2008). This number rose to 44% in 2010-2011, however this was in the three main groups (myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft) (NACR 2012).

Research examining the adherence to CR programmes is conflicting; however this may be due to the variation in which adherence is defined and measured (Dalal et al. 2010). Dalal et al, (2010) reviewed trials of home vs. centre based CR programmes and reported that no study found significantly higher adherence in centre-based programmes. Two studies within that review found significantly higher adherence in home-based CR programmes (Arthur et al. 2002; Marchionni et al. 2003). Home-based CR provides a more flexible, menu-driven approach to CR and therefore presents the opportunity to improve uptake and delivery of CR programmes (Blair et al. 2011). With the NHS undergoing major reform and budget cuts, the impact of lower public spending on population health has been considered (Stuckler et al. 2010). Programmes such as centre-based exercise CR may be at risk of closure (a situation that already exists at one of the London-based hospitals used in the present study), making home-based CR even more important. Exploring ways to make home-based CR effective and rewarding for patients are vital to ensuring successful clinical outcomes.

Centre-based rehabilitation programmes provide health benefits when patients attend (NACR 2012). Typical home-based CR programmes rely on self reporting from patients during follow-up phone calls or home/clinic visits at varying intervals (Jolly et al. 2003). With home-based programmes it is difficult to assess how hard patients work or how many exercise sessions they actually complete. For patients, the use of a monitoring device may help maintain motivation and also track their progress. For a clinician, monitoring devices can eliminate the subjective aspect of home-based CR programmes, allowing them to monitor patient progression through the programme. Sport science has used HR as a training guide for intensity for over 25 years (Schonfelder et al. 2011). The use of HR monitoring as a training tool to assess exercise intensity allows athletes to maximize training benefits, and avoid overtraining and injury (Arts & Kuipers 1994; Bamford 1999; Davis & Convertino 1975; Gilman & Wells 1993). Changes in the autonomic nervous system of athletes corresponding with harder training sessions (Iellamo et al. 2002), prompted the use of HRV as a monitoring tool to prevent over-reaching and overtraining (Bosquet et al. 2003; Hedelin et al. 2000; Manzi et al. 2009; Mourot et al. 2004a). The interaction between intensity, duration and HRV has become a tool in preventing staleness, overreaching or overtraining. These states are thought to develop as a result of excessive training loads, without adequate recovery in between. The use of telemonitoring equipment, such as a heart rate monitor has been demonstrated as a feasible tool for following adherence and providing sustained benefit of exercise training in HF patients (Smart et al. 2005). Therefore, the present study has several aims which will be categorized as either primary or secondary.

11.1.4 Aims

The primary aims of the present study were (i) to determine if a home-based cardiac rehabilitation programme using Ithlete as a biofeedback tool would be effective and beneficial for heart failure patients; (ii) to examine whether or not patients participating in the CR programme demonstrated a decrease in HRV following exercise as postulated in literature with healthy participants. The secondary aims were (i) to explore physiological characteristic differences by NYHA classes and gender; (ii) to determine the effectiveness of a home-based walking CR programme on improving fitness in each NYHA class; (iii) to determine the effectiveness of a home-based walking CR programme on measurements obtained during a 6MWT.

11.2 Methods

11.2.1 Recruitment of participants

The researcher attended clinics with either a Consultant Cardiologist or Heart Failure Nurse Specialist at three London hospital sites. Each participant was recruited in accordance with NHS Research Ethics Committee standards and expectations. Participants responded in the clinic or by phone and were given an information pack before agreeing to participate. This information pack included:

1. An information sheet with details of the requirements for each participant before and during the research study
2. An informed consent form
3. HRV measurement information package
4. A detailed demographic information sheet
5. Physical activity calendar

Participants were requested to read the information pack prior to attending the clinic to meet with the researcher and any questions or concerns were addressed. All procedures were approved by the local research ethics committee.

11.2.2 Participants

All participants were defined as patients with HF, with varying levels of impairment but all were deemed eligible by the medical team at the hospital they attended. Any patient who completed the one-month trial of Ithlete data collection were asked to go into phase two of the study which involved a home-based walking cardiac rehabilitation programme using Ithlete as a guide to exercise.

Inclusion Criteria: The participants were recruited from hospitals in the London area. The participants were heart failure patients within the New York Heart Association classifications of I, II & III aged at least 18 years of age. Heart failure treatment was under the control of the participant's consultant cardiologist.

Exclusion Criteria: Participants were excluded if they had any of the following conditions: consistent atrial fibrillation, unstable coronary artery disease with revascularization within the last 6 months or planned revascularization, planned heart valve surgery or planned transplantation, uncontrolled arterial hypertension, acute myocarditis, worsening clinical condition, inability to read the display of a handheld device or deemed unable to comply with home telemonitoring, inadequate understanding of English, or any visual or cognitive impairment sufficient to interfere with the participant's ability to use the device (Cleland et al. 2005; Dar et al. 2009; Scherr et al. 2009).

Participants completed their consent form in front of the researcher and the researcher countersigned the form. Participants were then given a demonstration of how to use the device to take HRV/HR measurements using Ithlete on an iPod touch. Patients took home all the paper work with the device which included detailed instructions on how to take measurements and how to fill in the calendar with daily physical activity.

11.2.3 Protocol

Phase 1: Following appropriate ethical approval from the NHS Southwest Research Ethics Committee and informed consent, participants were asked to visit the clinic at their hospital to meet with the researcher for a demonstration. Each participant was given a demonstration of how to use the Ithlete software on the iPod touch and required to complete two measurements in the presence of a researcher before taking the device home.

Then each participant was required to take an HRV measurement once every morning when they woke up for 1 month in succession. HRV (rMSSD in ms) and heart rate (HR in beats per minute (bpm)) were recorded via Ithlete software for the iPod touch (Ithlete 2009). Patients were also asked to take home a pedometer to wear daily to count their steps. Patientsô height and stride length were measured and input into the pedometer. Then the researcher demonstrated how to use the pedometer, and where it should be worn. Patients tried taking steps with the pedometer before leaving the clinic. Finally, patients were asked to record the following on a physical activity diary daily:

1. What (if any) exercise was performed the day before
2. Duration of that exercise
3. Intensity of that exercise (Low/Moderate/High)
4. Daily scale of how you are feeling on a scale of 0-100% (100% being the best)

Patients who successfully completed phase one, were then asked to move on to phase two.

Phase 2: During this phase patients were instructed to continue taking Ithlete measurements every morning; patients were also asked to wear a pedometer everyday and record the total number of steps at the end of each day on their physical activity diary.

Phase 3: This phase was an eight-week CR home-based walking programme. Participants spent the first month taking readings without following the Ithlete indications and then for the following month they were asked to follow the colour indications to rest (red), taper their workout (amber) or complete a full workout (green or blue) for each of their training days. Participants in this phase were asked to follow an incremental walking exercise programme where they had 4 walking levels to progress through.

To measure functional capacity, patients were asked to complete a six-minute walk test (6MWT) before the walking programme commenced. The 6MWT is a modification from the 12-minute walk/run test, which allows patients to be evaluated during normal physical activity, in a non-laboratory setting (Reybrouck 2003). It is a reliable test which correlates well with morbidity and mortality in heart and lung diseases (Arslan et al. 2007; Cote et al. 2008; Enright 2003; Rostagno et al. 2003). There is a good correlation between the distance covered by patients and maximal oxygen uptake, ventilator anaerobic threshold or risk of cardiac death (Arslan et al. 2007; Balady et al. 2010; Ross et al. 2010). The 6MWT is cost effective, non-invasive and does not need expensive equipment. The test has established standards for testing, reference values and is well tolerated by patients with a wide range of fitness and ability (Enright 2003; Solway et al. 2001).

The 6MWT is easy to administer as it is an exercise mode familiar to patients, and only needs a flat pre-measured surface and a timing device (Enright 2003; Ingle et al. 2005). Several measurement outcomes can be used, with distance covered being the primary measure (Enright 2003). Secondary measurement outcomes include fatigue (measured by the Borg or visual analogue scale) and arterial oxygen saturation (measured by pulse oximetry) (ibid). The prognostic value of the 6MWT has been demonstrated in patients with HF, with reference values indicating a distance covered of < or = 300 m signifying patients at higher risk of cardiac death (Arslan et al. 2007).

In the present study, the 6MWT was performed in a quiet indoor corridor in the hospital. Patients were instructed to walk on a flat surface between two cones situated 25 metres apart, as many times as possible in the permitted time. The test was performed under the control of a researcher with a Nurse Specialist present, and patients were encouraged during the test using phrases like óYou are doing wellô, and óGreat workô. During the test patients were informed each time a minute had passed and their rate of perceived exertion (RPE) was recorded. At the end of the six minutes, distance and RPE were recorded by the researcher.

Patients rested in clinic for at least 15 minutes before the test. Blood pressure (Omron bp508, USA), HR (Ithlete), HRV (Ithlete) and rate of perceived exertion score (Borg rate of perceived exertion scale) were recorded before and after the test. The Borg scale is a rate of perceived exertion scale used to document the intensity of exertion throughout the test. The Borg scale is a linear scale ranging from 6-20 and is thought to coincide with increases in heart rate as exercise intensity increases. Six corresponds to easy or very light intensity through to twenty, which corresponds to very hard or maximum intensity. After each minute of the 6MWT, patients stated which number their intensity corresponded to.

The levels of the walking programme are listed in table 11.1. Ithlete software was utilized throughout the CR programme. Ithlete software provides an indication of how the body has responded to exercise by displaying a colour behind the change in HRV (rMSSD). The change is denoted by colours on a weekly and monthly change scale; blue for normal recovery, green for good recovery, amber for not the best recovery, and red for bad recovery. During the second month of the CR programme, patients were encouraged to look at their recovery and reduce their training plans for that day when amber or red colours were displayed by the Ithlete software that morning.

Table 11.1 CR home-based walking programme

Level	Distance	Frequency
1	1500 steps (or 15 extra minutes) of walking	at least 3 days/week
2	1500 steps (or 15 extra minutes) of walking	at least 5 days/week
3	3000 steps (or 30 extra minutes) of walking	at least 3 days/week
4	3000 steps (or 30 extra minutes) of walking	at least 5 days/week

The walking programme was accompanied by an information sheet which discussed warm-ups, stretching, and building up exercises gradually. The information sheet encouraged patients to try to fit in exercise every day, even if it was just a few minutes of stretching. Patients were encouraged to warm-up slowly for five-minutes each day, before commencing the walking programme. Warm-up exercises included arm/leg stretches and instructed patients to walk at a slower pace for at least two-minutes before commencing their regular walking programme pace. Patients were expected to increase their stretching time and add more suggested stretches from the information sheet as they progressed to each new level. Patients were also encouraged to take breaks during the walking exercises whenever necessary, but were asked to consciously try to reduce the frequency or duration of the breaks over time. Patients were instructed to progress to the next level when they were able to complete the requirements for that level of the walking programme without taking breaks or feeling symptoms (i.e. shortness of breath or excessive tiredness following the exercise session). Tiredness was explained to HF patients as a temporary loss of strength and energy due to excessive hard physical or mental work (Piper 1993). Fatigue was explained to HF patients as persistent tiredness that creates the perception of difficulty in performing daily activities (Evangelista et al. 2008).

After completing the walking programme, patients completed another 6MWT and were asked to fill in a questionnaire regarding their use of the Ithlete device. Patients were given the option to fill out the questionnaire with the researcher posing the questions, or by them filling it out themselves in the clinic room. The primary measurement following the CR programme from the 6MWT was the distance covered. Fatigue (assessed by the Borg scale), BP and resting HR were also compared.

11.2.2.1 Heart rate variability analysis using the Ithlete for iPod touch

For HRV measurement a standard analogue ECG chest strap was worn in the middle of the chest just under the sternum. Real time heart and lung animation on the iPod touch facilitated paced breathing during measurements and indicated reception of each heart beat from the analogue chest strap. Participants followed a breathing frequency of 7.5 breaths per minute, designed to maximize RSA response (Brown et al. 1993). Each measurement took 1-minute, when this was complete the HR (bpm) and HRV (rMSSD in ms) were displayed on the screen and saved to the device. Ithlete recordings were transferred to a password protected PC via Ithlete software.

11.2.3 Statistical analysis

All statistical analysis was analysed using PASW 19.0 (SPSS: An IBM Company. Somers, NY, USA). Values are reported in the text as mean ± standard deviation. The median-split method was used with the HRV data to split each participantøs values into two data sets (days when exercise was reported vs. days when no exercise was reported). Exercise was coded as 1 and corresponded to everything above and equal to the median, anything below the median corresponded to no exercise and was subsequently coded 0. The median-split method was used to allow comparison between subjects objectively by making HRV values relative to each participant. The change in HRV from day-to-day was then calculated for each participant by subtracting the HRV value from the day before (i.e. HRV-day-2 minus HRV-day-1). Independent t-tests were then used to generate mean and standard deviation of the change in HRV from day to day. Participant cases were then weighted based on the number of recordings taken for each participant. From these data, participants were coded as dippers (those who showed a lower HRV when exercise was reported) or non-dippers (no dip in HRV when exercise was not reported).

The general linear model was then used to quantify the relationship between exercise and HRV. Univariate analysis was performed on the change in HRV at 24 and 48-hours after exercise was reported/ not reported. Participants were then grouped into those who had a dip in HRV when exercise was reported (dippers) vs. those who did not have a dip in HRV after exercise was reported (non-dippers). Binary logistic regression was then used to predict the presence or absence of exercise. A P-value of <0.05 was considered statistically significant.

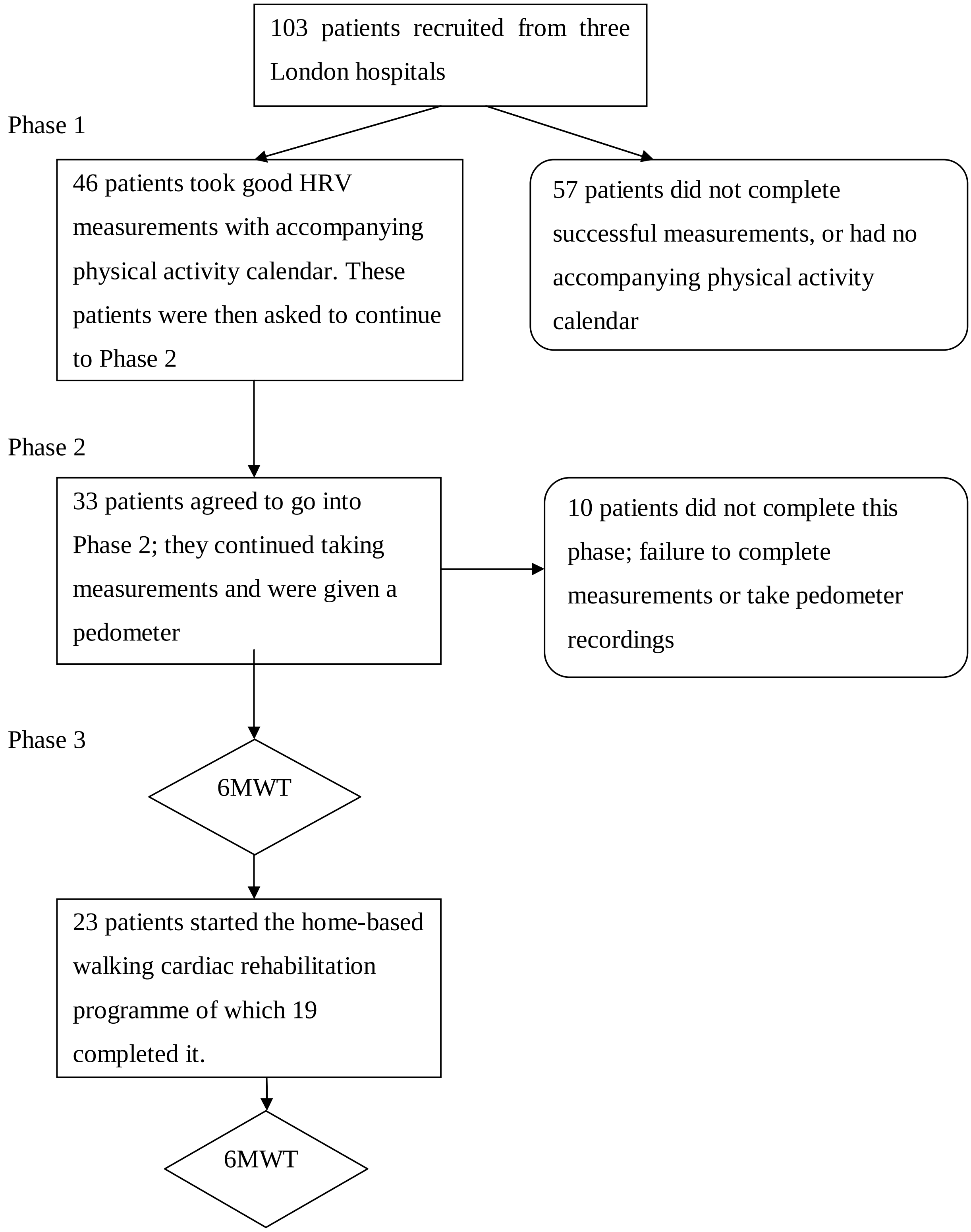
11.3 Results

In total, 103 participants responded within the clinics and agreed to participate in the study of which 70 were male and 33 were female. Participant age ranged from 24 to 87 years. Of those 103 participants, 46 took measurements for one calendar month (at least 28 days) and were then asked to enter phase two of the research study which involved the CR programme. Thirty-three of the 46 patients agreed to go into the next phase and from those 19 completed the CR programme. Patients progressed through the different levels at their own pace, but were encouraged to try to increase each time they completed a week successfully without excessive fatigue or other symptoms.

Using Ithlete the participants had a biofeedback tool to indicate how their bodies were responding to each workout. Participants were able to know when and how hard to train and how to identify the need for more rest and recovery from the last workout. Participants were asked to give feedback on how they felt each day through the day scale on their physical activity calendar (on a scale of 1-100, 100 being feeling great, one feeling very poorly). During the rehabilitation phase patients indicated if this agreed with the HRV reading that day (i.e. If Ithlete indicated a rest day, did they feel that was necessary or not).

Participants spent the first month taking readings without following the Ithlete indications and then for the following month they were asked to follow the colour indications to rest (red), taper their workout (amber) or complete a full workout (green or blue) for each of their exercise days. Figure 11-1 is a flowchart depicting how patients moved through the research study after recruitment. Patients were all recruited directly into phase one and then depending on their successful use of the device, were then recruited into phase two and the CR programme (phase three). Successful use of the device was characterized by consistent daily readings for at least 28 days with an accompanying physical activity calendar.

Figure 11-1 Patient flowchart



In table 11.2 the average age, HRV, HR and ejection fraction (EF) are displayed for cardiac rehabilitation participants divided into their NYHA classes. These classifications are determined by the Consultant Cardiologist or Heart Failure Nurse Specialist following their initial consultation with each patient.

Table 11.2 Average cardiac rehabilitation participant values for age, rMSSD, HR and ejection fraction (EF) by NYHA class

	NYHA I **N=3**	**NYHA II** **N=8**	**NYHA III** **N=8**
Age (years)	69.0 ± 7.1	63.0 ± 10.5	61.9 ± 12.5
rMSSD(ms)	81.3 ± 17.2	72.4 ± 12.9	72.3 ± 7.5
Heart Rate (bpm)	78.0 ± 7.9	81.5 ± 16.4	84.9 ± 4.4
Ejection Fraction (%)	41.0 ± 3.4	34.1 ± 8.6	33.8 ± 14.8

In the following table average components for each participant are displayed. Ithlete software provides an indication of how the body has responded to exercise by displaying a colour behind the change in HRV as displayed below on an Iphone beside daily and weekly change. These indications are displayed in the table as an average number which corresponds to one of the four colour indications (1-1.5=Blue for normal recovery, 1.5-2.5=Green for good recovery, 2.5-3.5=Amber for not the best recovery, 3.5-4=Red for bad recovery). TRIMP is displayed as an average of intensity of exercise multiplied by the duration of exercise and Day Scale (how patients felt on a scale of 0-100, 100 being the best and 1 being the worst) is displayed as a percentage. More specifically, amber represents the first day when HRV is more than 1 x SD (standard deviation of natural log transformed rMSSD) below the moving average of the previous seven days (so excluding the most recent recorded value); red represents the second day when this condition is true (i.e. two successive days when the current value is more than 1x SD below the moving average blue line) and green represents a rise of more than 2 x SD compared to the previous day. Green is intended to indicate good recovery and signifies that the body is ready for harder exercise. An example snap-shot from the Ithlete screen can be seen in figure 11-2.

Figure 11-2 Ithlete screen shot

Table 11.3 Average rMSSD, HR, Indication, TRIMP and Day Scale for cardiac rehabilitation participants by gender

Gender	Age	rMSSD	HR	Indication	TRIMP	Day Scale
M	62.1	77.5± 17.1	70.0± 8.6	1.5 ± 0.9	157.2 ± 184.0	63.8 ± 15.9
F	64.0	80.8± 11.5	74.7± 6.5	1.6 ± 1.1	133.8 ± 57.4	89.2 ± 2.8

Table 11.4 displays the mean predicted 6MWT distance for males and females in the present study, as predicted from the gender specific regression equations provided by Enright & Sherrill, (1998). Table 11.5 displays mean 6MWT results for each gender. Table 11.6 displays patientsô measurements divided into NYHA classes, obtained during the 6MWT. Walk one was completed the week before the CR programme commenced. Walk two occurred within two weeks of completion of the CR programme. Before the CR commenced, patientsô height, weight and blood pressure were recorded by the researcher.

Table 11.4 Mean predicted six-minute walk test distance with lower limit of the normal range (LLN) for each gender

	Predicted 6MWD	LLN
Male	543.7	390.7
Female	476.3	337.3

Table 11.5 Six-minute walk test results assessed by gender

	Male Walk 1	Male Walk 2	Female Walk 1	Female Walk 2
Age	62.1 ± 11.0	62.1 ± 11.0	64.0 ± 7.2	64.0 ± 7.2
Height (cm)	174.7 ± 8.5	174.7 ± 8.5	164.7 ± 7.6	164.7 ± 7.6
Weight (kg)	89.5 ± 20.7	90.3 ± 21.5	72.6 ± 0.9	71.0 ± 1.2
BP before test (mmHg)	118/74	120/74	126/77	123/78
HR before test (bpm)	72.3 ± 8.2	69.9 ± 9.4	86 ± 5.6	82.3 ± 6.0
Borg Scale Before test	8.3 ± 2.7	7.3 ± 1.7	11.0 ± 1.7	10.7 ± 1.5
Distance Covered (m)	303± 78	320 ± 66	302 ± 31	313 ± 51
BP after test (mmHg)	126/81	127/76	129/81	130/78
HR after test (bpm)	74.5 ± 10.0	71.0 ± 9,5	83.3 ± 6.4	80.0 ± 7.6
Borg Scale after test	12.1 ± 3.2	12.1 ± 3.1	14.3 ± 2.1	13.7 ± 2.1

Table 11.6 Six-minute walk test results assessed by NYHA Class

	NYHA I Walk 1 (n=3)	NYHA I Walk 2 (n=2)	NYHA II Walk 1 (n=8)	NYHA II Walk 2 (n=7)	NYHA III Walk 1 (n=8)	NYHA III Walk 2 (n=8)
Age	62.5 ± 9.2	62.5 ± 9.2	66.2 ± 13.2	66.2 ± 13.2	56.8 ± 12.3	56.8 ± 12.3
Height (cm)	171.0 ± 9.9	171.0 ± 9.9	175.7 ± 11.5	175.7 ± 11.5	177.8 ± 7.7	177.8 ± 7.7
Weight (kg)	91.9 ± 27.0	89.8 ± 25.8	80.9 ± 21.6	82.3 ± 22.3	103.5 ± 29.1	105.8 ± 30.8
BP before test (mmHg)	126/67	125/73	117/73	117/71	110/70*	119/73*
HR before test (bpm)	66.5 ± 9.2	64.5 ± 6.4	71.8 ± 8.3	67.8 ± 10.5	69.0 ± 8.0	65.3 ± 5.2
Borg Scale Before test	7.5 ± 2.1	7.0 ± 1.4	9.2 ± 3.4	7.6 ± 2.1	9.0 ± 3.6	7.8 ± 2.4
Distance Covered (m)	314.0 ± 48.1	328.5 ± 46.0	362.2 ± 102.7	364.1 ± 71.0	266.0 ± 57.3	309.2 ± 75.5
BP after test (mmHg)	123/70	128/74	123/78*	128/75*	119/89	118/69
HR after test (bpm)	69.5 ± 13.4	75.0 ± 7.1	82.8 ± 7.3	71.2 ± 13.6	70.3 ± 3.8	69.8 ± 1.7
Borg Scale after test	13.0 ± 2.8	13.5 ± 3.5	13.0 ± 1.9	13.8 ± 3.1	11.3 ± 5.6*	10.8 ± 3.3*

*Significant difference at $p < 0.05$

Results from the 6MWT demonstrate changes after the six-eight week CR programme. In each NYHA class there was an overall increase in the distance patients were able to cover after the CR programme. Sixty-six percent of participants in NYHA class I, increased the distance covered in the 6MWT. In NYHA class II it was 80% and in class III 75%. This increase could be attributed to the increased fitness levels that patients should incur after doing the walking CR programme.

Other improvements demonstrated in NYHA classes II and III after the CR programme included a lower resting HR and a lower initial RPE before the test commenced. In NYHA class I, no significant differences were demonstrated between any of the variables from walk one to walk two. In NYHA class II a significant difference was found in blood pressure between walk one and walk two; and in NYHA class III significant differences were found in the resting blood pressure taken before the 6MWT and the RPE after the test.

Table 11.7 displays the change in rMSSD measurements obtained for each subject during the cardiac rehabilitation programme on the day following exercise and 2 days following exercise.

Table 11.7 Change in rMSSD 24 and 48-hours after exercise for each CR participant

Patient	Number of recordings	24-hour change	Mean change after 24-hours	Standard Deviation	48-hour change	Mean change after 48-hours	Standard Deviation
1	22	No	3.13	17.26	No	5.01	27.12
2	22	Yes	-8.00	21.44	Yes	-9.30	24.68
3	12	Yes	-6.66	21.60	Yes	-8.31	22.41
4	23	Yes	-2.81	9.10	Yes	-2.30	13.01
5	25	Yes	-5.81	13.60	Yes	-7.55	17.80
6	27	Yes	-1.29	20.63	No	3.45	28.41
7	31	Yes	-3.47	19.25	Yes	-3.15	21.31
8	53	Yes	-1.29	11.58	Yes	-2.01	14.33
9	29	Yes	-0.83	19.43	Yes	-2.25	21.92
10	38	Yes	-0.60	22.28	No	4.38	29.26
11	27	No	1.43	14.83	Yes	-1.11	21.62
12	18	Yes	-2.52	22.31	Yes	-3.14	28.20
13	29	No	2.06	7.44	No	1.29	12.66
14	16	Yes	-13.45	20.86	Yes	-18.38	28.07
15	18	Yes	-5.73	24.77	No	3.66	29.37
16	27	No	5.44	19.00	Yes	-0.84	23.74
17	29	Yes	-0.74	14.79	Yes	-2.39	22.76
18	55	Yes	-0.32	15.24	Yes	-1.50	23.17
19	37	Yes	-0.45	13.01	No	0.45	13.82

* Number of recordings refers to the amount of recordings which had corresponding measurements at 24 and 48 hours following reported exercise. Any recordings that did not have both follow-up recordings were excluded.

11.3.1 General linear model: Univariate analysis

Univariate analysis revealed that 24-hours after exercise was reported, rMSSD was not significantly different F (0.164) (p=0.68). Forty-eight hours after exercise was reported rMSSD was also not significantly different F (0.427) (p=0.52). When no exercise was reported, the overall mean change in rMSSD after 24-hours was -1.56 (95% CI: -3.85 - 0.73) (n = 233); compared with -2.20 (95% CI: -4.28 - -0.13) (n = 305) when exercise was reported. The overall mean change in rMSSD 48-hours after no reported exercise was -0.99 (95% CI: -4.18 - 2.19) (n = 218); and -2.32 (95% CI: -5.26 - 0.59) (n = 283) when exercise was reported.

When participants were grouped into those who had a dip in rMSSD 24-hours after exercise was reported (dippers) vs. those who did not have a dip in rMSSD 24-hours after exercise was reported (non-dippers), the mean rMSSD was 72.6 for dippers, and 76.0 for non dippers. The mean change in rMSSD was -3.60 ± 3.71 for dippers and 3.02 ± 1.76 for non-dippers. Forty-eight hours after reported exercise, participants were again grouped as dippers and non-dippers with a mean rMSSD of 73.1 for dippers, and 74.0 for non-dippers. The mean change in rMSSD was -4.79 ± 4.97 for dippers and 3.04 ± 1.79 for non-dippers.

11.3.2 Binary logistic regression

In the present study, the presence of exercise appeared to have minimal effect on rMSSD 24-hours after exercise. An odds ratio of 1.123 (95%: CI 0.798 - 1.580) (p= 0.50) was demonstrated when exercise was reported, compared with 1.011 (95% CI: 0.980 - 1.043) when exercise was not reported. This demonstrated that there was very little difference in the odds of a dip in rMSSD on the day following exercise. For 48-hours following exercise the odds ratio of a dip in rMSSD was 1.229 (95% CI: 0.863 - 1.751) (p = 0.25) when exercise was reported. When exercise was not reported the odds ratio for a dip 48-hours after exercise was 0.987 (95% CI: 0.956 - 1.019). This suggests that exercise has more effect on rMSSD 48-hours following exercise. This was not a significant difference at p = 0.42.

11.4 Discussion

The primary aims of the present study were to assess the use of Ithlete HRV (rMSSD) measurement daily to gauge how patients with HF responded to exercise during a CR programme. A dip in rMSSD following exercise was also assessed. The present study also examined differences in physiological characteristics between NYHA classes and gender. The outcome of the 6MWT was used to assess the effectiveness of the home-based walking CR programme.

Patients reported that using the Ithlete device during the CR programme was beneficial because they enjoyed looking at measurements from day to day. Participants particularly liked seeing how their body was responding to exercise by looking at the indication given by Ithlete for whether or not they had good recovery following exercise. Participants also said it was a reassuring tool which they followed so that rest days were taken when suggested by the Ithlete software.

Average CR participant values for age, rMSSD, HR and ejection fraction (EF) were compared by NYHA class. rMSSD and EF were highest in NYHA class I and lowest in NYHA class III. Resting HR increased with NYHA class. These averages are not surprising, considering that NYHA Class I have the highest fitness level and therefore would be expected to have the healthiest averages when compared with the other NYHA classes.

The average age, rMSSD, day scale and HR values were higher for female participants. TRIMP was higher for males and Ithlete indications throughout the CR programme were in the good recovery range for both genders over 60% of the time. The present study found higher rMSSD values for females, which is consistent with the majority of the literature on gender differences (Antelmi et al. 2004; Gregoire et al. 1996; Liao et al. 1995). There are also several studies that have reported a lower HRV in females when compared with males (Christou et al. 2005; Pavithran et al. 2008; Ramaekers et al. 1998; Saleem et al. 2012). Day scale was higher in females when compared to males indicating that they generally felt better overall. This is in contrast to other research which reported worse general health and life satisfaction scores in females (Cline et al. 1999; Riedinger et al. 2001). A higher TRIMP in male subjects suggested that men within the present study were more active than their female counterparts.

11.4.1 6MWT results

The 6MWT demonstrated an improved in the distance covered for both genders in following the CR programme. A smaller increase was demonstrated in females, but there were only three participants within this group. Enright et al, (2003) tested over 2000 participants over the age of 65 to determine the average walking distance for that age group. The average walking distance covered by healthy men was 400 m and 367 m for healthy women (ibid). Within the present study, none of the participants reached those averages. In 1998, Enright & Sherrill published gender specific reference equations with a lower limit of the normal range. Using these equations within the present study, the mean percentage of the predicted 6MWT distance covered was 78.6% for males and 91.2% for females. Following the CR programme, three males and one femaleçs 6MWT distances were within the predicted healthy range, suggesting that the CR programme improved their exercise tolerance.

When split by NYHA classifications, the smallest increase in the distance covered was demonstrated in NYHA class I, but there were only three participants within this classification. NYHA classô II and III demonstrated an increase in at least 75% of participants (both groups with 8 members). The demonstrated increase in distance could be attributed to increased fitness levels that patients should incur after completing the CR programme. Other improvements demonstrated in NYHA classes II and III after the CR programme included a lower resting pulse and a lower initial Borg scale before the test was initiated. Results of the 6MWT indicated that overall, patients benefited from participating in CR. Unexpectedly the greatest distance covered within the present study was achieved by NYHA class II, followed by NYHA class III and then NYHA class I. All participants were exposed to the same procedure for both their pre and post-intervention testing, so this should not have impacted on the results. There was however a smaller number of participants in the NYHA class I group (n=3) compared to NYHA class II and III (n=8), which may have affected the results. Throughout the CR programme, patients were encouraged to monitor their own walking progress through the use of pedometers, which will be discussed in the next section.

11.4.2 Pedometer use in walking programmes

Pedometers respond to movements and some may have been interpreted as steps despite that not being the case. Steps are counted when vertical accelerations of the hip cause a horizontal spring suspended lever arm to moves up and down, opening and closing an electric circuit (Berlin et al. 2006). A key problem with pedometer measurements is the inability to distinguish between varying intensities of vertical displacement (ibid); running 50 steps versus walking 50 steps would register the same amount of steps despite evident differences in energy expenditure.

Pedometer derived step ranges proposed in healthy adults suggested that <5,000 steps/day indicated a sedentary lifestyle, 5,000-7,500 steps/day as low activity, 7,500-9,999 steps/day as somewhat active, 10,000 to 12,499 steps/day as active and >12,500 steps/day as highly active (Tudor-Locke & Bassett 2004). The average for HF patients within this research study fell within the sedentary range (2622 steps/day) which is very similar to the average cited for this particular population (2,840 steps/day), and for patients with coronary heart disease and related disorders (Tudor-Locke et al. 2011). This implies that participants in the present study were mostly sedentary and indicates a need for increased exercise within this population. This may help to explain why nearly half of the patients who took measurements successfully still decided not to participate in the CR programme; of those that did participate, some patients found it particularly difficult to progress through the different walking levels within the CR programme because they had a very low fitness level to start with. This is however a common characteristic of heart failure patients, which leads back to lifestyle changes that need to be made in order to improve their quality of life.

11.4.3 Overtraining and HRV

Ithlete software was designed to detect and prevent overtraining by monitoring restoration of vagal tone. In the present study, Ithlete measurements were assessed 24 and 48-hours after exercise, to see if a dip in HRV (rMSSD) occurred. A dip in rMSSD 24-hours following exercise was demonstrated in 78.9% of HF patients, 48-

hours following exercise 68.4% demonstrated a dip in rMSSD. This is in contrast to HF patients not involved in a CR programme (observed in chapter 9) who averaged 46.5%, 24-hours after exercise and 65.1%, 48-hours after exercise. This suggests that the walking programme provided enough intensity to facilitate alterations to vagal autonomic nervous system activity.

The dip in HRV in the days following exercise may be as a result of increases in sympathetic activity outlasting the cessation of exercise, which was originally thought to last for up to 24-hours (Furlan et al. 1993). Prolonged heavy exercise has been shown to cause attenuated cardiac vagal outflow for several hours following exercise, and participants with poorer cardiovascular fitness had decreased vagal outflow for a longer period (Hautala et al. 2001). Measurements of rMSSD from HF participants when they were not involved in CR, suggest that these patients were perhaps not engaging in exercise heavy enough to cause attenuated HRV following exercise. The results demonstrated in the present study indicate that the CR programme facilitated heavy enough exercise to cause a dip in HRV in almost 80% of patients, 24-hours after the cessation of exercise. Due to their symptoms, patients with HF, in NYHA classes II-IV have limitations to their ordinary ability to perform physical activity. This potentially makes it more difficult to perform exercise heavy enough to cause attenuation of HRV. When exercise heavy enough to produce attenuated HRV is performed by HF patients, a longer period of reduced vagal outflow would be expected.

Measurement of HRV in HF patients has implications in the measurement of cardiovascular status. Following exercise a decrease in HRV has been demonstrated in aerobically trained athletes (Mourot et al. 2004a), and overtrained female aerobic athletes (Uusitalo et al. 2000). A study assessing national level swimmers found that reduced HRV levels were associated with increased risk of illness (Hellard et al. 2011). Various studies have demonstrated that HRV reflects recovery status in untrained athletes (Pichot et al. 2002), male rowers from the Italian national team (Iellamo et al. 2004) and elite Olympic weightlifters (Chen et al. 2011). When using HRV as a guide to exercise, studies have demonstrated better results for those using HRV when compared with those using pre-planned exercise sessions (Kiviniemi et al. 2010; Kiviniemi et al. 2007). The use of HRV to guide exercise for HF patients has not yet been reported.

11.4.4 HRV guided exercise using Ithlete

HRV represents variations in heart rate representative of the sum relationship between the activity branches of the autonomic nervous system (ANS). In response to subconsciously perceived visceral sensations the ANS excites or inhibits glands, cardiac and smooth muscle (Tortoro & Derrickson 2006). The two branches of the ANS (parasympathetic and sympathetic) have opposing actions. The sympathetic increases HR, force of contraction and blood pressure, increasing blood flow to muscles during exercise while the parasympathetic reduces heart rate and blood pressure. The balance between the parasympathetic and sympathetic nervous systems indicates how relaxed the body is (the greater the parasympathetic input); the higher the HRV, the more relaxed the body is.

Autonomic activity becomes altered during exercise, characterized by a marked decrease in HRV during exercise (due to vagal withdrawal) which has been demonstrated with increased workloads (Bernardi et al. 1990; Blain et al. 2005; Perini et al. 2000). This suggests the harder the exercise bout, the bigger the decrease in HRV (Kaikkonen et al. 2007; Mourot et al. 2004b; Terziotti et al. 2001). During exercise an increase in sympathetic activity and a decrease in parasympathetic activity occur (Gladwell et al. 2010; Perini & Veicsteinas 2003); this could outlast the cessation of exercise by up to 24-hours (Furlan et al. 1993; Pober et al. 2004).

Following exercise the body needs a recovery period (Wenger & Bell 1986). In the present thesis, HRV Ithlete measurements have been demonstrated as an easy, non-invasive measure which can be used to assess how well the body has recovered from exercise. Using the moving average of the previous seven days, Ithlete indicates when HRV falls outside 1x SD of the moving average. With different colours indicating to the user how well the body has recovered (i.e. HRV 1xSD below represented by amber compared with HRV 2xSD above represented by green), making it easy for the user to recognize and change their exercise regime accordingly.

Periodization involves changing exercise in regular periods or intervals to make the body work hard for fitness gains but also provide adequate rest. Ithlete was developed for athletes who typically do systematic periodization involving specific training periods for their exercise training whereas the patients in this study do not necessarily follow that pattern. Patients within the present study were asked to follow an incremental walking exercise programme, where they had four walking levels to progress through. A meta-analysis of trials comparing training using periodization vs. non-periodization found greater training adaptations in those who did periodized training for all age groups, both genders and people of different training backgrounds (Rhea & Alderman 2004). This form of cardiac rehabilitation has been suggested as a useful tool for getting better fitness results (de Macedo et al. 2011). While the volume and intensity are a long way removed from that undertaken by athletes, patients following the CR programme in the present study were therefore, undertaking a form of periodization. The periodization occurred as patients progressed from one level to the other, and were instructed only to do so, when they had successfully completed the level before.

Success within the present study was characterized by patientõs achieving the required amount of steps for that week without reporting any severe symptoms of fatigue such as shortness of breath or of excessive tiredness following the exercise session. Patients could choose to remain on the same level for up to three weeks (especially if they were experiencing any symptoms). The potential benefit of Ithlete for the patients in the present study however, lies in its short measurement duration and detection of changes in HRV over time. Ithlete provides patients with daily feedback on their bodyõs response to the CR programme. Ithlete can also be used as an online tool, as patients can upload their measurements through email to their practitioner to get feedback from them on how they have performed. Patients were not asked to upload measurements within the present study, because they attended clinic every 4 weeks with the heart failure specialist nurse. After discussion with the clinical team, it was decided that there was not a sufficient amount of time to train patients on how to upload their measurements. Potential problems with patient confidentiality when sending measurements from the device were also a concern. Measurements were consequently downloaded and paperwork was collected each time patients attended the clinic (approximately every 4 weeks).

Another potential advantage of Ithlete would be the capability to prevent overexertion in patients with HF. To keep track of how patients are adapting to exercise, practitioners could monitor exercise training goals and follow Ithlete readings to see how patients are adapting to the exercise programme. With the use of Ithlete practitioners have a useful tool for helping both themselves and the patient assess their goals. The cost of the Ithlete kit (iPod touch + charger, Ithlete dongle, ECG chest strap) is approximately £230. This is considerably cheaper than other measurement devices typically used within the HF population for home telemonitoring. The cost of telemonitoring devices is not often reported, instead the overall cost of treatment including telemonitoring vs. normal care is often compared or the cost of hospitalization for a telemonitored group vs. a control group. The Honeywell HomMed Sentry system has been used in various studies (Alaoui et al. 2003; Dar et al. 2009; Levine et al. 2006; Martínez et al. 2006; Riley & Cowie 2009), with an approximate cost of $899 (£550). Telemedicine has been adopted as an efficient approach and important feature of heart failure management with decreased rates of morbidity and mortality (Clark et al. 2007; Clarke et al. 2011; Inglis et al. 2011; Klersy et al. 2009). Only a few selected studies have contradicted these results. Two random control trials in HF did not find reduced morbidity or mortality rates, along with another study including elderly patients with multiple health issues. However, overall results for telemonitoring find advantages to its use over normal care (Chen et al. 2013). Mobile phone monitoring has been demonstrated as useful tool for HF patients, providing improved quality of life through improved self care and clinical management (Seto et al. 2012).

11.4.5 Adherence to the cardiac rehabilitation programme

In the present study, 58% adhered to the CR programme by completing at least two levels of the home-based walking programme. Reasons cited by the patients who did not complete the programme were that the programme took up too much time, or that they did not feel comfortable enough to progress to the next walking level of the programme. Some patients fell ill, or had physical injuries such as knee, ankle or hip problems that became too painful during their walking exercises. Two patients went in for surgical procedures during the CR programme and were unable to complete the programme due to not feeling well enough to continue. The length of the CR programme in the present study was chosen based on the literature. The average CR programme lasts for approximately eight-weeks (Brodie et al. 2006). Delaney et al, 2005 assessed the effect of exercise training on cardiac autonomic function in a six-month CR programme, and reported the majority of changes in autonomic function occurred in the first three months (Delaney et al. 2005). Also an initial increase in cardiac autonomic activity was demonstrated in the first 12-weeks followed by a óplateauô effect (ibid).

Research examining adherence to CR programmes is conflicting, with a comparison often being made between home-based and centre-based CR programmes. Two reviews of CR programmes reported that most studies found no significant difference between the two methods (Dalal et al. 2007; Jolly et al. 2009). In the reviews, no studies reported higher adherence in centre-based programmes but two studies did report significantly higher adherence in home-based CR programmes (Arthur et al. 2002; Marchionni et al. 2003). Home-based rehabilitation provides a more flexible, menu-driven approach to CR and therefore presents the opportunity to improve uptake and delivery of CR programmes (Blair et al. 2011). With centre-based CR programme attendance averaging below 50% (Grace et al. 2011; Martin et al. 2012), offering alternatives to patients is important with the aim of increasing CR uptake and programme completion.

The definition of adherence differs between studies (Dalal et al. 2010). Therefore Dalal et al, (2010) reported adherence based on those who had follow-up data. In the present study, 82.6% of participants adhered to the CR programme; adherence was defined as those who attended their follow-up appointment and completed a second 6MWT. The present study had high adherence to the CR programme, which is in contrast to many CR programmes where reported attendance was below 50% (Beswick et al. 2005; Jolly et al. 2007). A major factor for non-adherence in home-based CR programmes was due to patientsô lack of motivation to do exercise on their own at home (Jolly et al. 2003). The use of a monitoring device may help to keep patients motivated.

Current delivery approaches are not suitable for everyone (Thomas 2007), and therefore other resources to help improve CR programme uptake are becoming more mainstream. For example, a new online CR programme called óActivate your heartô was launched in Leicestershire in early 2012 http://www.activateyourheart.org.uk/. The programme offers educational resources for patients to learn more about their diagnosis as well as the anatomy and physiology of the heart. Patients can interact with a CR specialist or other participants in the programme in a forum, and can monitor their weight, stress and exercise levels online through the website. Initiatives like this programme will go a long way towards helping improve both CR uptake and participation across the UK. This is the only programme of its kind at the moment so far, and it is important that if successful, it is put into effect all over the UK. Depending on patientsô preferences and needs for rehabilitation delivery, various options should be available to help maximize uptake (Jolly et al. 2009). The use of internet-based technology and mobile phone for programme delivery (ómHealthô) could provide a more effective and efficient ways to reach more people and get them involved in rehabilitation (Krishna et al. 2009). Therefore mobile applications such as Ithlete could improve CR uptake and compliance.

Walking may be most likely to appeal to inactive people (Scottish 2003). It has been suggested that the use of a combined programme including goal-setting and the use of pedometers was effective for increasing walking by up to 2500 steps/day (Bravata et al. 2007; Kang et al. 2009). In a systematic review focusing on walking interventions these authors found that individualised, focused interventions assisted extensively with increasing the physical activity levels of the most sedentary. They also found, however that improvements were often short term (less than 12 months) but that this may have been due to a lack of longitudinal data collected in studies (Ogilvie et al. 2007). Furthermore many of the studies in the systematic review did not provide much evidence on what occurs when wider implementation of walking interventions are put in place because they were based on small, volunteer or convenience samples (ibid). The present study provided patients with HF daily feedback on how their body responded to exercise while completing their walking programme. The present study sample was relatively small, but over 80% of patients reported they would like to continue using the device as an exercise-guidance tool to help them maintain their exercise regime. The low cost and easy accessibility to the device makes it more likely that patients would continue using the device through their own iPod touch or smartphone.

11.4.6 Cardiac rehabilitation programme recruitment

In the latest CR report for the UK, patient recruitment from those eligible for CR is still under 50% (BACPR 2012). For patients with HF in particular, recruitment is lower compared with the three main groups (MI, PCI, CABG) because 15% CR programmes in the UK exclude HF patients (ibid). Recruitment of patients proved to be a difficult task throughout the present research study. The study began at a hospital in London with a Consultant Cardiologist and a Specialist Heart Failure Nurse. The Consultant Cardiologist would see approximately 10-15 patients in each cardiology clinic and of those patients only three or four would meet the inclusion criteria. Of those that were suitable many of the older patients were reluctant to take home the device because it was too technical or thought to be too complicated. Some reported that they would not have the time to take daily measurements and keep record of daily physical activity. Patients also voiced concerns about having enough time to meet the walking requirements for each level in the CR programme, despite being told how beneficial it could be to their health. Some patients despite meeting the criteria were still not deemed suitable because of comorbidities such as chronic obstructive pulmonary disorder (COPD) or being wheelchair bound. Comorbidities are prevalent in heart failure patients with the most common being diabetes mellitus, renal insufficiency, COPD, sleep apnoea and anaemia (Widmer 2011). Due to this prevalence, maximizing recruitment was very important.

The researcher attended clinics 5 days/week for 17 months to maximize recruitment; this frequently involved attending one hospital in the morning and then another in the afternoon. Following up with patients became increasingly difficult as the study progressed and therefore patients had to be prioritized based on what stage in the research project they had progressed to. Some patients received a phone-call follow-up instead of in person if this was deemed appropriate, and patients were always offered an alternative time to see the researcher if they were not able to be present during their appointment time with either the consultant cardiologist or the heart failure specialist nurse. Telemonitoring together with structured telephone support provided a significant reduction in the risk for CHF hospitalization (Inglis et al. 2011), and therefore telephone support was also used within the present study.

Brisk walking is moderate-intensity physical activity, which is of sufficient intensity to provide health benefits (Ainsworth et al. 2011; Murtagh et al. 2002). Therefore each patient was given information about the benefits of walking. Patients were also given an information sheet about their home-rehabilitation plan with suggestions on how to structure their exercise. The importance of stretching daily was emphasized, along with recommendations on what stretches to execute (Page 2012). The information sheet discussed warm-ups, static stretching, building up exercises gradually and trying to fit in something every day, even if it was just a few minutes of stretching. When patients found that exercise sessions became easier (easy was defined as when patients were not breaking a sweat or breathing heavier during exercise), patients were encouraged to decrease breaks (either frequency or duration), increase the duration of exercise (by 5-7.5 minutes) or intensity of their exercise (increase walking speed or carry small weights of no more than 2kg to provide resistance). Improved muscular strength and reduced body fat are demonstrated outcomes of combined aerobic and resistance training in cardiac rehabilitation (Oka et al. 2000; Pierson et al. 2001).

11.4.7 Limitations

Before the CR programme commenced, several participants voiced concerns about having enough time to complete the exercise requirements at each stage of the exercise programme. This may have accounted for the number of participants who did not complete the CR programme. Participants were also asked to use a pedometer daily for measurements of their steps. Some patients reported that they forgot to wear the pedometer on some days, or only remembered to put it on part-way through the day. Other issues reported were loss of the pedometer, or the pedometer stopped working and this led to some inaccuracies in the amount of steps accounted for with some participants. A reported key problem with pedometer measurements in general, is the inability to distinguish between varying intensities of vertical displacement. This means that sprinting 100 steps vs. walking 100 steps would be counted as the same amount of steps despite differences in vertical displacement and therefore intensity of exercise (Berlin et al. 2006). This is however, less of an issue in the present study population; as patients with HF are unlikely to have large variation in the intensity of vertical displacement. Despite these inherent problems, pedometers have become an important tool for accurate measurement of ambulatory behaviour (ibid). Pedometers ability to capture intermittent or continuous activity participation throughout an assessment period (Berlin et al. 2006), make it advantageous for CR programmes. However using pedometers as both the intervention and the measurement tool is not ideal. Research has demonstrated that pedometer users increase their physical activity by an average of 27% (Bravata et al. 2007). To counteract this issue, patients served as their own controls in (Phase two) by wearing the pedometer initially for at least one month before commencing the CR programme.

Participants were also asked to record their exercise activity daily in calendars provided. Participants had to choose the workout zone for the rate of intensity they had achieved during their workout. The zones were low/moderate/high and this was a very subjective measure. For some patients this concept seemed hard to grasp as they did not have much energy to carry out their daily activities. They reported that everything they did felt like it was at high intensity because it took so much effort to carry out. This could have affected the comparisons between participants due to the subjectivity of the measurement. It was hard to gauge how well they adhered to the described intensity zones within one workout. If participants exercised in more than one zone within a given workout, they were instructed to only record the zone they thought they did the most exercise in. This again was quite subjective; however a large range of activity levels within the participants should have helped counter that effect.

11.5 Conclusion

The CR programme improved functional capacity in patients. Over 65% of patients who participated in the CR programme demonstrated a dip in rMSSD at 24 and 48-hours after exercise was reported. This is in contrast to HF patients not involved in a CR programme (observed in chapter nine). This suggests physiological adaptations occurred in the CR groups in the days following exercise as a result of the CR programme. The CR programme facilitated heavy enough exercise to cause a dip in rMSSD in almost 80% of patients for 24-hours after exercise was reported. These results are in agreement with research advocating HRV as a guide for exercise (Kiviniemi et al. 2010; Manzi et al. 2009). As there was such a high percentage dip after 24-hours, this advocates the use of Ithlete daily within the HF population during a CR programme to gauge recovery from exercise.

Due to their symptoms, HF patients in NYHA classes II-IV have limitations to their ordinary ability to perform physical activity, perhaps making it more difficult to perform exercise heavy enough to cause attenuation in HRV. This underlines the importance of finding exercises (such as walking) that patients can readily participate in and gradually increase. Ithlete measurements demonstrated attenuated autonomic function following exercise in patients with HF. The Ithlete device can be explored for further use in the clinical setting, to aid CR and provide patients and clinical staff with feedback on autonomic function. Ithlete appears to be an easy device to use for HRV assessment in the HF population. Ithlete is also cost efficient when compared to other medical devices and provides feedback to the user which can be easily interpreted.

11.6 References

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CHAPTER 12: SUMMARY, RECOMMENDATIONS AND CONCLUSIONS

The final chapter of this thesis presents a summary of the findings from each empirical chapter and discusses overall outcomes from the thesis. The summaries follow the British Medical Journal model in the form of brief bullet points. For each empirical data chapter what was already known prior to the study is stated, followed by what the research in that chapter adds to the body of knowledge. Directions for future research and overall conclusions are then drawn to supply the necessary significance and impact to conclude this thesis.

12.1 Review of empirical findings by chapter

Chapter 3: Comparison of heart rate and heart rate variability (rMSSD) analysis using Polar s810i and Ithlete

What is already known:

- Heart rate variability (HRV) is a reliable and reproducible technique for assessing autonomic activity; with high correlations between time and frequency domain measures of vagal activity suggesting they can be used interchangeably.
- Ultra-short HRV (rMSSD) measurements of 10 s have high correlations with the standard 5-minute short-term recording.
- Polar s810 models have been validated for HRV measurement against ECG and Holter devices.

What this study adds:

- With respect to HRV measurement Polar s810i and Ithlete can be used interchangeably for measurements of rMSSD.
- High Pearson correlation coefficients suggest Ithlete is a valid measure for rMSSD in both healthy and heart failure subjects.
- Narrow limits of agreement suggest Ithlete is a valid measure for rMSSD in both healthy and heart failure subjects.
- Measurements of HR using Ithlete had high correlations with the Polar s810i, however there were significant differences in HR for three out of four subjects.

Chapter 4: Measurement options for body composition using bioelectrical impedance analysis devices

What is already known:

- Bioelectrical impedance analysis (BIA) is a method for estimating body composition.
- BIA devices offer a variety of measurements which can include total body water (TBW), free fat mass (FFM), fat mass (FM).
- Tanita BIA scales have been validated against hydrostatic weighing and dual-energy x-ray analysis.

What this study adds:

- Good relative agreement was demonstrated for body composition measurements between five BIA devices.
- Good relative agreement suggests that it is acceptable to use any of those BIA devices, both at home and in the clinical setting.
- The difference between devices was not significant except for one device indicating that price may not be an important factor in deciding which BIA device to use.
- Use of BIA devices in the home and the clinical setting may be more affordable than previously thought.

Chapter 5: The relationship between Ithlete measurements and body composition assessed by bioelectrical impedance analysis body composition

What is already known:

- An impaired HRV is associated with an increased risk of CV disease, type II diabetes and insulin resistance.
- Increased body fat, BMI and weight are known as risk factors for increased CV disease, diabetes, metabolic syndrome etc.

What this study adds:

- Relationships were demonstrated between rMSSD, HR and body composition measurements when compared by gender, ethnicity, BMI and body fat %.

- This study found no significant ethnic or gender differences in rMSSD.
- HRV was negatively correlated with body fat and age.
- HR was negatively correlated with height, total body water, muscle, BMR, age and alcohol units.

Chapter 6: Heart rate variability in healthy Caucasian and South Asian participants

What is already known:

- Only two studies have assessed the differences in HRV between Caucasians and South Asians, neither of which were undertaken in the UK.
- Higher body fat percentage, abdominal obesity and higher liver fat content exist in the South Asian population when compared with their Caucasian counterparts of the same BMI.

What this study adds:

- No significant difference was found in rMSSD or HR between South Asian and Caucasian participants when controlled for gender and age.
- The average rMSSD values were 71.1 ± 10.1 ms in South Asians compared with 67.9 ± 10.5 ms in Caucasians.
- Significant differences in BMI, TBW and BMR were demonstrated between Caucasian and South Asian participants.

Chapter 7: The relationship between heart rate variability (HRV), body composition and aerobic capacity measurements in healthy participants with varying physical activity levels.

What is already known:

- Exercise capacity has been expressed as the best predictor of mortality.
- Decreased HRV is an independent risk factor for morbidity and mortality; increased HRV is a measure of good health and physical fitness.
- Different habitual levels of physical activity may cause changes in HRV.
- HRV is affected by body composition.

What this study adds:

- Resting rMSSD measurements obtained from Ithlete software were correlated with Vo_2 peak, HR, WC, weight and BMI.
- Resting HR was correlated with age.
- A significant correlation was demonstrated between rMSSD and Vo_2 peak.
- The average TBW for both male and female participants in this study was below the healthy average.
- The mean Vo_2 peak for males (29.52 ± 6.9 kg/ml/min) and females (25.68 ± 4.9 kg/ml/min) in this study were lower than published normal sedentary averages, suggesting poor fitness levels of the participants.
- HRV for male and female participants in this study were found to be similar to other studies despite the mean Vo_2 peak for both males and females being lower than average.

Chapter 8: Heart rate variability measurement in healthy subjects with varying physical activity levels using Ithlete software

What is already known:

- There are no established normal values for HRV which constitute a healthy measure; HRV is thought to be a very individual measure.
- Exercise training has a positive effect on HRV. An initial dip in HRV is expected following exercise; however over time exercise improves HRV.
- TRaining IMPulse (TRIMP) is a method for quantifying training and can be important for assessing how much impact training/exercise has on the body.

What this study adds:

- Using TRIMP, a dip in HRV following exercise was demonstrated for 24, 48 and 72-hours following exercise; the highest percentage of participants demonstrated a dip at 48 hours.
- Those who did at least 30-minutes of exercise had a lower resting HR.
- Ithlete is a feasible HRV measurement device for daily use to assess the bodyĝs response to exercise.

- The average rMSSD in healthy participants was 72.4 ± 7.4 ms for males and 69.3 ± 7.7 ms for females.

Chapter 9: Heart rate variability measurement in patients with heart failure with varying physical activity levels using Ithlete software

What is already known:

- Heart failure (HF) is associated with reduced autonomic function; depressed HRV levels are commonly identified as a risk factor for sudden cardiac death.
- HRV provides a non-invasive indirect measurement of autonomic control of the heart, making it an ideal measurement to use in patients with HF.

What this study adds:

- A dip in HRV 24 hours following exercise was found in 46.5% of HF patients; 48-hours following exercise, 65.1% demonstrated a dip in HRV.
- Ithlete measurements of rMSSD and HR in HF patients were completed on a consistent basis for at least twenty-eight days by 46% of patients, a further 23% were able to take measurements, but did not complete a full 28-day cycle.
- Participants reported that the device was easy to use and most did not have any trouble taking measurements on a daily basis.

Chapter 10: Adherence, reference values and user assessment of Ithlete heart rate variability (HRV) measurements in patients with heart failure

What is already known:

- Average HRV values have been published in various studies in both healthy and diseased populations; however there is still no clear standard reference.
- Clinical use of HRV has not yet been accepted as common practice.

What this study adds:

- Most participants reported that the device was quick and easy to use on a daily basis; 89.5% stated that they enjoyed using Ithlete.

- 100% of patients said they would recommend the device to other patients and 94% stated that the measurements were not too time-consuming.
- Average rMSSD values for HF patients were demonstrated within the range of 63.7-71.8 ms.

Chapter 11: Implementation and evaluation of a heart rate variability (HRV) guided cardiac rehabilitation programme with heart failure patients using the Ithlete

What is already known:

- Cardiac rehabilitation (CR) is a medically supervised programme designed to improve the health and wellbeing of people with heart conditions such as heart failure, but optimal physical activity levels of those participating in CR have not yet been established.
- CR has demonstrated improvement in physical health and a decrease in subsequent morbidity and mortality.
- There is a good correlation between the distance covered by patients in a 6MWT and maximal oxygen uptake.

What this study adds:

- Decreased rMSSD 24-hours following exercise was demonstrated in 78.9% of HF patients who participated in the CR programme, 48-hours following exercise 68.4% demonstrated a dip in HRV.
- The 6MWT demonstrated improvements in each NYHA class in the overall distance patients were able to cover in the test after the CR programme.
- Ithlete appears to be an easy device to use for capturing daily rMSSD and HR.
- Patients reported that it was easy to follow Ithlete indications on when to exercise and when to rest.
- Patients enjoyed receiving feedback from Ithlete and felt more secure about their exercise programme.
- Ithlete is also cost efficient when compared to other medical devices and provides feedback to the user which can be easily interpreted.

12.2 Evaluation of aims and objectives

The primary aim of this thesis was to explore the potential of using home-based devices such as Ithlete and bioelectrical impedance analysis (BIA) scales to supplement clinical care for patients with HF. Each empirical data chapter within this thesis provided evidence to support the use of these devices in both healthy and HF populations. Chapter three demonstrated that Ithlete is a valid measure of rMSSD in patients with HF and healthy participants. Chapter four demonstrated good relative agreement between several BIA devices. Chapter five demonstrated no significant differences in rMSSD between Caucasian and South Asian participants, but did find significant differences in BMI, TBW and BMR. Chapter six demonstrated a significant correlation between rMSSD and Vo_2 peak. In chapter seven, significant relationships were demonstrated between rMSSD, HR and body composition measurements. Chapter eight demonstrated Ithlete as a feasible measurement technique for capturing rMSSD daily in healthy participants. Chapter nine demonstrated the feasibility of Ithlete measurements daily in patients with HF. In chapter ten, approximately 90% of participants enjoyed using the Ithlete device and a reference range for HF patients using Ithlete was established (63.6-71.8 ms). Finally in chapter eleven, 90% completed the HRV-guided CR programme and reported that daily feedback from the device enhanced their CR programme experience.

This thesis also had several secondary aims, first was to determine the feasibility of collecting daily HRV measurements using a new personal HRV monitor (Ithlete) in participants with HF. The validity of Ithlete rMSSD measurements were tested against the Polar heart rate monitor and good correlations were found. Healthy participants and patients with HF completed measurements for at least 28 days to test the usability of the device. Normal ranges of rMSSD for both groups using the Ithlete device were also analysed. Forty-six percent of HF patients were able to take daily measurements for at least 28 days. In healthy subjects the normal range of rMSSD using Ithlete was 65.1-87.7 ms; in HF patients the normal range was 63.7-71.8 ms rMSSD. The difference in range was to expected as HF patients are known to have decreased autonomic function (Fauchier et al. 1997; Marijon et al. 2010; Nolan et al. 1998).

This thesis also examined how other correlates such as aerobic capacity, body composition, comorbidities and medication might affect daily rMSSD measurements. In healthy participants, correlations were demonstrated between rMSSD, body composition and aerobic capacity. As Ithlete is a quick and convenient measurement device, it has great potential for use in clinical practice. Since Ithlete rMSSD measurements have shown the same correlations with aerobic capacity and body fat in healthy participants as other measures, the use of Ithlete in conjunction with these other measurements could potentially improve patient care by highlighting those patients who are at increased risk. Originally participants with HF were to be tested using one of the body composition devices validated within this thesis (Chapter four), to test if those same correlations exist between Ithlete measures in HF patients. Circumstances however, led to that not being possible. The main issue was that an unforeseen amount of patients recruited within this study had implantable cardioverter defibrillators (ICD), which cannot be used with BIA devices.

Finally, the use of Ithlete software to monitor patients during a CR programme using daily rMSSD measurements was successful. Patients stated that they enjoyed getting feedback from the device daily and took rest days when the device advised them to.

This thesis has served as the spring-board for the potential use of the Ithlete device for CR. A few patients reported having trouble using the device or thought daily measurements were too time consuming and therefore did not complete the measurements. Approximately 50% of heart failure participants enrolled in the study completed the required amount of measurements and were satisfied with the device. A further 23% were satisfied with the device, but did not complete the required amount of measurements. Adherence to telemonitoring in patients with HF has been reported as low as 14% (Chaudhry et al. 2007) and as high as 95% (Scherr et al. 2009); therefore the results from the present study are encouraging. The majority of the previous telemonitoring studies based adherence on measurements taken at least three times per week. The present study however, based adherence on daily measurements and therefore HF patients needed a higher frequency of measurements in order to be considered compliant. Overall patients thought they benefitted from receiving feedback. The clinical staff involved in the study liked the idea of having another measure they could analyse and use as an indicator of increased risks i.e. worsening symptoms, sudden cardiac death.

12.3 Recommendations

The prognostic value of HRV measures in patients with heart failure has been demonstrated (Adamson et al. 2004; Bilchick et al. 2002; Chattipakorn et al. 2007; La Rovere et al. 2003; Ponikowski et al. 1997; Sandercock & Brodie 2006). Several studies have reported improvements in HRV in patients with HF following an exercise programme (Kubinyi et al. 2003; Murad et al. 2012; Routledge et al. 2010; Selig et al. 2004). The use of HRV as a training tool in HF has yet to be explored in full detail. With further development of reliable short-term HRV analysis devices, individuals and practitioners have easier access to HRV assessment tools at a lower cost. Because Ithlete works with smartphones or an iPod touch, it is easily accessible to the general public and costs less than other devices. Future research in a larger cohort of participants using Ithlete would help clarify its potential use in clinical populations. As the popularity of smartphones increases, the use of application software such as Ithlete in healthcare will be a useful tool for both patients and practitioners.

When considering the relationship between HRV measurements such as rMSSD and other cardiovascular risks, further research can elucidate what differences may occur between different populations and why. Making individuals aware that they are potentially at higher risk may have an affect on their lifestyle choices and consequently their health. Future research on the effects of exercise on HRV over various time periods with a large cohort of participants could be very beneficial in the assessment of the effect of exercise on the body over time. Monitoring body composition with BIA devices in clinical practice has potential but needs further investigation. Identifying what relationships may exist between HRV/HR and body composition in special populations such as heart failure and diabetes may help highlight those at increased risk. Knowledge of these relationships and how they develop over time could lead to improvement in care and prevention.

For patients with HF, the Ithlete device can be explored for use in the clinical setting to aid in CR and provide patients and clinical staff with daily feedback on autonomic function. Ithlete could also help keep patients motivated through staff and individual monitoring of responses to exercise over time. With Ithlete, patients can correlate their bodyø response with their exercise patterns and determine what exercise regime is best for them. Once patients have completed a six-eight week CR training programme, they can continue to use Ithlete to keep them on track and monitor their progress. There are a number of fitness applications on the market; this study has demonstrated the potential of one application. Future research should focus on finding other applications that could also be utilized to help patients keep active, monitor their progress and reach targets to improve their health and wellbeing.

12.4 Conclusions

Ithlete monitors the bodyø autonomic response to exercise volume on a daily basis. Since impaired autonomic function is associated with overtraining, Ithlete was developed as a tool to monitor recovery from exercise with the aim of preventing overtraining. Within this thesis, Ithlete was tested with both healthy participants and patients with HF and appears to be an easy device to use for HRV analysis. Ithlete is also cost efficient when compared to other medical devices and provides immediate feedback to the user which can be easily interpreted. The benefit of Ithlete for patients lies in its short measurement duration and detection of changes in rMSSD over time to give patients feedback on their bodyø response to exercise and stress. With increasing cutbacks in the NHS this tool could be used to help clinicians monitor patientsô recovery from an exercise programme. Ithlete could also be used to guide exercise intensity and volume changes throughout an exercise programme. Furthermore, clinicians could use Ithlete to monitor HRV over time to identify those at increased risk of cardiac events.

In addition, this thesis assessed the important interactions between clinical measures such as HRV, HR, aerobic capacity and body composition. Each measurement has independently been established as a risk factor for cardiovascular disease. The use of these measurements together may provide clinicians with a clearer idea of the patientsô increased risk for disease. Different tools were evaluated throughout this piece of work, many of which are at low cost compared to conventional medical devices and therefore contribute valuable information for clinicians as they try to improve patient care on increasingly lower budgets. This thesis provides evidence for the use of new technology in clinical practice and advocates more research to be undertaken to ensure patient care can indeed improve, despite the increasingly tough economic climate in healthcare. The findings of this thesis support the use of mobile applications as tools in medical practice and further encourage the use of HRV in patients with HF.

12.5 References

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APPENDIX I

Average HRV, HR, Indication, TRIMP and Day Scale for each healthy participant

Age	Gender	HRV	HR	Indication	TRIMP	Day Scale
30	F	78.6 ± 2.9	70.0 ± 3.6	1.33 (N)	83.1 ± 49.6	84.5 ± 7.8
25	F	60.1 ± 5.9	102.8 ± 8.1	1.46 (N)	44.6 ± 96.9	67.7 ± 13.3
33	F	65.9 ± 5.9	64.6 ± 3.6	1.44 (N)	106.1 ± 130.3	
30	M	59.4 ± 6.0	82.8 ± 7.7	1.48 (N)	123.6 ± 97.2	68.4 ± 40.3
32	M	77.5 ± 17.4	63.1 ± 11.4	1.25 (N)	n/a	n/a
25	M	73.4 ± 5.6	68.3 ± 3.6	1.29 (N)	125.6 ± 149	80.8 ± 28.3
28	F	80.3 ± 4.1	65.0 ± 4.1	1.44 (N)	105.0 ± 110.1	62.0 ± 13.0
32	M	78.4 ± 7.3	60.4 ± 6.0	1.37 (N)	71.7 ± 55.7	72.6 ± 8.9
34	M	73.1 ± 6.4	75.1 ± 9.1	1.62 (G)	59.2 ± 70.1	74.0 ± 7.5
64	M	83.1 ± 8.4	48.2 ± 3.9	1.22 (N)	50.0 ± 47.9	58.4 ± 9.9
28	F	68.8 ± 5.5	85.2 ± 9.7	1.33 (N)	n/a	n/a
31	F	76.1 ± 9.7	66.7 ± 8.4	1.22 (N)	149.0 ± 185.4	55.2 ± 12.7
25	F	70.0 ± 7.5	77.9 ± 7.5	1.45 (N)	34.1 ± 42.9	64.1 ± 15.5
36	M	78.4 ± 4.7	63.1 ± 4.0	1.41 (N)	0	62.7 ± 14.8
42	F	62.0 ± 14.2	67.2 ± 10.6	1.38 (N)	73.2 ± 86.7	47.0 ± 32.1
51	M	65.3 ± 4.1	80.0 ± 5.9	1.48 (N)	123.4 ± 76.2	88.3 ± 3.8
27	F	71.3 ± 7.0	75.2 ± 9.7	1.42 (N)	40.4 ± 32.8	90.0 ± 0.0
27	F	46.0 ± 12.7	95.9 ± 16.8	1.20 (N)	121.8 ± 215.8	46.4 ± 33.6
28	F	77.7 ± 15.4	64.9 ± 4.7	1.72 (G)	54.0 ± 48.1	71.7 ± 7.4
29	M	59.5 ± 6.2	79.5 ± 5.0	1.38 (N)	n/a	n/a
28	F	72.7 ± 6.2	74.6 ± 7.3	1.34 (N)	43.7 ± 43.0	72.7 ± 8.0
29	M	67.3 ± 6.9	62.5 ± 5.7	1.38 (N)	170.7 ± 158.4	87.9 ± 5.7

56	M	65.8 ± 14.5	76.1 ± 4.1	1.34 (N)	54.8 ± 58.3	69.3 ± 38.6
27	F	74.2 ± 6.2	70.5 ± 6.8	1.28 (N)	67.7 ± 70.4	76.1 ± 23.5
32	F	74.2 ± 6.2	70.5 ± 6.8	1.38 (N)	67.7 ± 70.4	76.1 ± 23.5
29	F	76.9 ± 6.2	65.4 ± 4.1	1.35 (N)	160.5 ± 176.2	78.9 ± 8.3
28	M	80.6 ± 6.6	63.3 ± 7.3	1.31 (N)	52.2 ± 71.6	84.9 ± 5.6
29	F	58.8± 4.7	100.0 ± 6.7	1.38 (N)	113.3± 76.7	90.7± 5.8
28	M	82.4± 3.9	57.2± 3.4	1.52 (G)	113.1± 88.2	78.3± 29.2

Appendix I is a table demonstrating average components for each healthy participant from Chapter 8. Age is displayed in years, HRV is displayed in rMSSD, HR is displayed in beats per minute (bpm), and Indication is displayed as an average number which corresponds to 1 of the 4 colour indications. These indications are displayed in the table as an average number which corresponds to 1 of the 4 colour indications (1-1.5=Blue for normal recovery, 1.5-2.5=Green for good recovery, 2.5-3.5=Amber for not the best recovery, 3.5-4=Red for bad recovery). More specifically, amber represents the first day when HRV is more than 1 x SD (standard deviation of natural log transformed rMSSD) below the moving average of the previous 7 days (so excluding the most recent recorded value); red represents the second day when this condition is true (i.e. two successive days when the current value is more than 1x SD below the moving average blue line) and green represents a rise of more than 2 x SD compared to the previous day. Green is intended to indicate good recovery and signifies that the body is ready for harder training. TRIMP is displayed as an average of intensity multiplied by duration and Day Scale is displayed as a percentage.

APPENDIX II

Average HRV, HR, Indication, TRIMP and Day Scale for each heart failure participant

Age	Gender	HRV	HR	Indication	TRIMP	Day Scale
48	M	74.2	86.7	1.4 ± 0.8	190.9 ± 113.9	65.6 ± 5.4
63	M	50	88.8	1.7 ± 1.3	44.7 ± 60.1	41.0 ± 15.6
59	M	68.4	75.4	1.5 ± 0.8	208.6 ± 234.5	58.3 ± 32.5
60	M	78.2	111.7	1.4 ± 0.8	183.6 ± 95.1	45.1 ± 6.0
82	M	87.3	82.4	1.8 ± 1.1	173.0 ± 189.7	30.7 ± 26.4
78	M	54.3	89.4	1.9 ± 1.2	32.1 ± 27.4	17.3 ± 34.5
74	M	87.6	81.9	1.5 ± 0.9	55.3 ± 97.0	75.8 ± 7.1
69	M	72.4	77.9	1.6 ± 1.0	308.1 ± 251.7	42.0 ± 36.1
54	M	88.4	76	2.1 ± 1.4	138.1 ± 126.1	58.6 ± 20.4
54	M	74	86	1.4 ± 0.8	165.4 ± 213.4	53.8 ± 35.4
69	M	77	84.7	1.5 ± 1.0	84.1 ± 68.0	57.5 ± 12.7
61	M	75.3	95.5	1.4 ± 0.7	22.9 ± 40.2	0
36	M	63.2	89.9	1.2 ± 0.6	90.0 ± 67.1	31.4 ± 20.5
68	M	84.2	76	1.7 ± 0.9	85.7 ± 85.0	64.7 ± 18.1
56	M	66.7	77	1.5 ± 0.9	61.7 ± 82.7	68.1 ± 5.7
56	M	90.8	71.9	1.6 ± 1.1	39.1 ± 17.3	66.5 ± 5.8
71	M	90.5	74.6	1.1 ± 0.4	69.1 ± 92.6	88.2 ± 3.1
44	F	75.3	79.3	1.1 ± 0.3	212.1 ± 109.4	73.6 ± 10.8
73	F	78.2	94.2	1.6 ± 1.0	127.1 ± 57.3	88.1 ± 5.4
80	M	70.2	80.9	1.5 ± 0.9	128.3 ± 90.6	80.0 ± 0
43	F	67.8	107.5	1.4 ± 0.9	48.6 ± 32.2	61.0 ± 34.3
65	M	85.4	67.1	1.2 ± 0.6	75.0 ± 46.7	0

68	M	87.4	81.3	1.5 ± 0.9	117.9 ± 106.9	62.5 ± 12.2
70	M	94.4	80.4	1.3 ± 0.7	120.0 ± 62.0	80.0 ± 16.9
56	M	66.4	91.2	1.3 ± 0.7	52.7 ±62.6	56.8 ± 6.6
71	F	85.5	70.1	1.5 ± 0.8	71.6 ± 58.5	47.0 ± 17.8
77	M	76.8	72.3	1.4 ± 0.8	185.0 ± 154.2	47.0 ± 23.4
64	F	69.1	83.6	1.5 ± 0.9	98.0 ± 57.9	72.7 ± 17.6
74	M	93.4	72.4	1.6 ± 1.1	35.6 ± 40.7	62.7 ± 10.5
74	M	74.5	79.2	1.6 ± 1.0	77.1 ± 49.9	55.7 ± 15.7
63	M	72.2	88.6	1.5 ± 1.0	129.4 ± 116.9	93.6 ± 3.1
63	M	76.6	86.9	1.5 ± 0.9	171.4 ± 95.1	87.1 ± 24.7
59	M	63.8	71.1	1.3 ± 0.8	135.0 ± 156.1	85.6 ± 5.1
59	M	71.9	70.7	1.5 ± 1.0	229.7 ± 214.8	81.0 ± 11.0
64	M	81.7	75.9	1.5 ± 1.0	16.1 ± 11.0	41.3 ± 6.4
60	M	72.7	77	1.3 ± 0.8	46.6 ± 31.3	0
78	M	80.2	85.1	1.2 ± 0.6	220.7 ± 103.2	0
74	M	94.7	81.4	1.4 ± 0.9	35.5 ± 30.3	63.2 ± 9.7
24	M	77.8	85.1	1.1 ± 0.5	23.9 ± 6.5	59.8 ± 7.5
43	M	76.7	86.1	1.5 ± 1.0	24.5 ± 23.2	88.3 ± 2.9
56	M	88.6	72.2	1.2 ± 0.5	76.7 ± 34.8	69.4 ± 12.2
65	M	74.9	87.3	1.5 ± 1.0	22.5 ± 23.4	46.2 ± 6.3
64	M	78.2	111.7	1.4 ± 0.9	192.5 ± 110.3	45.5 ± 5.8

APPENDIX III Heart failure patient statistics

Frequency of patient co-morbidities by percentage within the study population

Comorbidity	Patient Percentage
Ischaemic heart disease	38.8%
Dilated Cardiomyopathy	34.0 %
Hypertensive	21.4 %
Chronic heart failure	10.7%
COPD	7.7%
Myocardial Infarction	7.7%
Hypercholesterolemia	5.8%
Type 1 Diabetes	5.8%
Type 2 Diabetes	3.8%
Arthritis	3.8%

Coefficient of variation for rMSSD between HF patient taking/not taking the following medications

Medication	Yes	No
Beta Blockers	13.4	12.1
ACE Inhibitors	12.7	12.3
Diuretics	14.7	11.9
Angiotensin II Receptor	12.9	13.1
Aldosterone Antagonists	15.3	12.1
Nitrate	9.4	13.6
Digoxin	10.4	13.3
Diabetic medication	10.6	13.3
Amiodarone	12.6	13.3

Coefficient of variation of rMSSD for HF patient comorbidities

Comorbidity	Yes	No
Dilated Cardiomyopathy	11.8	15.6
Ischaemic Heart Disease	16.9	9.5
Hypertension	10.8	14.9
Diabetes	14.2	13.8

Binary logistic regression

Binary logistic regression was carried out on participant results to control for the different comorbidities and medication that patients were taking during the study to assess their impact on HRV. Without controlling for medication or comorbidities, HRV values had an odds ratio of 1.007 (CI 0.802, 1.264) (p= 0.95). For two days following exercise the odds ratio was 0.976 (CI 0.774, 1.230) (p= 0.84). When controlling for medication and comorbidities the odds ratios and confidence intervals are listed in the table below. An odds ratio of 1 indicates no difference in risk between the groups, if >1 the rate of that event is increased. The confidence interval indicates the range that is likely to contain the true value within it (in studies where only a sample of the whole population is tested). When given with odds ratios this confidence interval is statistically significant when it does not include 1 (no difference in odds). This means that none of the confidence intervals below are significant as they all include one; several of the odds ratios below are slightly over one but the values are all small amounts (<0.075) therefore the likelihood of HRV being different due to that medication or comorbidity is low.

Binary logistic regression values for HF medication and common comorbidities found in the present studyǿs patient population

Medication/ Comorbidity	Odds Ratio	P-Value	Confidence Interval
Beta blockers	0.996	0.397	0.987-1.005
Diuretics	1.057	0.667	0.821-1.361
ACE inhibitor	1.003	0.978	0.791-1.273
AngiotensinII receptor	1.020	0.884	0.783-1.329
Amiodarone	1.067	0.649	0.806-1.412
Aldosterone antagonist	1.002	0.989	0.777-1.291
Nitrate	1.052	0.802	0.709-1.560
Digoxin	0.954	0.860	0.565-1.610
Diabetic medication	0.897	0.505	0.653-1.234
Dilated cardiomyopathy	0.984	0.904	0.761-1.273
Ischaemic heart disease	1.075	0.579	0.833-1.388
Hypertension	0.850	0.252	0.644-1.123
Diabetes	0.925	0.632	0.674-1.271

APPENDIX IV Modified Bruce Protocol

Modified Bruce Protocol

Stage	Speed	Grade	Duration
1	1.7 miles per hour	0%	3 Minutes
2	1.7 miles per hour	5%	3 Minutes
3	1.7 miles per hour	10%	3 Minutes
4	2.5 miles per hour	12%	3 Minutes
5	3.4 miles per hour	14%	3 Minutes
6	4.2 miles per hour	16%	3 Minutes
7	5.0 miles per hour	18%	3 Minutes

Heart rate variability measured by a novel device in participants with heart failure

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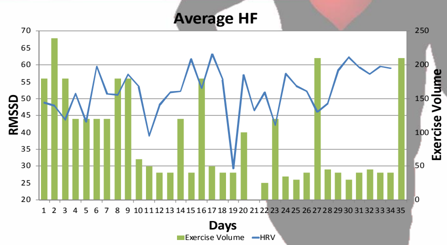
Background: Heart rate variability (HRV) is a non-invasive measure that examines autonomic influences on the heart, indicating how the body is trying to preserve its equilibrium. Thus HRV has the potential to monitor the autonomic response to exercise volume on a daily basis. A reduced level of HRV has been demonstrated to be a significant predictor of cardiac event and death.

Purpose: The aim of this study was to determine the feasibility of HRV measurements using a new personal heart rate variability monitor (Ithlete) while estimating the normal pattern for HRV in participants with heart failure.

Methods: Eighty-five participants were tested, of which 65 were male and 20 were female. Each participant received a device for daily measurement of HRV and heart rate (HR) in the seated position first thing in the morning. HRV and heart rate (HR) was measured in the seated position for at least 28 days. Participants were also asked to fill in a daily exercise diary which included exercise intensity and duration.

Results: Almost half of the 85 participants took sufficient correct measurements while they had the Ithlete device. The average HRV measurement found in this study was 48.6 ms (rMSSD). The relationship between HRV and HR was found to be negatively correlated.



Discussion: At rest HRV (rMSSD) was lower than that recorded in the literature for a healthy population. Participants with heart failure varied in their level of use of the device. Some found the device very easy to use while others cited problems. The relationship between HRV and HR was similar to the findings from other studies.

Conclusion: This study is the first to look at measurements of HRV in heart failure patients using the Ithlete device. This study could be the basis for more research into what HRV measurements are to be expected in this population and how they can be used to benefit the health and care of heart failure patients.

bucks new university

Ealing Hospital NHS Trust NHS

**This poster was published in May 2012, before the entire data collection process was completed.

Heart rate variability (HRV) in heart failure

- Study supervised by Dr Stuart D Rosen, Consultant Cardiologist and team
- Aim: to evaluate HRV daily using a new easy to use monitoring device in heart failure patients and compare the results in healthy volunteers.
- Involves simple 1-minute daily measurements
- For further information please contact: Dionne Matthew-PhD research student Bucks New University
- Tel: 01494522141extn 4415 or speak to your Cardiologist in the clinic
- Thank you for your time