THE EFFECTS OF STRESS AND RELAXATION ON HEART RATE VARIABILITY IN HEALTH AND DISEASE

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor of Philosophy by Joseph Peter Delaney, Department of Medicine, University Hospital Aintree. June 2002

DECLARATION

This thesis is the result of the work performed whilst registered as a candidate for the degree of Doctor of Philosophy at the University of Liverpool.

I declare that no portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or institute of learning.

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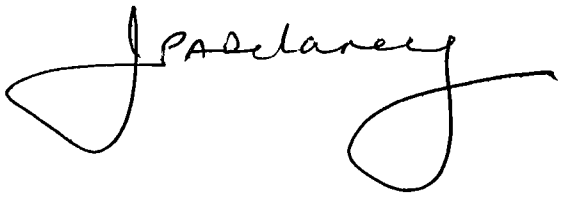

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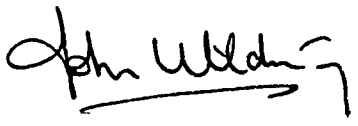

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MEMORANDUM

The author, with the following exception, performed the studies that form the basis of this thesis:

In Chapter Three, the idea and the design for the low-cost, real-time heart rate variability analysis system was from the author. The construction of the apparatus and development of the computer programme for the HRV system, under the supervision of the author, was carried out by Ian Drysdale and Dave Williams of the Electronics and Biomedical Engineering Department, Arrowe Park Hospital, Wirral, Merseyside.

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ABSTRACT

Stress management is considered to be any method that facilitates a level of arousal that is healthy, balanced and enjoyable. It can be achieved using techniques that either reduce activity of the sympathetic nervous system, increase parasympathetic tone or a combination of both. The main purpose of this thesis was to investigate the physiological and some of the psychological outcomes of several techniques popularly used to alleviate the effects of stress. To put into context the effects of the various stress management interventions, the effects of the stress response on the physiological and psychological markers used in the subsequent studies was investigated. Analysis of heart rate variability (HRV), a non-invasive method of assessing cardiac autonomic function, which describes the balance between the sympathetic and parasympathetic (vagal) components of the autonomic nervous system (ANS), was chosen as the principal method of assessing the physiological effects of the various interventions. The research investigated stress management in the form of guided imagery, music therapy, myofascial trigger-point massage therapy (MTPT), moderate aerobic exercise and certain breathing techniques. Also tested were the effects of various physical stressors (heart rate response to lying and standing and an exercise treadmill test) and stress-relieving pharmacological interventions on ANS function. Furthermore, during the course of the research a low-cost, real-time HRV system was developed and the details of its construction and validation are

reported. The results of the research show that massage therapy was effective in increasing HRV, improving cardiac autonomic tone and reducing blood pressure and subjective measures of emotional and muscle tension in both healthy and type 2 diabetic subjects. Music therapy was also effective in improving symptoms and inducing cardiovascular relaxation in type 2 diabetic patients but to a lesser extent than massage. Compared to a control group over a six-month period, cardiac rehabilitation predominantly based on moderate aerobic exercise training, proved effective in significantly increasing cardiac vagal tone and improving HRV in rehabilitation patients. Slow, rhythmical, deep breathing at six breaths per minute was shown to be highly effective in increasing HRV and baroreflex sensitivity in normal subjects. To a lesser extent mental relaxation using guided imagery also induced relaxation by significantly decreasing heart rate in normal subjects. Pharmacological blockade of the ANS yielded more variable results. In conclusion the results of this research demonstrate that several of the stress management procedures outlined above are effective in improving cardiac autonomic tone and enhancing quality of life. These techniques may prove beneficial when combined with orthodox treatments and further research should consider investigating the combined effects of some or all of these various stress reduction modalities.

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LIST OF ABBREVIATIONS

ACTH	Adrenocorticotropic hormone
AF	Autonomic function
ANS	Autonomic nervous system
AR	Autoregressive modelling
AT	Autogenic training
BMI	Body mass index
BRS	Baroreflex sensitivity
CGSA	Coarse graining spectral analysis
CHD	Coronary heart disease
CRH	Cortisol releasing hormone
DHF	Diastolic heart failure
ECG	Electrocardiogram
EMOT	Self-perceived emotional tension
ETT	Exercise treadmill test
FFT	Fast Fourier transform
GI	Guided imagery
HF	High frequency power
HPA	Hypothalamic – Pituitary – Adrenal
HR	Heart rate
HRV	Heart rate variability
LF	Low frequency power
LF/HF	The ratio of the power for the LF and HF components
MI	Myocardial infarction

MTPT	Myofascial trigger-point massage
MTrP	Myofascial trigger-point
nHF	Normalised high frequency power
nLF	Normalised low frequency power
NTS	Nucleus tractus solitarius
PC	Personal computer
PDN	Painful diabetic neuropathy
PMR	Progressive muscle relaxation
PSA	Power spectral analysis
PSD	Power spectral density
PNN50	Percentage of difference between adjacent normal RR intervals greater than 50 ms
PNS	Parasympathetic nervous system
QOL	Quality of life
RAS	Reticular activating system
RMSSD	Root mean square of successive differences
RPE	Rating of Perceived Exertion
R-R	R-R time interval
RSA	Respiratory sinus arrhythmia
SDNN	Standard deviation of normal R-R intervals
SHF	Systolic heart failure
SNS	Sympathetic nervous system
TP	Total power
VAS	Visual analogue scale
VLF	Very low-frequency power

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CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND

The prevalence of diseases or symptoms most frequently associated with stress such as high blood pressure, coronary heart disease (CHD), peptic ulcers, backache and breathing disorders is increasing. Many who have not had these severe symptoms have probably experienced milder ones such as generalised muscle stiffness, headaches, neck and shoulder tension, cold hands, and feelings of nervousness, irritability, apathy, boredom, dissatisfaction and even moderate levels of hostility. Although unpleasant, many people accept these symptoms as the cost of modern living (Arnetz & Wiholm 1997).

Stress is a term that has become synonymous with modern life (Maddock & Pariante 2001) and there is now greater public concern about how features of modern life pose threats to personal health (Arnetz 1997, Petrie *et al.* 2001). Success in life and maintenance of health in present society requires continuous adaptation of the body to a variety of extraneous influences. This can only be achieved by the balanced interaction of the nervous, endocrine and immune systems (Krueger & Krueger 1991). As the demands of life increase, the perceived and actual levels of stress also seem to be rising. Increasingly employees in modern office environments report suffering from psychosomatic symptoms and studies of employees in high-technology situations suggest that psychosomatic symptoms are related in part to high perceived mental demands and inadequate coping and 'stress management' skills (Arnetz & Wiholm 1997). Almost every week, new stress management strategies are promoted offering new and improved methods of coping designed to enable us to respond to stress more positively

in the high pressure environment of modern living and to help us achieve our individual targets more rapidly. From a psychophysiological standpoint the achievement of these 'deadlines' may be drawing closer to the truth than we realise.

1.2 STRESS

One of the basic problems with the term 'stress' is that it is used in a variety of quite different ways. It can be used to describe various unpleasant environmental events or stressors, which are perceived as harmful or threatening. Alternatively, it can be used to describe the physiological and behavioural responses, or strain that occurs when an individual is confronted by particular stressors. Furthermore, a third view of stress combines elements of the first two and describes the various transactions that take place between the person and the environment. According to this view, stress is not just a stimulus or a response but rather a process in which the individual is an active agent who can influence the impact of a stressor through behavioural, cognitive and emotional strategies.

In its broadest and most conventional use 'stress' is essentially the rate of all wear and tear caused by life (Selye 1976). Any threat or demand made upon the human system whether intrinsic, extrinsic, physical, psychological or social will affect the body's homeostatic mechanisms and help prepare for defensive action. In painful or threatening situations, whether real or imagined, the body's defensive mechanisms are activated.

1.2.1 THE DEFENCE-AROUSAL RESPONSE

The defence-arousal or stress response as it is more popularly known, (Hilton 1982, Henry 1986) is a mechanism, which in situations of danger either activates or depresses various biological processes. Its physiological and pathological effects vary from person to person depending on the individual's reaction to stress (Silvestrini 1991, Sapolsky 1994).

W.B.Cannon (1914), a forerunner in the field of human physiology, described the stress response as the 'emergency reaction' or 'fight or flight' response. According to Selye, this response is only the first in a series of events that the body makes when stress is long lasting. In his book 'The Stress of Life' (1976), Selye further describes the general and local adaptive processes of the human body in response to stressful situations. The General Adaptation Syndrome (GAS) is described as " a non-specific response to that which causes stress". It is characterised by three stages.

1. *The alarm reaction* – this describes the immediate physiological changes that take place in reaction to a stressor. It involves a neurohormonal response causing activation of the sympathetic nervous system (SNS) and release of stress hormones such as adrenaline and cortisol which lead to increases in heart rate (HR), and force of contraction, and mobilisation of energy stores such as liver glycogen and fat. As such this is similar to the 'emergency reaction' or 'fight or flight' response described by Cannon (1914).
2. *The stage of resistance* – if the stressor is not removed, the body begins to recover from the initial alarm and in order to cope it adapts and habituates to the stressful situation. According to Selye, in the

stage of resistance, physiological arousal declines somewhat but remains higher than normal. Baseline levels of physiological parameters such as blood pressure, blood glucose, glycogen and free fatty acid levels may be reset as part of the adaptive response. Cortisol-mediated immune function deteriorates and conditions such as asthma and ulcers may become more prevalent (Selye 1976). Despite continuous physiological arousal there may be few outward signs of stress. Impairment of normal function can render the organism increasingly vulnerable to health problems, which are described as diseases of adaptation (Selye 1976).

3. *The stage of exhaustion* – prolonged physiological arousal produced by severe long-term or repeated stress is costly (Sarafino 1990). During continual stress the body's energy reserves are depleted and the physical ability to resist is lost. The body fails to cope and at this point of catastrophe, the stage of exhaustion begins. Pathological conditions such as CHD, chronic fatigue and tension myositis syndromes often develop at this stage (Selye 1976).

1.2.2 Integrated Response to Stress

Both the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenocortical (HPA) system, mediate the response to stress. This integrated process, which has been referred to as the "ergotropic" response was first described by Hess (quoted in Best & Taylor 1990), and the ergotropic *zone* is said to extend from the anterior midbrain towards the hypothalamus. In animal studies when the ergotropic zone is electrically stimulated, it

consistently produces dilation of the pupils, increased blood pressure, increased respiratory rate and heightened motor excitability (Benson *et al.* 1974). Although at times any one of these responses may be emphasised, there are no specific foci that correspond to individual isolated responses such as those seen in the motor cortex (Hess & Bruger 1943). Nuclei in the diencephalon, particularly in the hypothalamus and amygdala play a central role in the integration of the mammalian response to threat.

The arousal response is not solely the product of simple reflexes (Spyer 1989). The collective action of a group of responses including responses of the ANS make their appearance in the form of synergistically associated mechanisms causing changes in respiration and cardiovascular output (Benson *et al.* 1974). In the human, responses to threatening situations or circumstances requiring behavioural adjustment mimics the activation of the fight or flight response observed in animal models (Benson *et al.* 1974).

The sympathetically-mediated, coordinated response is referred to in Gray's Anatomy (1999), where it suggests that the sympathetic nervous system is so called from the opinion entertained that "through it is produced a *sympathy* between the affections of distant organs".

1.2.3 Role of the Central Nervous System

Stress is perceived by many areas of the brain, from the cortex down to the brainstem. Major stressors activate both corticotrophin-releasing hormone (CRH) neurones and adrenergic neurones in the hypothalamus. The main function of the hypothalamus is the maintenance of homeostasis. To achieve this task, the hypothalamus continually receives information from all parts of

the body from a variety of inputs. The inputs include information from the nucleus of the tractus solitarius (NTS), the reticular activating system (RAS) and the limbic system.

The NTS collects all visceral sensory information from the vagus nerve and relays it the hypothalamus and other targets. Information from aortic and carotid baroreceptors travels via this route and is concerned mainly with the homeostatic regulation of blood pressure. Although in the immediate response to threat as far as the cardiovascular system is concerned, this is a preparatory reflex and not compatible with short-term homeostasis. Indeed during the initial alerting reaction, the baroreceptor reflex, which is homeostatic, is strongly inhibited (Hilton 1982).

The reticular formation, which forms part of the RAS, is a nucleus in the brainstem, which receives a variety of impulses from the spinal cord. Somatosensory information for example from temperature and pressure receptors in the skin is relayed via this route. The RAS is also known to play a part in regulating arousal levels (Eysenck 1967). It can enhance or inhibit incoming sensory stimuli. According to the theories linked to the biological basis of personality, extroverted personality types tend to inhibit the intensity of stimuli and introverts tend to increase the intensity (Eysenck & Eysenck 1985). Introverts dislike high arousal conditions because their RAS is already stimulated, whereas extraverts actively seek high arousal levels because their RAS lacks stimulation. This mechanism may partly explain some of the individual differences often observed in individual responses to stressful circumstances.

Limbic structures such as the amygdala, hippocampus and the olfactory cortex also refer information to the hypothalamus. These structures are concerned with regulating behaviours such as eating and reproduction and are further involved in the processing of emotional stimuli. The amygdala complex is composed of two almond-shaped, fingernail-sized structures that are richly and reciprocally connected to most brain areas, especially advanced sensory-processing areas. Its principal task is to filter and interpret sophisticated incoming sensory information in the context of survival and emotional needs, and then to initiate appropriate responses.

Once the hypothalamus detects a threat to homeostasis there are two main pathways in which it can produce a change and restore balance. It modulates neural pathways that influence the ANS and by sending biochemical signals to the pituitary gland.

1.2.4 The Autonomic Response

The lateral hypothalamus projects to the medulla, where the cells that drive the ANS are located. These include the parasympathetic vagal nuclei and a group of cells that descend to the SNS in the spinal cord. With access to these systems, the hypothalamus can influence heart rate (HR), vasoconstriction, digestion, sweating etc. (Table 1.1)

1.2.5 Hormonal Responses

Additionally, large hypothalamic cells send axons directly into the posterior pituitary, where the axon terminals release oxytocin and vasopressin into the blood stream. Smaller cells in the same area send their axons only as far as

TABLE 1.1

Responses of major organs to autonomic nerve impulses.

Organ	Sympathetic stimulation	Parasympathetic stimulation
Heart	Increased heart rate ($beta_1$ and $beta_2$ receptors) Increased force of contraction ($beta_2$ and $beta_2$ receptors) Increased conduction velocity	Decreased heart rate Decreased force of contraction Decreased conduction velocity
Arteries	Constriction ($alpha_1$) Dilation ($beta_2$)	Dilation
Veins	Constriction ($alpha_1$) Dilation ($beta_2$)	
Lungs	Bronchial muscle relaxation ($beta_2$)	Bronchial muscle contraction Increased bronchial gland secretions
Gastro-intestinal tract	Decreased motility ($beta_2$) Contraction of sphincters ($alpha_2$)	Increased motility Relaxation of sphincters
Liver	Glycogenolysis ($beta_2$ and alpha) Gluconeogenesis ($beta_2$ and alpha) Lipolysis ($beta_2$ and alpha)	Glycogen synthesis
Kidney	Renin secretion ($beta_2$)	
Bladder	Detrusor relaxation ($beta_2$) Contraction of sphincter (alpha)	Detrusor contraction
Eye	Dilates pupil (alpha)	Constricts pupil Increase lacrimal gland secretions
Submandibular and parotid glands	Viscous salivary secretions (alpha)	Watery salivary secretions

the base of the pituitary, where they empty chemical messengers such as corticotropin-releasing hormone (CRH) into the capillary system of the anterior pituitary.

CRH is considered to be a major mediator of the effects of stress mainly because of its analgesic properties. In this manner CRH can moderate the stressful effects of acutely painful circumstances (Dunn & Berridge 1990). Conversely, it has been suggested that chronic exposure to painful stress may result in hyperalgesia rather than analgesia and this may have further implications in the field of research into pain and stress management. (Lariviere & Melzack 2000).

These releasing factors induce the anterior pituitary to secrete any one of at least six hormones, including adrenocorticotropic hormone (ACTH), which stimulates the adrenal cortex thereby increasing production of glucocorticoids such as cortisol. Ultimately therefore the hypothalamus plays a major role in the stress reactivity and can control every endocrine gland in the body for example by altering blood pressure through vasopressin and vasoconstriction, body temperature and metabolism through thyroid stimulating hormone and ACTH secretion.

In addition to the above, increased activities of sympathetic nerve fibres to the adrenal medulla promote secretion of the catecholamines, adrenaline and noradrenaline into the bloodstream. This surge of adrenaline and consequent physiological activity is popularly referred to as 'the adrenaline rush'. This effect is experienced in many highly stressful circumstances and in many situations is actively pursued.

1.2.6 OTHER EFFECTS

Increased muscle tension is a further consequence of the arousal response. In his early work, Cannon (1929) demonstrated that the increase in adrenaline reinforces the dilation of muscle arterioles preparing muscles for action if the need to escape from a threatening situation arises. He demonstrated that in cats, blood is 'driven out' or shunted from visceral structures such as the intestines, kidneys and spleen into the skeletal muscles causing an increase in limb volume (Cannon 1929). This viscerosomatic process would meet the urgent demands of struggle or escape.

As a consequence of this redirection of resources, processes that are not required in the defence of the organism are curtailed. Further changes that occur during the arousal response include (Graham 1990):

- Muscles in the areas of the throat, neck and shoulders become tense.
- The mouth becomes dry as salivary secretions are reduced.
- Further digestive processes are curtailed so that blood is redirected to muscles for the purposes previously described.
- Blood clotting agents within the bloodstream increase in case of injury and blood loss.
- Carbohydrates and fats are mobilised to provide increased energy resources.
- Sweating increases in preparation for overheating and the electrical resistance of the skin is lowered.

According to Selye (1976), the general stress reaction involves almost every organ and chemical constituent of the body.

1.2.7 ADAPTATIONS TO CHRONIC STRESS

If the threat or perceived threat is successfully dealt with and the danger passes, then the arousal mechanism disengages allowing the body's 'homeostatic' or normalising processes to take over. If however the threat remains, or the body is subjected to prolonged or repetitive stress, then the organism's natural inclination to protect itself remains in force. As a consequence, defensive, adaptive processes take place and long term chronic changes follow.

In constant preparation to flee from danger, habitual physical stresses influence the body's musculature and connective tissues. Over time the body can become 'used to' or 'habituated' to these changes and they are gradually pushed from consciousness resulting in chronic muscle tension and reduced physical flexibility (Hanna 1988). In the process, the sensation of the tension can be lost. Ultimately these chronic tensions become as 'second nature' to us and contribute to a defensive muscular shield. This inner process has been described as 'visceral tissue armouring' (Hanna, 1988).

1.2.8 COMMONLY USED MARKERS OF STRESS

Increased levels of catecholamines, cortisol and various pituitary hormones are consistently raised during stressful events and therefore are commonly used as stress markers to measure the effects of various stressful events. Increased levels of the neurotransmitter noradrenaline result in elevation of heart rate and increased contractility of the heart muscle.

Other biochemical substances such as ß-endorphins, which are co-released with ACTH by the anterior pituitary during the stress response

(Farrell *et al.* 1982), have been suggested as valid markers of acute stress situations (Meyerhoff *et al.* 1988, Miller *et al.* 1993). Endogenous opioids, particularly ß-endorphins not only have analgesic and euphoric effects but have also been shown to regulate haemodynamic responses to stress by reducing sympatho-adrenergic activity (Fontana *et al.* 1998). Furthermore, they are also elevated following exercise and have been shown to be associated with a post-exercise hypotensive effect (O'Sullivan & Bell 2000). A link has also been suggested between the cardiovascular baroreceptor reflex arc and ß-endorphin associated pain regulatory systems (Randich & Maixner 1984 and 1986). The release of ß-endorphins during stressful situations is also considered to be dependent on personality factors such as subjective control attributions, (Schedlowski *et al.* 1995) once again highlighting individual patterns of stress-responsiveness.

1.2.9 Psychological Effects of Stress

Although Selye (1976) considered the general adaptive syndrome to be non-specific with reference to the type of stressor, there are at least two reasons why this presents a problem. Firstly, some stressors elicit a stronger emotional response than do others and secondly cognitive appraisal processes appear to play a role in physiological responses to stress (Tennes & Kreye 1985).

Sapolsky (1994) suggests that major physical stressors produce a fairly stereotypical response among individuals. He explains that few of us for example, would fail to secrete catecholamines or glucocorticoids if being

mauled by a lion. In contrast, there is far greater interindividual variability in the magnitude and quality of responses to more psychological stressors.

Bodies and psyches differ tremendously in their vulnerability to stress (Sapolsky 1994) and in the realm of our everyday experiences, what might be pathologically stressful for one person could be something another may do for recreation. Therefore in the face of constant physical challenge to homeostasis it is important, particularly in the context of the stress management, to be aware of the psychological factors that modulate the magnitude of the resultant stress response.

Henry (1986) also suggests that much stress is of psychological origin and due to emotional arousal. Furthermore, in updating Selye's concept of stress, Levine (1985) points out that stimuli, which evoke the stress response, are often psychological in nature involving complex multiple response systems.

1.2.10 Hormonal Responses to Psychological Stress

Various psychosocial factors appear to trigger different hormonal systems. Unpredicatability, lack of control, inadequate outlets for frustration and aggression, and lack of hope for the future, have all been suggested as important psychological factors that increase levels of stress and initiate the response of different hormonal axes within the body (Sapolsky 1994). The first of these is the adrenocortical system, which is thought to respond primarily to situations where a high degree of 'uncertainty' or indecision is involved (Miller 1980).

A second group of hormones is regulated by the gonadotrophic system, which is responsible for the secretion of androgens, oestrogen and progesterone. Both suppression and elevation of these hormones appears to be determined by the extent to which the organism feels secure and in the case of androgens, the sense of 'power' i.e. the dominance and control that the individual has over a challenging situation (Henry 1985). A rise in testosterone can enhance the libido and attractiveness of the individual to potential sexual partners and an increase often occurs after any competition for status especially following exercise and in competitive sport (Mazur & Lamb 1980).

Thirdly the catecholamine 'fight or flight' sympathetic adrenomedullary axis is crucially involved in response to situations that require attention or vigilance (Levine 1985). When the situation involves an aggressive, directed attack, noradrenaline is said to be involved, and where levels of uncertainty and anxiety increase, both adrenaline and noradrenaline are involved (Henry & Stephens 1977).

In summary it can be seen that stress is the specific response of the individual to a variety of non-specific demands. However, the process of adaptation is complex and varies considerably from person to person. Various stressors, including both intrinsic and extrinsic events trigger the stress response and reactivity. Both have physiological, cognitive and behavioural components that in the long-term can be maladaptive and harmful to the individual. Therefore in order to counteract stress or at least lessen its effects, various measures need to be taken to manage its various components. Having addressed the various effects of stress and the stress response it is now appropriate to examine the effects of its counterpart the relaxation response.

1.3 RELAXATION

According to the Concise Oxford English Dictionary (1996), to relax is defined as; at ease, unperturbed or to become less stiff, rigid or tense. Relaxation is also described as the restoration of equilibrium following disturbance. In the context of the work of this thesis relaxation is considered to be an integrated hypothalamic response, which results in a generalised decrease in sympathetic nervous system activity (Friedman *et al.* 1996), enhanced parasympathetic nervous system activity (Sakakibara *et al.* 1994) or both. Relaxation involves the elicitation of the relaxation response, which has been described as a simple, no-cost, non-pharmacological mechanism without side-effects (Benson *et al.* 1974) and its initiation forms the basis of many stress management interventions.

1.3.1 THE RELAXATION RESPONSE

The relaxation response is the physiological opposite of the fight or flight, or stress response, first described by Cannon in 1914. When particular areas within the anterior hypothalamus are stimulated, a hypoarousal state occurs which Hess described as the 'trophotropic response' (Best & Taylor 1990) and involves PNS dominance. Stimulation of the 'trophotropic zone' consistently causes reductions in HR and blood pressure along with slower deeper breathing. Hess theorised that this response functioned as a protective mechanism against excessive stress, countering the potentially harmful effects of the defence-arousal response (Hess & Bruger 1943).

1.3.2 PSYCHOLOGICAL EFFECTS OF RELAXATION

Stress is often accompanied by anxiety, mood disturbance and reduced quality of life measures and these symptoms have all been shown to improve as a consequence of relaxation training. Elicitation of the relaxation response by various means has proven to be effective in treating the psychological symptoms of stress in many disease states. In cancer patients, depression, anxiety and hostility all significantly improved following relaxation training (Luebbert *et al.* 2001) and relaxation induced by Transcendental Meditation (TM) has been shown to alleviate symptoms of anxiety and depression in patients suffering from cardiac syndrome X (Cunningham *et al.* 2000). In a study of 1,312 patients with stress disorders, relaxation training when combined with other behavioural interventions, such as cognitive restructuring and diet modification, has proven effective in reducing both physical and psychological symptoms of anxiety (Nakao *et al.* 2001).

Training in relaxation (Benson's Relaxation Response) has also been shown to be effective in treating the psychological symptoms of tension-anxiety and depression in women suffering from menopausal hot flushes (Irvin *et al.* 1996). Furthermore, practice of the relaxation response (Benson *et al.* 1974) has also helped patients prepare for cardiac surgery and, along with reducing the incidence of post-operative supra-ventricular tachycardia, it has also produced lower ratings of tension and anger in the same patients (Leserman *et al.* 1989).

The specific behavioural and physiological changes associated with the trophotrophic (relaxation) response have been found to be reproducible

through a variety of stress management interventions (Mandle *et al.* 1996) and various commonly used methods to induce relaxation are considered below.

1.3.3 Relaxation for the Treatment of Pain

Pain is a condition that requires continual behavioural adjustment and can cause considerable stress and have profoundly damaging effects on quality of life (Chester *et al.* 2000). Pain and similar stressful behavioural states are often characterised by organised neural responses of the somatomotor, somatosensory (analgesia), autonomic and neuroendocrine systems (Janig 1995). The pathogenesis of pain often involves activation of the afferent sympathetic pathway and a frequent consequence of pain, especially when severe, is the activation of the stress response. Therefore any method, including activation of the relaxation response, which causes a reduction in sympathetic activity, may contribute to the alleviation of pain and improvement in quality of life.

Relaxation as induced by progressive muscle relaxation and guided imagery has been shown to be successful in the treatment of cancer pain and, Sloman (1995) proposes that the relaxation response may break the pain – muscle tension – anxiety cycle in cancer patients facilitating pain relief through a calming effect.

Mind/Body (cognitive/behavioural) interventions including relaxation training, meditation and stress management have shown positive results in treating chronic pain in a large health maintenance organisation (McCarberg & Wolf 1999) and in treating patients with Fibromyalgia Syndrome (Singh *et al.* 1998).

1.4 STRESS MANAGEMENT

There are a number of options to consider when looking at the prevention of stress (Cooper & Cartwright 1997). Three levels of management exist that address different stages of the stress process (Murphy 1988). Primary prevention is mainly concerned with taking action to modify or eliminate sources of stress in the environment, thereby reducing the negative impact on the individual.

Secondary measures are concerned with the prompt detection and management of experienced stress by increasing awareness and improving coping skills. As such secondary prevention is one of damage limitation (Cooper & Cartwright 1997). This method is focussed mainly on developing self-awareness and educating the individual to deal with the effects of stress 'in the moment'. Learning to relax by becoming more aware of the somatic sensations and symptoms linked to the arousal response can help the individual to counteract the various effects as they manifest and therefore reduce any consequent long-term damage.

Techniques such as slow deep breathing, autogenic training, meditation and guided imagery all fall into this category of stress management. A further method of secondary prevention, which is being more commonly employed, especially in large organisations, is the provision of cardiovascular exercise training schemes. This method of health promotion is considered to help the individual adapt more favourably and deal more effectively with the consequences, rather than the sources of stress (Cooper & Cartwright 1997).

Tertiary prevention is concerned with the treatment, rehabilitation and recovery processes of individuals who are suffering from the long-term effects of stress. Interventions at this level include the provision of a counselling service aimed at improving the psychological wellbeing of the individual and remedial treatments such as massage are provided to reduce muscle tension and promote feelings of wellbeing.

1.5 RELAXATION THERAPIES

Relaxation therapies are the cornerstone of any stress management programme and most include some form of progressive relaxation training (Legeron 1993). In recent years the potential benefits of relaxation training has generated widespread interest in both the lay and professional literature (Sims 1987). Relaxation is a learned response and a variety of techniques exist to facilitate its induction. According to Benson (1975), the most effective techniques are those which are the simplest to learn. All share the common goal of countering the physiological effects of the stress reaction. Some procedures can involve long and exacting training, but once learned the time and effort required to bring about relaxation is considerably reduced, producing success quickly and on demand.

In its various forms, relaxation therapy (RT) has been used to treat a variety of psychological and physical conditions. It has proven effective in reducing anxiety (Rasid & Parish 1998, Clum *et al.* 1993), panic disorder (Ost & Westling 1995, Barlow 1990), social phobia (Heimberg 1989) and anger, hostility and aggressive behaviour (Hazaleus & Deffenbacher 1986). Furthermore, other conditions that have responded favourably to RT include

Alzheimer's Disease, asthma and fibromyalgia (Suhr *et al.* 1999, Vazquez & Buceta 1993, Buckelew *et al.* 1998).

Stress management in the form of RT contributes to many cardiac rehabilitation programmes. RT has been shown to be effective in controlling mild essential hypertension (Agras *et al.* 1983) and in helping individuals reduce their anti-hypertensive medications (Glasgow et *al.* 1989). Relaxation-based interventions are also considered to have a prophylactic effect against heart disease (Dath *et al.* 1997, Patel *et al.* 1981, van-Dixhoorn 1998).

The stress response can be accompanied by dramatic, unexpected episodes of intensely disturbing somatic symptoms that are often accompanied by extreme fear (Friedman & Thayer 1998). This enigma of *panic anxiety* has been the subject of extensive investigation since Da Costa's landmark study of the "irritable heart" in the 1870's and numerous labels have been historically used to these phenomena (Friedman & Thayer 1998). Terms such as "nervous heart", "cardiac neurosis", "functional cardiovascular disorder" and "anxiety neurosis have been used to describe this phenomenon and the most frequently reported symptoms in these panic attacks are palpitations and tachycardia (Barlow 1988). Other commonly reported features include sweating, shaking, shortness of breath and chest pain; collectively, these signs suggest disturbances of the ANS (Friedman & Thayer 1998).

Focussing on these symptoms and becoming more "body-aware" forms a major component of most stress management programmes. Traditionally its application has been related to psychosomatic and psychotherapeutic interventions (Noeker *et al.* 2000). Beyond this classical approach, behavioural medicine has more recently emphasised the relevance

of this interoceptive process and adequate attribution patterns concerning bodily sensations, as a major source of adequate coping (Noeker *et al.* 2000). There are a variety of techniques, which make this process possible, including progressive muscle relaxation, autogenic training and guided imagery, and these are described below.

1.5.1 Progressive Muscle Relaxation

Progressive muscle relaxation (PMR) is commonly used in stress management to reduce muscle tension. Muscle relaxation is considered to be an active rather than a passive process and requires learning how to turn off motor unit activity (Basmajian 1973). In its original form (Jacobsen 1938), PMR involves active tension of specific muscle groups followed by a rapid 'letting-go' process. This isometric 'squeeze - relaxation' technique has been shown to be effective in treating anxiety and is considered more useful than other techniques for individuals who find difficulty using mental imagery (Weinstein & Smith 1992).

PMR has also been shown to be effective in treating tension headaches (Blanchard *et al.* 1990, idiopathic insomnia (Borkovec 1979), and dysmenorrhoea (Sigmon & Nelson 1988) and has proven to be effective in enhancing immune function in HIV-positive men (Taylor 1995).

Various modifications of the original PMR technique exist and include Applied Relaxation, Differential Relaxation, and Rapid Relaxation. These are often combined with other modalities to reduce the effects of stress (Bernstein & Carlson 1993).

1.5.2 Autogenic Training

Autogenic training (AT) is a technique that involves the use of a series of self-suggestions, instructing various body parts to relax. This eventually leads the individual into a state of passive concentration or detached alertness, which has been termed the 'rest and digest' state. It is said that in this state the practitioner often experiences a different mode of perception (Ernst & Kanji 2000).

The subject focuses attention on various body parts e.g. the limbs, lungs, heart, diaphragm and head and attempts to induce feelings of heaviness and warmth in the target areas. In stress management programmes, AT is often combined with physical relaxation methods such as slow rhythmical deep breathing and mental imagery to further potentiate the relaxation effect.

AT is considered to be more effective than progressive muscle relaxation (PMR) in treating conditions associated with ANS disorder, whereas PMR appears to be more effective in reducing somatic tension (Lehrer *et al.* 1980). Most of the studies investigating AT have been concerned with its benefits in the reduction of stress and anxiety. In a study of 50 nurses, Bailey (1984) demonstrated that those who trained in AT over a six-week period, had significantly fewer days of absence due to sickness than the no treatment control group. In a 10-session, 5-week, group-administered stress management program for nursing students using AT in combination with visual imagery for stress reduction, Charlesworth *et al.* (1981) showed reductions in trait anxiety in nursing students when compared to a no-treatment control group. Further studies have also reported on the

psychological benefits of AT and reductions in state anxiety (Crocker & Grozelle 1991, Scallet *et al.* 1976).

A few studies have also explored the physical effects of AT training. In an experiment examining the psychophysiological effects of stressful imagery on frontalis muscle electromyograph (EMG) activity, AT training sessions were shown to produce a "cultivated low-arousal state" (Reynolds 1984). Additionally, AT has been reported to improve respiratory function in asthmatic patients (Henry *et al.* 1993).

1.5.3 Guided Imagery

Guided Imagery (GI) is a technique that usually involves listening to instructions given either verbally by an instructor, for example, or on a tape-recording. The instructions guide the subject to create or visualise a mental picture or to capture or recall a memory or emotional feeling. Relaxation with GI has been successfully used for stress management, controlling acute pain, reducing anxiety and emotional distress in various pathological conditions (Vines 1994). GI is a simple, inexpensive, non-invasive technique, which in combination with other techniques forms a major part of many stress management programmes. It has been shown to be successful in facilitating improvement in health behaviours and is often used to promote self-care, increasing patient coping abilities particularly in areas such as cancer care. In the 'Chemotherapy Experience Survey' 1993, when used in combination with standard antiemetic medication, GI was successfully used, by means of chemotherapy-specific guided-imagery audiotape, to reduce chemotherapy-

related nausea and vomiting and significantly improve feelings of wellbeing when compared with a non-GI control group (Troesch *et al.* 1993).

Again in a controlled study using instructions on an audio-cassette tape, GI has been shown to be effective in reducing stress-related anxiety in student nurses unused to giving injections to patients (Speck 1990). It has also been proposed as an effective method to combat post-surgical depression in elderly patients (Leja 1989). In addition to reducing surgical stress, GI has also been shown in a randomised controlled trial to be effective in reducing plasma cortisol levels and promoting wound healing in patients undergoing cholecystectomy (Holden-Lund 1988). In younger patients, stress management and relaxation training with GI has proven successful in reducing symptoms of upper respiratory tract infection (Hewson-Bower & Drummond 2001). In the same study, levels of secretory immunoglobulin A, a marker of immune function, increased towards the end of treatment. The authors suggested that the psychological intervention had in some way interrupted the chronic illness cycle.

Pre-menstrual distress is another condition that has responded favourably to the use of GI and normalisation of menstrual period cycle-length has also been demonstrated (Groer & Ohnesorge 1993).

In smoking cessation programmes, GI (power-imagery) and relaxation training have both been shown to significantly improve (both $P < 0.05$) success rates and to help participants to 'kick the habit' with less stress when compared with a placebo-controlled group (Wynd 1992). Smoking quit rates were 67% for the power imagery group, 69% for the relaxation group, and 27% for the control group. At a three-month follow-up, the power imagery

group had a continued abstinence rate of 52%, the relaxation group had an abstinence rate of 55%, and the control group cessation rate remained at 27%. These success rates for GI and relaxation therapies are higher than those normally seen with nicotine replacement therapies either used alone or in combination with the pharmaceutical agent buproprion hydrochloride (Zyban) which generally achieve smoking cessation rates of around 20% (Roth & Westman 2001, Silagy *et al.* 2001).

Although research on GI in stress management has increased over the last decade most studies report on psychological outcomes. Few appear to have explored the physiological effects of GI and there are none that investigate its effects on cardiac autonomic function.

1.5.4 EXERCISE THERAPY

Over the past 40 years there have been many studies confirming the important role of regular physical activity for increasing function, improving health and extending longevity, and also in the prevention of coronary heart disease (CHD). There is also evidence to suggest that psychological abnormalities, particularly depressive illness, anxiety states and mental stress are involved in triggering clinical cardiovascular events and that these conditions also contribute to development of atherosclerosis (Lane *et al.* 1999, Esler & Kaye 2000).

Additionally several studies have indicated a relationship between the risk of cardiovascular disease and environmental and psychosocial stressors (Knardahl 2000, Maschke *et al.* 2000, Levenstein *et al.* 2001). Further factors such as job strain, social isolation and personality factors are also considered

to contribute to the progression of CHD (Sacker et *al.* 2001, Peter & Siegrist 2000, Weidner 2000, Kawachi *et al.* 1999). The mechanisms of increased cardiac risk attributable to mental stress are not entirely clear, but activation of the SNS seems to be of prime importance (Esler & Kaye 2000).

According to the British Heart Foundation (BHF 2001) CHD is the most common cause of death in the United Kingdom. Over 270,000 heart attacks occur each year, and of these patients, about 43% die within twenty-eight days of their heart attack.

People who are physically active live longer (Sherman *et al.* 1999) and in the UK, physical inactivity is considered the most common risk factor for heart disease with seven out of 10 adults not taking enough regular physical exercise. Even though physical inactivity is so common eight out of 10 adults still believe that they are physically fit (BHF 2001). Similar to the British Heart Foundation, the American Heart Association also cites physical inactivity as a major risk factor for heart disease (Fletcher et *al.* 1999).

Until recently the quantity and intensity of physical activity required for the primary prevention of CHD has been unclear. According to BHF physical activity equivalent to 30 minutes brisk walking five times per week, roughly halves the risk of developing CHD and reduces the risk of having a stroke and following exercise training the risk of developing diabetes is reduced (BHF 2001). Evidence from the Harvard Alumni Study, which examined the physical activity profiles of a total of 13, 485 males (mean age 57.5 years) over a 16 year period (Lee & Paffenbarger 2000) supports these claims. It suggests that light activities (< 4 Mets (i.e. multiples of resting metabolic rate)), are not associated with reduced mortality rates, moderate

activities (4 to 6 Mets) appear somewhat beneficial and vigorous activities (> 6 Mets) clearly predict lower mortality rates.

Five decades of epidemiological research from the Framingham Heart Study has shown that behaviour modification and alteration in lifestyle are prerequisites for reducing risk factors for heart disease and Framingham research confirms that physical inactivity is positively associated with risk for CHD (Sherman *et al.* 1994).

Besides the tangible benefits for the cardiovascular system, other health benefits derived from physical training include increased levels of energy, alleviation and prevention of depression, reduced levels of anxiety and considerable benefits to self-esteem (Fentem 1994). Aerobic exercise in particular has been shown to have positive effects on wellbeing and has proven effective in reducing stress (Norris *et al.* 1990).

In combination with other lifestyle modifications, physical exercise confers wide-ranging benefits across all age ranges. Ornish *et al.* (1990) demonstrated that comprehensive lifestyle changes, including increased physical activity and stress management training, reduce the risk of coronary atherosclerosis after only 1 year. In a study of 147 adolescents, high intensity aerobic exercise was shown to be effective in reducing stress, depression and hostility (Norris *et al.* 1992). In older persons with depressive illness a 16-week exercise-training programme was shown to be an effective alternative to antidepressants, although the initial therapeutic response was slower than with medication (Blumenthal *et al.* 1999).

Besides the psychological benefits, exercise training produces numerous metabolic, cardiovascular and autonomic effects. Abnormalities in

autonomic physiology, especially increased sympathetic activity, reduced vagal tone, and delayed heart rate recovery have been associated with increased mortality (Goldsmith *et al.* 2000, Rosenwinkel *et al.* 2001).

With regular exercise, a variety of physiological effects are evident (O'Sullivan & Bell 2000). Exercise training is associated with a relative enhancement of vagal tone and a reduction in resting heart rate (Ekblom *et al.* 1968, Kenney 1985, Shi *et al.* 1995). There is also evidence for reduced sympathetic cardiac tone (Smith *et al.* 1989) and an inherent reduction in the discharge frequency of the sinoatrial node (Katona *et al.* 1982). Vasomotor sympathetic outflow is decreased at rest following exercise training (McAllister 1998, Ray 1999), conferring such potentially beneficial effects as reduced peripheral resistance and decreased resting blood pressure. The concept of treating heart disease, especially hypertension with exercise training, has been suggested as an attractive alternative to the problems arising from using pharmacological interventions (Kenney & Zambraski 1984)

Baroreflex sensitivity has also been shown to improve following exercise training (Iellamo *et al.* 2000) and altered responses to the Valsalva manoeuvre and isometric exercise have also been reported following participation in an exercise training regime (O'Sullivan & Bell 1999).

Following myocardial infarction, physical activity as part of a rehabilitation programme reduces the risk of mortality by 20% (BHF 2001).

1.5.5 Massage Therapy

Massage therapy is older than recorded time, and 'rubbing' was a primary form of medicine until the pharmaceutical revolution of the 1940's (Field

1998). Therapeutic massage involves manipulation of soft tissue areas to bring about generalised improvements in health (Vickers & Zollman 1999). In its various forms it has been shown to reduce blood pressure (Cady & Jones 1997), facilitate relaxation (Labyak & Metzger 1997), reduce muscle tension (Nordschow & Bierman 1962) and reduce anxiety and depression (Weinberg & Hunt 1979, Field *et al.* 1996). Furthermore, following massage therapy, patients have reported reduction in pain and increases in feelings of warmth and wellbeing (Kaada & Torsteinbo 1989, Ferrell-Tory & Glick 1993 and Nixon *et al.* 1997).

More specifically, myofascial trigger point massage therapy (MTPT) is an advanced neuromuscular procedure that is commonly used in sports medicine to induce relaxation for the treatment of pain and muscle tension following injury or other trauma (Peppard 1983).

1.5.6 MUSIC THERAPY

Music is a universal language with many purposes and is commonly used to aid in stress reduction and anxiety management (Covington & Crosby 1997). It is well tolerated, inexpensive, has good compliance and few side effects (Myskja & Lindbaek 2000).

Music therapy has been used in a wide variety of health settings and has been shown to reduce HR, blood pressure and plasma stress hormone levels (Scheufele 2000, Watkins 1997, Chlan 1995). It has also been shown to be an effective intervention to reduce stress and anxiety in critically ill patients (Chlan & Tracy 1999) and during childbirth (Browning 2000). In a study of 468 patients, music combined with other relaxation therapies was

shown to be effective in reducing post-surgical pain following abdominal operation (Good *et al.* 2001). Furthermore, using power spectral analysis of HRV to measure the effects of music therapy on cardiac autonomic tone, White (1999) demonstrated increased high frequency power in patients following myocardial infarction (MI). High frequency power is associated with cardiac vagal tone and therefore this study indicates that music therapy may cause cardiovascular relaxation as a result of increased vagal activity (White 1999). Music therapy is best applied in a quiet, low-stimulus, restful environment and when combined with other relaxation modalities may increase the relaxation effect. Some forms of music have also been shown to have profound beneficial effect on breathing (Fried 1990).

1.5.7 Breathing Techniques

Breathing exercises in various forms constitute a major part of stress management programmes and are often combined with simple stretching exercises such as those practised in the discipline of Yoga. Breathing can be viewed as an independent variable, which affects emotion, cognition and behaviour as well as a dependent variable, which reflects changes in emotion, cognition and behaviour. According to Ley (1999), this bi-directional interaction is basic to an appreciation of breathing in terms of its relevance in research and application.

The underlying premise of using breathing exercises in stress management is that since breathing is a behaviour that is under both voluntary and reflex control, it can be modified according to the principles of operant and classical Pavlovian conditioning. This would consequently allow a

certain amount of control over emotional state thereby facilitating relaxation and reducing stress. This theory may further explain the widely held view that many yogic breathing techniques, when practised regularly, offer a certain amount of 'emotional cleansing' (Iyengar 1970).

Pranayama is one such yogic breathing practice, which involves slow rhythmical deep breathing and is known experientially to produce a profound calming effect on the mind (Pratap *et al.* 1978). Slow, deep breathing has been shown to improve the condition of patients suffering from stress-induced hyperventilation syndrome and anxiety disorders (Han *et al.* 1996) and respiratory retraining in the form of a slow breathing procedure has been used in the treatment of insomnia (Choliz 1995). The author suggested that as a consequence of reduced ventilation, an increase in carbon dioxide (CO_2) occurs which causes a sedative effect on the central nervous system (CNS) thereby assisting patients to relax. Although a study by Pratap *et al.* (1978) found no significant changes in blood gases following slow breathing practice and the authors suggested that the calming effect observed in the subjects was more likely to be neurally mediated.

Furthermore, breathing exercises are often used to help patients deal with the trauma of acute asthma attacks and Vedanthan *et al.* (1998) have shown that when used in combination with yoga stretching exercises, slow deep breathing (pranayama) significantly increases relaxation and positive attitude and also improves exercise tolerance.

Breathing exercises have also been shown to produce significantly greater increases in perceptions of physical and mental energy and feelings of

alertness and enthusiasm than progressive relaxation and visualisation techniques (Wood 1993).

Device-guided, slow-breathing exercises when practised regularly have also been shown to significantly reduce blood pressure in hypertensive patients (Rosenthal *et al.* 2001) although exact mechanisms for this effect are unclear.

1.5.8 PHARMACOLOGICAL INTERVENTION

Anxiety, fear and tension are commonly associated with activation of the stress response and can pose serious complications especially to patients with pre-existing cardiopulmonary disorders (Tolksdorf & Siefort 1992). Numerous medications are available including, neuroleptics, barbiturates, beta-blockers and benzodiazepines for treatment of these conditions. Commonly used cardiovascular medications have neuropsychiatric effects (Keller *et al.* 1999) and agents like beta-blockers because of their anti-adrenergic effects are used to treat performance anxiety and psychocardiac disorders. Certain drug exposures can contribute to the biopsychosocial aetiology of depressive symptoms and disorders (Patten & Love 1997) and there is evidence that beta-blockade, particularly propanolol, have adverse effects on mood. Gatchell *et al.* (1986) demonstrated that a behavioural stress management intervention was equally as effective as beta-blockade in reducing psychophysiological reactivity in post-MI patients and the authors suggest that when beta-blocker therapy is contraindicated that a non-pharmacological stress management approach may be more appropriate.

1.6 HEART RATE VARIABILITY

1.6.1 Historical Background

Heart rate variability (HRV) is the beat-to-beat variation in the R-R interval of the ECG. The first documented observation of HRV is often credited to Stephen Hales who in 1733 described an intricate relationship between arterial blood pressure, the respiration cycle and the cardiac inter-beat interval in the horse (Hales 1733). In more modern times the clinical potential of HRV analysis was realised when in 1965 Hon and Lee discovered that foetal viability correlated with HRV. They demonstrated that foetal distress was preceded by variations in R-R intervals before any appreciable change in heart rate (HR) itself. It was suggested that foetal hypoxia led to depression of the central nervous system (CNS) subsequently affecting autonomic control of the heart and leading to reduced HRV (Hon & Lee 1965). Clinical interest in HRV was also rekindled in cardiology by the early work of Wolf who focussed on the contribution of CNS factors in sudden cardiac death (Wolf 1967). He viewed HRV as reflecting brain – vagal – heart communication and this relationship has since provided an important bridge between clinical research and psychophysiology (Berntson *et al.* 1997).

In the 1970s further research focussed on the underlying physiological mechanisms responsible for fluctuations in R-R intervals. The effects of mental workload on HRV were explored in field and laboratory settings, (Sayers 1973, Mulder & van der Mulder 1973) and Luczack & Laurig (1973) evaluated the best mathematical models available at that time to measure the effects of mental strain on HRV. Also in the 1970s, a battery of simple

bedside tests was devised by Ewing to assess autonomic function in patients with diabetes by measuring short-term R-R interval and blood pressure variations, to assorted manoeuvres. (Ewing & Clarke 1982, Ewing *et al.* 1985). These tests are still often used today to test autonomic function in various populations and are commonly referred to as Ewing's Battery (see Chapter 2). In 1981 Akselrod and co-workers introduced the frequency domain or power spectral approach to HRV analysis for the quantitative evaluation of beat-to-beat cardiovascular control (Akselrod *et al.* 1981).

The application of HRV analysis has gradually been extended from basic research into clinical investigation. With the advent of new and more powerful computer-based analysis programmes, HRV analysis represents a sensitive, non-invasive technique, which can be used to identify cardiac autonomic disturbances. It has been used in the early sub-clinical detection of autonomic dysfunction in diabetes mellitus (Pagani *et al.* 1988) and as a prognostic marker following myocardial infarction (Kleiger *et al.* 1987). A reduction in HRV is associated with an increased risk of coronary heart disease (Liao *et al.* 1997), cardiac sudden death (Singer *et al.* 1988) and all-cause mortality (Tsuji *et al.* 1994). HRV from short-term recordings has also been proposed as an indicator of compromised health in the general population (Dekker *et al.* 1997).

1.6.2 Physiological background of Heart Rate variability

The synergistic action of the parasympathetic (vagal) and sympathetic components of the autonomic nervous system (ANS) mediate HRV. The motor neurones forming the vagus nerves originate in the dorsal motor

nucleus and the nucleus ambiguus. They run down the neck alongside the carotid arteries and into the thorax (Hainsworth 1995). The most obvious effect of vagal stimulation is to slow or even stop the heart (McCraty & Watkins 1996). Mechanical neck suction and massage in the area of the carotid sinus are often used to stimulate vagal activity and reduce HR (Schweitzer & Teichholz 1985, Waxman *et al.* 1988). Active contraction of neck muscles and chin pressure in the jugular notch has also been shown to alter vagally mediated baroreflex responsiveness (Lepicovska *et al.* 1992).

Sympathetic nerves originate in the intermediolateral column of the spinal cord in the upper thoracic region. White rami synapse in the sympathetic ganglia. Grey rami run with preganglionic vagal fibres over the mediastinum, forming a plexus of cardiac nerves and parasympathetic ganglia, which supply the various parts of the heart. (Hainsworth 1995). Pharmacological blockade of sympathetic nerves in this region is frequently used to reduce sympathetic activity in the treatment of painful conditions such as refractory angina and can modify HRV (Fujiki *et al.* 1999).

Neural control of heart rate is achieved by membrane processes at the sino-atrial (SA) node, which is the dominant pacemaker of the heart (Task Force 1996). Both sympathetic and parasympathetic nerves innervate the SA-node and in the absence of any sympathetic, parasympathetic or hormonal input to the sinus node, it fires at its intrinsic rate, usually about 100 to 120 beats per minute (McCraty & Watkins 1996). In a healthy individual, the HR at any given time represents the net affect of the cardiac parasympathetic and sympathetic nerves. When vagal effects predominate the HR is less than the

intrinsic rate; when sympathetic effects predominate, the HR is greater than the intrinsic rate (Goldberger 1999) (Figure 1.1).

Vagal and sympathetic responses have a different time constant. Vagal stimulation results in an immediate response within one or two heartbeats after its onset and following cessation of stimulation HR rapidly returns to its previous level. Sympathetic stimulation produces a much slower effect and requires about 15 to 20 seconds to elicit a response (McCraty & Watkins 1996). This difference in adrenergic and cholinergic responsiveness is partly due to processes within the synaptic cleft. Re-uptake of noradrenaline mainly occurs in sympathetic nerve terminals, or it is washed out in the coronary circulation, whereas acetylcholine is enzymatically hydrolysed within the same nerve terminals (Levy & Martin 1979). Post-synaptic effects also contribute to the time differential. Beta-adrenoceptors are coupled to a cAMP pathway, while muscarinic receptors are coupled to specific sarcolemmal potassium channels that trigger membrane hyperpolarisation within 100 ms. of the initiation of vagal stimulation (Levy & Martin 1979). These differences set the basis for the short-term measurement of HRV using spectral analysis (Altimiris 1999).

A further factor affecting neural control of the heart is the phenomenon described as 'accentuated antagonism' (Yang & Levy 1984). The accelerative effects of the SNS on HR are highly dependent on the background level of vagal activity. Using a bipolar electrode implant around the right cervical vagus, Stramba-Badiale *et al.* (1991) demonstrated this vagal – sympathetic effect in conscious dogs during resting conditions and exercise. They showed that gradual increases of the frequency of vagal

stimulation slowly enhanced the inhibitory effect on HR both before and during exercise. Similar demonstrations of the phenomenon of accentuated antagonism have been described in experiments on children and adults (Miyazoe *et al.* 1998, Uijtdehaage & Thayer 2000), showing that sympathetic HR effects are substantially smaller with high levels of vagal tone than with low background vagal activity. Furthermore, vagal effects become progressively stronger with increasing sympathetic background activity.

Since the cardiovascular system is a 'pressure' controlled system, factors that alter blood pressure will primarily govern fluctuations in HR. Several biological sensors including mechanoreceptors in the atria, ventricles and lungs, and baroreceptors in the carotid sinus and aortic arch respond to perturbations in blood pressure and/or volume. These biological sensors act as servo loops to oppose the changes in blood pressure on a beat-to-beat basis. Afferent impulses from baroreceptors travel via the glossopharyngeal and vagal nerves to the cardio-inhibitory, vasomotor centres and other parts of the CNS where they modulate the parasympathetic nervous system (PNS) outflow to the heart and the sympathetic nervous system (SNS) outflow to the heart and blood vessels (La Rovere 1995). Numerous reflexes and regulatory mechanisms affect the ANS and may subsequently alter HRV. These include: blood pressure oscillations called Mayer waves, which occur in approximately 10-second cycles (Ori *et al.* 1992), thermoregulatory mechanisms (Kitney 1975, Fleisher *et al.* 1996) and peripheral vascular resistance (Rosenbaum & Race 1968).

Other reflexes that can influence HRV include, peripheral artery chemoreceptors located in aortic and carotid bodies that produce variations in

the depth and rate of breathing. Furthermore, the coronary chemoreflex (Bezold-Jarisch reflex) and reflexes emerging from the pulmonary arteries, lungs and muscles also contribute to variations in HRV (Hainsworth 1995). The integration of sympathetic and parasympathetic activity with afferent signals from these various receptors produces the beat-to-beat changes in R-R interval (Figure 1.2).

Under resting conditions, in healthy subjects, a periodic variation in cardiac interbeat intervals exists which is linked to breathing and is referred to as respiratory sinus arrhythmia (RSA). This variation is due to fluctuations in vagal tone reflexly mediated by different phases of respiration and results in acceleration of HR when breathing in and slowing of HR when breathing out (Hirsch & Bishop 1981). Respiratory effort causes changes in the intra-pleural pressure secondary to diaphragmatic movement resulting in pressure changes in the aortic arch (Sayers 1973). The variations in aortic arch pressure activate baroreceptors, which cause a compensatory change in HR.

Pharmacological intervention has been shown to alter the mechanics of RSA. The anticholinergic agent atropine reduces RSA and beta-adrenergic blockade increases RSA (Coker *et al.* 1984). Stimulation of carotid baroreceptors by mechanical neck suction at the respiratory frequency has also been shown to restore RSA during periods of apnoea (Piepoli *et al.* 1997). This provides further evidence for the interrelationship between baroreceptor function and RSA. These studies demonstrate that RSA is predominantly under vagal control and consequently, the magnitude of RSA is often used to provide an index of vagal activity (Eckberg 1983, Kollai & Mizsei 1990, Hayano *et al.* 1991 and Porges 1995). Cardiac vagal function as assessed by

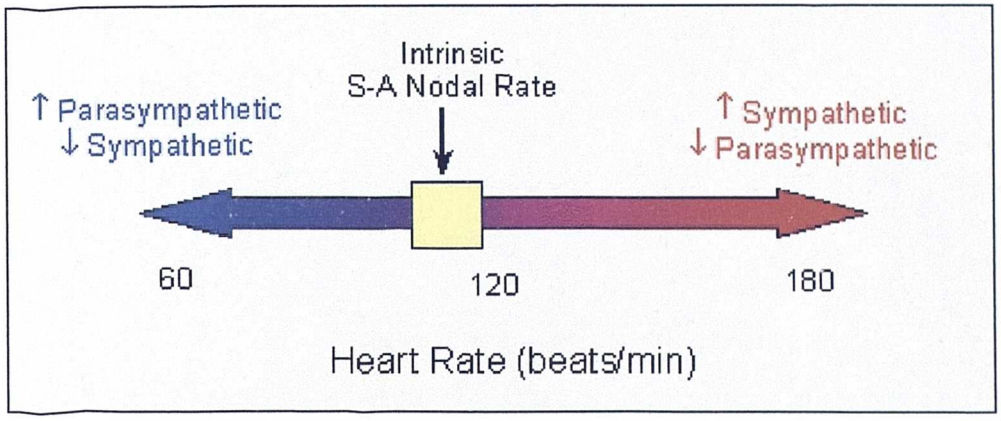


Figure 1.1 Intrinsic heart rate

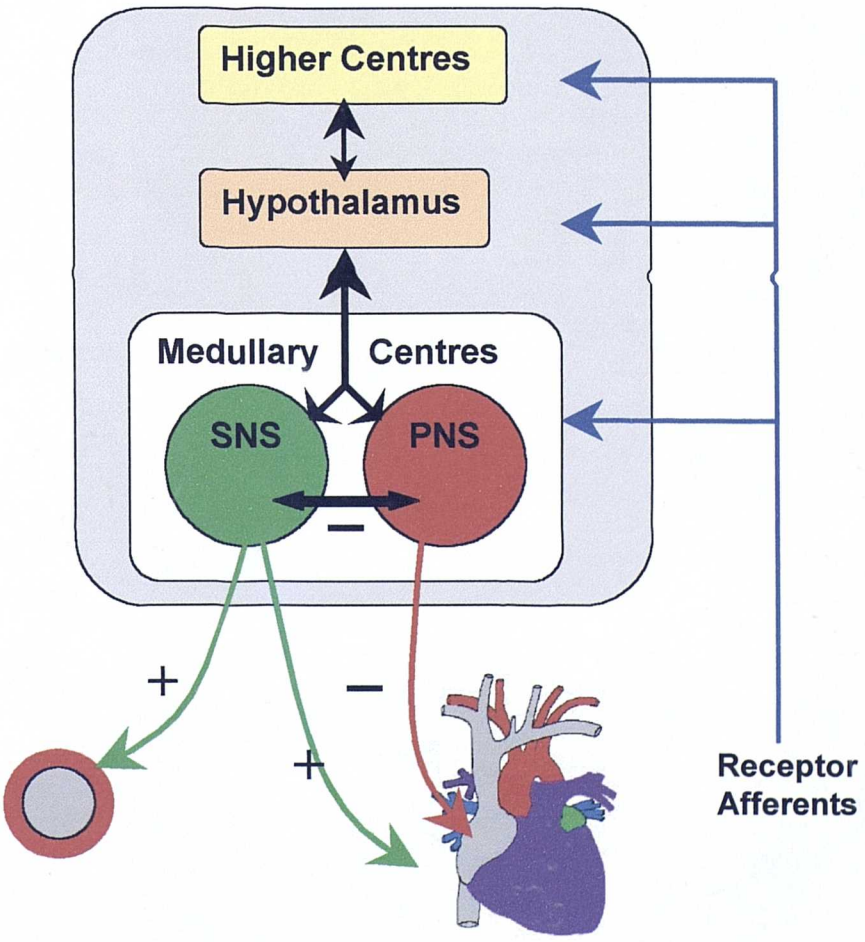


Figure 1.2 A schematic representation of the integrated actions of the sympathetic and parasympathetic branches of the autonomic nervous system.

deep breathing induced HRV has been shown by May and co-workers to be reduced in older people and in individuals on cardiac medication, with left ventricular hypertrophy or ECG signs of myocardial infarction (MI). They also demonstrated that in healthy subjects, parasympathetic function is inversely associated with age and left ventricular mass (May *et al.* 1999).

Other factors that affect HRV include cognitive stimuli from the higher cortical centres (Toichi *et al.* 1999) and emotional input from the areas of the amygdala and hypothalamus (Jordan *et al.* 1980, Spyer 1989). Furthermore, it has been proposed that genetic factors contribute towards a substantial proportion of the variance in HRV (Singh *et al.* 2001).

1.6.3 Methods of Analysing Heart Rate Variability

HRV can be assessed in two ways, either as a time domain analysis or in the frequency domain by power spectral analysis. In either method the time intervals between each successive normal QRS complex of the ECG are first determined (Figure 1.3).

1.6.4 Collection of Data for Heart Rate Variability

In studies researching HRV, the duration of recording is dictated by the nature of each investigation. At the start of the work presented in this thesis, short-term analysis of HRV was still in its early stages. Most of the larger studies, at the time used data that were obtained from 24-hour electrocardiogram (ECG) tape recordings that were collected using ambulatory monitoring devices called Holter monitors. These instruments are mainly used in clinical cardiology and form part of an established monitoring and diagnostic

procedure. They store information for off-line heart rhythm analysis and also have a facility to download R-R interval data. The R-R interval data can be further processed off-line to compute HRV statistics and power spectrum. Various problems have been identified with the collection of R-R interval data by this method (Pinna 1994). Although Holter recordings permit analysis of very slow R-R interval fluctuations, they do not allow for control of common factors such as posture and physical activity. Further variables that may cause inefficient sampling of R-R intervals include inadequate sampling frequency, tape speed distortion, inter-recorder differences and analysis system differences. These factors must be taken into consideration before viable data can be assured and will be considered more fully in Chapter Three.

1.6.5 EDITING OF THE R-R INTERVAL SEQUENCE

Achieving an artifact-free R-R interval time series is essential for accurate analysis of HRV. Introduction of errors in the time-series data is usually associated with periods of low signal quality, artifacts in the QRS detection routine or the presence of ectopic beats (Task Force 1996). Therefore prior to analysis, it is necessary to remove all abnormal or aberrant beats not generated by sinus node depolarizations (Figure 1.4). In long-term recordings this process is usually performed using automatic filtering procedures after initial arrhythmia analysis has been completed. For example, one method might exclude intervals from the original R-R interval sequence if there is more than 20% difference from the previous interval (Task Force 1996). These automatic methods may further complicate the procedure and a clean signal is not always assured. Therefore when using statistical-time domain and/or

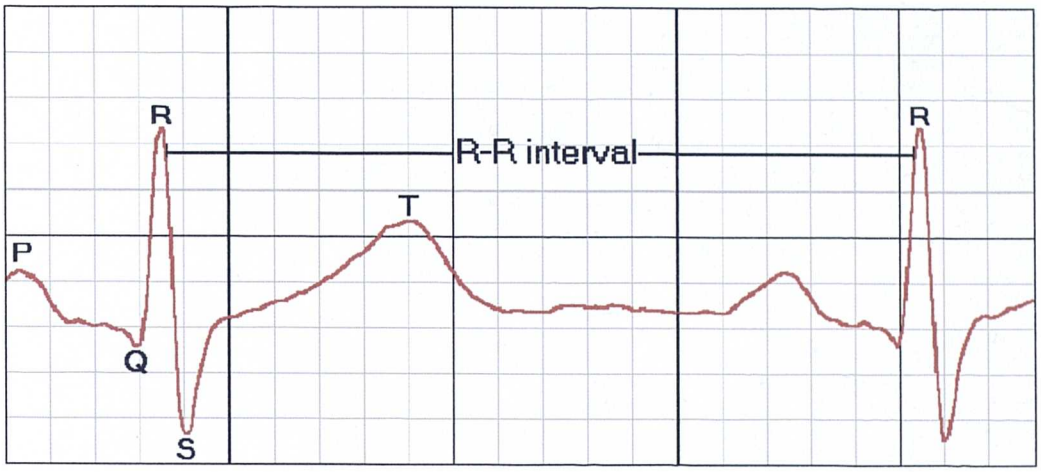


Figure 1.3 A segment of electrocardiogram showing a cardiac interbeat R-R interval.

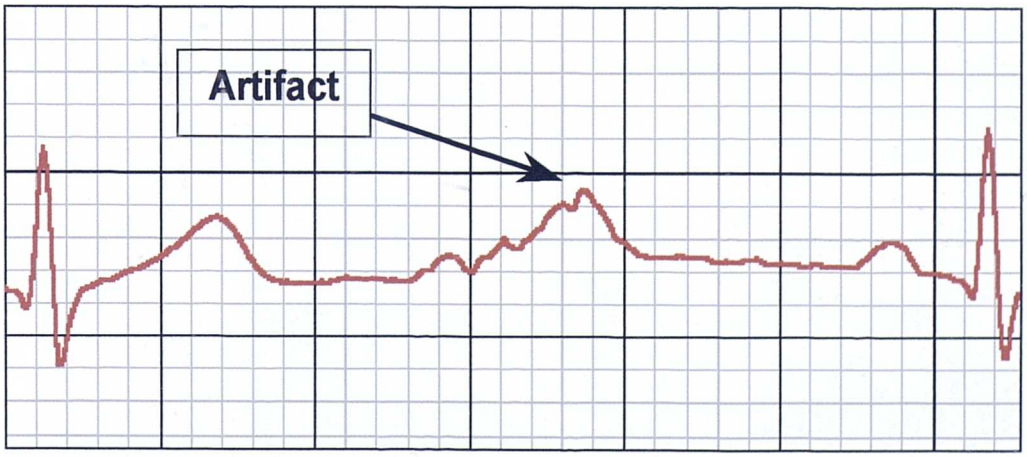


Figure 1.4 A section of ECG containing an artifact that would require removal before HRV data analysis.

frequency-domain methods the editing of R-R interval data must be performed to a high standard. For the short-term analysis of HRV used in this work, visual inspection of the R-R interval tachogram for abnormal beats and where possible inspection of corresponding QRS complex was carried out, before any manual editing was performed.

There are no specific recommendations concerning the maximum number of artifacts that can be removed before the sample becomes unusable. As a usual practice, the data are discarded when more than 5% of the beats need correction (Mulder 1992, Pitzalis *et al.* 1996, Altimiris 1999). In this study these recommendations were followed and when data were edited they were replaced using the mean of the five preceding and five successive R-R intervals. Following signal-cleaning procedures time- and frequency- domain analysis can be performed.

1.6.6 TIME DOMAIN ANALYSIS

HRV can be evaluated by a number of methods. Many of the common time-domain statistical measures have been summarised in the report of the Task Force of the European Society of Cardiology and The North American Society for Pacing and Electrophysiology (1996). Time domain measures are the simplest to calculate and with these methods either the HR at any point in time or the intervals between successive normal ECG complexes are determined (Fig 1.5). Simple time-domain measures include the mean HR, the mean R-R (N-N) interval and the difference between the longest and shortest R-R interval. (N-N interval is a term used to describe the so-called normal-to-normal intervals or all intervals between adjacent QRS complexes

resulting from sinus node depolarizations. In this study it should be assumed that the term R-R interval when used is synonymous with N-N interval and results from a clean or cleaned signal). Further time-domain measurements that can be used are derived from variations in HR secondary to respiration, lying to standing, tilt, Valsalva manoeuvre and various other procedures.

From a series of instantaneous HR or cycle intervals more complex time-domain measures can be calculated. These are divided into two groups, (a) those derived from direct measurements of the R-R interval or instantaneous HR or (b) those derived from the differences between inter-beat intervals (Kleiger *et al.* 1995). These variables may be derived from analysis of the total ECG recording such as a 24-hour Holter recording or can be calculated using smaller segments or shorter recording periods. The latter method allows comparison of HRV to be made during various activities or following certain interventions and forms the basis of the work in this thesis.

1.6.7 Time Domain Units

The Task Force has recommended four standard time-domain units to calculate HRV. They consist of three statistical measures and one geometrical measure. These are SDNN, SDANN, RMSSD and the HRV triangular index. SDANN and the HRV triangular index are normally performed on 24-hour recordings and therefore are not used in this work. In this study in addition to SDNN and RMSSD a further time-domain measure, pNN50 is used.

1.6.7.1 SDNN

This measure represents the standard deviation of the N-N interval. Standard deviation is the square root of variance and since variance is mathematically equal to the total power of spectral analysis, SDNN reflects all the cyclical components responsible for variability within the period of recording. It is inappropriate to compare SDNN measures from different lengths of recording therefore duration of recordings, used to determine SDNN values and other measures of HRV should be standardised (Task Force 1996). Nominal 24-hour, long-term recordings and five-minute recordings are recommended as appropriate options.

1.6.7.2 RMSSD

This represents the square root of the mean squared differences of successive R-R intervals. Each R-R interval difference is squared, summed, the result is then averaged and then finally the square root is calculated. This variable is used to provide an estimate of the short-term components of HRV.

1.6.7.3 pNN50

This measure represents the proportion of differences between adjacent normal R-R intervals that are greater than 50 ms. and again provides an estimate of short-term variation (STV) of HRV. All of these measurements of STV estimate high-frequency variations in HR and are thus highly correlated (Task Force 1996).

The advantages of time-domain methods are their simplicity, reproducibility and proven prognostic power in certain clinical disorders

(Fallen 2000). A disadvantage of time domain assessment of HRV is that it is not possible to discern and therefore quantify the relative contributions of sympathetic and parasympathetic activity (Fallen 2000). In the time-domain the most common way to plot beat-to-beat changes associated with sympathovagal interaction is in the form of an R-R interval tachogram (Fig 1.6).

In the work performed in this thesis short-term recordings of five-minute and 10-minute duration were used. Five-minute recording periods of HRV have been shown to be stable over months and are characteristic of individuals (Sinnreich *et al.* 1998). Short-term ECG recordings for analysis of HRV have also been proposed as a simple but effective means of contributing to risk stratification in patients with severe CHF (Lucreziotti *et al.* 2000). Measures of R-R interval variability calculated from short (two to 15 minutes) ECG recordings have also shown to be remarkably similar to those calculated over 24-hours. It has been suggested that these short-term methods of measuring HRV represent excellent predictors of all cause mortality and sudden death (Bigger *et al.* 1993). Reproducibility of HRV results has also been found to be high in normal subjects (Kleiger *et al.* 1991), in patients with CHF (Stein *et al.* 1995), and in patients with previous MI or ventricular arrhythmias (Bigger *et al.* 1992).

1.6.8 Frequency Domain Analysis

In addition to time domain analysis methods, procedures exist to decompose the heart rate signal into its power spectral components. HRV is composed of well-defined rhythmical fluctuations (Sayers 1973, Akselrod *et al.* 1981) and

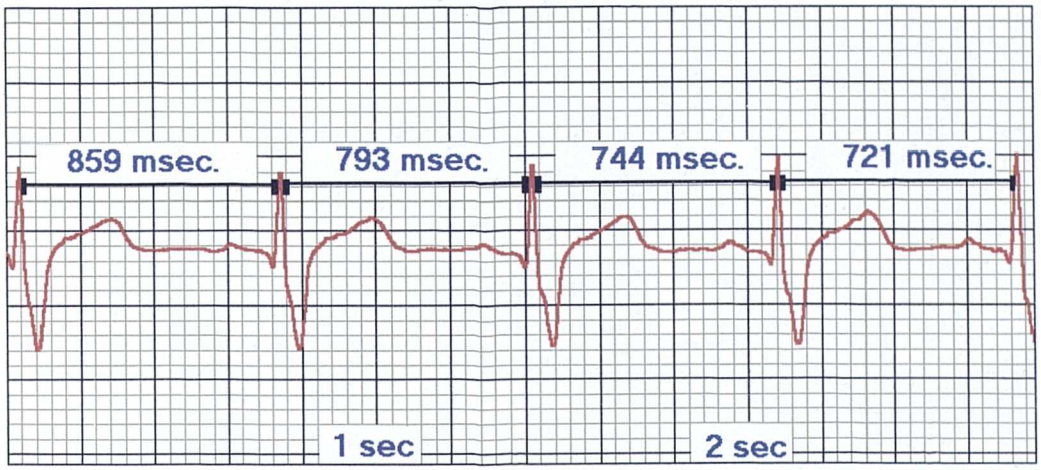


Figure 1.5 A series of cardiac interbeat R-R intervals.

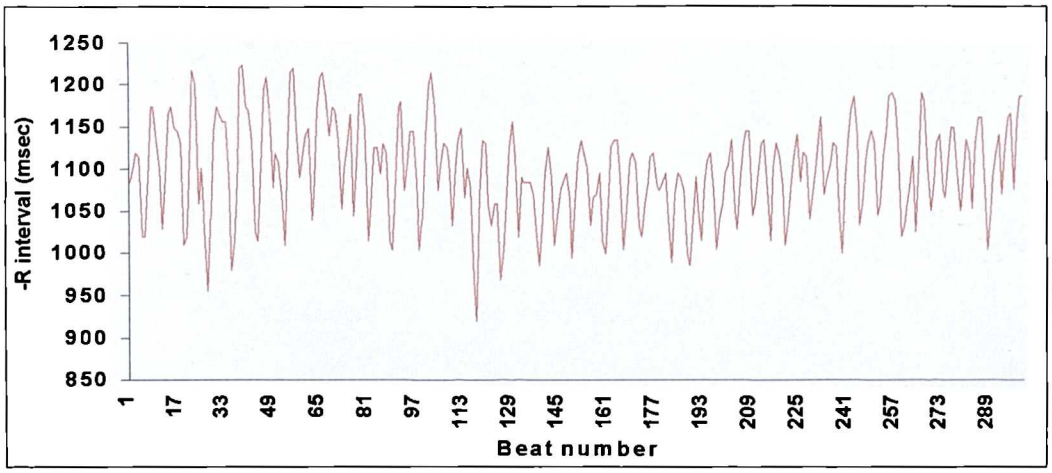


Figure 1.6 An R-R interval tachogram.

by applying filtering techniques and spectral analysis to the R-R interval tachogram, different frequency components can be discerned and analysed. Using power spectral analysis (PSA), the intensity of each frequency component can be quantified in terms of 'power' (Hartikainen *et al.* 1998).

For optimal reliability and reproducibility, the heart rate signal must meet a number of conditions that are prerequisites for meaningful PSA: ideally the signal should be *random* meaning that it should contain sequences that cannot be determined or defined by a unique mathematical expression or rule. It should be *stationary* – a random process is considered to be stationary if its statistical characteristics do not significantly change over time. Although strict stationarity does not exist in biological systems (Malliani *et al.* 1994), using parametric algorithms as opposed to non-parametric methods and shorter recording periods can partially overcome this problem (Altimiris 1999). Finally, the signal should be *sufficiently long* because assuming constant stationarity the consistency of power spectral estimates improves with an increase in the duration of the signal. If these criteria are not met and heart period modulations of a certain frequency are unstable during the recording period then interpretation of results becomes difficult (Task Force 1996).

In addition to the presence of artifacts and/or ectopic beats a further factor that may influence signal quality is the sampling rate of the ECG. A low sampling rate may produce a jitter in the estimation of the R-wave fiducial point, (i.e. the electronically detectable reference-point used to measure R-R interval length), altering the spectrum considerably. The optimal range for sampling is 250 to 500 Hz (Task Force 1996) although

Pinna has considered higher rates as appropriate (Pinna 1994). Additionally, pre-processing of data by proper de-trending and filtering is mandatory to ensure accurate power spectral analysis (Ori *et al.* 1992).

1.6.9 POWER SPECTRAL ANALYSIS

Methods for the calculation of power spectral analysis (PSA) are classified as either non-parametric or parametric. There are two main methods that are used to obtain PSA of HRV. They are the fast Fourier transform (FFT), which is a non-parametric method and the autoregressive model (AR), which is a parametric technique (Figure 1.7).

1.6.9.1 FAST FOURIER TRANSFORM

The fast Fourier transform is an efficient algorithm developed from the classical Fourier transform discovered by the French mathematician and physicist, Jean Baptiste Fourier (1768 – 1830). Fourier discovered that any periodic function of time (signal) can be resolved into an equivalent infinite summation of sine and cosine waves. In other words the Fourier transform is used to move a calculation from amplitude as a function of time to amplitude as a function of frequency. These frequencies start at 0.00 Hz and increase in integer multiples of a base frequency (Harris 1978). The classical Fourier transform (FT) is theoretically defined for signals of infinite duration and therefore is not appropriate for spectral analysis of HRV. Since HRV analysis uses discrete event series, modification of the FT is necessary. The FFT is an abbreviated calculation of the discrete Fourier transform (DFT) which is an improved model of the FT (Kay & Marple 1981).

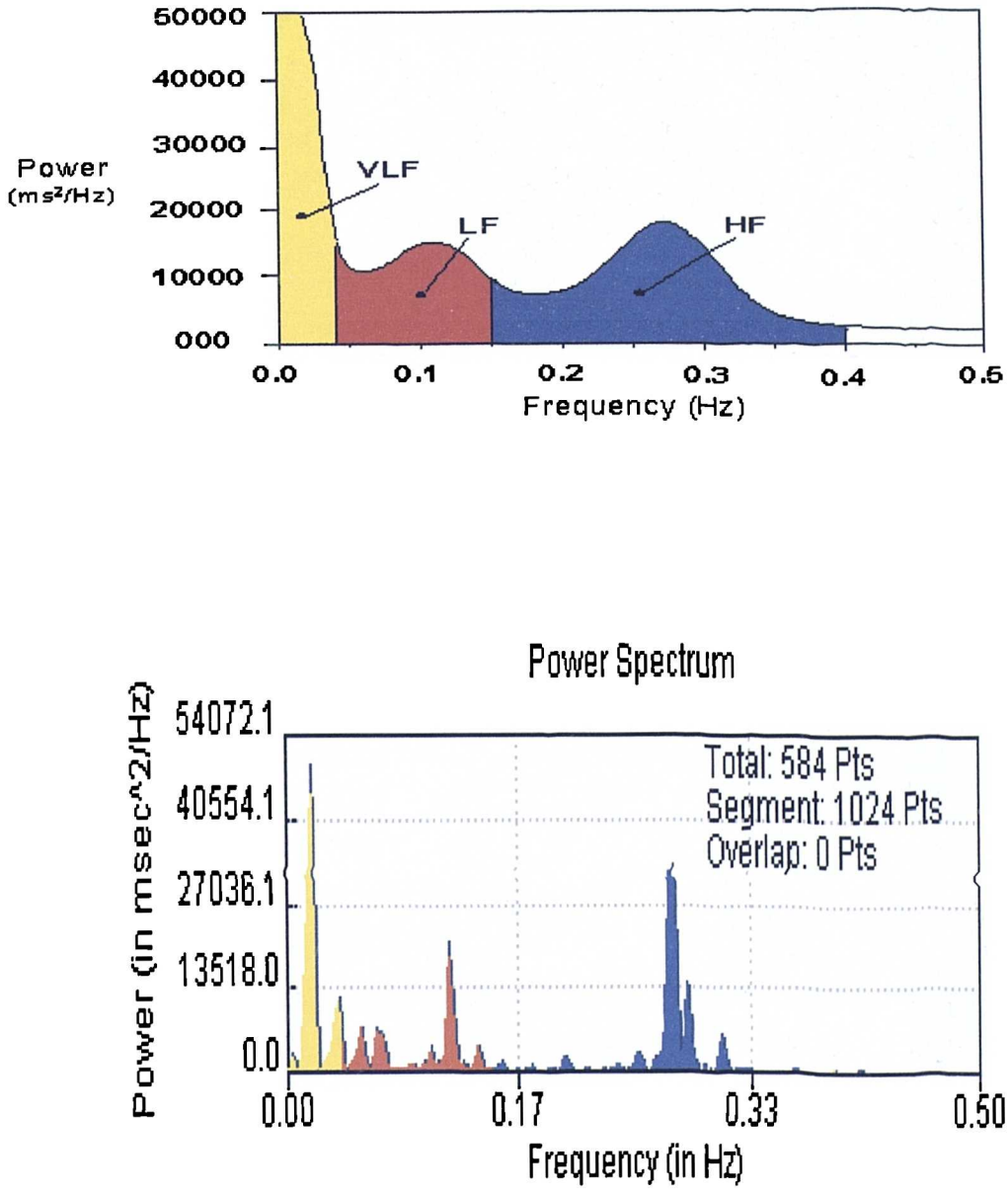


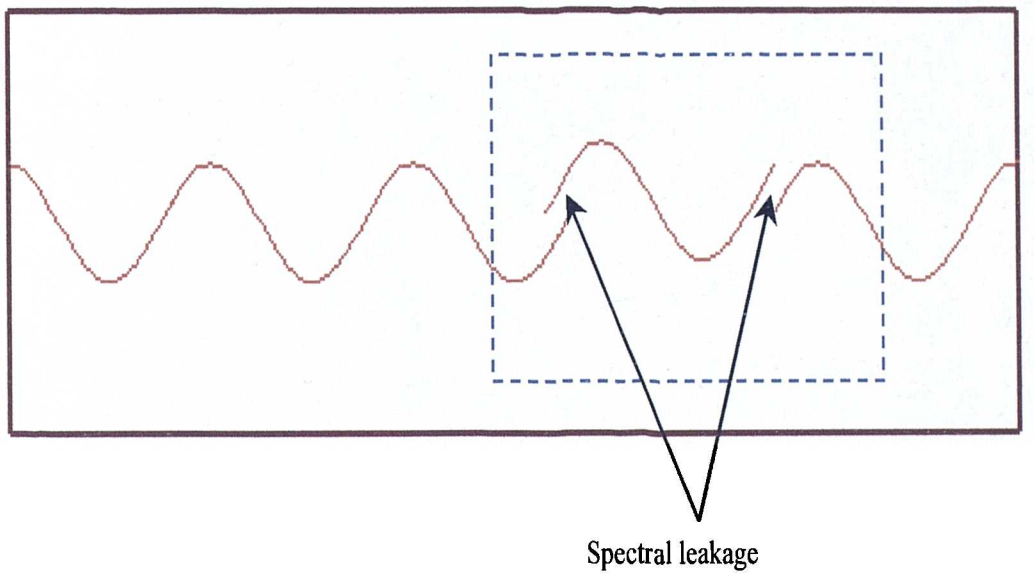
Figure 1.7 An example of **(top)** an autoregressive HRV power spectrograph and **(bottom)** a fast Fourier transform spectrograph.

The major drawback of the DFT is that it uses a complex algorithm and is consequently very slow. The FFT, sometimes referred to as the Cooley and Tukey algorithm after its inventors (Cooley & Tukey 1970) is a non-parametric method that is computationally efficient and produces rapid results for a large class of signal processes (Kay & Marple 1981). In spite of these advantages, there are several inherent performance limitations to the FFT approach. Disadvantages include lack of frequency resolution i.e. the ability to distinguish the spectral responses of two or more signals, and the problem of spectral leakage.

Spectral leakage or truncation effect, is a phenomenon that occurs when energy in the main lobe of a spectral response 'leaks' into the sidelobes, obscuring and distorting other spectral responses that are present (Figure 1.8) (Kay & Marple 1981). Various 'data windowing' and 'overlap' techniques exist to reduce leakage by decreasing the signal amplitudes near the boundaries of the discrete samples (Trethewey 2000). These techniques are mainly used before computing the FFT spectrum of the data segment, and their purpose is to smooth or otherwise shape the resulting spectrum. Examples of windowing techniques include the Hamming, Blackman-Harris, and Hanning windows. The latter, also known as the cosinus taper, is the most commonly used in HRV studies (Altimiris 1996).

1.6.9.2 AUTOREGRESSIVE MODELLING

Autoregressive modelling (AR) is a popular alternative to FFT for PSA of HRV (Kay & Marple 1981). The AR method is a parametric procedure that uses mathematical modelling of a time series based on the assumption that



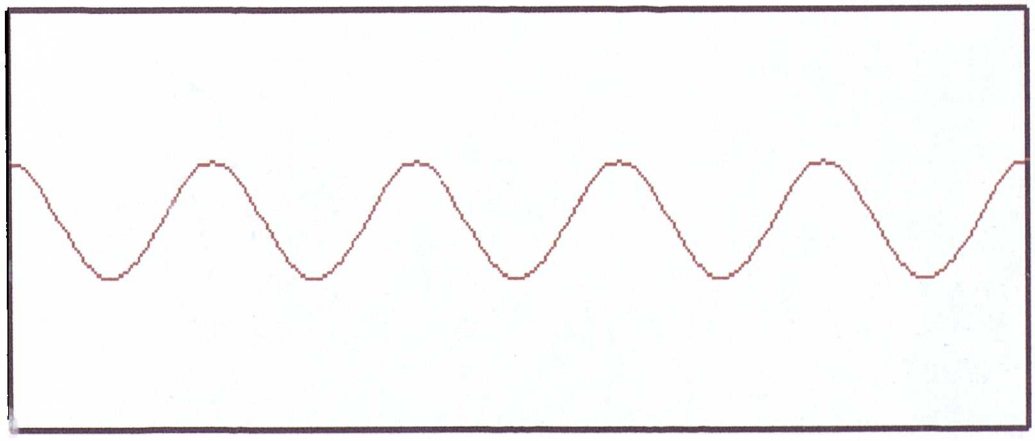


Figure 1.8 A representation of a signal showing (**top**) spectral leakage and (**bottom**) following the use of a data 'windowing' procedure.

each value of the series depends only on a weighted sum of the previous value of the same series plus "noise" (http://www.cbi.polimi.it). AR spectral estimates provide a visually attractive representation of the dynamics of interbeat intervals (Burr & Cowan 1992) and they achieve good frequency resolution i.e. smoother spectral curves, and excellent statistical stability on short segments of R-R interval data (Burr & Cowan 1992). This allows easy post-processing of the spectrum with an automatic calculation of low and high frequency power components and easy identification of the central frequency of each component. It also permits accurate estimation of power spectral density (PSD) even on a small number of samples (Task Force 1996). The basic disadvantage of parametric methods is that the order of the AR must be explicitly chosen and should conform to Akaike's Information Criteria (Burr & Cowan 1992). A comparative study of FFT and AR in the spectral decomposition of short-term HRV has shown that both methods yield similar qualitative results but differences in quantitative results (Fagard *et al.* 1998).

1.6.9.3 Coarse Graining Spectral Analysis

Coarse-graining spectral analysis (CGSA) is a more recent procedure that is used to further refine the power spectrum. The conventional FFT method is unable to separate harmonic oscillations such as respiratory and Mayer (10-second) waves from the 1/f fluctuation which is thought to represent underlying fractal dynamics i.e. a specific form of chaos. The term 'chaos' implies an aperiodic, seemingly random behaviour in a deterministic system. Essentially the coarse-graining technique is used to analyse power law fractals i.e. time-series which exhibit power law behaviour in the Fourier spectrum

(Yamamoto & Hughson 1991). This has the effect of removing noise and cleaning the HRV signal.

1.6.10 Spectral Components of Heart Rate Variability

FFT and AR methods generate peaks in three main frequency ranges or bands: very low frequency (VLF) 0.0 to 0.04 Hertz (Hz); low frequency (LF) 0.04 to 0.15 Hz; and high frequency (HF) 0.15 to 0.40 Hz (see Figure 1.9). The area under the curve is the power attributed to each frequency band (Cerutti *et al.* 1995, Task Force 1996, Hartikainen *et al.* 1998). PSA of HRV can be used to analyse the sequence of R-R interval data from short-term recordings or from an entire 24-hour period. Using 24-hour recordings the results yield an additional frequency band termed the ultra-low frequency component (ULF). Although the physiological explanation of the ULF component is still not well understood, it is thought that these oscillations are linked to circadian rhythms (Gronfier *et al.* 1999).

VLF, LF and HF power components are generally reported in absolute values of power (ms^2), but LF and HF are also given in normalised units (N.U.) representing the relative value of each power component in proportion to the total power minus the VLF component. (Pagani *et al.* 1986, Malliani *et al.* 1991). The representation of LF and HF in normalised units is said to emphasise the controlled and balanced behaviour of the two branches of the ANS (Task Force 1996). Moreover, normalisation is reported to minimise the effect on the values of LF and HF components of the changes in total power (Pagani *et al.* 1986, Malliani *et al.* 1991). Both absolute and normalised units

should always be quoted together to describe the distribution of power within the power spectrum (Task Force 1996).

In addition to the use of normalised units, the ratio of low frequency power and high frequency power (LF/HF ratio) is commonly used to describe the balance between the sympathetic and parasympathetic components of the cardiac autonomic system. Since numerous complex interactions occur between the inputs to the sinus node the components of the ANS do not function solely in a reciprocal manner (Berntson *et al.* 1993, Porges 1995). A broader *doctrine of autonomic space* has been developed to describe in more detail these complex interrelationships and indicates how the two autonomic branches can vary reciprocally, independently or co-actively. (Berntson *et al.* 1991). Despite widespread use of a variety of HRV parameters as indices of the interaction of the two branches of the ANS, controversy still remains in the use of the term 'sympathovagal balance' for the reasons previously stated (Goldberger *et al.* 1999, Eckberg 2000).

1.6.10.1 HIGH FREQUENCY POWER

Periodic components of HRV tend to accumulate within several frequency ranges or bands. In the range 0.15 Hz and 0.40 Hz in healthy individuals, there is a high frequency (HF) component often referred to as the respiratory component of HRV (Ori *et al.* 1992). These RSA-linked fluctuations are generally associated with cardiac parasympathetic (vagal) activity (Cerutti *et al.* 1995, Hartikainen *et al.* 1998). HF oscillations are caused partly by inhibition of vagal tone during inspiration (Altimiris 1999) and are evoked centrally within the cardiovascular centre. Peripheral reflexes arising from

thoracic stretch receptors also contribute to this so-called respiratory sinus arrhythmia. Atropine or vagotomy, abolish RSA (Coker *et al.* 1984), and the power at the HF frequency is commonly used as an index of vagal activity (Eckberg 1983, Kollai & Mizsei 1990 and Hyano *et al.* 1991 Porges 1995).

Several studies have reported on the effect of breathing on HRV parameters. Pagani *et al.* (1986) demonstrated that metronome paced breathing at 20 breaths per minute increased HF power and reduced LF/HF ratio when compared with spontaneous breathing. Although neither breathing frequency or tidal volume significantly influences average R-R intervals (HR), significant variations have been reported within the frequency domain. Brown *et al.* (1993) confirmed that breathing parameters influence the HF (parasympathetic) component of HRV and showed that when breathing frequency fell below 9 breaths/minute (0.15 Hz) the power in the LF region increased. Tidal volumes also affect PSA of HRV. R-R interval power at respiratory frequencies is significantly greater at tidal volumes of 1500 ml than 1000 ml (Brown *et al.* 1993).

1.6.10.2 LOW FREQUENCY POWER

The low frequency (LF) component of HRV is characterised by an oscillatory pattern with a period around 10 seconds or 0.1 Hz. This rhythm originates in the vasomotor area of the baroreflex loop as a result of negative feedback (Madwed *et al.* 1989). It is commonly associated with synchronous fluctuations in blood pressure known as Mayer waves (Mayer 1876, Penaz 1978). The LF range is generally considered to fall between 0.04 Hz and 0.15 Hz. In several studies this frequency range has been termed the mid-

frequency range (Mulder 1992), but the designation low-frequency is more common and is used within this work.

Fluctuations in LF power are said by some authors to reflect mainly sympathetic outflow (Malliani *et al.* 1991, Malliani *et al.* 1994) although most investigators consider them to be of both sympathetic and vagal origin (Akselrod *et al.* 1985, Pomeranz *et al.* 1985, Koh *et al.* 1994). In animal models muscarinic and beta-adrenoceptor antagonists are known to change the area of the LF region. In the dog, the LF component appears to be mainly mediated by the parasympathetic nervous system (Akselrod *et al.* 1985) while in rats, the sympathetic influence accounts for 80% of the LF region (Cerutti *et al.* 1994). Sympathetic activation during tilt or standing has been shown to increase power in the LF region (Pomeranz *et al.* 1985, Pagani *et al.* 1986). Therefore, particularly when expressed in normalised units, LF power is regarded as a marker of SNS activity (Cerutti *et al.* 1995, Task Force 1996, Hartikainen *et al.* 1998).

1.6.10.3 VERY LOW FREQUENCY POWER

Other R-R interval fluctuations occur at frequencies below 0.04 Hz. These have been designated variously, but commonly used bands include very low frequency (VLF) and ultra low frequency (ULF) frequencies. ULF are obtained from 24-hour recordings and are thought to be associated with neuroendocrine processes related to circadian rhythms and therefore fall outside the scope of this work (Gronfier *et al.* 1999). Some workers have described the VLF band from 0.003 to 0.05 Hz (Mulder 1992) but in this work VLF is described from 0.0 Hz (DC) to 0.04 Hz.

The exact mechanisms underlying VLF oscillations remain uncertain (Cerruti *et al.* 1995, Task Force 1996). They are thought to be mainly associated with thermoregulatory cycles (Sayers 1973, Kitney 1975, Fleisher *et al.* 1996) and with fluctuations of renin activity on arterial pressure. Akselrod *et al.* (1981) demonstrated that blockade of the renin-angiotensin-aldosterone system (RAAS) in conscious dogs caused increased activity of R-R variability within the VLF region of the power spectrum. These results have been supported by long-term studies in post-MI patients treated with angiotensin converting enzyme (ACE) inhibitors (Bonaduce *et al.* 1994). Reductions of VLF R-R interval oscillations are associated with increased risk for cardiac and dysrhythmic death (Bigger *et al.* 1992 and 1993). Additionally, Lepicovska *et al.* (1992) proposed that reduced VLF fluctuations may represent increased risk in patients prone to vasodepressor syncope. Discrete VLF oscillations have been reported in patients with advanced CHF (Ponikowski *et al.* 1996). They are thought to be related to severely impaired autonomic regulation and suppression of baroreceptor function, with enhancement of hypoxic chemosensitivity. The authors hypothesised that the discrete VLF rhythm represents an enhanced chemoreflex harmonic oscillation and may have application for arrhythmogenesis. Furthermore, an anti-baroreflex mechanism associated with VLF oscillations has been proposed in some patients with advanced CHF (Ponikowsi *et al.* 1997).

Although VLF oscillations are influenced by the RAAS as low and high frequency R-R intervals, Taylor *et al.* (1998) suggested that VLF rhythms depend primarily on parasympathetic outflow. They further proposed that the prognostic value of VLF oscillations derive from the

fundamental importance of parasympathetic mechanisms in cardiovascular health. VLF R-R interval variability is also influenced by physical activity and any attempts to predict cardiovascular prognosis on the basis of HRV should take into account the confounding effect of physical activity (Bernardi *et al.* 1996).

1.6.11 Heart Rate Variability in Health and Disease

Analysis of HRV has also been used to highlight the importance of the autonomic nervous system in both health and disease (Kristal-Boneh *et al.* 1995, Sleight 1997). Karemaker & Lie (2000) suggested that HRV is not only useful as a 'telltale' of disease but can also be considered a valuable indicator of good health. Several factors affecting HRV in both health and pathological states and are considered below.

1.6.11.1 Gender effects

Many studies have reported on the effects of gender on HRV. Ryan *et al.* (1994) observed that HF power of HRV (associated with parasympathetic activity), and the overall complexity of heart rate dynamics was higher in women than men. It was suggested that these factors contributed to the lower cardiovascular risk and greater longevity in women. The possible cardio-protective effects of physical activity in post-menopausal women were also explored by Davy *et al.* (1996) and in a further study by Ramaekers *et al.* (1998), cardiac autonomic modulation, as described by HRV, was shown to be significantly lower in healthy women in comparison to healthy men. They hypothesised that these seemingly paradoxical results suggested that the lower

SNS activity, (as measured by LF power) in women provided protection against arrhythmias and the development of CHD. The effects of gender on HRV have also been reported in patients with cardiac disease. In a recent large study, Milicevic *et al.*. (2001) analysed 24-hour Holter recordings from 2578 cardiac patients aged 15 to 91 years. Differences in HRV by age, sex and type of patient were identified. The results showed that females had a higher mean HR but more pronounced vagally modulated activity than males.

1.6.11.2 AGE EFFECTS

The effect of ageing on ANS cardiac control is progressive and continuous throughout an 18 – 80 years age range (Fluckiger *et al.* 1999). VLF, LF and HF powers of HRV decrease significantly with age, both during awake as well as sleep periods (Yeragani *et al.* 1997). Age-related reductions in HRV were initially attributed to a decline in cardiac vagal tone (Eckberg 1983, Shannon *et al.* 1987) however PSA of HRV has shown that LF power also decreases with age indicating a fall in cardiac sympathetic activity (Lipsitz *et al.* 1990, Korkushko *et al.* 1991). Kuo *et al.* (1999) described a linear decline of HRV with age and demonstrated that the gender-related difference in parasympathetic regulation of the heart reduced after age 50 years whereas a significant time delay for the disappearance of sympathetic dominance occurs in men. Other workers however have reported that the ratio between high and low frequency components of HRV, representing vagal and sympathetic branches of the ANS, remains stable with advancing age (Pagani *et al.* 1986, Schwartz *et al.* 1992).

1.6.11.3 CIRCADIAN VARIATION

Similar to other human physiological systems the ANS is considered to exhibit circadian variation (Ori *et al.* 1992). Normally HRV increases at night during sleep due to increased cardiac parasympathetic activity and reduction in sympathetic tone (Ewing *et al.* 1991). This was demonstrated by Furlan *et al.* (1990) using 24-hour ECG recordings. They showed pronounced and consistent reduction in nocturnal LF activity and increased HF activity in normal, healthy controls. Similar studies have confirmed these findings (Burger *et al.* 1999, Badilini *et al.* 2000). Additionally, Wennerblom *et al.* (2001) reported that in the early morning hours, in preparation for waking, there is normally a rapid withdrawal of cardiac vagal activity and an increase in sympathetic tone. They proposed this as the mechanism underlying the increased incidence of sudden cardiac death in the early morning hours. However, Hayano *et al.* (1991), using hourly recordings for PSA of HRV, demonstrated greater vagal power during the morning hours compared to late afternoon and in the same study showed that the power in the respiratory component (HF) decreased 30 minutes after food intake.

Disordered circadian variation of HRV has been demonstrated in several disease states. PSA of HRV from 24-hour recordings has shown reduced day-night oscillations in ambulant hypertensive subjects (Hayano *et al.* 1991). Following MI, Lombardi *et al.* (1992) showed that an alteration exists in neural control mechanisms as indicated by the presence of signs of sympathetic activation and attenuation of the nocturnal increase in vagal tone. Casolo *et al.* (1991) used spectral analysis to investigate the differences between normal and CHF patients. They noted that normal but not CHF

patients exhibit circadian variation of HRV. Further studies demonstrating irregular circadian variations of HRV have also been reported in other pathological conditions. In a study by Burger *et al.* (1999), circadian differences in both time and frequency domain HRV parameters have been reported in different groups of subjects. Normal subjects demonstrated the greatest day-to-night variability, patients with diabetes mellitus exhibited the least variability and patients with chronic angina showed intermediate values.

1.6.11.4 EXERCISE TRAINING

Heart rate variability is a characteristic that is potentially increased by physical activity (Schuit *et al.* 1999). In a recent review of Sports Medicine in the British Medical Journal, Raold Bahr (2001) suggests that one of the most important advances in medicine is the documentation that regular physical activity reduces the risk of premature mortality, coronary heart disease, colon cancer, obesity and diabetes mellitus (Bahr 2001). Substantial health benefits can be obtained by undertaking a moderate amount of physical activity on most, if not all, days of the week (Surgeon General, JAMA 1996,276:522).

In recent years the number of studies reporting on the effects of exercise and physical training on HRV in various populations has increased considerably. Most studies demonstrate that increased physical fitness and exercise training are associated with increased HRV (Fujimoto *et al.* 1997, Malfatto *et al.* 1998, Schuit *et al.* 1999, Deligiannis *et al.* 1999, Stahle *et al.* 1999 and Tygesen *et al.* 2001). However, a small number have failed to demonstrate any association. In a small study of 12 endurance-trained athletes compared with 12 untrained controls, Reiling & Seals (1988), using

the magnitude of respiratory sinus arrhythmia (RSA) as a measure of cardiac vagal tone, found no significant differences between groups. Boutcher & Stein (1995) were also unable to demonstrate significant variations in HRV following a 24-session moderate intensity aerobic training programme in middle-aged men (n = 19) when compared with controls (n = 15).

The effect of exercise training on HRV has been studied across all age ranges. Regular exercise has been shown to improve fitness and body composition in obese children and has a favourable effect on spectral measures of HRV (Gutin *et al.* 2000). In healthy young athletes, the effects of different physical training regimes on HRV using spectral techniques has also been compared to sedentary controls (Aubert *et al.* 2001). In a group of 140 normal subjects aged 40 to 77 years, HRV as measured by the time-domain measure SDNN was associated with increased high physical training level (Molgaard *et al.* 1991). Regular exercise in older men and women has been shown to specifically increase the VLF and LF components of HRV (Schuit *et al.* 1999). Furthermore, parameters consistent with cardiac vagal modulation have been shown to be superior in older athletes following regular training sessions (De Meersman 1993, Yataco *et al.* 1997). Goldsmith *et al.* (1997) have suggested that the decline in vagal modulation, represented by HF power, often attributed to increasing age may instead be due to the result of a decline in physical fitness.

In elite athletes HRV analysis has been used to detect ANS disturbances in conditions of overreaching and overtraining. These states, which are thought to represent an imbalance between training and recovery, are characterised by increased sympathetic and reduced vagal tone (Hedelin *et*

al, 2000, Uusitalo *et al.* 2000). HRV analysis has also been used to test the effects of dynamic exercise in athletes (Shin *et al.* 1995) and to compare the effects of different lifestyles, (smokers, sedentary and aerobically fit persons) on cardiovascular regulatory mechanisms (Gallagher *et al.* 1992). Additionally, breathing associated HRV has also been suggested as a measure of aerobic fitness (Hrushesky & Schraufek 2001).

Exercise and physical training has also proven effective in improving cardiac ANS activity in certain disease states. Deligiannis *et al.* 1999 demonstrated that in patients with renal disease receiving haemodialysis, physical training significantly increases HRV as measured by SDNN. It was proposed that physical training augmented cardiac vagal activity and decreased vulnerability to arrhythmias. In congestive heart failure (CHF), physical training has also been shown to maintain and improve circadian variation of HRV (Adamopolous *et al.* 1995). Furthermore, also in CHF, others have suggested that physical training, leading to improved exercise capacity ameliorates the autonomic derangement by increasing the parasympathetically mediated component of HRV (Kiilavuori *et al.* 1995).

Exercise training is the major component of many cardiac rehabilitation (CR) programmes and at the start of this work the number of studies reporting the effects of CR on HRV was small. Although study numbers remain limited, analysis of HRV has yielded positive information on the role of the ANS in the cardiac recovery process. In an early study using time and frequency domain measures of HRV, Malfatto *et al.* (1996) demonstrated an increase in parasympathetic tone following an eight-week exercise programme in uncomplicated MI patients. The same authors

reported on the combined effects of beta-blocker and exercise therapy in 53 patients also following a first uncomplicated MI. They showed that the effects of exercise rehabilitation and beta-blockers are complementary to each other and that their association induces a more favourable sympathovagal balance, accelerating the recovery of a normal profile (Malfatto *et al.* 1998). More recently, Pardo *et al.* (2000) examined the effects of a 12-week exercise rehabilitation programme on HRV in cardiac patients. The results showed a significant decrease in HR and increases in SDNN, pNN50, total and HF power. The authors suggest that the results supported the concept that exercise training lowers the risk of sudden cardiac death by improving vagal tone. They also reported a dose-related effect of exercise on HRV and suggested that improved vagal tone as a result of exercise training is likely to beneficially alter ventricular fibrillatory and ischaemic thresholds. Using PSA of HRV a further recent study by Carunchio *et al.* (2000) has reported similar findings on the effects of an eight-week exercise-training programme in patients recovering from a recent uncomplicated MI.

1.6.11.5 MYOCARDIAL INFARCTION

Following myocardial infarction (MI) cardiac sympathetic and parasympathetic activity becomes disordered. Generally this results in loss of vagal reflexes and increased sympathetic activity (Casolo *et al.* 1992). These effects occur during the period when the risk of arrhythmic events is at its highest. Sympathetic hyperactivity has been shown to predispose towards ventricular fibrillation in animal models (De Ferrari *et al.* 1991) while vagal reflexes are believed to have a cardio-protective effect (Task Force 1996). In

a study by Kleiger *et al.* (1987) involving 808 post-MI subjects, reduced HRV as measured by the standard deviation of all normal R-R intervals (SDNN) over 24-hours, was associated with an increased risk of terminal ventricular arrhythmias. The relative risk of mortality was calculated to be 5.3 times higher in the group with reduced HRV (SDNN < 50 ms.) than the group with a higher HRV (SDNN > 100 ms.). Lombardi *et al.* (1987) reported a relative increase in LF and decrease in high frequency heart rate fluctuations in 70 subjects, 2-weeks after MI. They demonstrated that LF/HF ratio showed a trend towards control values after a 12-month period. The association between post-infarction mortality and altered ANS function was further confirmed in a large study by Bigger *et al.* (1992). Frequency domain measures of HRV were evaluated in 715 subjects, two weeks after MI. The population was followed for up to four years. Following adjustment for known risk predictors, the association between mortality and total, ULF and VLF power remained significant and strong. In comparison LF and HF powers were only moderately strong. VLF power was the only variable that was a more powerful predictor of arrhythmic death than cardiac or all-cause mortality.

A further measure of ANS function that is associated with a good prognosis following MI is the baroreflex function. In a study of autonomic tone and reflexes after myocardial infarction (ATRAMI) analysis of vagal reflexes by baroreflex sensitivity methods, was shown to significantly add to the prognostic power of HRV following MI. Analysis of vagal reflexes had significant prognostic value independently of left ventricular ejection fraction (LVEF) and of ventricular arrhythmias (La Rovere *et al.* 1998).

Site of infarct also determines the size of effect on HRV. Anterior wall MI results in a considerably larger reduction in HRV than inferior wall infarction (Pipilis *et al.* 1991).

1.6.11.6 HYPERTENSION

Increased vascular resistance is the basic haemodynamic abnormality in systemic hypertension (Ori *et al.* 1992). Intrinsic vascular muscle defects and autonomic abnormalities have been postulated as the underlying contributory mechanisms (Julius *et al.* 1975, Korner *et al.* 1973 Abboud, 1982). Guzzetti *et al.* (1991) studied spectral parameters of HRV from 24-hour recordings using an AR model in subjects with mild hypertension. They demonstrated an increase in the LF component of HRV and a blunting of circadian patterns when compared to normal controls. The authors proposed that hypertension is characterised by depressed circadian rhythmicity. Similar findings were obtained in a study by Chakko *et al.* (1993). They performed PSA of HRV on 24-hour Holter recordings from hypertensive patients with left ventricular hypertrophy and compared results with age-matched normal controls. Significant differences were observed in HRV measures with the hypertensive patients exhibiting lower HF values reflecting diminished vagal tone. Additionally the control groups exhibited normal circadian rhythms in HRV while in the hypertensive group circadian variation was absent. Langewitz *et al.* (1994) used PSA of HRV to compare LF and HF components of HRV in normal, borderline and hypertensive subjects at rest and under conditions of mental stress. Spectral energy in the HF band revealed the most prominent differences between groups. Hypertensive patients were found to have

significantly reduced parasympathetic activity when compared to normal controls although these results may be confounded by physical inactivity.

Two large population studies, the Atherosclerosis Risk in the Communities (ARIC) study and the Framingham Heart Study have used analysis of HRV to investigate the underlying causes of hypertension. The ARIC group used spectral estimates of HRV and reported that an imbalance of sympathovagal function as a result of reduced vagal tone is associated with a risk of developing hypertension (Liao *et al.* 1996). The Framingham study showed that autonomic dysregulation is present in the early stages of hypertension and that reduced HRV in both men and women is associated with systemic hypertension. It was also observed that among normotensive men, a lower HRV was associated with a risk of developing hypertension.

Hypertension is twice as frequent in diabetic patients than in the general population (Perin *et al.* 2001). In studies using HRV analysis sympathetic activation has been considered as a link between insulin resistance, hyperinsulinaemia and hypertension in type-2 diabetics (Laitinen *et al.* 1999). Vecchione *et al.* (2000) suggested that vascular insulin resistance is a type of endothelial dysfunction that impairs the insulin modulation of the vascular effects of sympathetic nervous activation. Using PSA of HRV Takahashi *et al.* (2001) further investigated the association between insulin resistance and autonomic dysregulation in Type-2 diabetics. From the results of the study the authors concluded that essential hypertension acts synergistically with Type-2 diabetes to depress cardiac vagal and sympathetic function and they also suggested that insulin resistance may play a pathogenic role in these autonomic processes.

1.6.11.7 HEART FAILURE

Within the last 15 years several studies have investigated HRV and congestive heart failure (CHF). The results of these studies have substantially demonstrated that HRV, measured both in the time and frequency domains, is significantly different in CHF patients compared to controls. Moreover, some variables particularly SDNN and the LF component of HRV seem related to an increased mortality in CHF (Guzzetti *et al.* 2001). In CHF, Sopher *et al.* (1990) proposed that HRV is altered mainly due to attenuated vagal tone and augmented sympathetic activity. More recently Malfatto *et al.* (2001), using LF/HF ratio as an index of sympathovagal balance demonstrated that patients with heart failure had a greater sympathetic activation at baseline in comparison to patients with idiopathic dilated cardiomyopathy.

Reduced HRV based on 24-hour monitoring has also been demonstrated in CHF when compared to normal conditions and several studies suggest that depressed HRV has independent prognostic value in CHF (Boveda *et al.* 2001, Ponikowski *et al.* 1997, Brouwer *et al.* 1996). Lucreziotti *et al.* (2000) used 5-minute ECG recordings to assess HRV in 75 ambulatory patients with severe CHF to investigate the relationship between HRV and clinical, neurohormonal and haemodynamic parameters and to determine its predictive power. No correlation was found between New York Heart Association (NYHA) class and HRV, whereas significant correlations were identified between plasma levels of noradrenaline, several haemodynamic and spectral measures of HRV. The authors concluded that PSA of HRV represents a simple but effective means of contributing to risk stratification in patients with severe CHF. Moreover in CHF, the prognosis

for women is better than for men. Using time and frequency domain analyses of HRV from 24-hour Holter recordings, Aronson & Burger (2000) found that women with non-ischaemic CHF had enhanced vagal responsiveness compared to men. The authors suggested that gender-based differences in autonomic responses are related to the female survival advantage.

1.6.11.8 OTHER CARDIOVASCULAR DISEASES

Results from the Atherosclerosis Risk in Communities (ARIC) study demonstrated that in general, reduced HRV is associated with a higher risk of death and in elderly subjects with a higher incidence of coronary heart disease (CHD) (Dekker *et al.* 2000). Reduced HRV mainly affecting vagal tone has been reported in patients with stable coronary artery disease (CAD) (Wennerblom *et al.* 2000, van Boven *et al.* 1998). In a study of 265 patients with CAD, Huikuri *et al.* (1999) using SDNN as a marker of HRV demonstrated that reduced HRV, analysed from 12-hour recordings was shown to predict rapid progression of the disease. Sympathetic activation without parasympathetic augmentation has been proposed as the possible mechanism for the genesis of coronary artery spasm in patients with nocturnal variant angina (Miwa *et al.* 1998). Moreover, in patients with coronary syndrome X, HRV studies have indicated that vagal withdrawal, represented by reduced RMSSD and HF spectral power is involved in the pathogenesis of dynamic myocardial ischaemia, which is commonly seen in these patients.

1.6.11.9 CARDIAC TRANSPLANTATION

Cardiac transplantation results in extrinsic denervation of the transplanted heart. Following heart transplant, HRV is considerably reduced in comparison to normal subjects (Sands *et al.* 1989). A visual display of spectral analysis after transplant reveals reduced total power and resembles broad-band noise with no significant peaks (Fig 1.9). HRV studies demonstrating the reappearance of cardiac innervation following transplantation show mixed results. Koskinen *et al.* (1996) reported that donor HRV increases with post-transplantation time and in a study by Fallen *et al.* 1988 after 33 months, one from a group of eight transplant patients displayed an HRV spectrum indistinguishable from normal controls. Ramaekers *et al.* (1996) suggested that increases in the HF component of HRV are compatible with parasympathetic reinnervation following heart transplant. HRV monitoring has also been proposed as a marker of allograft rejection (Sands *et al.* 1989) but Ramaekers *et al.* (1996) showed that in five patients with acute allograft rejection HRV monitoring was unsuccessful in detecting rejection. The HRV data of patients with MI and malignant ventricular arrhythmias proved similar to the transplant recipients. Rodrigues *et al.* (1996) compared HRV measurements from a group of transplant r cipients to patients who have had MI with and without malignant arrhythmias. The authors suggested that myocardial autonomic denervation plays an important role in the genesis of malignant arrhythmic events. Moreover, Bernardi *et al.* (1990) studied HRV measurements between normal and transplant patients, under conditions of submaximal dynamic exercise. They suggested that at peak exercise, a non-autonomic mechanism, possibly

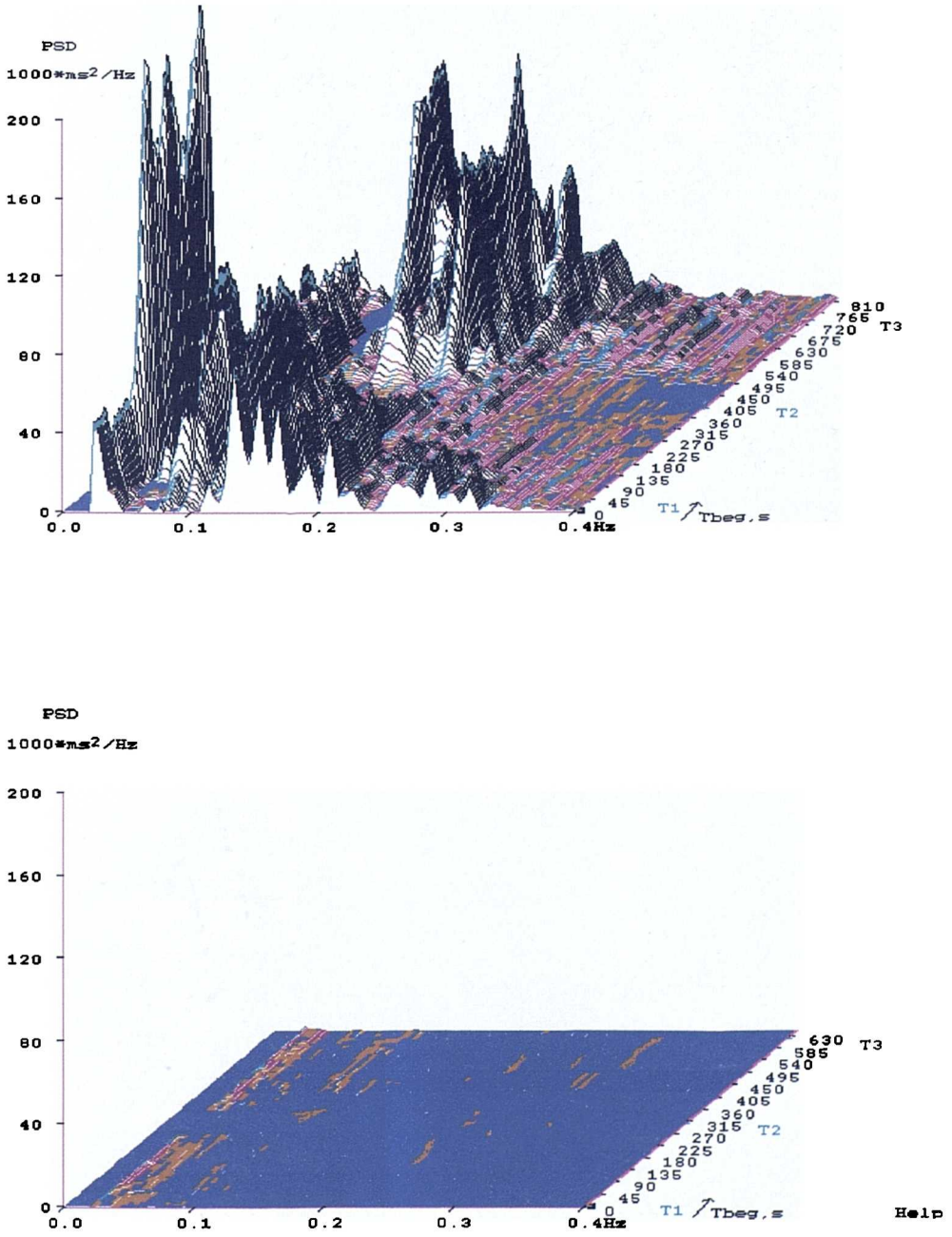


Figure 1.9 HRV power spectral graphs of (**top**) a healthy 46 years old male runner and (**bottom**) a 51 years old male cardiac transplant patient three months post-transplant.

intrinsic to the heart accounted for heart rate oscillations linked to ventilation in both the intact and denervated human heart.

1.6.11.10 DIABETES MELLITUS

Autonomic neuropathy is a common complication of diabetes (Hosking *et al.* 1978, Fedele & Giugliano 1997). HRV measures used in studies concerning diabetic neuropathy are mainly derived from autonomic function tests such as those used in Ewing's Battery (Stalberg & Nogues 1989, Ewing *et al.* 1981). More recently spectral analysis of HRV has been employed in the detection of sub-clinical diabetic autonomic neuropathy (DAN). Power spectral measures of HRV are said to be more sensitive than time-domain measures in the detection of DAN and can be used to quantify the severity of disease (Bianchi *et al.* 1990). The clinical significance of early and reliable detection of DAN, as is possible using PSA of HRV is obvious. (Ravenswaarj-Arts 1993). Five-year mortality rate in diabetic subjects with autonomic neuropathy is increased fourfold compared to those without autonomic neuropathy (O'Brien *et al.* 1991, Ewing *et al.* 1981).

In diabetic patients some workers have proposed that parasympathetic damage occurs more commonly than sympathetic damage (Hosking *et al.* 1978, Ewing *et al.* 1980, Bellavere *et al.* 1985) while others suggest that the initial manifestation of diabetic neuropathy involves both limbs of the ANS. This was demonstrated by Bernardi *et al.* (1992) who showed a total reduction in HRV in DAN patients but no significant differences for normalised LF and HF units of HRV when compared to normal controls. Abnormalities in HRV have also been reported in diabetic patients in supine conditions and in

response to orthostatic stress. Pagani *et al.* 1988 demonstrated that R-R interval variability was reduced both at rest and during response to tilting, in diabetic patients in comparison to normal controls. Furthermore it was shown that the diabetic group revealed normal LF/HF ratio during supine conditions but had a lower LF/HF ratio during tilt. This evidence suggested reduced sympathetic activation during orthostasis in diabetic patients. The results of the study also demonstrated that a comparison of power spectral estimates recorded during supine and tilt conditions is more sensitive for identifying abnormal autonomic function than testing in the supine state alone.

1.6.11.11 PHARMACOLOGICAL INTERVENTION

HRV can be influenced by various groups of pharmacological agents. Within the last decade the effects of many types of chemical substances on the ANS, from alcohol and antidepressants to zinc, have been tested using HRV analysis (Reed *et al.* 1999, Agelink *et al.* 2001, Merialdi *et al.* 1999). More relevant to the work presented in this thesis are the studies that have examined the influences of beta-blockade on HRV and to a lesser extent, the effects of angiotensin converting enzyme (ACE) inhibitors and calcium channel blockers (CCBs) on autonomic tone. Beta-blockers reduce mortality following MI (Yusuf *et al.* 1985) and in healthy subjects have been shown to reduce HR and increase HRV (Coker *et al.* 1984, Ewing *et al.* 1984). These effects are said to occur because of reduced sympathetic drive and increased vagal tone (Sandrone *et al.* 1994). In cardiac rehabilitation, Malfatto *et al.* (1998), examined the effects of a combination of exercise training and beta-blocker therapy in patients following a first, uncomplicated MI. The authors

suggested that the combination induced a more favourable sympathovagal balance, as assessed by time and frequency domain analysis of HRV, accelerating the recovery of a normal autonomic profile. Along with other medications, beta-blocker therapy is commonly used in the treatment of hypertension (Ferdinand 2001) and evidence for the effectiveness of beta-blockers in the management of patients with heart failure is also compelling (Marinone *et al.* 2001).

Calcium channel-blockers, which are generally used in the treatment of hypertension and ischaemia, have also been shown to exert influences on the ANS. Bekheit *et al.* (1990) reported that diltiazem but not nifedipine reduced SNS activity as indicated by reduced LF power. They suggested that this represented a similar action to that of beta-blockers. Further studies of the CCBs, verapamil and felodipine have demonstrated increases in both time and frequency domain components of HRV. Verapamil appears to exhibit a more powerful effect causing significant increases in SDNN, RMSSD and pNN50 in the time domain and in increases in the VLF, LF and HF spectral components with a reduction in HR and LF/HF ratio. The results indicate a shift towards parasympathetic predominance. Felodipine caused significant increases in only SDNN and VLF (Bonaduce *et al.* 1997).

Angiotensin converting enzyme (ACE) inhibitors reduce blood pressure without reflex tachycardia and have also been shown to exert an effect on HRV but studies remain limited. Kontopoulos *et al.* (1997a) compared the effects of various ACE inhibitors on cardiac autonomic tone in 90 patients after uncomplicated MI. Using time and frequency domain indices of HRV they demonstrated that quinapril, lisinopril and captopril

improved frequency domain HRV indices related to vagal tone whereas cilazapril and enalapril had no effect. The same authors further substantiated the vagal enhancing effect of quinapril in a group of 40 diabetic patients with diabetic autonomic neuropathy (DAN). HRV results showed that quinapril increased parasympathetic activity in patients with DAN, 3 months after the start of treatment and sustained the effect until the end of the monitoring period. They suggested that this might contribute to the reduction of risk for malignant ventricular arrhythmias in patients with DAN (Kontopolous *et al.* 1997b).

Double pharmacological blockade is often used in HRV studies to test the function of both branches of the ANS. The most commonly used agents are propanolol and atropine. Propanolol reduces beta-adrenergic function and parasympathetic blockade is achieved with full dose atropine, which is a competitive antagonist of acetylcholine at smooth muscle, cardiac muscle and various glandular cells. It increases HR by reducing the effects of vagal nerve stimulation and accelerating the effects of the sympathetic nervous system. (Stanley *et al.* 1996, Warren *et al.* 1997, Jokkel *et al.* 1995). Phenylephrine, is a further pharmacological agent used in testing autonomic function. It has a direct effect on alpha-adrenergic receptors causing constriction in resistance and capacitance blood vessels. This increases total peripheral resistance resulting in increased systolic and diastolic blood pressure. By measuring HRV and blood pressure variability analysis (BPV) responses to phenylephrine infusion, assessment of cardiac sympathetic and vagal tone can be made and baroreflex sensitivity (BRS) established (Goldberger *et al.* 2001,

Takahashi *et al.* 1999). Further details of BRS measurement are given in the General Methodology section 2.4.7.

1.6.11.12 BEHAVIOURAL STATE

HRV analysis has been used to investigate the various effects of mental and emotional conditions on autonomic function across all age ranges. In a study by Steward *et al.* (2001) reduced HRV was associated with behavioural deficits in a population of infants with failure to thrive. The authors proposed a physiological basis for the behaviours exhibited by these infants compared to matched healthy group. In older, middle school children the impact of an emotional self-management programme was shown not only to improve behavioural outcomes and coping skills but also to significantly increase HRV (McCraty *et al.* 1999). In a previous study by McCraty *et al.* (1995) the effects of different emotional states on short-term HRV were examined in twenty-four healthy, middle-aged men and women. Anger was shown to reduce HRV whereas a shift to a positive emotional attitude significantly improved HRV.

Personality type has also been shown to affect HRV. Type-A, coronary prone behaviour which is generally associated with such characteristics as impatience, competitiveness and time urgency is associated with increased sympathetic activity and reduced vagal tone during stressful tasks compared to the more tolerant 'laid back', Type-B personality subjects (Kamada *et al.* 1992, Schmied & Lawler 1989, Lawler & Schmied 1988). Additionally, Type-A subjects demonstrate significant baseline differences

compared to type-B suggesting greater lability in sympathovagal function (Dembroski *et al.* 1977).

The link between mental and emotional state and cardiovascular disease has been strengthened by research commonly reporting increased HR and reduced HRV in various forms of depression. Using data from 24-hour Holter recordings, Stein *et al.* (2000) demonstrated that severe depression is associated with markedly reduced HRV in patients with stable CHD. The authors suggested that the increased risk of mortality in these patients is related to impaired cardiac autonomic modulation. Psychiatric depression is also associated with increased morbidity and mortality in patients with coronary artery disease (CAD) (Carney *et al.* 1988, Frasure-Smith *et al.* 1993) and Krittayaphong *et al.* (1997) showed that in patients with CAD, higher depression scores were associated with increased reduction of HRV. They suggested that the findings may be related to the reported relationship between depression and survival risk in patients with CAD. Similar findings have been shown in other forms of depression and in major depressive disorder (MDD),

Balogh *et al.* (1993) using 5-minute ECG recordings demonstrated that increased HRV was associated with successful treatment. They proposed that increased HRV reflecting improved autonomic function decreased the risk of cardiovascular mortality in patients with MDD and further suggested that short-term measures of HRV could be developed as a useful adjunctive physiological measure of treatment response to pharmacotherapy.

Tentative hypotheses have also been proposed linking panic disorder (PD) with coronary artery disease (Fleet *et al.* 2000). Yeragani *et al.* (1993) reported that patients with PD had disordered autonomic responsiveness

compared with normal controls. Using PSA of HRV they demonstrated a decrease in cholinergic and a relative increase in adrenergic responsiveness in patients with PD. The emerging view of panic as a disorder involving reduced flexibility across biological, affective and behavioural dimensions was discussed in a recent study by McCraty *et al.* (2001). Using 24-hour analysis of HRV in thirty-eight patients with PD they showed significantly reduced HRV compared to healthy age- and gender-matched controls. They suggested that the findings were consistent with the high rate of cardiovascular morbidity and mortality in this population.

Similar decreases in ANS responsiveness have been observed in patients suffering from post-traumatic stress disorder (PTSD). Cohen *et al.* (1998) showed that in comparison with normal controls, PTSD subjects demonstrated almost no response to a mental stressor. The PTSD patients demonstrated a degree of autonomic activation at rest that was comparable to normal subjects reaction to the stress model. It was suggested that the PTSD group experienced so great a degree of ANS hyper-activation at rest that they were unable to marshall any further defences in stressful circumstances.

Analysis of HRV has also been used to examine ANS function in other pathological behavioural conditions and recently a link between cerebral cognitive and peripheral ANS activities has been demonstrated in 53 patients with schizophrenia (Toichi *et al.* 1999). The authors proposed that this link appeared to be mediated through the PNS.

1.7 THE AIMS OF THE STUDY

The main purpose of this thesis was to investigate the physiological and some of the psychological effects of several common techniques popularly suggested as means to alleviate the effects of stress by inducing relaxation. To put into context the effects of the various stress management interventions under investigation, it was first considered necessary to test the effects of the stress response, on the physiological and psychological markers used in the subsequent studies. The chronology of the research work is shown below (Figure 1.10).

The effects of stress and relaxation on the heart were used as a surrogate measure of a generalised response of the sympathetic and parasympathetic systems. Analysis of heart rate variability (HRV) was chosen as the principal method of assessing the physiological effects of the various interventions. HRV analysis is a non-invasive method of assessing cardiac autonomic function and describes the balance between the sympathetic and parasympathetic (vagal) components of the autonomic nervous system (ANS) innervating the heart. Activation of the sympathetic nervous system (SNS) is considered to reflect a state of physiological arousal, described as the 'stress response' and increased parasympathetic nervous system (PNS) activity indicates reduced arousal or activation of the 'relaxation response' (Benson 1974).

In the context of this work, stress management was considered to be any method that facilitates a level of arousal that is healthy, balanced and enjoyable, either by reducing SNS activity, increasing PNS tone or a combination of both. The techniques under investigation were relaxation

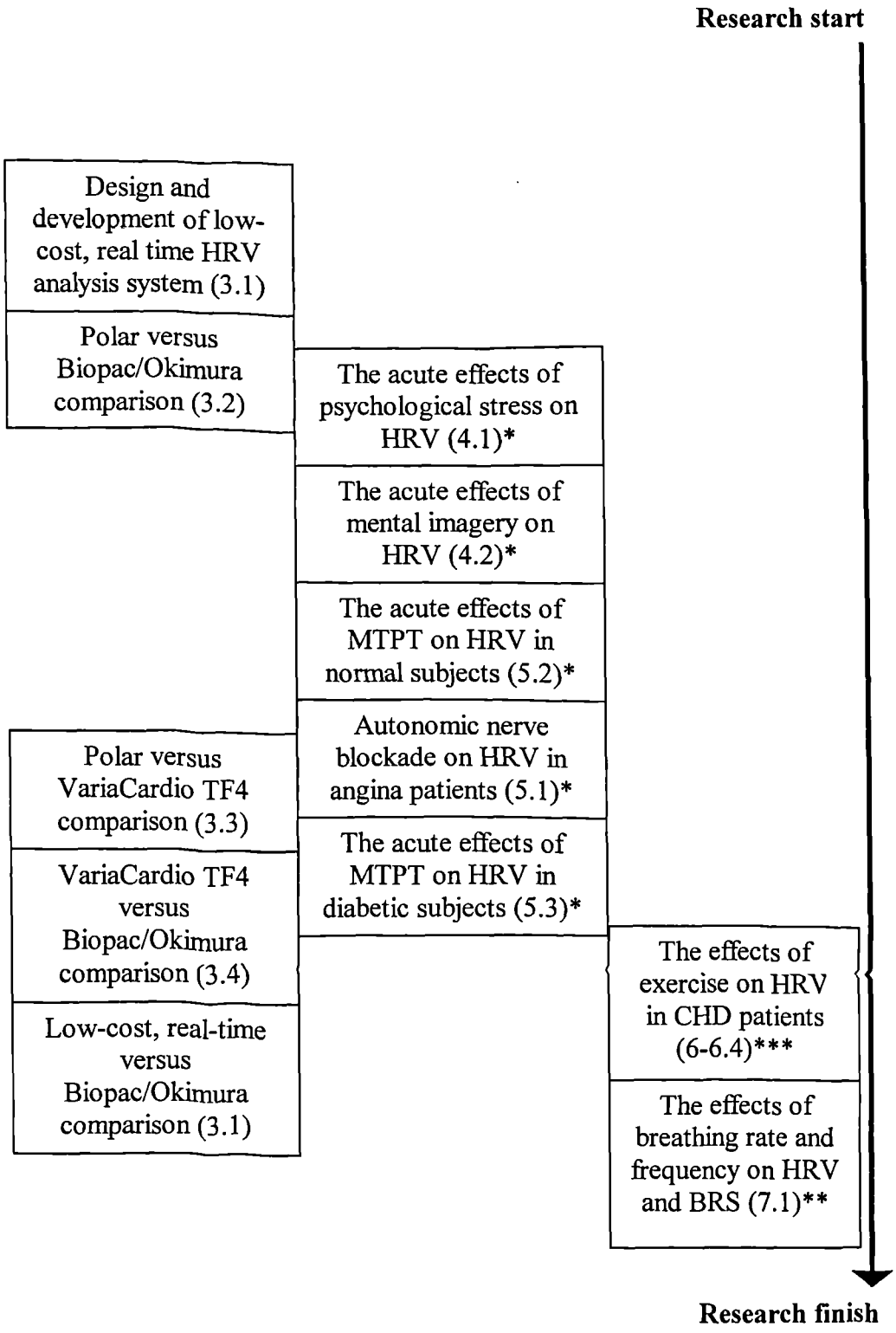


Figure 1.10 Schematic representation of the systematic approach and time course of the work undertaken in this thesis. Also indicated are the HRV analysis systems used. § = Reynolds Holter system* = Polar NV-Advantage system, ** = Biopac/Okimura system, *** = VariaCardio TF4 system. Heart rate variability (HRV), Myofascial trigger-point therapy (MTPT), Baroreflex sensitivity (BRS) and coronary heart disease (CHD).

therapy in the form of guided imagery, myofascial trigger-point massage, aerobic exercise, music therapy and certain breathing techniques.

The effects of various stressors (heart rate response to lying and standing and an exercise treadmill test) and stress-relieving pharmacological interventions on ANS function were also studied.

The thesis has been written so that each chapter 'stands alone' and therefore can be interpreted in its own right. An abstract has been presented at the start of each section to assist this process. As a consequence of the slightly different approaches used there is a certain amount of repetition of text particularly in the introductory, methodology and discussion sections. Where possible the author has kept this to a minimum and hopes that the reader will forgive the repetition and understand the need for this in view of the different emphasis of each chapter.

CHAPTER TWO

GENERAL METHODOLOGY

2.1 DATA ACQUISITION FOR HEART RATE VARIABILITY

The appropriate local Research Ethics Committees approved all of the studies contained within this work and fully informed consent was obtained from all subjects prior to testing. Data acquisition was performed in quiet, lightly illuminated, temperature-controlled (20 – 24 °C) conditions. Where appropriate, a sign was placed on the door of the research environment, informing that experimental procedures were taking place and requesting quietness. Unless otherwise stated, all subjects were asked to refrain from smoking, drinking alcohol, tea and coffee or taking other sympathomimetics for at least eight hours prior to testing. They were also asked not to undertake any strenuous exercise within the same time period. In the majority of cases subjects were allowed a light meal up to two hours before testing.

2.2 DIFFERENT HRV SYSTEMS USED

During the course of the research work, different methods of HRV data collection and analysis were used. The various systems all had particular advantages and disadvantages when compared to one another. Chapter Three describes in more detail the various attributes of each system and reports the validation methods used to compare the systems. The different methods of data acquisition and the various processes for data transformation are described below.

2.2.1 REYNOLDS SHERPA II – PATHFINDER SYSTEM.

The Sherpa II – Pathfinder system consisted of a two channel, three-lead, Holter 24-hour, ambulatory ECG data acquisition monitor, using Ag/AgCl

ECG electrodes (ADI Instruments, Hastings, UK) and a Pathfinder 500 (P500) Holter analyser (Reynolds Medical Ltd, Hertford, UK). The electrocardiogram (ECG) signal was sampled at 128Hz and recorded onto a magnetic cassette tape (TDK D60). Following ECG acquisition, R-R interval data were obtained using the Reynolds RR-Tools Version 3.33 (Research Workstation) contained within the P500 System. The data files were then e-mailed to colleagues at the Institute of Heartmath, Boulder, Colorado, USA, where both time-domain analysis and power spectral analysis of HRV was performed using a DADiSP software package (DSP Development Corp, MA, USA).

2.2.2 BIOPAC – OKIMURA SYSTEM

The BIOPAC system consisted of 3-lead system using 3M™ Red Dot™ repositionable electrodes (3M United Kingdom PLC, Berkshire, UK), an electrocardiogram amplifier module (ECG100B), a signal-conditioning unit (UIM100) and an analogue to digital (A/D) signal converter (MP100). The ECG signals were sampled at 200 Hz and were transmitted to the MP100 using 2mm shielded cables. From the MP100 module the signals were then transferred onto a desktop computer and stored on AcqKnowledge software (Biopac Systems Inc, Santa Barbara, CA) for further off-line analysis.

2.2.3 POLAR NV – ADVANTAGE SYSTEM

The Polar NV-Advantage System (Polar Electro Oy, Kempele, Finland) used a telemetric acquisition system to collect and store R-R interval data. Subjects were fitted with an electrode belt that incorporated a Polar Coded Transmitter

(PCT). The 'ribbed' electrodes were coated in electrode gel to ensure maximum conduction and the transmitter was positioned centrally, directly below the xiphisternum. The belt was attached tightly enough so that the movement of the electrodes was held to a minimum and did not cause any discomfort or interfere with breathing. The R-R interval data were transmitted by the PCT to a Polar Advantage Interface and stored on a laptop computer for further off-line analysis using Polar Precision Performance Software Version 2. The R-R interval data were sampled at 1000 Hz. PSD of HRV was performed using an autoregressive method with a model order of 18.

2.2.4 VARIAPULSE – TF4 SYSTEM

The VariaPulse – TF4 system (MIE, Medical Research Ltd., Leeds, UK), similar to the Polar system used a chest strap and telemetric transmitter/receiver method to collect data. Again the data were stored on a laptop computer where it was later analysed off-line. Unlike the Polar system the Varia Pulse – TF4 system contained a facility to collect and store ECG segments for accurate identification of artifacts and/or ectopic beats and subsequent editing if necessary. Also similar to the Polar system when using this equipment it was essential that the transmitter belt was not attached too tightly for the reasons previously described. The R-R interval data sampling frequency was also 1000 Hz. PSD of HRV was achieved using an FFT algorithm incorporating a coarse-graining spectral analysis (CGSA) filtering technique (Yamamoto & Hughson 1993).

2.2.5 THE LOW-COST, REAL-TIME SYSTEM

The low-cost, real-time system, which was developed during this research, used a standard three-limb lead ECG acquisition system and Biotab ECG electrodes (Norlite Medical Ltd, Aberdeen, UK). Data were acquired directly onto a standard desktop computer for real-time analysis and then stored onto the hard-drive for further off-line processing. The ECG sampling frequency was 1000Hz and PSD of HRV was performed using an FFT algorithm with a Hanning data windowing technique. An in-depth description of this system can be found in Chapter Three.

2.3 ANALYSIS OF HEART RATE VARIABILITY

Data were collected by the various methods described above. HRV analysis was calculated, following removal of any abnormal beats, in both the time and frequency domains. Measurements in the time domain consisted of the mean R-R interval and the standard deviation of normal R-R intervals (SDNN), which is the primary measure of HRV in the time domain. Additionally, root mean square of successive differences (RMSSD) and the proportion of differences between adjacent normal interbeat intervals that are greater than 50 milliseconds (pNN50) were used. These measurements of short-term vari bility estimate rapid variations in heart rate and are generally associated with parasympathetic nervous system (PNS) activity (Task Force of the European Society of Cardiology and The North American Society of Pacing and Electrophysiology 1996).

Power spectral analysis of HRV indirectly measures cardiac autonomic tone and generates peaks at three frequency bands (Leong *et al.* 2000). The

following frequency domain indices of heart rate variability were calculated by the various methods as described above. They were 1) Very low frequency power (VLF) from 0.00 Hz - 0.04 Hz. 2) Low frequency power (LF) from 0.04 Hz - 0.15 Hz. 3) High frequency power (HF) from 0.15 Hz - 0.40 Hz.

2.4 Supine – Standing – Supine Orthostatic Test

Subjects were requested to lie down for at least ten minutes prior to testing to exclude relevant emotional or external influence on the autonomic nervous system. After this resting phase the data acquisition was started. Data were collected for five-minutes in three positions (supine1 – standing –supine 2).

2.5 Baroreflex Sensitivity Testing

Following an appropriate resting period, a Portapres Model II pressure cuff (TNO, Amsterdam Netherlands) was applied to the midphalanx of the third finger for continuous blood pressure monitoring and three ECG limb leads were attached to the subject's forearms. Five-minutes of continuous blood pressure (BP) and ECG data were recorded onto the hard-drive of a standard desktop PC into via the MP100 ECG acquisition system. The AcqKnowledge software package (Biopac Systems Inc, Santa Barbara, CA) was used to further process the signals before spectral analysis.

Baroreflex sensitivity (BRS) was determined from the continuous BP and ECG data by the transfer function technique using the CARSPAN programme (Pro GAMMA, Groningen, Netherlands). This programme allows discrete Fourier transformation of non-equidistant samples of blood pressure and R-R interval series (Saul *et al.* 1991). The analysed time-series were

corrected for artifacts and edited if necessary. BRS is defined as the mean modulus between spectral values of systolic blood pressure variability and heart rate variability in the 0.07 – 0.15 Hz frequency band with a coherence of more than 0.30. BRS is expressed in ms/mm/Hg. A measure of 10ms/mmHg indicates that a rise of 1 mm/Hg in systolic blood pressure will induce 10ms of R-R interval lengthening.

2.6 Self – Perceived Measures of Emotional State, Muscle Tension and Pain

Self-reports of emotional state, feelings of muscle tension and pain scores were measured before and after various treatments using a 100mm visual analogue scale (VAS) with verbal anchors at either end (Appendix 1). VASs have been used previously to examine self-assessment of health and quality of life (Maddox & Douglas 1973, Wright 1987, Grunberg *et al.* 1996, Kaplan *et al.* 1996).

2.7 Exercise Treadmill Test (ETT)

Prior to the ETT a medical evaluation was carried out to check for contraindications (Appendix 2). This reduces the risk of untoward cardiac events during exercise testing and included the following components:

- Medical Diagnosis
- Symptoms
- Risk Factors for atherosclerotic disease progression
- Recent illness, hospitalisation, surgical procedures
- Medication dose, schedule, drug allergies

- Other habits
- Exercise history
- Work history

In addition to the evaluation a brief physical examination was performed by the physician in charge and included:

- Body mass, height and body mass index (BMI)
- Resting heart rate and rhythm
- Resting blood pressure
- Auscultation of the chest, (if warranted)
- Resting ECG.

After completing the evaluation and examination, subjects read and signed informed consent (Kelly 2001).

2.7.1 PREPARATION

In order to record a high quality ECG, subjects were shaved in the general areas of electrode placement, cleansed with an alcohol-saturated wipe and then the skin was abraded using fine gauze. Ag/AgCl ECG electrode (ADI Instruments, Hastings, UK) placement was carried out with subjects standing and followed ACSM Guidelines for Exercise Testing and Prescription (2000).

The exercise test carried out was a sign/symptom limited maximal stress test employing the modified Bruce protocol (see Appendix 3). The modified Bruce protocol has been used extensively in clinical settings and is well suited to a coronary population due to the relatively low intensity of the initial workloads (AACVPR, 1999). It has excellent reproducibility and is a familiar form of exercise for the majority of the population including heart

disease patients (AACVPR, 1999 and ACSM, 2000). All testing for the study was carried out using a Marquette motorised treadmill (Marquette, Manchester, UK) interfaced to a computer allowing for automatic protocol selection, speed and incline.

2.7.2 DATA COLLECTION

Sequence Of Measurement

Pre test

- 12 lead resting ECG in standing position.
- Ausculatory blood pressure and heart rate recorded in standing Position

During Exercise

- 12 lead ECG monitored continuously
- Blood pressure recorded in the final minute of each work stage and heart rate recorded in the final 15 seconds.
- Ratings of perceived exertion (RPE), Angina & Dyspnoea recorded in the final 15 seconds of each work stage.
- Other comments or information

Post exercise

- 12 lead ECG
- Heart rate
- Symptomatic ratings obtained if symptoms persist after exercise.

2.7.3 SUBJECTIVE RATINGS

Rating of Perceived Exertion: Borg's 6 - 20 category scale (1985) was used to assess RPE (Appendix 4). Subjects were given clear and concise instructions in the use of this tool before testing.

Angina & Dyspnoea: A 5-point scale was used to rate symptoms during testing for both angina and dyspnoea (Appendix 5). Again prior to testing subjects received complete instruction in the use of both of these measures.

2.7.4 TERMINATION OF ETT

Absolute and relative indications for terminating the exercise test follow ACSM Guidelines for Exercise Testing and Prescription (2000) and are given at Appendix 6.

Ordinarily the formula of 220 beats per minute minus the patient's age is used for setting maximum heart rate (MHR). However because of the effect of beta-blockade on HR a separate normogram was developed by Brodie *et al.* (1998). This normogram has been shown to be reliable and valid for use of both termination of ETT and for exercise prescription (Kelly 2001).

2.8 MYOFASCIAL TRIGGER-POINT MASSAGE THERAPY

Subjects were not required to undress for the massage therapy and wore light cotton T-shirts. Following baseline recordings they remained seated in an upright chair. In order to maintain consistency, the same therapist, a fellow of the International Council of Health, Fitness and Sports Therapists, performed all massages. The massage procedure, which took 20 minutes, employed the techniques of effleurage, petrissage, cross-fibre stroking and tapotement as

described by Goats (1994). Deeper more focused pressure and circular frictions were applied to myofascial trigger-point areas in the upper, middle and lower trapezius muscle region and the sub-occipitalis region. Gentle circular frictions and palmar kneading was also applied in the areas of the frontalis and temporalis muscles together with linear stroking to the sternocleidomastoid muscles. The anatomical locations of the MTrP used in this study can be found in detail in *The Trigger Point Manual* (Travell & Simmons 1983).

2.9 Statistical Methods

Once the hypothesis for each chapter had been developed, 'a priori' power calculations (effect size calculations) were performed. These procedures were conducted under the supervision of the Medical Statistics Department of the University of Liverpool and used normative data obtained from previous departmental studies and also information from similar studies available from current medical literature.

For further information regarding exact statistical methods the reader is referred to each individual chapter.

CHAPTER THREE

DEVELOPMENT & COMPARISON OF DIFFERENT HEART RATE VARIABILITY MEASUREMENTS

3.1 A LOW-COST, REAL-TIME, HEART RATE VARIABILITY ANALYSIS SYSTEM

ABSTRACT

Heart Rate Variability (HRV) is increasingly being accepted to represent changes in the parasympathetic and sympathetic components of the autonomic nervous system. This paper describes a system that was developed during the course of the research work of this thesis. It calculates the R-R interval in real-time, displays it in the form of a tachogram and at the end of the collection period, generates the standard time-series and frequency domain parameters of HRV. The measures used have been shown to be associated with the assessment of risk after acute myocardial infarction (AMI) and the early sub-clinical detection of autonomic dysfunction in diabetes mellitus. (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). The equipment includes an analogue/digital converter sampling at 10 kHz, which generates the ECG on the computer monitor, a simple to operate graphical user interface, software to generate the tachogram and HRV measures, and a high-resolution spectral analysis graphics package allowing easy identification of frequency changes. The system meets European Health and Safety requirements by incorporating an optical isolation system tested for flashover to 6KV. The merits of this system include a) a real-time ECG display enabling continuous observation for abnormalities, (b) an unlimited number of R-R intervals for data analysis, (c) two additional analogue ports for simultaneous display of other biological signals and (d) the capacity to present information to the subject (such as

required breathing frequency for biofeedback purposes and to entrain HRV). Components for the system cost approximately £100 and it operates through a standard Pentium MMX 300 computer with 64 megabytes of RAM. Comparison with other commercial systems shows high correlation in the time and frequency domains for all measures and results comply with the normal values of standard measures of HRV as recommended by the Task Force (1996).

INTRODUCTION

Within the last decade, analysis of heart rate variability (HRV) has become of considerable interest in the disciplines of physiology, clinical medicine and clinical pharmacology (Adelmann 1999). The functional assessment of the autonomic nervous system (ANS) by observation of the activity of its sympathetic and parasympathetic components has emphasised the importance of autonomic regulation in different physiological conditions, in several disease states and under drug therapy (Task Force 1996).

As previously described, assessment of heart rate variability (HRV) can be achieved using time or frequency domain analysis and until recently ECG data acquisition and HRV analysis was performed using 24-hour ECG ambulatory Holter monitoring devices. Following acquisition, data were downloaded and analysed off-line using expensive commercial equipment (see Section 1.6.4). The main aim of the work in this thesis was to investigate the short-term effects of various interventions on autonomic function. Analysis of HRV was the means used to assess cardiac sympathovagal interactions. At the start of the research work no suitable method for short-term analysis was available and therefore a 24-hour Holter system was used as previously described (see Sections 1.6.4 and 4.1). Unfortunately the use of this equipment proved problematic and other more suitable methods of HRV measurement were sought. A suitable system was still not available after considerable enquiry and therefore it was decided to attempt to construct a simple measuring device based on a conventional ECG acquisition system. To this end the author enlisted the assistance of two biomedical engineering

colleagues (ID & DW) and set about the construction of the apparatus. The details of which are described below.

METHOD

The low-cost, real-time (LCRT) HRV acquisition and analysis system described in this chapter was constructed from 'scratch' and the basic components used in its construction cost approximately £100. Figure 3.1.1 shows these components inside a home-made casing which fits into the compact disc compartment of a standard desktop personal computer (PC). The PC used in this study to run the LCRT was a Pentium MMX 300 computer with 64 megabytes of RAM.

Manufacture of the printed circuit board

The design of the ECG printed circuit board (PCB) was based on an instrumentation differential amplifier TL084 (Sedra & Smith 1997) and the artwork was produced using a computer assisted design package (CAD). An acetate print of the artwork was overlaid onto a blank copper-clad photosensitive PCB, which was then exposed for three minutes to ultra-violet light from a standard PCB exposure light box. Following removal of the acetate, the PCB was developed and etched using commercial solutions RS-1535 and RS-1536 (RadioShack, Texas, USA). After rinsing, cleansing and drying, 0.75mm holes were drilled in the board and it was then populated with the basic components. These were then manually soldered into place. The equipment was bench-tested using a standard power supply and oscilloscope and an ECG simulator was used to calibrate for a 1mV span. The ECG lead

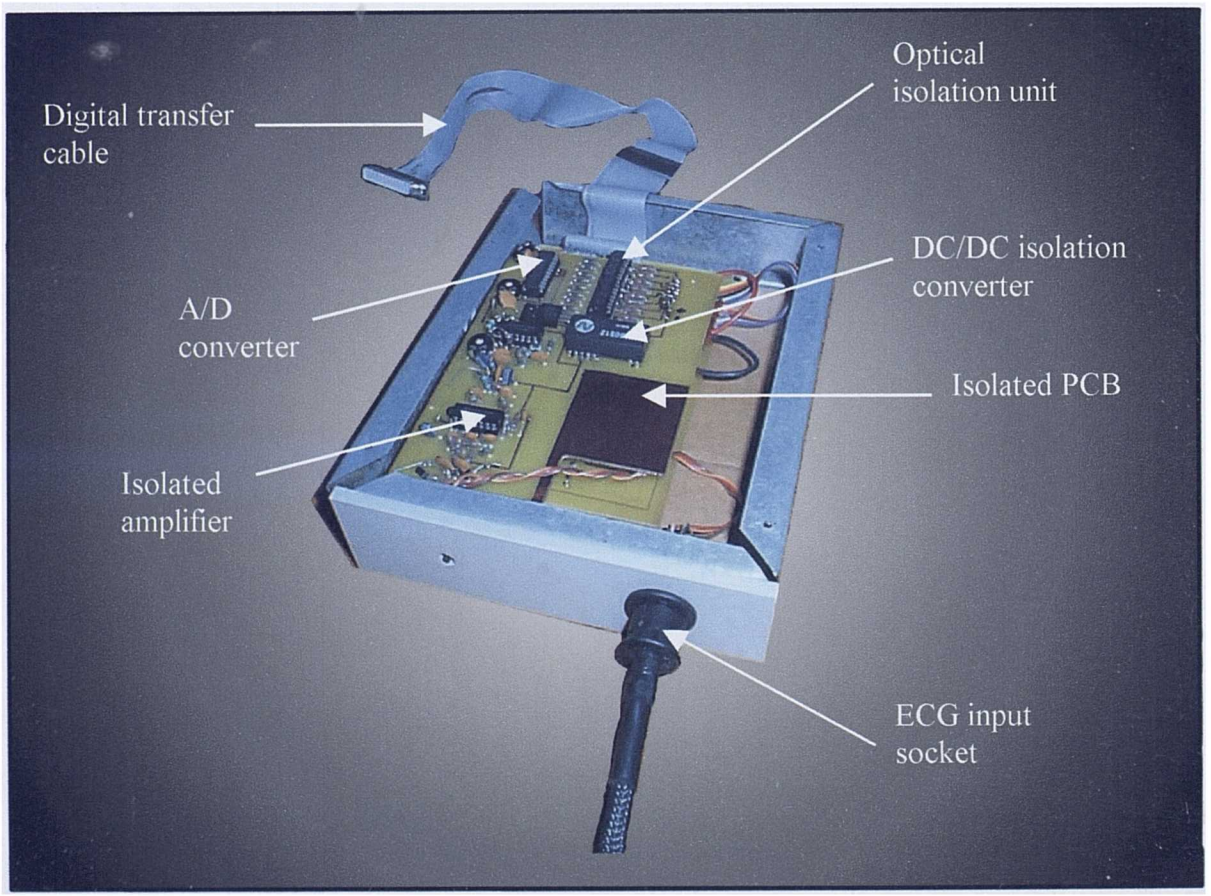


Figure 3.1.1 Basic components of the low-cost, real-time, HRV data acquisition system. A/D = analogue/digital, DC = direct current, PCB = printed circuit board.

for the LCRT was constructed using three screen-shielded signal cables, which were wrapped in a shrink-fit braid. The patient isolation socket at the computer end of the ECG lead was of a unique design dedicated to the LCRT. The patient end of the cable comprised of 3 x 4mm connectors to fit standard Ag/AgCl ECG electrodes or Biotab electrodes. The system (Figure 3.1.2) meets European Health and Safety requirements by incorporating an optical isolation system tested for flashover to 6 KV.

Data processing and analysis software

Microsoft Visual Basic (VB) Version 6 was used to design the graphical user interface. Following optical isolation, the computer sampled the eight-bit digital signal. The data were read off the Industry Standard Architecture (ISA BUS) at 1kHz and following signal averaging was displayed graphically as an ECG trace. An R-wave detection algorithm was devised to provide clear labelling of the QRS fiducial point (see section 1.6.4). This provided R-R interval timings, which were accurate to 1msec. Data were captured as an array in real-time stored as data (.dat) files onto the hard drive of the computer.

Visu al breathing guide

Microsoft VB software was also used to design a pre-set frequency curve so that subjects could follow a known respiratory pattern. This visual-breathing guide (VBG) could be set to represent any breathing frequency from 3 to 30 breaths per minute. As data acquisition took place subjects were able to

follow the VBG, which was clearly situated at the right side of the computer screen (Figure 3.1.3).

Data-editing and calculation of time domain measures of HRV

Following acquisition of the R-R intervals the signal could be visually scanned for ectopic or aberrant beats. The editing software was designed to automatically label a beat if it was 20% different from the previous beat. Following guidelines from the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996) aberrant beats were not removed automatically. Visual inspection of the raw signal portions of ECG related to aberrant R-R intervals, is considered a prerequisite for accurate data processing. By 'clicking' on the appropriate R-R interval, the portion of ECG corresponding to the marked beat could be clearly seen on the computer screen (Figure 3.1.4). If the ECG trace was considered to be abnormal then the R-R interval was rejected. Following rejection of an R-R interval a 'gapfill' technique was employed, which calculated an average result from the five intervals either side of the aberrant. This then replaced the rejected beat. Following the editing procedure, common time-domain parameters of HRV as suggested by the 'Task Force' were calculated. These included: MIN, MAX and MEAN of R-R intervals, standard deviation of normal R-R intervals (SDNN), root mean square of successive differences (RMSSD) and the proportion of differences between adjacent normal R-R intervals that are greater than 50 ms (pNN50) were calculated.

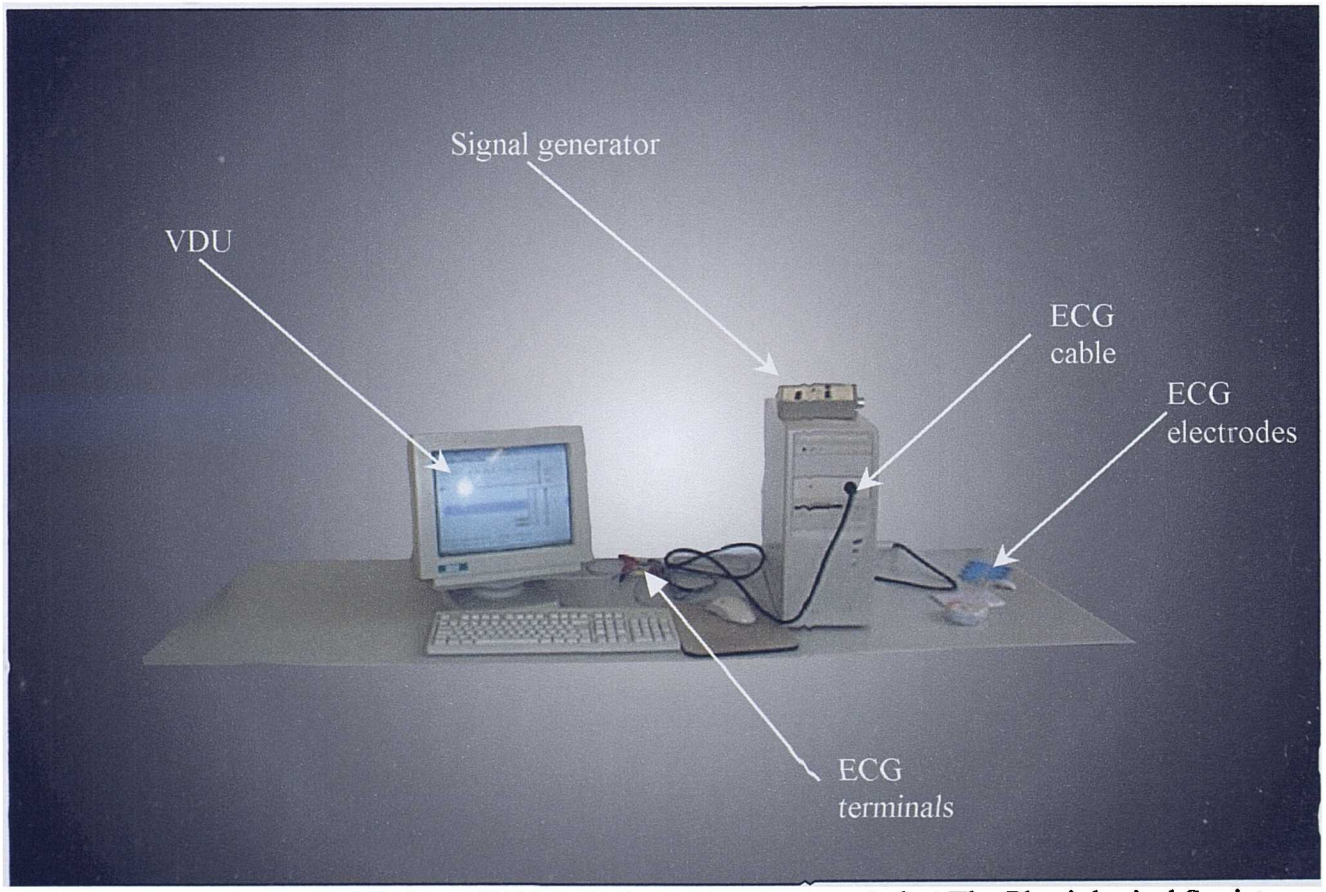


Figure 3.1.2 Low-cost, real-time, HRV analysis system as presented at The Physiological Society Meeting, University of Oxford, March 2001.

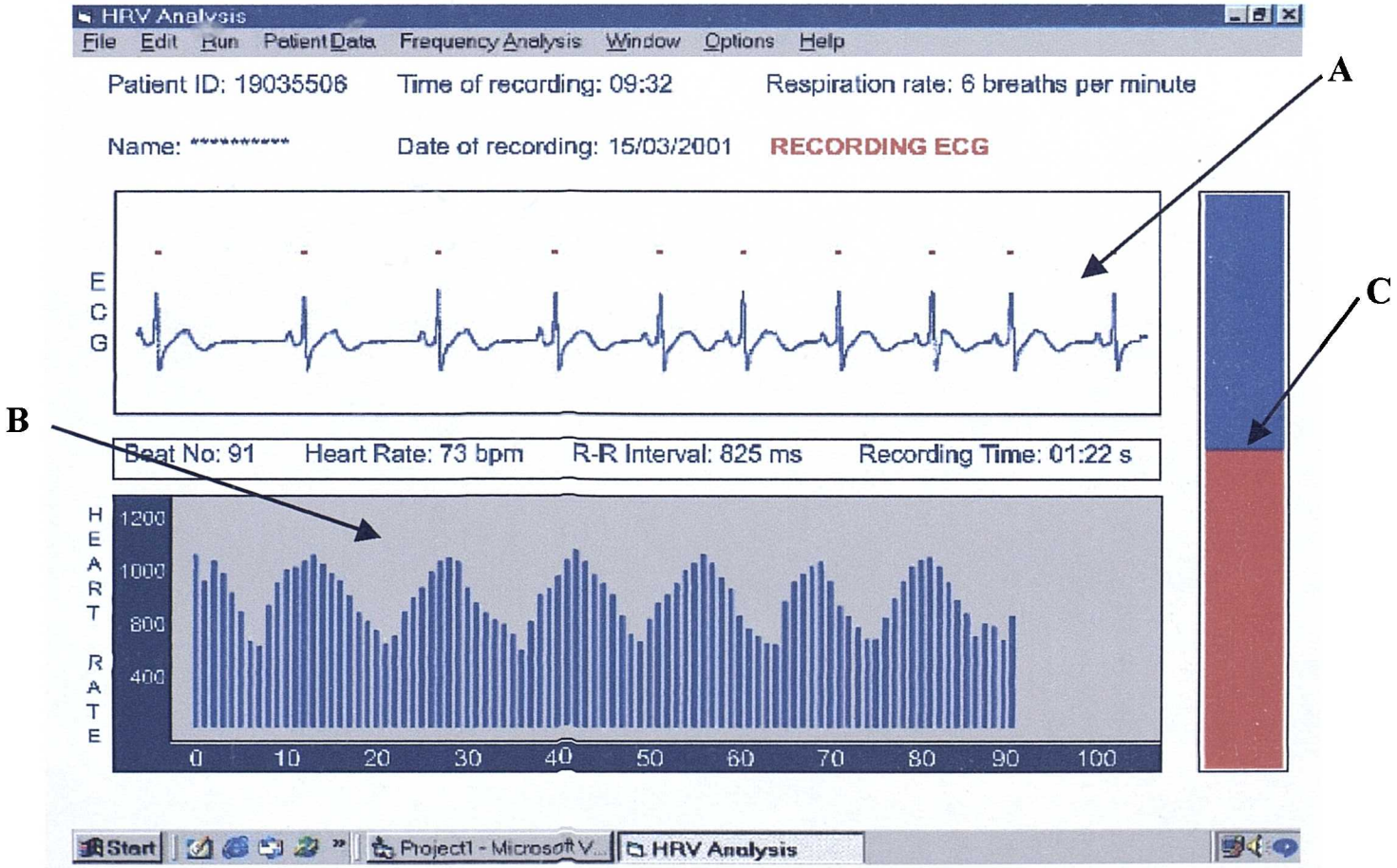


Figure 3.1.3 Screen capture of the low-cost, real-time, HRV system showing development of the ECG waveform (**A**), R-R interval tachogram (**B**) and visual breathing frequency guide (**C**).

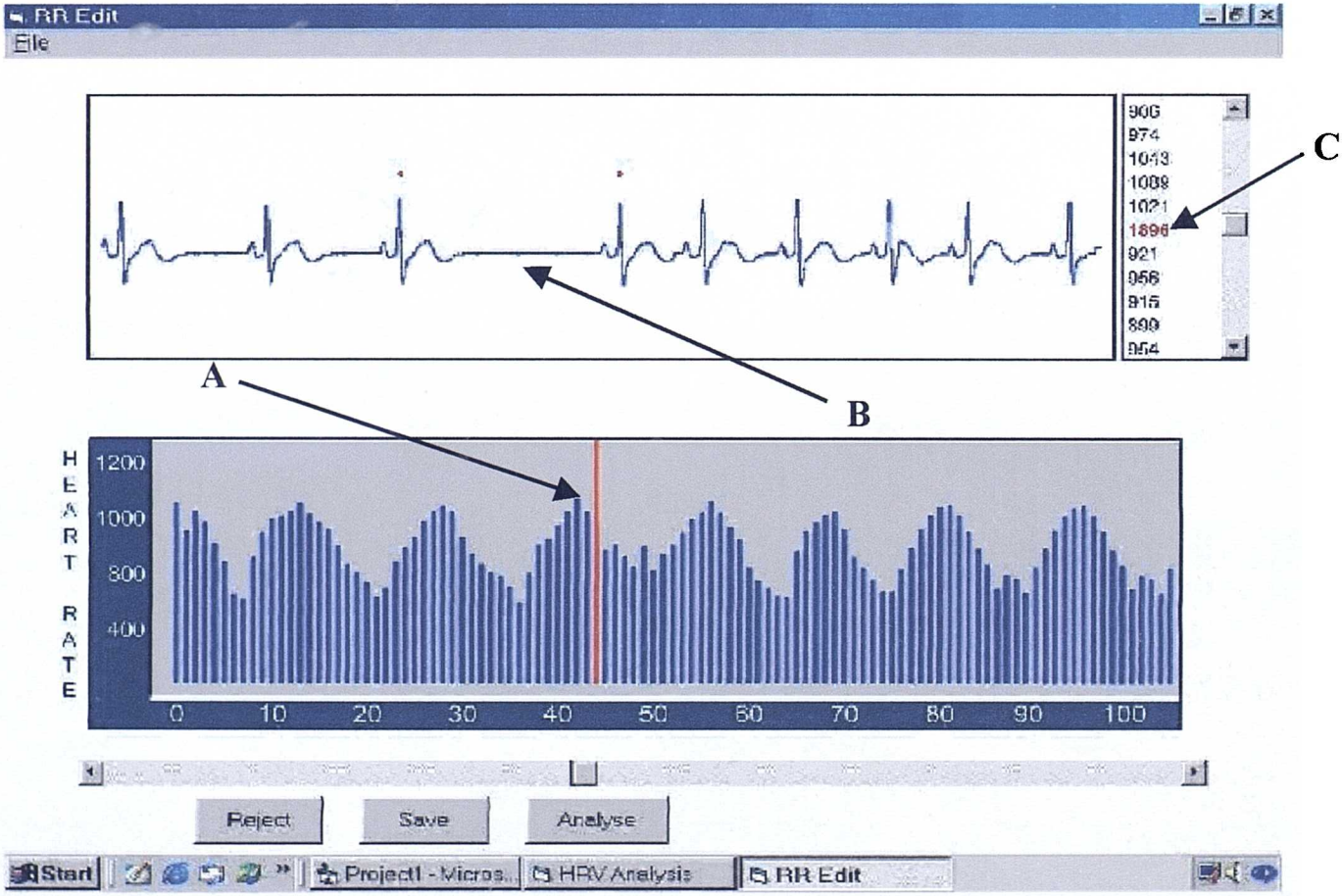


Figure 3.1.4 Screen capture of the low-cost, real-time, HRV editing facility highlighting an aberrant R-R interval (**A**), corresponding ECG segment (**B**) numerical value (**C**).

Power spectral analysis

Following time-domain calculations the interval data were presented to a Fast Fourier Transform (FFT) algorithm, which was based on a 256-point numerical harmonic analysis (Stroud 1984). A Hanning data window was used to smooth the signal and reduce spectral leakage prior to transformation (see Section 1.6.9.1). A power spectral graph was drawn and the spectral components were quantified in the ranges, 0 – 0.04 Hz (very low frequency), 0.04 – 0.15 Hz (low frequency) and 0.15 – 0.4 (high frequency). An example of the power spectral graph is shown in the final results sheet.

Results sheet

Following data acquisition, signal cleaning and time and frequency domain calculations, the results were printed on a final presentation sheet (Figure 3.1.5). They were set out so that the R-R interval tachogram and power spectral graphs could be easily observed alongside the commonly used time and frequency domain parameters of HRV. Normalised values for low frequency (LF) and high frequency (HF) components were also given along with an indication of the percentage of aberrant beats in the acquisition and the breathing rate that was used during data acquisition.

Validation of the LCRT

To test the validity of the sampling methodology and calculation of time domain parameters the LCRT system was compared to the Polar NV-Advantage system. The sampling methodology of the Polar system had previously been compared to another commercial system (Biopac/Okimura)

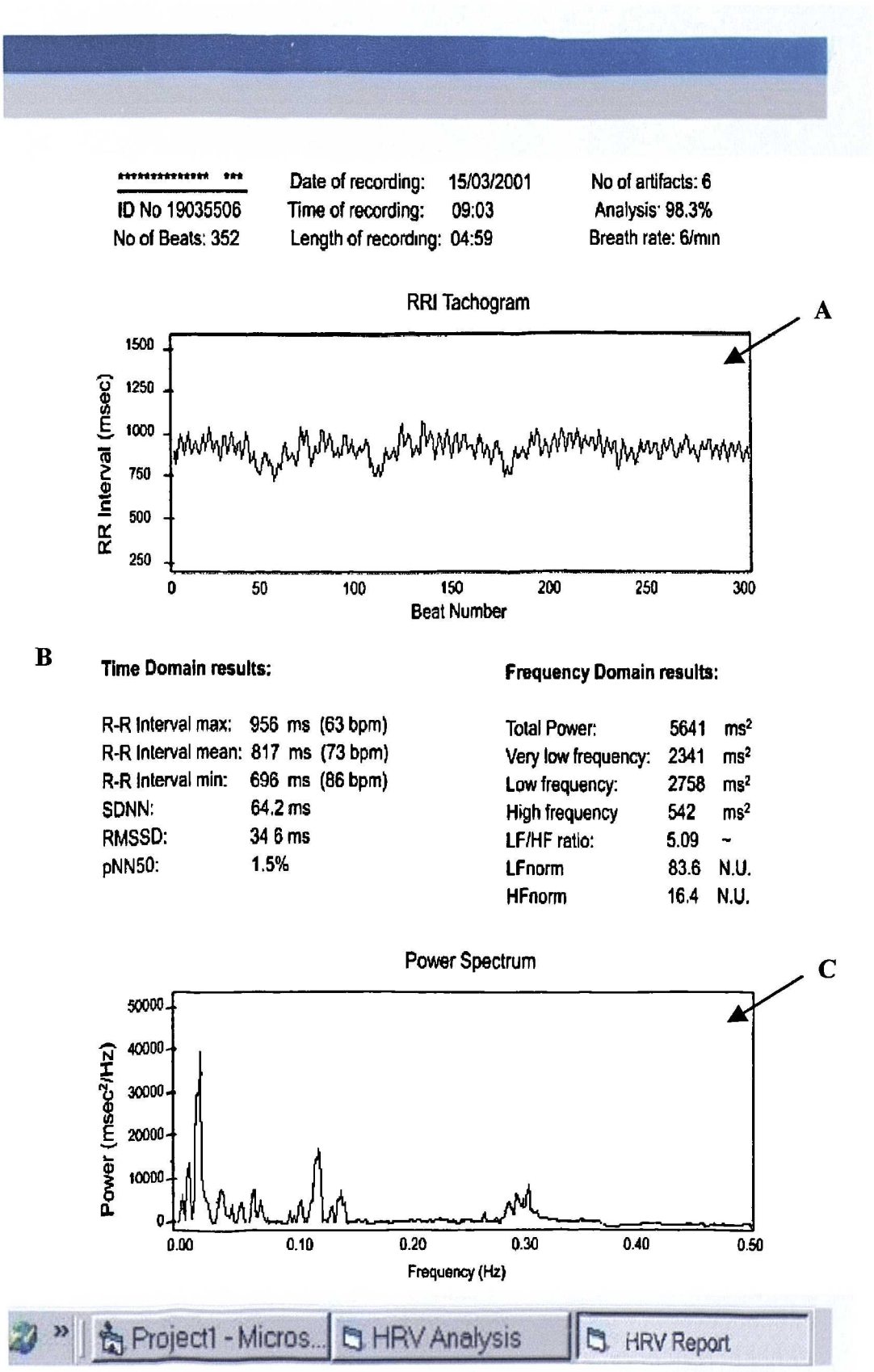


Figure 3.1.5 A screen capture (top and bottom sides 'cropped') showing the low-cost, real-time system's HRV analysis results sheet, displaying an (**A**) R-R interval tachogram, (**B**) time and frequency domain results and (**C**) a fast Fourier transform power spectral graph.

and found to have identical sampling methodology (see section 3.2). HRV data were collected from eight normal healthy volunteers comprising six females and two males (aged 37.9 ± 11.5 years: mean ± standard deviation). They were measured for five minutes while sitting quietly in a high-backed chair. Movement was kept to a minimum during recording. They were fitted with both systems and these were tested simultaneously. The Polar NV-Advantage, used radio-telemetry from a chest strap to acquire R–R interval data and the LCRT system used a standard three-lead ECG system attached to the subjects forearms. Biotab electrodes were used in the acquisition procedure.

To validate the LCRT spectral analysis software, 16, five-minute R-R interval recordings that had previously been collected (see Section 8.1) were offered up to the FFT algorithm after data smoothing using a Hanning window technique.

Statistical analyses

A Passing and Bablok regression equation for method comparison was used to compare both systems (Passing & Bablock 1983) along with Bonferroni comparison of means. Data are given as mean ± standard error. A probability of less than 0.05 was considered statistically significant.

RESULTS

Table 3.1 shows the means, standard error, correlation coefficients and Bonferroni comparisons for all variables. The correlation coefficients

between methods for all variables ranged from 0.87 to 0.99. Linear regression plots of the time and frequency comparisons are shown in Figure 3.1.6.

DISCUSSION

This study reports on the design and manufacture of a low-cost heart rate variability (HRV) system capable of collecting, editing and storage of ECG and R-R interval data. During acquisition the system also displays the real-time ECG along with the developing R-R interval trace. This enables the operator to determine the signal quality as it occurs and make appropriate adjustments as necessary. Following data collection, both time and frequency domain, measures of HRV are calculated along with the R-R interval tachogram and power spectral graphs, which are displayed, on a single page printout.

The system was designed because previous attempts to measure short-term changes in HRV using a device more suited to 24-hour recordings had proved unsuccessful. During the construction of the LCRT apparatus, the Polar NV-Advantage, R-R interval system became available and so the construction of the LCRT became less important. Work on its completion therefore only took place towards the end of the research. Consequently the LCRT was not used in any of the experimental work of this thesis but considerable interest was shown when it was presented at two meetings of The Physiological Society. Enquiries were taken from colleagues from many scientific disciplines but most interest came from the field of Veterinary Medicine. It is hoped therefore to further develop the system for use in these various fields of interest.

TABLE 3.1

Means, standard errors, correlation coefficients and Bonferroni comparison of means for all variables.

Variable	Units	Low-cost/real-time system		Polar NV/Biopac systems		Correlation	Bonferroni
		M	SE	M	SE	r-value	P-value
Mean R-R interval	ms	947	54.6	946	54.3	0.99	0.29
SDNN	ms	61.4	17.1	61.7	17.3	0.99	0.21
RMSSD	ms	45.3	11.5	43.8	11.8	0.97	0.73
pNN50	%	9.3	3.4	10.6	3.9	0.97	0.09
Total power	ms^2	3278	632	3057	592	0.93	0.37
Very low frequency power	ms^2	1033	190	1169	278	0.87	0.54
Low frequency power	ms^2	1398	365	1171	280	0.96	0.08
High frequency power	ms^2	846	229	716	171	0.95	0.14
Normalised LF power	N.U.	60	4.7	61	4.2	0.95	0.36
Normalised HF power	*N.U.*	*40*	4.7	39	4.2	0.95	0.36
LF/HF ratio	~	1.7	1.0	1.6	0.64	0.94	0.39

LF = low frequency, HF = high frequency, N.U. = normalised units. LCRT time domain variables compared with Polar system and frequency domain variables with the Biopac system.

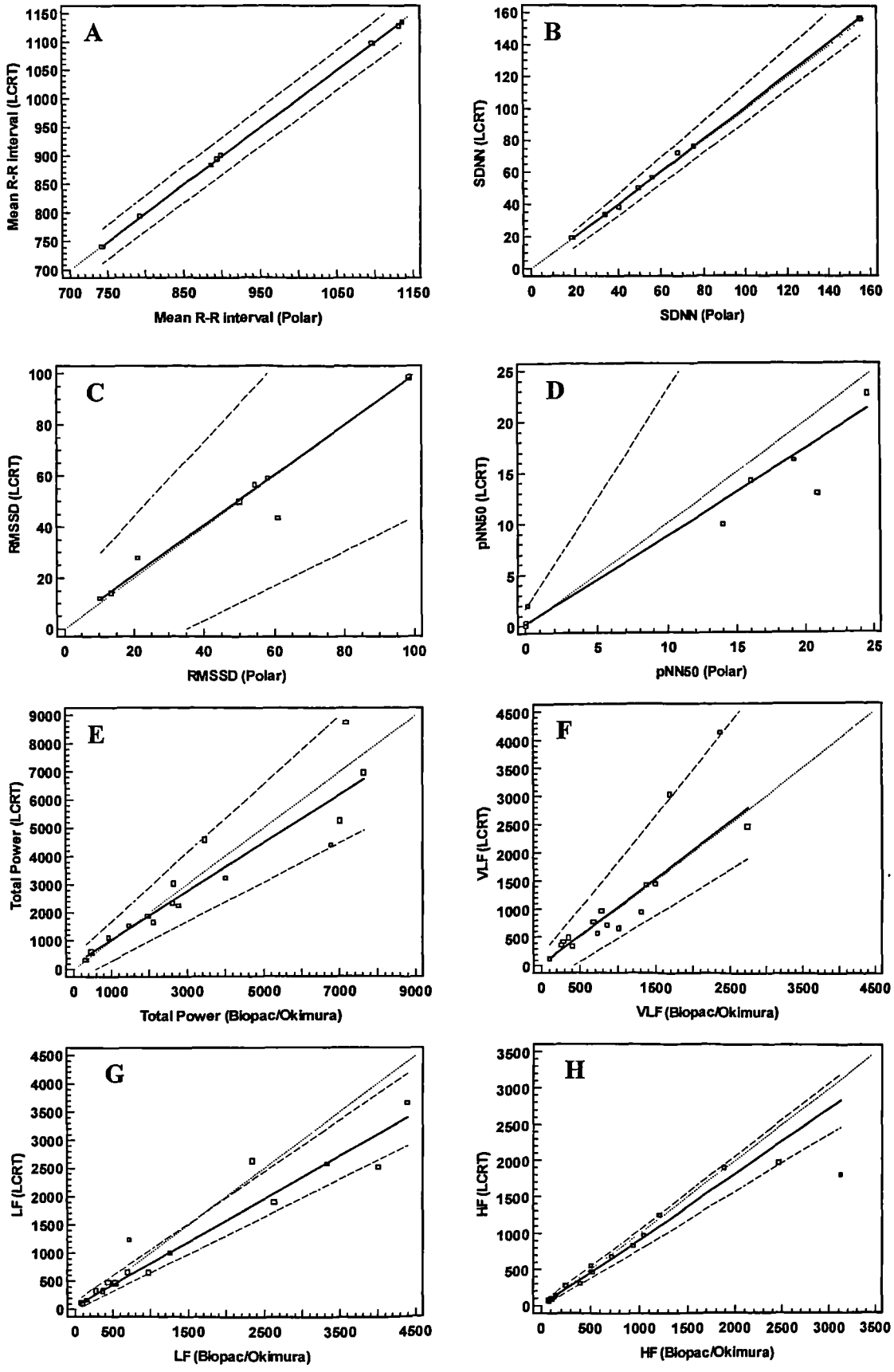


Figure 3.1.6 Polar v LCRT validation comparisons for (**A**) Mean R-R interval (**B**) SDNN (**C**) RMSSD (**D**) pNN50 Biopac/Okimura v LCRT validation comparisons for (**E**) TP (**F**) LF/HF ratio (**G**) LFnorm (**H**) HFnorm.

To compare sampling methodology and HRV analysis for validation purposes, the LCRT system was measured against the Polar NV-Advantage and Biopac/Okimura systems commercial systems and found to be highly compatible. The results comply with the normal values of standard measures of HRV as recommended by the Task Force (1996).

3.2 Short-term Power Spectral Analysis of Heart Rate Variability: A Comparison of the Method of data acquisition and analysis.

Analysis of heart rate variability (HRV) is an indirect measure of cardiac autonomic tone. It can be assessed using time or frequency analysis. There are three main frequency peaks in the heart rate spectrum, which are modulated by neuro-hormonal and other influences. The high frequency peak at 0.15 – 0.40 Hz is principally mediated by the parasympathetic nervous system. The low frequency peak at 0.04 – 0.15 Hz is under both sympathetic and parasympathetic control and influenced by the baroreceptor reflex arch. The very low frequency peak below 0.04 Hz may be influenced by the renin-angiotensin system, peripheral vasomotor function and chemoreceptor activity. HRV is reduced in several conditions associated with increased cardiovascular risk such as in diabetes and myocardial infarction. The purpose of this study was to compare two proprietary methods of data acquisition and HRV analysis both in the time and frequency domains. As costs of the two systems differ by a factor of 10 this becomes relevant in the context of health resourcing. Thirteen healthy subjects (8M, 5F) aged 35.7±7.6 years took part in the study. They were measured sitting quietly for 10 minutes and tested simultaneously using the two different methods. One method (NV-Advantage, Polar Electro Oy) used radio-telemetry from a chest strap to acquire R–R interval data, followed by an autoregressive model to quantify the components of the power spectrum. The other system used a standard three-lead ECG system (Biopac MP100, Biopac Systems Inc.) to

acquire the data followed by a fast Fourier transform using a Hamming window technique (PowerMedic Version 1, Okimura Taiwan Co.) to calculate the power in the frequency domain. The results showed that the sampling methodology (R-R interval) was identical and there was a no significant difference in the estimation of any of the time or frequency domain variables (unrelated t-test with Bonferroni adjustment). The results confirm that in resting conditions with healthy subjects, the systems used in this study are equally valid. The use of the chest strap with radio-transmission is less intrusive than ECG electrodes, permits freedom of movement and is more acceptable to females. The cost of the Polar system is considerably less than the alternative. Although for this specific application differences were shown to be negligible, it must be recognised that the Biopac/Okimura system offers a range of additional features. These include the selection of different windowing techniques, re-sampling rates and time points for analysis. There are also facilities to use up to six channels and it has functions for correlation, ECG waveform inspection and editing. As HRV analysis becomes more common in medical diagnosis it is important to ensure that an economical system is available in any calculations of cost-effectiveness.

INTRODUCTION

Heart rate variability represents the beat-to-beat alterations in heart rate (HR) and these can be measured and quantified using a number of different methods. As previously described in Section 1.6.7, the most common methods are based on time and frequency domain analysis. Time domain measures are the simplest to calculate and with these methods either the HR at any point in time or the intervals between successive normal ECG complexes are determined (Task Force 1996). The advantages of time-domain methods are their simplicity, reproducibility and proven prognostic power in certain clinical disorders. A disadvantage of time domain assessment is that it is not possible to discern and therefore quantify the relative contributions of sympathetic and parasympathetic activity (Fallen 2000).

In addition to time domain methods, procedures exist to decompose the HR signal into its power spectral components. There are several different methods to calculate these frequency domain components but as yet there is still no general consensus on the methods to be used. Autoregressive (AR) modelling and fast Fourier transform (FFT) have been the most commonly used methods for PSA in clinical research, but even these methods have differed among laboratories (Fagard *et al.* 1998). In 1996 the Task Force of the European Society of Cardiology and the North American Society for Pacing and Electrophysiology proposed certain standards for the analysis of HRV. Despite the publication of these standards, to date there are still few comparative methodological studies that have investigated different techniques for PSA (Malliani *et al.* 1994, Fagard et al. 1998).

The purpose of this study was to compare the results with different methods for both time domain and PSA measures of HRV in healthy subjects under standardised laboratory conditions.

METHOD

Participants

Thirteen healthy subjects (8M, 5F) aged 35.7 ± 7.6 years (mean ± standard deviation) took part in the study. All subjects were in good general health with no medical conditions known to affect HRV. No subject was taking any prescription drugs known to affect the cardiovascular system. They were requested to refrain from smoking or drinking any caffeine-containing beverages for at least two hours prior to testing. They were measured sitting quietly for 10 minutes and tested simultaneously using the Polar NV-Advantage and Biopac Okimura systems as described in Section 2.2.

Statistical analyses

The Passing and Bablok regression equation for method comparison was used to compare both systems (Passing & Bablock 1983) along with Bonferroni comparison of means. Data are given as mean ± standard error unless otherwise stated. A probability of less than 0.05 was considered statistically significant.

RESULTS

Table 3.2 shows the means, standard errors, correlation coefficients and Bonferroni comparisons for all variables. The correlation coefficients

between methods for all variables ranged from 0.73 to 0.99. Linear regression plots of the time and frequency comparisons are given in Figure 3.2.

DISCUSSION

The present study was designed to compare two proprietary methods for the assessment of short-term heart rate variability both in the time and frequency domains. The study took place in a group of normal healthy adults under standardised laboratory conditions. Recordings were performed for 10 minutes while subjects relaxed quietly in an upright, seated position.

The study demonstrated that within the time domain there was high correlation between methods and no significant differences were observed for any variables. This indicated that the sampling methodology used was identical for both methods. During the study very few 'aberrant' beats were detected by both systems. This is probably because the subjects used were in good health and because the recordings took place during quiet resting conditions. It is more likely that abnormal beats would be generated during movement and therefore future studies should compare methods during an orthostatic test for example. This might reveal differences in the quality of sampling and data-editing procedures.

Various spectral methods have been used in the analysis of the HRV and in the present study fast Fourier transform (FFT) and autoregressive (AR) modelling algorithms were compared. Power spectral density (PSD) analysis provides the basic information about how variance distributes as a function of frequency (Task Force 1996). The methods for the calculation of PSD are generally classified as non-parametric (e.g. FFT) and parametric (e.g. the AR

TABLE 3.2

Means, standard errors, correlation coefficients and Bonferroni comparison of means for all variables.

Variable	Units	Biopac/Okimura system		Polar NV-Advantage system		Correlation	Bonferroni
		M	SE	M	SE	r-value	P-value
Mean R-R interval	ms	788	33	788	33	0.99	0.67
SDNN	ms	39.8	4.6	39.4	4.6	0.99	0.23
RMSSD	ms	27.8	3.8	25.9	4.1	0.94	0.19
pNN50	%	4.7	*1.5*	*3.9*	*1.3*	*0.94*	*0.12*
Total power	ms^2	1892	618	1746	419	0.98	0.52
Very low frequency power	ms^2	595	166	688	106	0.73	0.36
Low frequency power	ms^2	942	469	719	282	0.99	0.26
High frequency power	ms^2	*355*	*94*	*339*	88	0.96	0.56
Normalised LF power	N.U.	65.1	5.2	66.4	5.8	0.96	0.44
Normalised HF power	N.U.	34.9	5.2	33.6	5.8	0.96	0.44
LF/HF ratio	~	2.7	0.95	2.1	1.5	0.85	0.19

LF = low frequency, HF = high frequency, N.U. = normalised units.

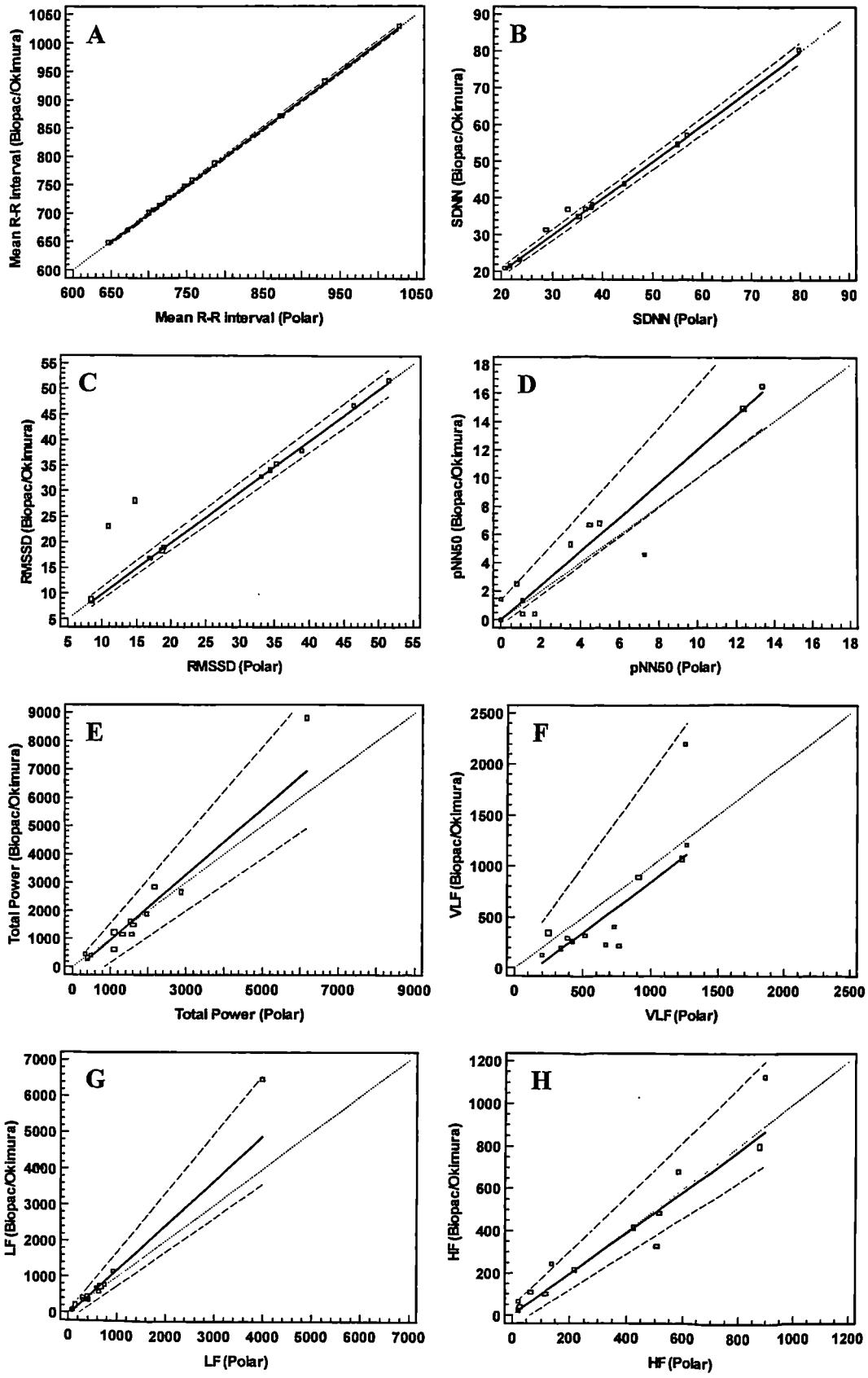


Figure 3.2 Biopac/Okimura v Polar validation comparisons for (**A**) Mean R-R interval (**B**) SDNN (**C**) RMSSD (**D**) pNN50 (**E**) TP (**F**) VLF (**G**) LF (**H**) HF.

approach). Non-parametric methods have the advantages of having simple algorithms and a high processing speed, whereas the advantages of parametric methods are smoother spectral components, easy post-processing and an accurate estimation of the PSD even on a small number of samples. The basic disadvantage of the parametric method is the need for verification of the suitability of the chosen model, and variations of this model order within or between subjects may make quantitative comparisons of results invalid. In the present study a model order of 18 was used by the Polar system, which could not be changed. A more detailed account of these procedures is given in Section 1.6.8. No significant differences were identified between methods for measurement of any variables in the frequency domain.

Overall, the results of the study confirm that in resting conditions in normals subjects both techniques are equally valid. The use of the chest strap with radio-transmission is less intrusive than ECG electrodes, permits freedom of movement and is more acceptable to females. The cost of the Polar system at £300 is considerably less than the Biopac/Okimura system costing approximately £3,400. Although for this specific application differences were shown to be negligible, it must be recognised that the Biopac/Okimura system offers a range of additional features. These include the ability to select different windowing techniques, re-sampling rates and time points for analysis. There is also the facility to use up to six channels for various other signal inputs and it has functions for correlation, ECG waveform inspection and editing. As HRV analysis becomes more common in medical diagnosis it is important to ensure that an economical system is available in any calculations of cost-effectiveness.

3.3 A COMPARISON OF TWO COMMERCIALLY AVAILABLE HEART RATE VARIABILITY MONITORS.

Abstract

Heart rate variability (HRV) has 'provided adequate information for risk stratification and evaluation of autonomic tone after myocardial infarction' (Lombardi & Mortara, Heart, 1998, 80:**3** 213-214). The purpose of this study was to compare two independent systems, which both measured HRV but used slightly different methods for data collection and analysis. An appreciation of any differences in results should inform the independent approaches to the same process. Nineteen healthy subjects (16 M, 3F) aged 44 ± 15 years, were measured. They were tested simultaneously using the VariaPulse TF4 (Advanced Medical Diagnostics Ltd) and the NV-Advantage (Polar Electro Oy Ltd) heart rate variability monitors which both use short range telemetry from a chest strap. The cardiovascular autonomic function test used was an orthostatic load test comprising five minutes lying, then standing and then lying. The results showed a non-significant difference for mean R–R interval and high frequency power and LF/HF ratio. There were, however, significant differences for total power ($P < 0.002$), low frequency power ($P < 0.01$) and very low frequency power values ($P < 0.001$) between the two systems. The results confirm that the data sampling methodology is identical. The VariaPulse TF4 uses a coarse-graining spectral analysis with a Fast Fourier Transform as suggested by Yamamoto and Hughson (Yamamoto & Hughson, J App Phys, 1991, 71:**3**, 1143-50) whereas the NV-Advantage uses autoregressive modelling. It is clear that an interpretation of the

sympathetic component of HRV will be distinct when using different systems. Although of less importance when the patient is his/her own control, cross-study comparisons need to recognise the impact of different approaches to the same measurement.

INTRODUCTION

As described in Section 3.2 the two main methods used for PSA of HRV are the fast Fourier transform (FFT), which is a non-parametric method and the autoregressive model (AR), which is a parametric technique. These methods decompose the waveform into its harmonic components and are typically used to analyse HRV components related to low (less than 0.15 Hz) and high (greater than 015 Hz) frequency variations. Also contained within the signal are very low frequency (VLF) components, which oscillate below 0.04 Hz. Previous authors (Butler *et al.* 1992, Yamamoto *et al.* 1995, Fortrat *et al.* 1999) have suggested that VLF fluctuations, in addition to representing genuine physiological input also contain signal 'noise', which can smear the short-term spectra. The conventional method of FFT is unable to separate harmonic oscillations such as respiratory and Mayer (10-second) waves from non-harmonic 'chaotic' components. Coarse-graining spectral analysis (CGSA) is a relatively new procedure that has been developed to refine the power spectrum. It discards the broadband non-harmonic 'noise' component, which contaminates the lower frequencies (1/f component) of HRV.

The purpose of this study was to compare two independent systems, which both measured HRV but used slightly different methods for data collection and analysis.

METHOD

Participants

Nineteen healthy subjects (16M, 3F) aged 44.0 ± 15 years (mean ± standard deviation) took part in the study. All subjects were in good general health

with no medical conditions known to affect HRV. No subject was taking any prescription drugs known to affect the cardiovascular system. They were requested to refrain from smoking or drinking any caffeine-containing beverages for at least two hours before testing.

HRV data acquisition and analysis

Subjects were tested simultaneously using two different systems. These were the Polar NV-advantage and the Varia-Pulse TF4 systems and are described fully in Section 2.2. Data were collected for five-minutes in the three positions of an orthostatic test (supine1 – standing – supine 2) and the data from the three positions were used for the comparisons.

Data editing

Both systems contained automatic aberrant beat detection algorithms, which identified and marked abnormal beats and this methodology was compared. With the VariaPulse TF4 system it was possible to observe the portion of ECG that corresponded to any detected abnormal beats. This facility was not available with the Polar NV-Advantage system, which only provided R-R interval 'spikes'.

Statistical analyses

The Passing and Bablok regression equation for method comparison was used to compare both systems (Passing & Bablok 1983) along with Bonferroni comparison of means. Data are given as mean ± standard error. A probability of less than 0.05 was considered statistically significant.

RESULTS

Of the 57, 5-minute recordings that were collected, four were discarded because no signal was detected. This may have been the result of some interference or 'cross-talk' between the two telemetric transmitter/receivers. No significant differences were observed between the automatic editing facilities for both systems. The Polar system identified and marked 45 abnormal beats and the Varia-Pulse system identified and marked 43 beats.

Table 3.3 shows the means, standard errors, correlation coefficients and Bonferroni comparisons for all variables. The correlation coefficients between methods for all variables ranged from 0.14 to 0.99. Linear regression plots of the time and frequency comparisons are also given in Figure 3.3.

DISCUSSION

This study was designed to compare the sampling methodology and power spectral analysis (PSA) techniques of two commercial HRV systems. One system, the Polar NV-Advantage used an autoregressive (AR) model to identify and quantify spectral components while the other system, the VariaPulse-TF4 used a coarse-graining filtering technique followed by a fast Fourier transform for PSA of HRV. Both methods used radio telemetry to collect R-R interval data.

The study showed that there were no significant differences in the sampling and editing facilities used by both the systems, however in terms of power spectral analysis measures in the frequency domain, considerable differences were evident.

Coarse-graining spectral analysis (CGSA) of HRV is a waveform

TABLE 3.3

Means, standard errors, correlation coefficients and Bonferroni comparisons for all variables.

Variable	Units	VariaCardio/TF4 system		Polar NV-Advantage system		Correlation	Bonferroni
		M	SE	M	SE	r-value	P-value
Mean R-R interval	ms	874	22	875	22	0.99	0.93
Total power	ms^2	1626	277	2087	247	0.90	0.002
Very low frequency power	ms^2	81	23	313	46	0.14	0.001
Low frequency power	ms^2	833	187	1139	174	0.84	0.01
High frequency power	ms^2	711	116	636	116	0.90	0.6
Normalised LF power	N.U.	56	69	3.2	3.1	0.70	0.003
Normalised HF power	N.U.	44	31	3.2	3.1	0.70	0.003
LF/HF ratio	~	1.2	0.4	1.8	1.2	0.74	0.63

LF = low frequency, HF = high frequency, N.U. = normalised units.

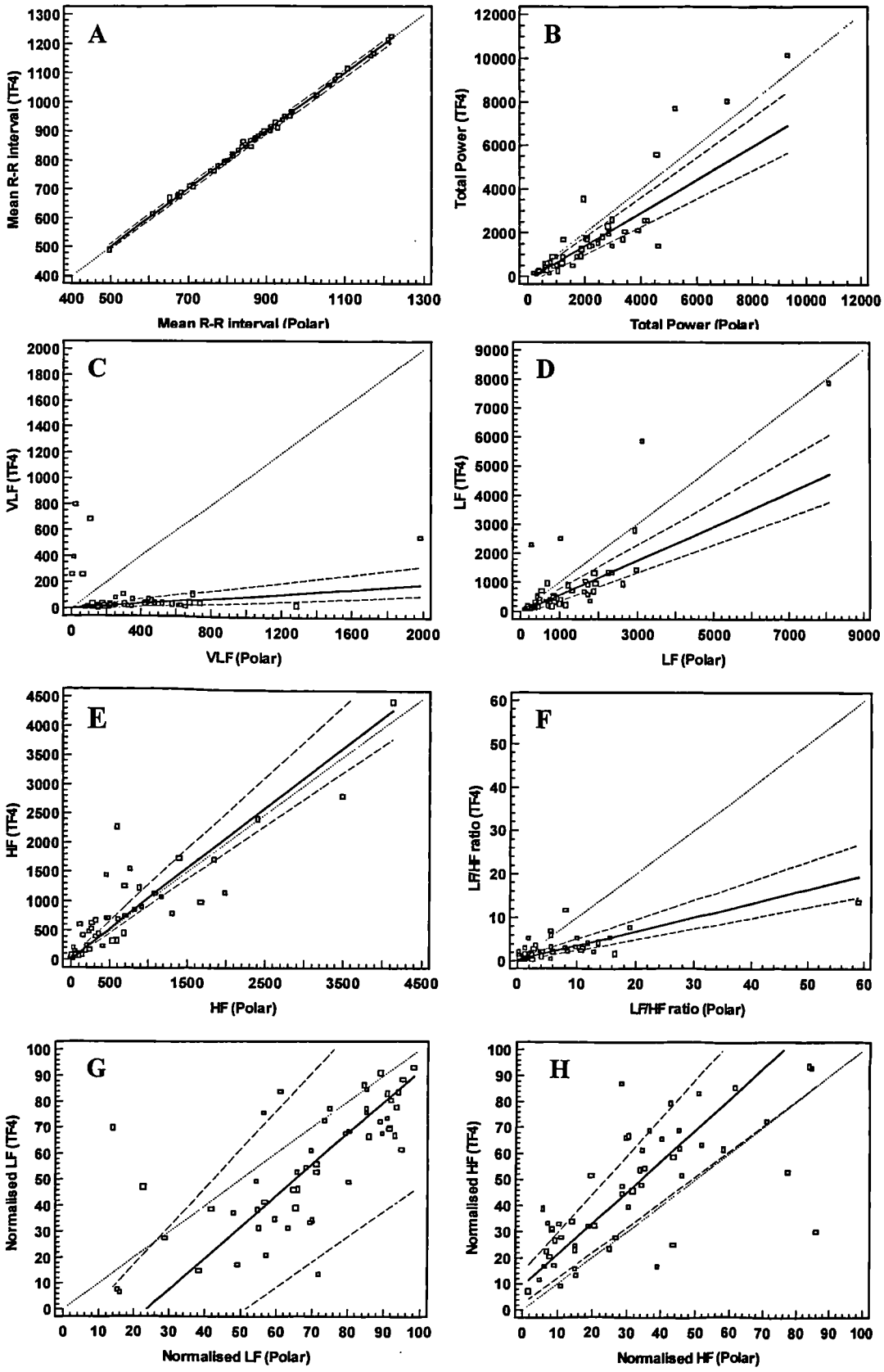


Figure 3.3 TF4 v Polar validation comparisons for (**A**) Mean R-R interval (**B**) Total Power (**C**) VLF (**D**) LF (**E**) HF (**F**) LF/HF ratio (**G**) LFnorm (**H**) HFnorm.

filtering method first described by Yamamoto and Hughson (1991). It is specifically designed to remove the so-called 1/f component which is thought to represent underlying fractal dynamics and is considered to interfere with the harmonic analysis of R-R intervals to determine HRV characteristics (see Section 1.6.9.3). This 1/f component is generally found in the VLF and LF ranges of the HRV signal. Therefore using CGSA the results for these components would be expected to be reduced compared with other spectral analysis techniques. This was clearly evident in the present study. In terms of the total power of HRV (i.e. the sum of VLF, LF and HF power), TP was 28% significantly lower for CGSA than for AR ($P < 0.002$). Within the VLF range there was a large difference identified between methods (CGSA 81ms^2 v AR 313ms^2, $P < 0.001$). In the LF region when compared to the Polar system, the VariaPulse TF4 demonstrated a 37% significant reduction ($P < 0.01$). The results confirm that the Varia Pulse system is removing portions of the VLF and LF components of HRV. A non-significant 11% reduction in HF was also observed. It was not expected that the CGSA technique would significantly affect the high frequency (HF) range of the power spectrum. This was confirmed by a non-significant reduction in the HF component.

In terms of cost, the Polar system as mentioned previously, is £300 whereas the VariaPulse system costs approximately £6000. Although it should be recognised that in addition to incorporating the coarse-graining filtration methodology, the Varia system contains further features that are not available with the Polar system. These include the ability to store the ECG waveform for accurate identification of aberrant beats, re-sampling rates and time-points for analysis and furthermore the TF4 receiver is able to detect a

signal a considerable distance away from the transmitter whereas the Polar has only a short one-metre pickup facility. The Varia system is also able to display a power spectral graph alongside the HRV results, which is not available on the Polar system.

The study clearly demonstrates that an interpretation of the sympathetic component of HRV will be distinct when using different systems. Although of less importance when the patient is his/her own control, cross-study comparisons need to recognise the impact of different approaches to the same measurement.

Because the CGSA method used in this study is based on the FFT and to make comparisons more meaningful it was considered appropriate that the CGSA method should be further compared to a system that also uses the FFT algorithm for measurement of spectral components. This was achieved in the following Section 3.4.

3.4 A Comparison of Fast Fourier transform and Coarse Graining Spectral Analysis for the Estimation of Heart Rate Variability

Power spectral analysis (PSA) of heart rate variability is an indirect measure of cardiac autonomic tone and there are several methods used to decompose time-series data into frequency domain components. Of these the fast Fourier transform (FFT) is the most commonly used. Coarse graining spectral analysis is a technique that combines FFT with a filtering method that extracts harmonic from non-harmonic components of the signal. This has the effect of removing noise and cleaning the HRV signal. The purpose of this study was to compare two proprietary methods of FFT analysis with and without coarse-graining methodology. Sixteen healthy subjects (8M, 8F aged 33.9 ± 10 years, mean ± SD) were measured sitting quietly for five minutes and tested simultaneously using the two different systems. One system (Varia-Pulse TF4) used radio-telemetry from a chest strap to acquire R–R interval data, followed by a coarse-graining spectral analysis model to quantify the components of the power spectrum. The other system used a standard three-lead ECG system (Biopac MP100, Biopac Systems Inc.) to acquire the data followed by a fast Fourier transform using a Hamming window technique (PowerMedic Version 1, Okimura Taiwan Co.) to calculate the power in the frequency domain. The results showed no significant differences for mean R–R interval, high frequency power and LF/HF ratio. There were however significant differences for total power ($P < 0.001$), low frequency power ($P < 0.01$) and very low frequency power values ($P < 0.001$) between the two

systems. The results confirm that the data sampling methodology for both systems is identical but similar to the previous study it is evident that an interpretation of the sympathetic component of HRV as measured by the VLF and LF components will be distinct when using the different systems.

INTRODUCTION

The conventional FFT method is unable to separate harmonic oscillations such as respiratory and Mayer (10-second) waves from the 1/f fluctuation which is thought to represent underlying fractal dynamics which may smear the signal and cause erroneous results (see Section 1.6.9). Coarse-graining spectral analysis (CGSA) is a more recent procedure that is used to refine the power spectrum by removing the 1/f component, which effectively removes 'noise' and cleans the HRV signal. (Yamamoto & Hughson 1991). The purpose of this study was to compare two proprietary methods of FFT analysis with and without coarse-graining methodology.

METHOD

Participants

Sixteen, normal healthy volunteers (8M, 8F aged 33.9 ± 10.0 yr., mean ± SD) were recruited via e-mail bulletin boards and from verbal requests for volunteers. They comprised 12 members of the University Hospital staff and four friends who were not part of the University. Most of the subjects engaged in a modest amount of physical activity weekly. None were involved in regular, high intensity physical activity. Ethical committee agreement and informed consent was obtained prior to testing. All subjects were in good general health with no medical conditions known to affect HRV. No subject was taking any prescription drugs known to affect the cardiovascular system.

HRV data acquisition and analysis

Subjects were tested simultaneously using the Biopac/Okimura and VariaPulse/TF4 systems. Full descriptions of these systems are given in Section 2.2. Data were acquired with subjects sitting quietly in a high-backed chair for five minutes.

Data editing

The Biopac/Okimura system did not contain an automatic aberrant beat detection system and for editing purposes the ECG recording was scanned for unusual segments. Following identification of abnormal segments these could be marked and the corresponding irregular R-R interval data removed. Using the VariaPulse TF4 system it was possible to observe the portion of ECG that corresponded to any marked abnormal beats and then to manually reject them if required.

Statistical analyses

The Passing and Bablok regression equation for method comparison was used to compare both systems (Passing & Bablok 1983) along with Bonferroni comparison of means. Data are given as mean ± standard error unless otherwise stated. A probability of less than 0.05 was considered statistically significant.

RESULTS

Because the study was conducted with normal, healthy subjects in a resting state very few abnormal beats were detected. From the 16, 5-minute

recordings only 14 aberrant beats were detected by the VariaPulse TF4 system. Using the Biopac/Okimura system, these beats were also identified as irregular segments of ECG. This suggested that the aberrant beat marking and editing methodology used by both systems was similar.

Table 3.4 shows the means, standard errors, correlation coefficients and Bonferroni comparisons for all variables. The correlation coefficients between methods for all variables ranged from 0.87 to 0.99. Linear regression plots of the time and frequency comparisons are also given in Figure 3.4.

DISCUSSION

Similar to the previous study in Section 3.3, this experiment was conducted to test two proprietary methods of power spectral analysis of heart rate variability (HRV). Unlike the previous study, which compared a fast Fourier transform (FFT) algorithm against an autoregressive (AR) model, this study compared two different methods of FFT. One was a standard FFT with a Hamming window technique to reduce spectral leakage and the other was an FFT incorporating a coarse-graining filter designed to remove the 1/f component reputed to contaminate the VLF and LF segments of the frequency domain (Yamamoto & Hughson 1991).

Both systems used different data sampling methodologies. The VariaPulse TF4 used a telemetric transmitter/receiver system to acquire data and the Biopac/Okimura used a standard 3-lead ECG system. Following the editing procedure, no significant difference was found for mean R-R interval measures, suggesting that the data sampling methodology is identical.

TABLE 3.4

Means, standard errors, correlation coefficients and Bonferroni comparisons for all variables.

Variable	Units	VariaCardio/TF4 system		Biopac/Okimura system		Correlation	Bonferroni
		M	SE	M	SE	r-value	P-value
Mean R-R interval	ms	867	32	868	32	0.99	0.98
Total power	ms^2	1620	304	3045	591	0.96	0.001
Very low frequency power	ms^2	275	52	996	195	0.87	0.001
Low frequency power	ms^2	707	178	1358	359	0.91	0.01
High frequency power	ms^2	637	160	691	174	0.98	0.83
Normalised LF power	N.U.	53	5.7	62	4.7	0.89	0.004
Normalised HF power	N.U.	47	5.7	38	4.7	0.89	0.004
LF/HF ratio	~	1.1	0.8	2.0	1.0	0.89	0.23

LF = low frequency, HF = high frequency, N.U. = normalised units.

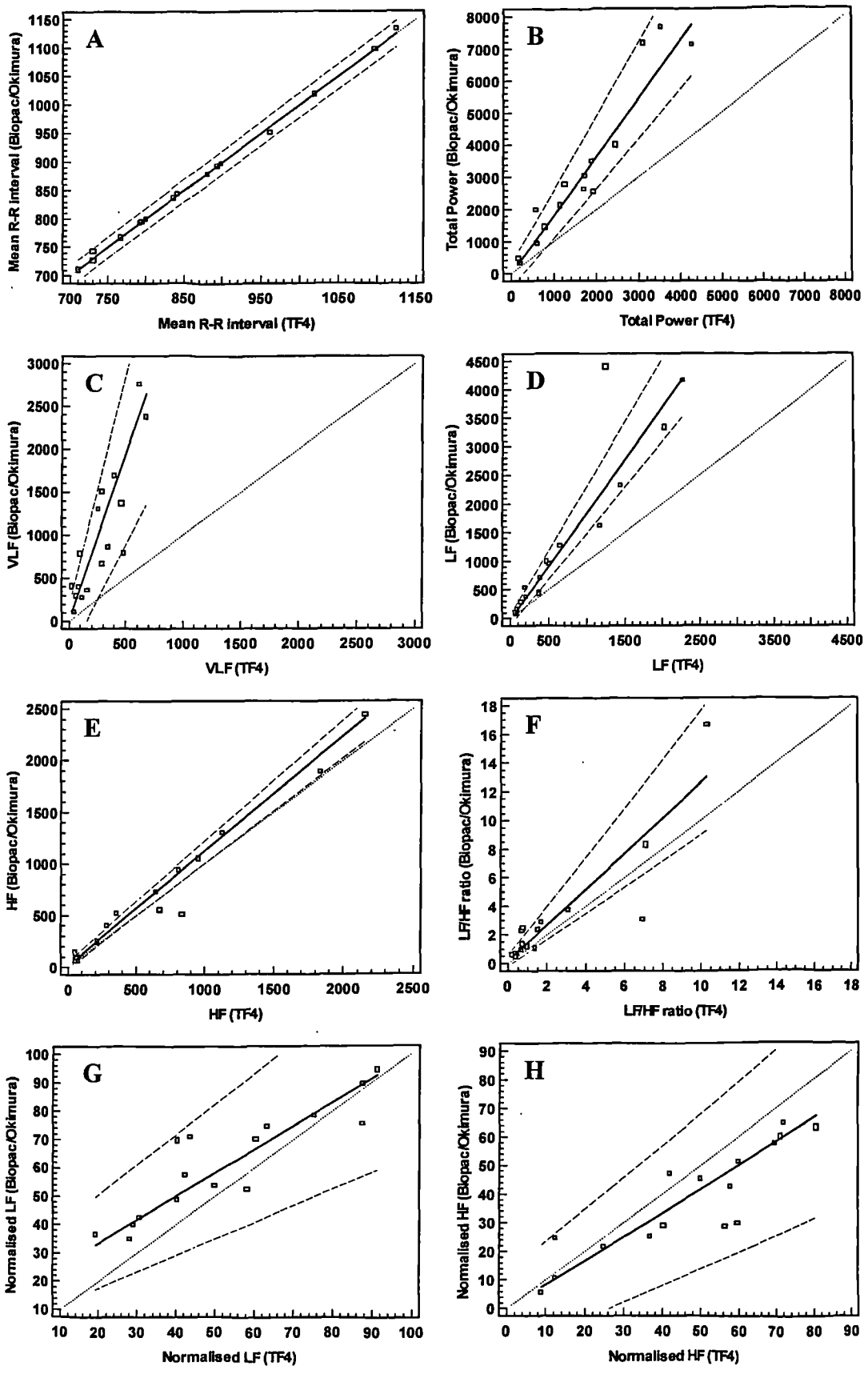


Figure 3.4 Biopac/Okimura v TF4 validation comparisons for (**A**) Mean R-R interval (**B**) Total Power (**C**) VLF (**D**) LF (**E**) HF (**F**) LF/HF ratio (**G**) LFnorm (**H**) HFnorm.

In the frequency domain, total power (TP) was 28% significantly lower for coarse-graining spectral analysis (CGSA) than for AR ($P < 0.001$). A large difference was identified between methods for estimation of VLF power (CGSA 275ms^2 v AR 996ms^2, $P < 0.001$) and compared to the Biopac/Okimura system, the VariaPulse TF4 showed a 92% reduction ($P < 0.01$) in LF power. A non-significant 8% reduction in HF was also observed.

The results from this study are remarkably similar to those obtained in the previous study, which compared an autoregressive model with the coarse-graining FFT method. The results provide further evidence to demonstrate that at least in healthy subjects both AR and FFT are equally valid for the analysis of short-term HRV recordings.

In terms of cost, the Biopac/Okimura system is about £3,400 whereas the VariaPulse system costs approximately £6000. Both systems offer similar features and although the Biopac system additionally includes facilities to use up to six channels to input various other physiological data, the advantage offered by the VariaPulse is its capacity to pick up the ECG signal at a considerable distance from the transmitter.

In conclusion the present study has further highlighted the differences between the standard FFT method and one that incorporates a coarse-graining facility. Similar to the previous study it is evident that an interpretation of the sympathetic component of HRV as measured by the VLF and LF components will be distinct when using the different systems. Although of less importance when the patient is his/her own control, cross-study comparisons need to recognise the impact of the different approaches to the same measurement.

CHAPTER TWO

PSYCHOLOGICAL STRESS AND RELAXATION

4.1 THE EFFECTS OF SHORT-TERM PSYCHOLOGICAL STRESS ON THE TIME AND FREQUENCY DOMAINS OF HEART RATE VARIABILITY

Abstract

The purpose of this study was to test the hypothesis that short-term psychological stress produces significant changes in sympathovagal activity. A simple, non- invasive method was used measuring the timing and frequency of heart rate variability (HRV). Thirty normal healthy subjects (16F, 14M aged 32.7 ± 6.3 years; mean ± SD) were assigned into two age- and sex-matched groups. In the experimental condition a 5-minute psychological stress test, predominantly based on the Stroop Word Colour Conflict Test, was employed in a competitive setting and included a financial inducement to produce psychological strain. Analysis showed that during psychological stress a significant reduction in the timing and frequency of HRV was observed. The standard deviation of interbeat intervals decreased. A significant increase in heart rate was also observed. Within the frequency domain, a significant reduction in the high frequency component of HRV and a significant increase in the low frequency component were observed. There was also a significant increase in the low frequency to high frequency ratio. Self evaluation of physical tension and emotional state measured by visual analogue scales also showed significant increases during psychological stress. No significant differences were observed on any variables within the control group. The results indicate a shift towards sympathetic predominance as a result of parasympathetic withdrawal and demonstrate that this psychological stress test used is effective in provoking a characteristic defence-arousal

reaction. This simple, cost-effective method of analysing heart rate variability is suitable for the detection of short- term changes in sympathovagal balance.

INTRODUCTION

With the advent of new and more powerful computer-based analysis systems, the assessment of heart rate variability (HRV) has rapidly expanded in cardiovascular research. It is commonly used as a robust yet sensitive measurement of autonomic nervous system function (Pomeranz *et al.* 1985, Malliani *et al.* 1991, Janssen *et al.* 1995, Nolan *et al.* 1996). Analysis of HRV has also been used to assess changes in sympathovagal tone in various emotional, (Rechlin *et al.* 1994, McCraty *et al.* 1995) and mental states (Carney *et al.* 1995).

Rechlin, *et al.* (1994) used supine subjects to examine differences between normal and depressive persons. Although McCraty, *et al.* (1995) used seated subjects, the method of measurement involved ECG electrodes, which are considered intrusive. Both authors used a fast Fourier transform to obtain the power spectrum and Carney, *et al.* (1995) also comparing normal with depressive persons, only used time domain analysis based on a 24-hour Holter recordings. The present study had the advantage of measuring HRV by both frequency and time series analysis. Also used was a radio transmission system from a simple chest strap that removed the necessity for direct wiring and was therefore less intrusive. Another advantage of this study was that the procedure involved an autoregressive model for the HRV, which produces smoother spectral components (Task Force of the European Society of Cardiology and The North American Society of Pacing and Electrophysiology 1996). The autoregressive model is preferable for accurate estimation of power spectral density even on a small number of interbeat samples (Task Force, 1996). This study has a further benefit compared with other published

work because the cost of the equipment is considerably less than other commercial systems.

The Stroop Word Colour Conflict Test (Stroop, 1935) is commonly used to produce psychological strain for various research applications and in its original form involves a lengthy procedure. The test has been described as an active coping task involving sensory rejection (Boutcher & Stocker, 1996) and has been used as a model of the defence-arousal mechanism in humans. (Freyschuss *et al.* 1988). Cardiovascular reactivity to psychological stressors such as this test typically involves an increase in heart rate, systolic blood pressure and the circulating catecholamines, adrenaline and noradrenaline (Freyschuss *et al.* 1990). The mathematical transformation of HRV into power spectral density permits clarification regarding autonomic nervous system function and has been used to indicate sympathovagal interaction in conditions of psychological strain. (Pagani *et al* 1991, Hoshikawa & Yamamoto, 1997).

On a beat to beat basis fluctuations in heart rate (HR) are the net result of sympathovagal interaction and any sudden large changes in heart rate are parasympathetically mediated. (Akselrod *et al.* 1985). Power spectral analysis is a procedure, which can help distinguish sympathetic from parasympathetic regulation of the sino-atrial node by allowing identification of component frequencies of the heart rate variability spectrum.

The purpose of this study was to investigate cardiovascular reactivity to short term psychological stress using power spectral analysis of HRV to determine sympathovagal balance.

METHOD

Participants

Thirty normal healthy volunteers (16 woman, aged 25 to 36 years, M: 30.9 ± 3.9; 14 men, aged 18–45 years, M: 34.4 ± 8.7) were recruited via e-mail bulletin boards and from verbal requests for volunteers. They comprised 21 students and four staff all from a further education college in the north west of England as well as five friends who were not part of the college. Physical activity profiles were normal for the age group with most subjects engaging in modest physical activity weekly. None were involved in regular, high-intensity physical activity. Informed consent was obtained prior to the study. Subjects were assigned into two age- and sex-matched groups. The 15 subjects in Group 1 participated in the short-term psychological stress test. The fifteen subjects in Group 2 acted as controls. All subjects were in good general health with no history of cardiovascular disease and were not taking any prescription drugs known to affect cardiovascular function. Subjects had no prior knowledge of the parameters being measured. They were requested to refrain from smoking, eating or drinking anything, with the exception of taking water for 4 hours before the test. The subjects were also asked not to undertake any exercise or strenuous activity within the same period. Throughout the study they were requested to refrain from making any exaggerated body movements or intentionally altering their respiration.

Stroop Test procedure

The Stroop Word Colour Conflict Test is a task that was originally designed to test the automatization of sub-components in skilled activities and is used

to induce a violent response conflict. (Stroop, 1935). In its conventional form the test involves a fairly lengthy procedure. In this study a 5-minute psychological stress test predominantly based on the Stroop test was used. There was in addition a mental arithmetic component as mental arithmetic has been previously shown to produce psychological strain. (L'Abbate *et al* 1991, Sloan *et al* 1991). Subjects were given a set of 4 laminated A4-sized sheets. Sheet 1 contained 22 nonsensical words, such as ZYP and WOPR. The subjects were required to name, as quickly as possible, the colour in which the word was printed. Sheet 2 contained a series of simple mathematical questions such as, 1+2-3+4+5=? The subjects were required to give an answer to the problem as quickly as possible. Sheet 3 contained 22 words denoting various colours such as **BLUE** although the colour ink in which the word was printed was of a different colour such as green. Subjects were instructed to name the colour in which the word was printed. Finally, sheet 4 contained 22 words popularly associated with a particular colour such as **GRASS** and the colour ink was printed in a mismatched colour such as red. Once again the subjects were required to name the colour in which the word was printed. If the subjects finished the test within the 5-minute period they were instructed to start again. Before testing, subjects were allowed approximately twenty seconds to practise. They were instructed to answer as quickly and as accurately as possible. To provide further demand the subjects were told that the person who gave the most correct answers within the specified time would receive a cash prize. Subjects in the control group engaged in light conversation in place of the test period. The rationale for permitting light conversation was because if we had insisted on silence it may

have caused a specific respiratory pattern to be adopted. As the experimental subjects were talking in response to the questions asked, it was considered appropriate to permit a modest level of conversation with the control to minimise the differences in respiratory pattern between the groups.

Data collection

Subjects were allowed to rest comfortably for approximately 10 minutes prior to the baseline recording procedure. During this time they were fitted with a flexible electrode belt which incorporated a Polar Coded Transmitter, (Polar Electro Oy, Kempele, Finland). The 'ribbed' electrodes were coated in electrode gel in order for ensure maximum conduction and the transmitter was positioned centrally, directly below the xiphoid. The belt was attached tightly enough that the movement of the electrodes would be held to a minimum, but not cause discomfort.

Immediately before the test period and at the end of the test period subjects were required to describe, using a simple analogue scale from 1 to 10, how they felt with regard to emotional state and muscle tension at that moment. At the lower end of the scale for muscle tension figure 1 read, 'Calm, Relaxed and Composed' and figure 10 read, 'Stressed'. Visual analogue scales have been used by Grunberg *et al.* (1996), by Kaplan & Camacho (1983), by Maddox & Douglas (1973) and by Wright (1987) to examine self-assessment of health and quality of life.

Each subject sat in a straight, high-backed chair to minimise postural change. The chair was positioned adjacent to a Polar Advantage Interface (Polar Electro Oy, Kempele, Finland), which received signals from the

transmitter. The procedure took place in quiet, warm, temperature controlled environment (22°C-25°C) and when not testing, normal conversation was allowed to continue throughout.

Interbeat interval was determined on a beat-to-beat basis as the difference in the time of the peak voltage of the R-wave and the peak voltage of the subsequent R-wave. HR was calculated from the interbeat interval data.

Heart rate variability was calculated following removal of 'aberrant' beats. This consisted of an automatic default filtering procedure contained within the Polar Precision Performance Software package (Polar Electro Oy, Kempele, Finland). In addition the tachogram was visually scanned to remove any further aberrant beats manually.

Measurements in the time domain consisted of the standard deviation of all 'normal' R-R intervals, along with the root mean square of successive differences and the pNN50, which represents the proportion of differences between adjacent normal R-R intervals that are greater than 50 msec. These measurements reflect short-term variation of heart rate variability and are used to estimate high frequency, beat-to-beat variations in HR. These variables are highly correlated with high frequency activity and give an estimate of parasympathetic activity (Kleiger *et al.* 1987).

The following frequency domain indices of HRV were calculated using the Polar software system: (1) Very low frequency power from 0.00 - 0.04Hz. (2) Low frequency power from 0.04 - 0.15Hz. (3) High frequency power from 0.15 - 0.40Hz. An autoregressive model was used to generate heart rate spectra. This has been suggested as the optimal method for short-duration recordings. (Task Force, 1996).

Heart-rate values from the Polar system have been compared with ECG recordings (Karvonen *et al.* 1984). This provided evidence that the data collection procedure is highly valid and this was confirmed by our own unpublished study that compared three commercially available systems. We have also compared the HRV results with another commercial system and all variables in the frequency domain were highly correlated. A further study by Loimaala *et al* (1999) has validated the HRV variables with a 24-hour recorder (Oxford Medilog) and inter-method differences were negligible.

Statistical Analyses

Statistical analysis involved a repeated measures *t* test which was used to compare values for all variables before and during treatment with the exception of the comparison of muscle tension, emotional stress, normalised high frequency power (HFnorm) and normalised low frequency power (LFnorm). These variables did not have a normal distribution; therefore the Wilcoxon signed-rank sum test was employed to compare results using the sum of the ranks for positive and negative differences for each group. A probability of < 0.05 was considered significant. A Pearson product-moment correlation coefficient was used to compare high frequency power with root mean square of successive differences and pNN50.

RESULTS

Table 4.1. summarises the means, standard deviations and measures of change for baseline and treatment conditions for experimental and control groups.

TABLE 4.1

Means, standard deviations, change, percentage change and P-values for all variables.

Variable	Units	Experimental Group						Control Group					
		Baseline		Treatment				Baseline		Treatment			
		M	SD	M	SD	Change	† Diff	M	SD	M	SD	Change	† Diff
Heart rate	bpm	77.0	12.7	85.8	15.3	8.8	11.4*	72.7	10.3	72.8	9.7	0.1	0.1
SDNN	ms	64.0	16.7	56.5	16.3	7.5	11.7*	60.8	14.6	60.5	15.9	0.3	0.5
RMSSD	ms	39.6	14.0	29.1	12.5	10.5	26.5*	40.4	17.6	36.6	12.6	3.8	9.4
pNN50	ms	7.9	5.9	4.6	4.6	3.3	41.8*	9.4	8.0	8.1	5.6	1.3	13.8
Total power	ms^2	4999	2793	3601	2000	1398	28.0*	4814	2556	4771	1844	43	1.0
Very low frequency power	ms^2	2391	1201	1881	1055	510	21.3*	2601	1835	2841	1291	240	9.2
Low frequency power	ms^2	2003	1562	1455	1182	548	27.4*	1605	744	1447	626	158	9.8
High frequency power	ms^2	606	442	265	228	341	56.3*	609	710	483	399	178	23.3
Normalised LF power	N.U.	76.7	13.1	83.7	9.7	7	9.1*	75.8	12.8	77.2	10.9	1.4	1.8
Normalised HF power	N.U.	23.3	13.1	16.3	9.7	7	30.0*	24.2	12.8	22.8	10.9	1.4	5.8
LF/HF ratio	~	6.3	7.6	8.1	6.5	1.8	28.6*	4.4	3.2	4.2	2.0	0.2	4.5
Self-perceived muscle tension	~	4.0	1.3	5.7	2.1	1.7	52.5*	3.1	1.2	3.3	1.3	0.2	6.5
Self-perceived emotional state	~	5.1	1.6	7.4	1.7	2.3	45.1*	4.1	1.6	3.5	1.6	0.6	14.6

*$p<0.05$. †% of baseline. N.U. = normalised units, LF = low frequency, HF = high frequency.

DISCUSSION

Heart rate is modulated by the synergistic action of the sympathetic and parasympathetic branches of the autonomic nervous system. Within the time domain standard deviation is used as the primary index of heart-rate variability. The present study shows that short-term psychological stress caused a significant increase in heart rate ($P < 0.0001$) and an overall reduction of autonomic nervous system activity as represented by a decrease in the standard deviation of normal R-R intervals ($P < 0.03$).

Also within the time domain root mean square successive difference ($P < 0.001$) and pNN50 ($P < 0.01$) were significantly reduced. These short-term changes in HRV reflect the rapid alterations characteristic of the parasympathetic nervous system. This contrasts with the more gradual changes normally seen in the sympathetic nervous system.

Within the frequency domain the reduction in autonomic nervous system activity was indicated by the significant decrease in total power as represented by the sum of all power frequencies ($P < 0.01$). Long period rhythms are contained in the very low frequency range. This range falls below 0.04Hz and it is assumed that this component accounts for long-term regulatory mechanisms probably relating to thermoregulation and to the renin-angiotensin system, which regulates peripheral vascular resistance (Ori *et al.* 1992). When broken down into its individual components, there was no significant difference found in very low frequency power during short-term psychological stress.

In the low frequency range, between 0.04 - 0.15Hz there is a rhythm centred around 0.1Hz. An increase in power is generally accepted as a marker

of sympathetic activity (Malliani *et al* 1991). Low frequency power calculated in normalised units most closely represents those fluctuations in sympathetic tone.

It is generally accepted that the power of the high frequency oscillations found between 0.15 - 4.0Hz corresponds to the heart rate variations related to the respiratory cycle. This is often referred to as respiratory sinus arrhythmia and is considered to reflect efferent vagal input to the heart (Malliani *et al.* 1991, Ori *et al.* 1992). High frequency power is also said to be highly correlated with the time domain variables of root mean square successive difference and pNN50. (Kleiger *et al.* 1987). The present study yielded significant correlations between these variables both in baseline and experimental conditions. The correlation between baseline high frequency power with root mean square successive difference was 0.78 and with pNN50 was 0.99. For experimental high frequency with root mean square successive difference was 0.99 and with pNN50, 0.96.

In terms of absolute units both high frequency power and low frequency power demonstrated significant reductions (high frequency, $P < 0.001$ and low frequency $P < 0.01$). Taken in isolation these results may lead to an erroneous interpretation of the overall response. However, following normalisation of low frequency and high frequency, the latter component of the power spectrum showed a significant decrease (HFnorm, $P < 0.02$) and the low frequency component showed a significant increase (LFnorm, $p < 0.02$). The normalisation process involves calculating the relative value of each power component in proportion to the total power minus the very low frequency component. High frequency power was reduced by 30% and low

frequency power increased by 9.1% percent during psychological stress.

The representation of low frequency and high frequency in normalised units emphasises the controlled and balanced behaviour of the autonomic nervous system. The normalisation process tends to minimise the effect of changes in total power on the values of both components. This study is consistent with the 1996 recommendation of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, which suggests the necessity of reporting both absolute and normalised units in order to describe completely the distribution of power spectral components and to prevent misinterpretation of results.

A significant increase in the LF/HF ratio, ($P < 0.02$), was also found, indicating the marked effect of short-term psychological stress on sympathovagal balance in this study. Taken as a whole the results suggest a parasympathetic withdrawal along with a sympathetic increase as being responsible for the increase in the ratio.

Subjective self reports also indicate a significant increase in feelings of emotional stress ($P < 0.001$) and muscle tension ($P < 0.004$). During the defence-arousal response, in order to prepare for fight or flight, digestive processes are curtailed as a result of the activation of $beta_2$ receptors and alpha receptors throughout the gastrointestinal tract. This leads to mild to moderate contraction of sphincters and may account for the increased gut feelings leading to increased emotional tension.

Another feature of the defence-arousal mechanism is that increased activity of nerve fibres to the adrenal medulla increases secretion of adrenaline into the bloodstream. This increase in adrenaline reinforces the

dilation of muscle arterioles that fill with blood preparing muscles for action. This set of physiological circumstances is probably responsible for the significant increase in subjective feelings of muscle tension.

In the present study the effects of short-term psychological stress were evaluated by spectral analysis of heart rate variability using the Polar NV-Advantage system. The psychological stress test used was a 5-minute modification of the Stroop Word Colour Conflict Test and included a mental arithmetic component. The results indicate a characteristic activation of the defence-arousal system during short-term psychological stress as suggested by a decrease in heart-rate variability and HFnorm and an increase in LFnorm, heart rate and low frequency/high frequency ratio. Subjective self-reports indicate an increase in muscle tension and increased feelings of emotional stress also characteristic of the defence-arousal mechanism. The results of the present study are consistent with other workers although differing times of application of psychological strain were used. (Pagani *et al.* 1991, Hoshikawa & Yamamoto 1997). The stressor used in this study was of much shorter duration. The study demonstrates that a non-invasive measure is highly responsive to psychological stress and provides the basis for future work on sino-atrial control.

4.2 THE EFFECTS OF SHORT-TERM MENTAL RELAXATION ON THE TIME AND FREQUENCY DOMAINS OF HEART RATE VARIABILITY IN HEALTHY SUBJECTS

ABSTRACT

Mental relaxation training forms a major part of many stress management interventions and is induced by several methods. Guided imagery (GI) is one such technique that uses specific instructions combined with visualisation to induce relaxation. Relaxation is characterised by an increase in parasympathetic nervous activity and the defence-arousal (stress) response is associated with increased sympathetic nervous activity. Time and frequency domain analysis of heart rate variability (HRV) is a simple, non-invasive method of assessing cardiac autonomic tone. The purpose of this study was to use HRV analysis to measure the effects of a single session of mental relaxation on cardiac sympathovagal activity in subjects unfamiliar with relaxation training. Self-evaluation of muscle tension (MT) and emotional state (EMOT) using visual analogue scales were also assessed before and after each intervention. Thirty healthy subjects (26M, 4F aged 18.2 ± 1.0 years, mean ± SD) took part in the study. They were assigned into two age- and sex-matched groups. In the experimental condition a 5-minute GI procedure, using phrases predominantly based on the Schultz method of autogenic training was used to induce relaxation. Subjects in the control group sat quietly for the same time period. Analysis showed that during GI, there was a significant reduction in heart rate ($P < 0.001$), breathing rate ($P < 0.005$) and EMOT ($P < 0.05$). No significant differences were observed for any variables

in the control group. No significant differences were observed for any HRV parameters during relaxation but there were trends suggesting increased parasympathetic activity associated with an increased relaxation response. The results indicate that GI has a relaxing effect on cardiac autonomic tone and is beneficial in improving feelings of wellbeing.

INTRODUCTION

Mental relaxation in its various forms is regularly used as a means of inducing relaxation in stress management training programmes. There are several commonly used mental techniques, which include Autogenic Training (Kanji & Ernst 2000), Transcendental Meditation (Barnes *et al.* 1999) and Guided Imagery (Speck 1990). Guided Imagery (GI) is a simple, inexpensive, non-invasive technique, which is often used in combination with other techniques for relaxation purposes. In addition to being used in the management of stress it has also been successful in controlling acute pain and reducing anxiety and emotional distress in various pathological conditions (Vines 1994).

Although research on GI for stress management has increased over the last decade most studies have reported only on psychological outcomes (Speck 1990, Leja 1989, Wynd 1992, Troesch *et al.* 1993, Groer & Ohnesorge 1993). Relatively few have explored its physiological effects (Leja 1989, Zachariae *et al.* 1990, Hewson-Bower & Drummond 2001) and to the best of the author's knowledge none have investigated the effects of GI on cardiac autonomic function as measured by HRV. The purpose of this study was to assess the effects of a single, five-minute session of guided imagery on cardiac autonomic tone and on subjective measures of emotional state and muscle tension. Analysis of HRV both in the time and frequency domains was used to measure the changes in cardiac sympathovagal tone.

METHOD

Participants

Thirty normal healthy volunteers (26 male and four female aged 18.2 ± 1.0 years, mean ± SD) were recruited via e-mail bulletin boards and from verbal requests for volunteers. Subjects were all students from a further education college in the north west of England studying for a National Diploma in Sports Science. As part of the course, subjects engaged in several sessions of moderate to vigorous physical activity per week. Informed consent was obtained prior to the study. Subjects were assigned into two age- and sex-matched groups. The 15 subjects in Group One participated in the short-term mental relaxation procedure. The 15 subjects in Group Two acted as controls. All subjects were in good general health with no history of cardiovascular disease and were not taking any prescription drugs known to affect cardiovascular function. Subjects had no prior knowledge of the parameters being measured. They were requested to refrain from smoking, eating or drinking anything, with the exception of taking water for four hours before the test. The subjects were also asked not to undertake any exercise or strenuous activity within the same period. Throughout the study they were requested to refrain from making any exaggerated body movements or intentionally altering their respiration.

Guided Imagery Procedure

The relaxation procedure used in this study was based on a technique first developed by Schultz & Luthe (1969). In its original form the Schultz procedure requires the subject to adopt an attitude of passive awareness and to

focus on certain specific body areas and sensations. Schultz described particular 'autogenic' formulas or phrases which allowed subjects to focus on feelings of warmth and heaviness in the arms, legs, areas of the chest, heart and abdomen finishing with a sensation of coolness in the region of the forehead. In this study subjects listened to a five-minute taped recording containing instructions, which guided them to use their imagination to systematically focus on the specific body regions previously described.

Subjects relaxed with their eyes closed and listened to the instructions through cushioned headphones. They were also given instructions to imagine the colour red to represent a warm, glowing and soothing feeling and the colour blue to represent a cool feeling of alertness. The instructions were given in the following manner:

- Before starting make yourself as comfortable as possible, sitting upright in the chair with your feet firmly on the ground. Now close your eyes and imagine yourself being filled with a sense of calmness and relaxation as you start to become aware of the area of your right arm. Feel that your right arm is becoming heavier and heavier. You are starting to feel completely calm as you become aware of a beautiful, glowing, colour, red. A feeling of red, glowing warmth completely fills your right arm and dissolves away any pain and tension. Your arm feels heavier and heavier, as the red warmth completely fills your arm and you sink deeper and deeper into a calm state of relaxation.
- Now become aware of your left arm and as before imagine that your left arm is becoming heavier and heavier as you feel more and more calm and

relaxed as the warm red glow fills your left arm etc.

- Next focus on the area of your chest and heart. Feel the tension in your chest dissolve away and feel that your heart is beating calmly and strongly as you sink deeper and deeper into a state of relaxation and peacefulness. See and feel the gentle red glowing warmth as it flows through your heart bringing relaxation and calmness. Your chest is open and free from tension and your heart is relaxed and strong. It feels powerful and full of vitality but is relaxed, calm and comfortable etc.
- Now become aware of the area of your solar plexus and abdomen. Feel for any pain and tension in the region of your abdomen and allow the red glowing warmth to fill your abdomen as your insides unwind into a state of calm relaxation.
- Now become aware of the areas of your left and right legs etc.
- Finally become aware of the area of your forehead and imagine an ice-cool blue colour touching and chilling your brow. This colour blue brings with it a sense of clear thinking and alertness. You feel calm and relaxed but you are able to think clearly in this beautiful state of peacefulness. Your body feels heavy and completely relaxed but your mind is clear, calm and alert.
- In the last remaining moments scan your whole body and allow any remnants of pain and tension to dissolve away.

Subjects in the control group also wore the cushioned headphones and sat for five minutes in silence with their eyes closed while HRV data were acquired. They were asked to try to relax as much as possible, again avoiding any unnecessary movement and not intentionally altering their breathing pattern.

Data Acquisition

Before baseline recording, subjects were allowed to rest comfortably for approximately 10-minutes. During this time they were fitted with a flexible electrode belt which incorporated a Polar Coded Transmitter, (Polar Electro Oy, Kempele, Finland) as previously described in the General Methodology section. Immediately before, and at the end of the test period, subjects were required to describe, using a simple analogue scale from 1 to 10, how they felt with regard to emotional state and muscle tension at that moment (see Appendix 1).

Breathing rate was assessed by monitoring chest movement during baseline and experimental conditions and verified by observing the pattern of respiratory sinus arrhythmia (RSA) from individual R-R interval traces.

Statistical Analyses

A repeated measures *t* test was used to compare values for all variables before and during treatment with the exception of the comparison of RMSSD, total power (TP), very low frequency power (VLF) and LF/HF ratio. These variables did not have a normal distribution; therefore the Wilcoxon signed-rank sum test was used to compare results using the sum of the ranks for positive and negative differences for each group. A probability of < 0.05 was considered statistically significant.

RESULTS

At baseline there were no statistically significant differences between groups for any variables in the time and frequency domains of heart rate variability or

for self-perceived measures of emotional, muscle tension and breathing rate (Table 4.2). The results of the study show that in the experimental group, GI caused an overall decrease in both heart rate (HR) ($P < 0.001$) and breathing rate ($P < 0.005$) compared to baseline. There were no significant differences in HR or breathing rate in the control group. In the time domain and frequency domains of HRV no statistically significant differences were observed for any variables in both the test and control groups following intervention.

DISCUSSION

The purpose of this study was to test the effects of a commonly-used guided imagery relaxation technique on cardiac autonomic tone in subjects unfamiliar with this method of relaxation. Analysis of HRV in the time and frequency domain was used to measure cardiac autonomic status. Heart rate is modulated by the synergistic action of the sympathetic and parasympathetic branches of the autonomic nervous system. The present study shows that short-term mental relaxation caused a significant reduction in heart rate ($P < 0.01$), which was not evident in the control group. Except for a non-significant 11% increase in root mean square of successive differences (a time domain measure of parasympathetic activity) there were no notable differences for other time-domain variables.

In the frequency domain there were no significant differences for any variables in the control group. In the experimental group, again there were no remarkable changes in any HRV variables following mental relaxation with the exception of a non-significant 41% increase in LF power. Low frequency

TABLE 4.2

Means, standard deviations, change, percentage change and P-values for all variables.

Variable	Units	Experimental Group						Control Group					
		Baseline		Treatment				Baseline		Treatment			
		M	SD	M	SD	Change	† Diff	M	SD	M	SD	Change	† Diff
Heart rate	bpm	70.3	10.0	67.0	10.0	3.3	4.7**	67.6	10.6	68.5	10.4	0.9	1.3
SDNN	ms	74.3	24.5	75.1	27.3	0.8	1.1	75.8	24.9	80.8	28.0	5.0	6.6
RMSSD	ms	51.3	28.5	57.2	35.1	5.9	11.5	56.4	29.3	53.8	23.8	2.6	4.6
pNN50	ms	13.4	10.1	14.1	10.1	0.7	5.2	14.0	9.2	13.1	7.9	0.9	6.4
Total power	ms^2	6740	5217	7235	5858	495	7.3	7301	4473	7706	4530	405	5.5
Very low frequency power	ms^2	3611	3241	3175	2754	436	12.0	2838	2114	3122	2200	284	10.0
Low frequency power	ms^2	1566	929	2215	1838	649	41.4	2898	2689	3337	3329	439	15.0
High frequency power	ms^2	1563	1816	1844	2690	281	18.0	1565	2140	1248	1360	317	20.2
Normalised LF power	N.U.	59.3	21.8	64.4	22.2	5.1	8.6	65.4	23.6	68.8	22.2	3.4	5.2
Normalised HF power	N.U.	40.7	21.8	35.6	22.2	5.1	12.5	34.6	23.6	31.2	22.2	3.4	9.8
LF/HF ratio	~	2.6	2.7	3.6	4.2	1.0	38	4.4	5.0	5.6	6.7	1.2	27
Breathing rate	cpm	11.0	2.5	9.7	2.6	1.3	11.8**	11.2	0.84	10.8	0.85	0.4	3 7
Self-perceived muscle tension	~	4.0	1.5	3.2	1.2	0.8	20.0	3.8	1.4	3.3	1.6	0.5	13
Self-perceived emotional state	~	4.1	1.5	3.1	1.7	1.0	24.3*	3.9	1.5	3.5	1.3	0.4	10 2

*$p<0.05$. **$p<0.01$. †% of baseline. N.U. = normalised units, LF = low frequency, HF = high frequency. cpm = cycles per minute.

variations in the range 0.04 to 0.15 Hz of the power spectrum are generally considered to reflect cardiac sympathetic activity and in the range 0.15 to 0.40 Hz, high frequency oscillations are linked to respiratory sinus arrhythmia and reflect cardiac parasympathetic activity. The HF range is also often referred to as the respiratory frequency. Although these definitions are somewhat simplistic and interpretation of HRV results based on these ideas can lead to confusion. Some workers have suggested that if breathing frequency falls below 9 cycles per minute (0.15 Hz) then the respiratory frequency will be reflected by an increase in LF power (Goldberger 1999, Eckberg 2000). In the present study following mental relaxation the experimental group demonstrated a significant reduction in breathing frequency which was not observed in the control group. Breathing rate fell from 11.0 cpm to 9.7. It is therefore likely that a proportion of the 41% increase in LF power is due to a 'spillover' effect due to increased parasympathetic rather than sympathetic activity. This would also account for the reduction in heart rate. Taken together the results indicate an increased cardiac relaxation effect which is related to a more generalised relaxation response as demonstrated by a significant reduction in self-perceived feelings of emotional tension ($P < 0.05$). There are relatively few studies that have examined the short-term effects of relaxation techniques on cardiac autonomic parameters, most have measured the longer-term outcomes of relaxation training. In a study by Fried (1987), biofeedback-assisted guided imagery was shown to reduce breathing rate and induce electroencephalogram changes associated with a hypoarousal state. Mishima *et al.* 1999 have also shown that standard autogenic training induces significant reductions in heart rate and systolic blood pressure

responses.

From the results of the study it can seen that mental relaxation using guided imagery appears to induce a relaxation state and is associated with a reduction in breathing rate. Therefore this suggests that breathing rate may have an important influence on cardiac autonomic activity and to this end further research into the effects of breathing on HRV is needed. This was undertaken and the results of the additional research are reported in Chapter Seven.

CHAPTER FIVE

THERAPEUTIC MASSAGE, AUTONOMIC NERVE BLOCKADE AND HEART RATE VARIABILITY

5.1 The Short-term Effects of Myofascial Trigger Point Massage Therapy on Cardiac Autonomic Tone in Healthy subjects

Abstract

No studies have reported on the effect of back massage on autonomic tone as measured by heart rate variability (HRV). This is especially relevant to the nursing profession, as massage is increasingly available as a therapy complementary to conventional nursing practice. The purpose of this study was to investigate the effects of myofascial trigger-point massage therapy (MTPT) to the head, neck and shoulder areas on cardiac autonomic tone. In this experimental study, subjects were initially placed in age- and sex-matched groups and then randomised to treatment or control by alternate allocation. The study involved 30 healthy subjects (16 female and 14 male, aged 32.47 ± 1.55 years, mean ± standard error). A 5-minute cardiac inter-beat interval recording, systolic (SBP) and diastolic blood pressure (DBP) and subjective self-evaluations of muscle tension (MT) and emotional state (EMOT) were *taken before and after intervention. Autonomic function was measured* using time and frequency domain analysis of HRV. Following MTPT there was a significant decrease in heart rate ($P < 0.01$), SBP, ($P = 0.02$) and DBP ($P < 0.01$). Analysis of HRV revealed a significant increase in parasympathetic activity ($P < 0.01$) following MTPT. Additionally both MT and EMOT, showed significant improvement ($P < 0.01$). In normal healthy subjects MTPT to the head, neck and shoulder areas is effective in increasing cardiac parasympathetic activity and improving measures of relaxation.

INTRODUCTION

Nursing in a number of contexts (such as palliative care, oncology and cardiac rehabilitation) is increasingly exposed to complementary therapies. A PUBMED Medline search using the combined terms 'nursing' and 'complementary therapies' revealed 527 citations between 1980 and 1990 and 1653 citations between 1990 and 2000. More particularly, the use of therapeutic massage is re-emerging as a popular nursing modality as evidenced by an increase in journal articles. Again using the PUBMED Medline, database, the terms 'nursing' and 'therapeutic massage' revealed 54 citations between 1981 and 1991 in comparison to 248 citations between 1991 and 2001. The evidence base for these is increasing, but clinical governance requires further information on the efficacy of such interventions. In general, the present status of certain complementary therapies is that they are offered in conjunction with conventional nursing practice. It would be acceptable, for example, to see the opportunity for reflexology, autogenic training and aromatherapy advertised in conjunction with a coronary care unit. Nurses may be unsure of the merits of such therapies because it is not part of their training and the scientific validity is currently in its infancy. Massage is used across the entire age range and in many different nursing settings. For instance, massage has been used to reduce symptoms and improve quality of life in children with quadriplegic cerebral palsy (Stewart 2000). It is also among the battery of non-pharmacological methods commonly used to relieve children's post-operative pain (Polkki *et al.* 2001). In the field of cancer care, massage has been shown to provide meaningful relief from suffering and a relatively short period of massage has been shown to result in physical and

emotional benefits for cancer patients (Billhult & Dahlberg 2001). Back massage as a form of intervention has previously been shown to induce general relaxation (Fraser & Kerr 1993) but no study has previously reported the impact of massage on cardiac autonomic tone. As autonomic tone is implicated in so many common diseases (including diabetes, peripheral vascular disease and coronary artery disease) it will be beneficial to appreciate the measurement, implications and potential of HRV as a measure of autonomic tone. Massage therapy was chosen because it is known to the nursing profession as a prospective form of relaxation but it is not commonly practised within mainstream nursing. The selection of healthy subjects, in the first instance, was to ensure quality baseline data before including the confounding variables of disease and types of medication. It is intended to undertake further work on specific patient groups, such as diabetes and recent post-myocardial infarction, now the specific benefits of massage therapy on cardiac autonomic tone for normal subjects has been established.

Therapeutic massage is the manipulation of the soft tissue of body areas to bring about generalised improvements in health (Vickers & Zollman 1999). A number of studies have reported on the subjective effects of massage on muscle relaxation and psychological state. In an evaluation of the use of massage on the well-being of cancer patients, Corner *et al.* (1995) reported that patients found massage to be beneficial in assisting relaxation and reducing physical and emotional symptoms. Wilkinson *et al.* (1999) reported that patients in a palliative care setting considered massage to be beneficial in reducing anxiety, tension, pain and depression. In her article 'Massage Therapy Effects', Tiffany Field gave a history of massage and

describes many studies researching the numerous effects of massage in various populations and in many different settings (Field 1998). Relaxation appears to be the most important benefit of massage (Wilkinson 1996). Research into massage therapy is increasing yet the number of studies documenting objective physiological changes following therapeutic massage still remains limited. Several studies examined various massage techniques on heart rate and blood pressure variables but the results of these studies are equivocal (Fakouri & Jones 1987, Reed & Held 1988, Meek 1993, Ferrell-Torry & Glick 1993, Fraser & Kerr 1993, Stevenson 1994). To the best of the author's knowledge the present study is the first to examine the effects of MTPT on cardiac autonomic tone using analysis of HRV to assess effects of treatment.

MTPT is an advanced neuromuscular technique commonly used in the field of sports therapy for the alleviation of pain and to induce muscle relaxation following injury (Peppard 1983). It combines a variety of massage strokes with deeper more focussed pressure at myofascial trigger-points (MTrP). As such it is similar to acupressure, which involves applying pressure or massage to traditional acupuncture points (Filshie & Abbot 1991). When combined with exercise, MTPT has been shown to reduce the number and intensity of MTrP and to be effective in treating MTrP in the neck and shoulder areas (Gam *et al.* 1998).

MTrP are small discrete hyperirritable areas within a taut band of muscular tissue or fascia. They are painful on compression and can evoke characteristic referred pain in areas far away from their actual location (Travell & Simmons 1983). In 1977 Melzack *et al.* reported a remarkably

high degree (71%) of correspondence between MTrP and acupuncture points associated with pain. Stimulation of these MTrP can cause changes within the peripheral autonomic nervous system, such as local excessive perspiration, piloerection, local vasodilation, and erythema (Travell & Simmons 1983).

As previously detailed in Section 1.6, analysis of HRV is a sensitive, non-invasive, indirect technique, which has been used to highlight the importance of the autonomic nervous system in both health and disease (Kristal-Boneh *et al.* 1995, Sleight 1997).

This study investigated the effects of MTPT to the head, neck and shoulder areas on cardiac autonomic tone as assessed by HRV analysis and evaluated the psychological outcomes of the treatment.

METHOD

Participants

Thirty normal, healthy volunteers [16 females, 30.94 ± 1.72 years, mean ± standard error (SE); 14 males, 34.4 ± 2.74 years, mean ± standard error SE] were recruited via e-mail bulletin boards, posters and from verbal requests for volunteers. They comprised 22 students and five staff all from a further education college in the north west of England as well as three friends who were not part of the college. Most of the subjects engaged in a modest amount of physical activity weekly. None were involved in regular, high intensity physical activity. Ethical committee agreement and informed consent was obtained prior to testing.

All subjects were in good general health with no medical conditions known to affect HRV. No subject was taking any prescription drugs known to

affect the cardiovascular system. Subjects were randomly assigned into two age- and sex-matched groups (8F, 7M in each). They were requested to refrain from smoking or drinking any caffeine-containing beverages for at least eight hours prior to testing but were allowed a light breakfast at least two hours before the test. Throughout the study, subjects were requested to refrain from making any exaggerated body movements or intentionally altering their respiration.

Protocol

Subjects in Group One received MTPT to the head, neck and shoulder areas for 20 minutes and the subjects in Group Two relaxed by sitting quietly for the same time period thus acting as controls. Data acquisition took place between 09.30h and 11.30h in a quiet, warm, temperature- controlled environment (22 - 24°C). Subjects were seated in a straight, high-backed chair to minimise postural changes. The chair was positioned adjacent to a Polar Advantage Interface (Polar Electro Oy, Kempele, Finland) that received signals from the transmitter.

Subjects were allowed to rest comfortably for at least 10 minutes prior to the baseline recording procedure. During this time they were fitted with an elasticated electrode belt, which incorporated a Polar Coded Transmitter, (Polar Electro Oy, Kempele, Finland). The 'ribbed' electrodes were coated in electrode gel to ensure maximum conduction and the transmitter was positioned centrally, directly below the xiphisternum. The belt was attached tight enough to minimise movement of the electrodes but did not cause any discomfort. Heart rate data acquisition took place for 5 minutes at baseline

and for 5 minutes immediately following treatment. Systolic and diastolic blood pressure recordings were also taken at baseline and following treatment using an automated blood pressure recorder (Omron Healthcare, Europe). They were measured twice on the right arm and the mean of the duplicate results was recorded.

Measurements of emotional state and muscle tension.

Self-reports of emotional state and feelings of muscle tension were measured before and after treatment using a 100mm visual analogue scale (VAS) with verbal anchors at either end. (see Appendix 1). VASs have been used previously by Grunberg *et al.* (1996) Wright (1987) Kaplan & Camacho (1983) and Maddox & Douglass (1973) to examine self-assessment of health and quality of life.

Massage Procedure

The massage procedure employed in this study is described in detail in the General Methodology section, 2.8.

Data Analysis

Data collection and analysis using the Polar NV-Advantage system have also been described in detail previously both in the General Methodology section 2.2.3, and in Delaney & Brodie (2000).

Statistical analyses

Data are given as mean ± SE. All variables were tested for normality using the Kolmogorov-Smirnov test. The LF/HF ratios alone did not have a normal distribution and therefore were log-transformed prior to statistical analysis. An F-test was used to compare test and control groups for differences in variance. A repeated measures t-test was used to compare the test and control groups for all variables at baseline. A paired t-test was used to compare values before and after treatment for test and control groups. A two-tailed probability of $P < 0.05$ was considered statistically significant.

RESULTS

At baseline there were no statistically significant differences between both groups for all variables in the time and frequency domains (Table 5.1.1) or for self-perceived measures of emotional and muscle tension (Table 5.1.2). The P-value for emotional tension approached significance at 0.059, so the results for this variable may represent a type-2 statistical error. Additionally no significant gender differences were observed at baseline or following treatment.

In the time domain, the results show that MTPT caused an overall decrease in heart rate as indicated by an increase in average R-R interval length ($P < 0.01$). (Table 5.1.1). SDNN increased by 26.8% ($P < 0.01$), RMSSD by 46.8% ($P < 0.01$) and pNN50 by 55.8% ($P < 0.01$) following MTPT. There were no significant changes observed in the time domain measures in the control group. (Table 5.1.1).

In the frequency domain a 73.5% increase was observed in TP ($P < 0.01$) along with an 84.5 % increase in VLF power ($P = 0.03$) and a 90% increase in HF power ($P = 0.02$). No significant changes in LF power were seen in both groups. A 17% decrease in LF to HF ratio ($P = 0.04$) was observed in the massage group. There were no significant changes in the control group for any frequency domain measures (Figure 5.1).

Additionally there was a 39% reduction in muscle tension and emotional state improved by 32% following MTPT ($P < 0.01$) (Table 5.1.2). No significant differences were observed in the control group for muscle or emotional tension. In the massage group systolic blood pressure was significantly reduced ($P = 0.02$), as was diastolic blood pressure ($P = 0.01$).

DISCUSSION

To the best of the author's knowledge this is the first study to examine the effects of myofascial trigger-point massage therapy to the head neck and shoulders using HRV analysis to measure cardiac autonomic tone. The results of the study suggest that MTPT to the head, neck and shoulder areas for 20 minutes is highly effective in increasing HRV and cardiac parasympathetic activity in normal subjects. This is demonstrated in the time domain by a decrease in heart rate, and an increase in SDNN, RMSSD and also pNN50. In the frequency domain this is demonstrated by an increase in TP and HF power and a reduction in LF/HF ratio.

A simple decrease in heart rate by itself may be considered a sign of relaxation although the exact mechanisms causing the decrease would be unknown. An increase in parasympathetic activity or a decrease in

TABLE 5.1.1

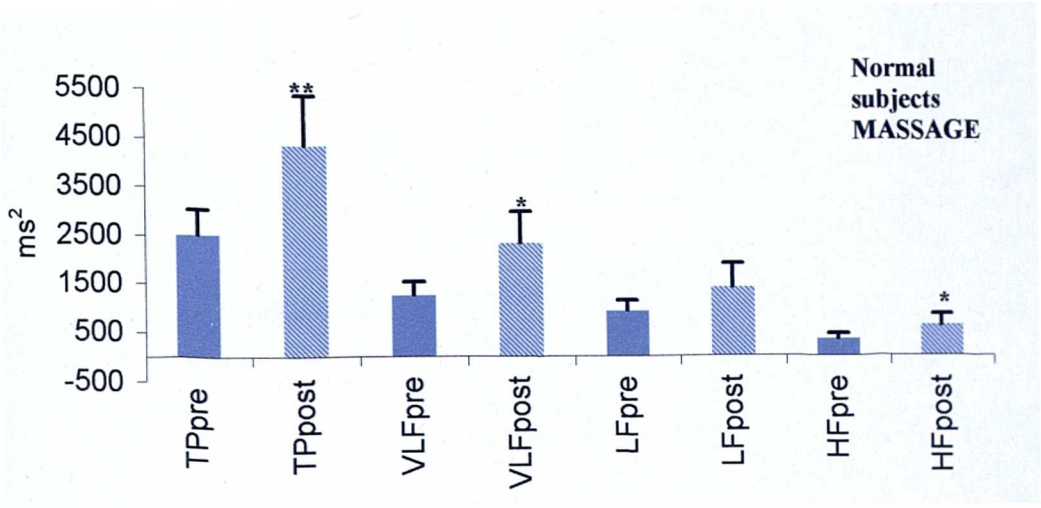
Means, standard errors, and P-values for time and frequency domain variables.

Variable	Units	Experimental Group					Control Group				
		Baseline		Post-MTPT			Baseline		Postrelaxation		
		M	SE	M	SE	P-value	M	SE	M	SE	P-value
R-R interval	ms	845	25.5	918	31.6	<0.01	825	27.4	848	26.1	0.12
SDNN	ms	60.8	5.3	77.1	7.2	<0.01	58.6	5.2	62.9	6.1	0.15
RMSSD	ms	36.5	4.1	53.6	7.0	<0.01	32.3	4.0	32.3	4.6	0.99
pNN50	ms	5.2	1.5	8.1	2.0	<0.01	6.0	1.4	5.5	1.3	0.34
Total power	ms^2	2485	521	4311	1011	<0.01	2490	612	2947	592	0.12
Very low frequency power	ms^2	1248	280	2303	638	0.03	1195	321	1508	290	0.15
Low frequency power	ms^2	910	221	1390	489	0.12	1003	286	1177	335	0.16
High frequency power	ms^2	327	121	618	219	0.02	292	75	262	49	0.49
LF/HF ratio (log transformed)	~	1.52	0.28	1.26	0.26	0.04	1.36	0.21	1.49	0.23	0.43

TABLE 5.1.2

Means, standard errors, and P-values for emotional tension, muscle tension and blood pressure.

Variable	Units	Experimental Group					Control Group				
		Baseline		Post-MTPT			Baseline		Postrelaxation		
		M	SE	M	SE	P-value	M	SE	M	SE	P-value
Self-perceived muscle tension	mm	41	3.0	25	4.4	<0.01	35	5.0	33	3.1	0.27
Self-perceived emotional tension	mm	47	3.2	32	3.9	<0.01	38	5.2	35	3.4	0.49
Systolic blood pressure	mmHg	125	3.5	119	3.4	<0.02	122	2.7	120	2.7	0.06
Diastolic blood pressure	mmHg	79	5.2	79	2.3	0.01	76	2.9	74	2.5	0.14



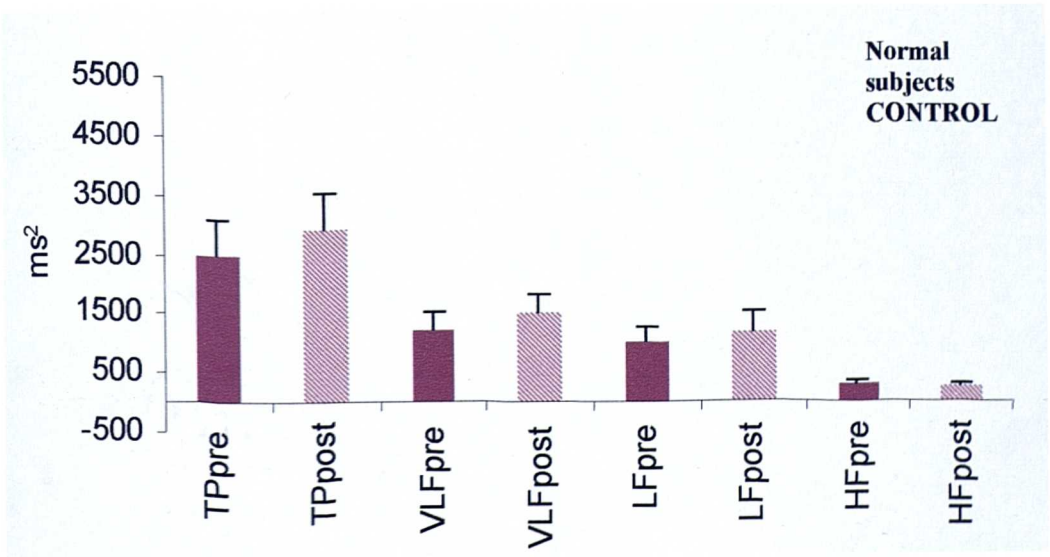


Figure 5.1 Frequency domain values for total power (TP), very low frequency (VLF), low frequency (LF) and high frequency power (HF) at baseline (pre) and following experimental (massage) and control (relaxing) conditions. * = $P < 0.05$, ** = $P < 0.01$.

sympathetic activity would cause a decreased heart rate. The purpose of using analysis of HRV is to try to determine the exact change in sympathovagal balance.

It is generally accepted that the power of the HF oscillations found between 0.15 to 0.4 Hz, is an indirect marker of efferent parasympathetic (vagal) input to the heart. In this study, following MTPT, a significant increase in HF power was observed. An increase in parasympathetic nervous system activity has been associated with the relaxation response (Benson *et al.* 1974).

In the range between 0.04 - 0.15 Hz there was a non-significant increase in LF power following treatment. The LF range is generally accepted as a marker of sympathetic nervous system activity associated with fluctuations around 0.1Hz corresponding to blood-pressure control oscillations known as Mayer waves (Pomeranz *et al.* 1985).

Increases in both LF and HF power have been reported following sensory stimulation by acupuncture needling (Haker *et al.* 2000). Sensory stimulation in healthy persons may be associated with changes in both the sympathetic and parasympathetic nervous system depending on the site of stimulation. This may account for the increases in both LF and HF power in the present study, although the increase in HF power is significantly greater following MTPT. Hence, the reduction in LF/HF ratio seen in this study ($P = 0.04$) again suggests a shift toward cardiac parasympathetic activity.

Interestingly, the VLF component, which is generally associated with thermoregulatory mechanisms (Hyndman *et al.* 1971) and the renin-angiotensin system (Akselrod *et al.* 1985), shows a significant increase

following MTPT. Previous studies in humans have shown that the VLF component may be mediated by cardiac parasympathetic activity (Taylor *et al.* 1998), therefore the significant increases in HF power following MTPT may have mediated the increase in VLF power. Care must be taken in the interpretation of these results as only a 5-minute data acquisition period was used in this present study. Further investigation using longer recording periods is needed to explore this particular area of research.

In this study MTPT was also shown to be effective in significantly reducing both SBP ($P = 0.02$) and DBP ($P = 0.01$). Felhendler & Lisander (1999) have demonstrated that non-invasive stimulation of acupressure points also significantly influences the cardiovascular system by reducing SBP, DBP and heart rate.

As previously mentioned, acupressure points and MTrP are thought to represent the same phenomena and the techniques used in this study may be activating similar mechanisms to produce blood pressure reduction. It should be pointed out that in addition to deep focussed pressure at trigger-point sites, the massage procedure used in this study did additionally contain some general effleurage strokes. It has been previously shown that these less complicated massage procedures alone can be effective in lowering blood pressure (Cady & Jones 1997).

With reference to quality of life measures, subjects reported feeling less muscle tension and significant improvement in mood following MTPT. These findings are probably the result of an increased relaxation response and an overall reduction in the defence-arousal (stress) response and are possibly mediated by increased parasympathetic activity.

Although there was a non-significant difference in the groups at baseline, the values for emotional tension of P=0.059 recognises the possibility of type-2 error. This limitation is appreciated and future studies would benefit from larger group sizes or matching baseline groups for psycho-physiological variables. A further limitation to this study is that any effect could potentially be due to some type of exchange between the therapist and the subject, irrespective of MTPT. Sham treatments to control for this effect have been incorporated in subsequent studies and it is recommended that future researchers consider a sham massage, perhaps using unskilled or random massage, avoiding myofascial trigger points. The limited number of blood pressure measurements may limit the conclusions. Regular measurements using a pressure cuff could be a confounding variable because of the level of discomfort. Future studies would be advised to take more frequent recordings using a less intrusive system such as a finger cuff.

The present study shows that MTPT is a safe, non-invasive technique that is effective in inducing a relaxation effect in normal subjects. It is a relatively simple technique to learn and under correct instruction could be taught to the partners or spouses of patients who could benefit from massage therapy.

It is imprudent to generalise from a healthy population to those with disease processes. However certain conditions are characterised by increased sympathetic tone and reduced HRV. It is possible to speculate that these conditions could show a relaxation response following massage that may benefit the sympathovagal balance.

Patients who may benefit include those recovering from a myocardial infarction (MI). These patients are usually in a high state of anxiety and tension and generally have increased sympathovagal tone as the result of reduced cardiac parasympathetic activity (Task Force 1996). Heart failure patients also have reduced HRV and increased levels of stress as indicated by increased levels of circulating catecholamines (Saul *et al.* 1988). MTPT could help reduce stress and improve autonomic function by increasing HRV and parasympathtic activity.

Patients with uncomplicated essential hypertension may be another group that could benefit from the effects of MTPT. These patients have elevated blood pressure and increased sympathovagal balance (Manolis *et al* 1995; Guzzetti *et al.* 1988). In previous studies, treatment using beta-blockade (Liao *et al.* 1996) and ACE inhibitors (Kontopoulos *et al.* 1997) has been shown to improve prognosis in these patients. MTPT may prove a useful adjunct to conventional treatment by enhancing cardiac vagal tone and leading to restoration of sympathovagal balance.

A further group who may benefit from MTPT are diabetic patients with autonomic neuropathy. These patients commonly have reduced autonomic function as indicated by decreased HRV (Mackay *et al.* 1980). They may also have pain as the result of peripheral neuropathy, thereby increasing levels of stress and anxiety thus further exacerbating the condition. Additional studies using MTPT in these patient groups need to be performed to confirm these hypotheses (see next section 5.2).

5.2 THE ACUTE EFFECTS OF MYOFASCIAL TRIGGER-POINT MASSAGE THERAPY ON SYMPTOMS AND HEART RATE VARIABILITY IN PATIENTS WITH CHRONIC PAINFUL DIABETIC NEUROPATHY

ABSTRACT

The purpose of this study was to investigate the short-term effects of myofascial trigger-point massage therapy (MTPT) on symptoms and cardiac autonomic tone using heart rate variability (HRV) in Type 2 diabetic patients with chronic painful neuropathy. Fifteen patients (9 male and 6 female), mean age 60.3 years (range 45 to 79 years) received MTPT and on a separate occasion listened to relaxing music for 30 minutes. Eight received MTPT first. Self-evaluation of muscle tension (MT), emotional state (EMOT) and pain, using 100mm visual analogue scales; systolic (SBP) and diastolic (DBP) blood pressures and HRV were assessed before and after each intervention. HRV was measured in the time and frequency domains using standard deviation of inter-beat intervals (SDNN) and an autoregressive model respectively. Analysis of the results showed that MT, (43 to 24, $P = 0.001$), EMOT, (46 to 21, $P = 0.001$) and pain scores (36 to 23, $P = 0.02$) all improved following MTPT but relaxation music only improved EMOT, (42 to 29, $P = 0.02$). Both relaxation music and MTPT lowered mean SBP (146 to 138 mmHg $P = 0.01$ and 144 mmHg to 133 mmHg, $P = 0.002$ respectively). Mean DBP was lowered by MTPT only, (87 to 82 mmHg, $P = 0.02$). MTPT increased mean R-R interval (786 to 820 ms, $P < 0.003$) and HRV to a greater extent than music (mean SDNN: music from 21 to 26 ms, $P = 0.04$, MTPT: 22 to

29 ms, P = 0.002) indicating increased cardiac vagal activity. In the frequency domain total (TP) and very low power (VLF) increased with MTPT (TP: 588 to 1026, P = 0.02, VLF: 400 to 770, P = 0.01) but music only increased VLF power (VLF: 392 to 704, P = 0.05). MTPT is more effective at reducing pain, muscle tension and emotional tension in patients with painful diabetic neuropathy compared to music therapy. These changes are associated with a cardiovascular relaxation response. MTPT might be a useful adjunct to other modalities for the treatment of painful diabetic neuropathy.

INTRODUCTION

Diabetic neuropathy is a common complication of diabetes. It is associated with considerable morbidity such as painful polyneuropathy or neuropathic ulceration and increased mortality (Vinik *et al.* 2000). Autonomic neuropathy is often associated with reduced heart rate variability (HRV), impaired haemodynamics and impaired activation of the baroreflex loop resulting in poor blood pressure regulation (Weck *et al.* 1997). The pain associated with painful diabetic neuropathy can last for many years and severely impair quality of life (Benbow & MacFarlane 1999).

Therapeutic massage involves manipulation of soft tissue areas to bring about generalized improvements in health (Vickers & Zollman 1999). In its various forms it has been shown to reduce blood pressure Cady & Jones 1997), facilitate relaxation (Labyak & Metzger 1997), reduce muscle tension (Nordschow & Bierman 1962) and reduce anxiety and depression (Weinberg & Hunt 1979, Field et *al.* 1996). Furthermore following massage therapy, patients have reported reduction in pain and increases in feelings of warmth and well being (Kaada & Torsteinbo 1989, Ferrell-Torry &Glick 1993, Nixon *et al.* 1997)

More specifically, myofascial trigger point massage therapy (MTPT) is an advanced neuromuscular procedure that is commonly used in sports medicine for the treatment of pain and muscle tension following injury or other trauma (Peppard 1983). Myofascial trigger points (MTrP) are small discrete hyperirritable areas within a taut band of muscular tissue or fascia. They are painful on compression and can evoke characteristic referred pain in areas far

away from their actual location (Travell & Simmons 1983). MTrP are classified as either active or latent and are commonly seen in both health and disease. Active MTrP cause pain but latent MTrP are painless and often cause restriction of movement and weakness in affected muscles. Active MTrP most commonly occur in the postural muscles of the neck, shoulder, and pelvic girdles. The upper trapezius, scalene, sternocleidomastoid, levator scapulae and quadratus lumborum muscles are also often involved.

MTrP are commonly activated directly by acute overload, overwork fatigue and direct trauma and can be indirectly activated by visceral disease and emotional distress (Travell & Simons 1983). They are found by palpation as sharply circumscribed spots of exquisite tenderness and moderate sustained pressure causes or intensifies pain. The pain referred from MTrP does not follow a simple segmental or neurological pattern, nor does it follow the known patterns for referred pain of visceral origin. Stimulation of MTrP can cause changes within the peripheral autonomic nervous system such as local excessive perspiration, piloerection, local vasodilation, and erythema (Travell & Simons 1983).

Treatment of MTrP includes ischaemic compression, which is firm digital pressure applied to the MTrP until tenderness disappears, deep stroking and kneading massage. Other treatments include stretch-and spray procedures using vapocoolants, application of moist heat, ultrasound and acupuncture (Travell & Simons 1983). There is a high degree of correspondence (71%) between MTrP and acupuncture points associated with pain and brief, intense stimulation of

MTrP frequently produces prolonged relief of pain (Melzack *et al.* 1977). Needling of acupuncture points has previously been shown to be effective in treating patients with chronic painful diabetic neuropathy (CPDN) (Abuaisha *et al.* 1998). In combination with exercise, MTPT reduces the number and intensity of MTrP and is effective in treating MTrP in the neck and shoulder areas (Gam *et al.* 1998).

Analysis of HRV is a sensitive, non-invasive, technique, which can be used to identify cardiac autonomic disturbances, such as in the early sub-clinical detection of autonomic dysfunction in diabetes mellitus (Pagani *et al.* 1988) and following myocardial infarction (Kleiger *et al.* 1987). HRV analysis has also been used to assess changes in sympathovagal tone in various mental (Carney *et al.* 1995) and emotional states (McCraty *et al.* 1995, Rechlin *et al.* 1994).

The purpose of this study was to investigate the short-term effects of MTPT to the abdomen, head, neck and shoulder areas on symptoms in Type 2 diabetic patients with CPDN and also, using HRV analysis, to measure the effects of massage on cardiac autonomic tone.

METHOD

Participants

Fifteen type 2 diabetic patients 9 male and 6 female, with a mean age 60.3 years (range: 45 to 79 years), mean duration of diabetes 6.9 years, with chronic painful neuropathy were recruited from an adult hospital diabetic clinic (Table. 5.2.1). All subjects had typical neuropathic pain such as tingling, burning and shooting

TABLE 5.2.1

Basic demographic details of the fifteen patients (mean ± SE).

n	15
Age (years)	60.3 (2.6) range 45 to 79
Sex (M/F)	9/6
BMI	30.0 (0.9)
Years of diabetes	6.9 (0.7)
Years of pain	3.7 (0.5)
VAS (mm)	30.5 (5.1)
HbA1c (%)	7.9 (0.5)
Retinopathy	7 (3 laser-treated)
Diabetes treatment	
Diet only	1
OHA	14

VAS, visual analogue pain score; OHA, oral hypoglycaemic agents.

pain, often with nocturnal exacerbation, for at least 12 months, principally affecting the lower limbs. All subjects had reduced perception of pressure using a 10g monofilament (5.07 Semmes-Weinstein) on the plantar surface of the foot (Kumar *et al.* 1991). They had received past treatment for painful diabetic neuropathy but at the time of the study only 12 were taking medication for pain (six tricyclic antidepressants, five NSAIDs and one benzodiazepine). Other medications taken by patients included ACE-inhibitors (4), beta-blockers (2), alpha-blocker (1), calcium channel blocker (1) and nitrates (1). Subjects were excluded if they had uncontrolled hypertension or atrial fibrillation.

Protocol

On the morning of the study, subjects omitted both their breakfast and all morning medication and refrained from smoking, drinking tea, coffee or other caffeine containing substances. During HRV recording they were asked to refrain from making any exaggerated body movements or intentionally altering their respiration. Following baseline recordings, patients were randomized, by alternate allocation, to receive either MTPT to the abdomen, head, neck and shoulder areas or listened to a compilation recording of relaxing music. One-week later subjects received the alternate therapy and acted as their own controls. During music therapy subjects listened to relaxation music through cushioned headphones. For the first ten minutes they lay supine on a massage bed and for a further twenty minutes they listened to the music sitting in an upright chair. This replicated the posture of the massage. The volume of music was adjusted to suit

individual requirements. The music included forest sounds, a recording of a canoe gently paddled on a lake, various types of birdsong and rainwater falling; all of these sounds were accompanied with gentle background instrumental music.

Massage procedure

The massage procedure used in this study was similar to that described in Section 5.1 and 2.8, except that following baseline recordings, subjects were massaged for the first ten minutes while lying supine on a massage bed and then for the remainder of the massage they were seated in an upright chair. The massage procedure in this study incorporated deeper more focused pressure and circular frictions to MTrP of the diaphragm and abdomen and lasted for 30 minutes.

HRV and blood pressure measurement

Data acquisition took place as described in Section 2.2.3, between 09.00h and 11.30h in a quiet warm, temperature- controlled environment (22 - 24°C).

Systolic and diastolic blood pressure recordings were also taken at baseline and following treatment using an automated blood pressure recorder (Omron Healthcare, Europe). They were measured on three occasions on the right arm, one minute apart and the mean of the results was recorded.

Self-reports of emotional state, feelings of muscle tension and pain scores were measured before and after treatment using a 100mm visual analogue scale (VAS) as described in Section 5.1. VASs have been used previously in the

assessment of pain and following treatment in diabetic patients with painful neuropathy (Benbow *et al.* 1998, Hamza *et al.* 2000, Somers & Somers 1999). Metabolic control was assessed by glycated haemoglobin. (HPLC, Menarini, Italy).

The local Ethics Committee approved the study and written informed consent was obtained from all participants. All subjects were given the opportunity to bring a friend or spouse, or a chaperone was available if requested.

Data analysis

As previously described in General Methodology section 2.3.

Statistical analyses

All variables were tested for normality using the Kolmogorov-Smirnov test. A repeated measures t-test was used to compare values before and after treatment and also to compare baseline values. The LF/HF ratios did not have normal distribution and therefore were analyzed using the Mann-Whitney U-test. A two-tailed probability of $P < 0.05$ was considered statistically significant.

RESULTS

Of the 15 patients who took part in the study eight received massage therapy first and seven received music first. At baseline there were no statistically significant differences between the treatment groups for self-perceived measures of pain, muscle tension, emotional tension, and blood pressure (Table 5.2.2) or for any

TABLE 5.2.2

Means, standard errors, and P-values for time and frequency domain variables.

Variable	Units	Experimental Group					Control Group				
		Baseline		Post-MTPT			Baseline		Postmusic		
		M	SE	M	SE	P-value	M	SE	M	SE	P-value
R-R interval	ms	786	34	820	40	0.003	817	29	823	29	NS
SDNN	ms	21.6	2.9	29.3	3.5	0.002	20.9	2.7	26.1	3.0	0.04
RMSSD	ms	15	3.9	14.7	3.2	NS	11.8	1.9	12.1	2.1	NS
pNN50	ms	1.9	1.5	1.5	0.8	NS	0.4	0.2	0.3	0.1	NS
Total power	ms^2	588	133	1026	269	0.02	558	134	914	268	NS
Very low frequency power	ms^2	400	94	770	196	0.01	392	89	704	200	0.05
Low frequency power	ms^2	85	23	131	36	NS	97	24	136	43	NS
High frequency power	ms^2	103	44	124	56	NS	70	25	74	35	NS
LF/HF ratio	~	2.8	0.8	3.4	1.0	NS	3.0	0.6	3.2	0.6	NS

LF =low frequency, HF = high frequency

TABLE 5.2.3

Means, standard errors, and P-values for emotional tension, muscle tension, pain scores and blood pressure.

Variable	Units	Experimental Group					Control Group				
		Baseline		Post-MTPT			Baseline		Postmusic		
		M	SE	M	SE	P-value	M	SE	M	SE	P-value
Self-perceived muscle tension	mm	43	6.2	24	5.6	0.001	39	7.1	35	6.5	NS
Self-perceived emotional tension	mm	46	6.8	21	4.8	0.001	42	8.2	29	5.8	0.02
Self-perceived pain	mm	36	5.5	23	4.9	0.02	25	3.8	21	3.9	NS
Systolic blood pressure	mmHg	144	4.3	133	4.8	0.002	146	5.9	138	6.5	0.01
Diastolic blood pressure	*mmHg*	*87*	*2.5*	*82*	*2.0*	*0.02*	*87*	2.6	86	2.6	NS

variables in the time and frequency domains of HRV (Table 5.2.3). Additionally no significant differences were observed at baseline or following treatment between males and females for all variables.

Following MTPT self-perceived measures of pain showed a significant reduction of 36% ($P = 0.02$), muscle tension (MT) was reduced by 44% ($P = 0.001$) and emotional state (EMOT) improved by 54% ($P = 0.001$). Following music therapy, only EMOT showed significant improvement, reducing by 31% ($P = 0.02$). Massage reduced systolic blood pressure (SBP) by 11mmHg ($P > 0.002$) and diastolic blood pressure (DBP) fell by 5mmHg ($P = 0.02$), but only SBP showed a significant reduction of 8mmHG ($P = 0.01$), after music therapy. In the time domain MTPT caused an overall decrease in heart rate as indicated by an increase in average R-R interval length ($P = 0.003$) (Table 5.2.3) and SDNN increased by 36% ($P = 0.002$). Following music there was no significant change in heart rate but SDNN increased by 25% ($P = 0.04$). Within the frequency domain following MTPT, a 74% increase was observed in TP ($P = 0.02$) together with a 93% increase in VLF power ($P = 0.01$). Following music there was a non-significant increase of 64% for TP ($P = 0.06$) and a significant increase of 80% for VLF power ($P = 0.05$)(see Figure 5.2). No significant changes were observed for LF, HF and LF/HF ratio following massage or music.

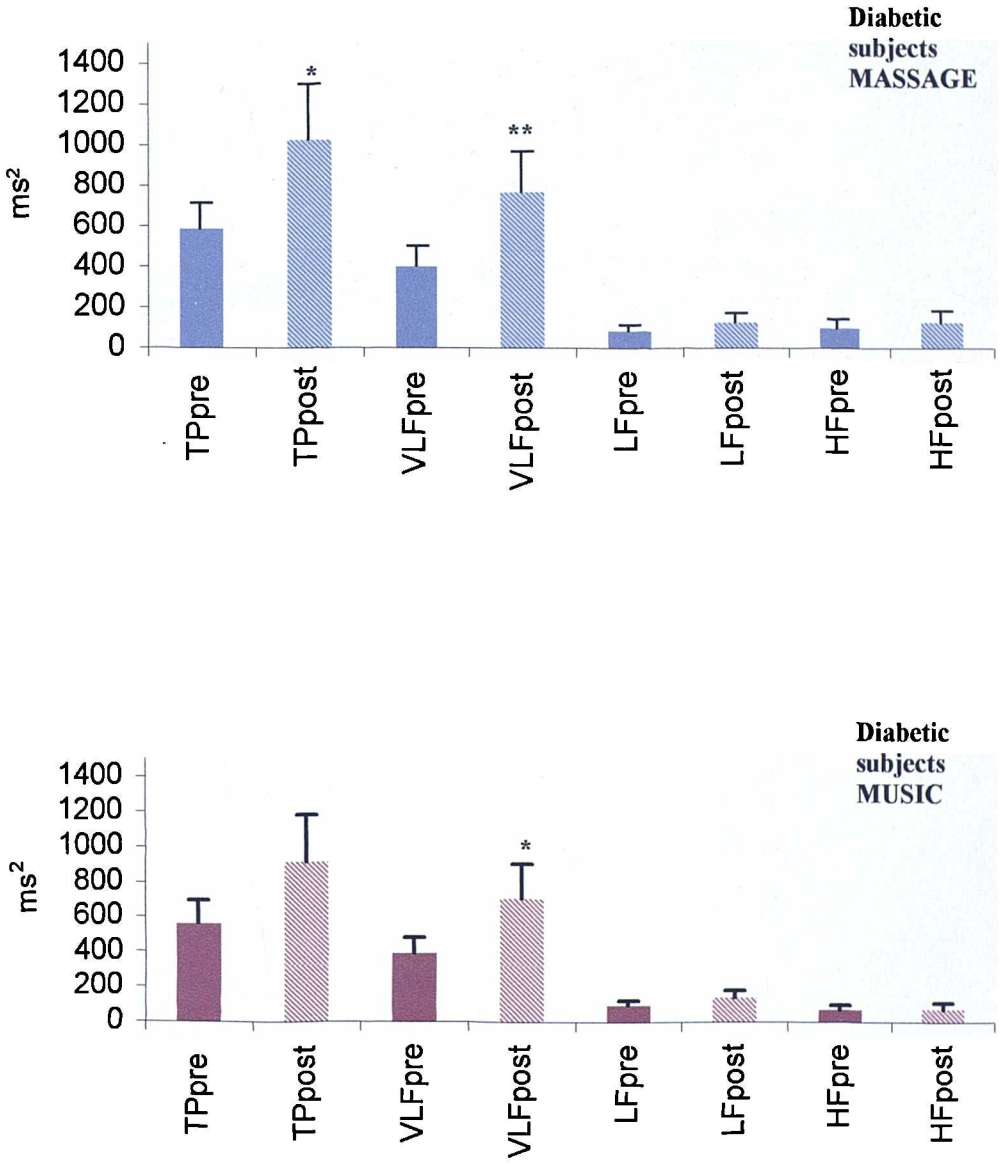


Figure 5.2 Frequency domain values for total power (TP), very low frequency (VLF), low frequency (LF) and high frequency power (HF) at baseline (pre) and post massage and music conditions. * = $P < 0.05$, ** = $P < 0.01$.

DISCUSSION

Chronic painful diabetic neuropathy is often difficult to treat, is distressing for the patient and reduces quality of life (Benbow & MacFarlane 1999, Galer *et al.* 2000). In this study there was a reduction in pain and muscle tension and significant improvement in mood following massage. The changes seen in heart rate variability suggest that these benefits are related to increased parasympathetic activity, which may reflect an overall reduction in stress associated with the relaxation response. The feelings of warmth and well being, experienced by some of the subjects have been described previously following therapeutic massage and have been associated with increases in ß-endorphin concentration (Kaada & Torsteinbo 1989). Whether similar mechanisms are activated following MTPT is unknown but may warrant further investigation.

Heart rate is modulated by the synergistic action of the sympathetic (SNS) and parasympathetic (PNS) branches of the autonomic nervous system (ANS). Heart rate was significantly reduced following massage, but not following music. Both massage and music caused an overall increase in ANS activity as shown by increases in SDNN, which is generally used as the primary measure of HRV in the time domain (Task Force 1996). Massage increased SDNN by 36% and music by 25%. Unexpectedly no significant differences were observed for either RMSSD or pNN50 following MTPT or music therapy. These variables represent rapid variations in heart rate generally associated with PNS activity. In a previous study examining the effect of trigger point massage to the head, neck and shoulders in healthy subjects significant increases in RMSSD and pNN50

following were observed following massage (Delaney *et al.* 2002). It is possible that autonomic neuropathy associated with diabetes may have lessened the expected effect of relaxation and massage on these time domain variables.

All of the subjects who participated in the study suffered with painful peripheral symptoms, principally in the lower extremities. MTrP were detected in all patients but the number, intensity and locations differed from person to person. This study was carried out to assess physiological responses to MTPT and to measure the associated symptomatic changes and effect on the ANS. The areas of massage used were chosen because experience has shown that patients with chronic painful conditions, such as painful diabetic neuropathy, tend to adopt characteristic postures to lessen the effects of pain. In time, this can lead to chronic muscle tension and postural abnormalities, further exacerbating the underlying condition. Abdominal massage a frequently used therapy to induce relaxation was included. Diabetic patients occasionally experience abdominal discomfort (Chan *et al.* 1990) and experimentally produced diabetes has been shown to increase abdominal muscle tension in animal models (Krishnamurthy *et al.* 1992). The massage therapy consisted of deep, focussed pressure at myofascial trigger-point sites in combination with general massage strokes. Therefore it was not possible to specify which particular type of massage had the most effect. Future studies are needed to investigate the effect of stimulation at specific trigger-point sites.

Within the frequency domain the increase in HRV following MTPT was indicated by a 74% significant increase in total power (the sum of all power

frequencies). An increase in HRV indicates an increase in ANS activity (Task Force 1996). Following music a similar increase of 64% was also observed but this did not reach statistical significance.

The HRV power spectrum is usually divided into three frequency ranges or bands. The VLF band below 0.04 Hz is influenced by the renin-angiotensin system, peripheral vasomotor function and chemoreceptor activity (Ori *et al.* 1992). In this study significant differences were observed in VLF following both MTPT and music. Previous studies in humans have suggested that the VLF component may also be partly mediated by cardiac vagal activity (Taylor *et al.* 1998), therefore the significant increases in VLF could be associated with increased parasympathetic activity, independent of the HF band and may be related to an increased relaxation effect. Previously the author has demonstrated a significant increase in the VLF component following massage in non-diabetic subjects following MTPT to the head neck and shoulders (Delaney *et al.* 2002)

The LF range, between 0.04 - 0.15 Hz, is under both SNS and PNS control and is influenced by the baroreceptor reflex arc. The power of the HF oscillations found between 0.15 - 4.0 Hz corresponds to the heart rate variations related to the respiratory cycle. This is referred to as respiratory sinus arrhythmia (RSA) and is considered to reflect efferent vagal input to the heart (Ori *et al.* 1992). Following massage and music there were non-significant increases in both LF and HF power (Table 5.2.3).

In this study MTPT was also shown to be effective in significantly reducing both SBP ($P = 0.002$) and DBP ($P = 0.02$). A previous study, in healthy

male subjects, demonstrated that non-invasive stimulation of acupressure points also significantly influences the cardiovascular system by reducing SBP, DBP and heart rate indicating an increase in vagal tone (Felhendler & Lisander 1999). However whether the techniques used in this study activate similar mechanisms to acupuncture to produce blood pressure reduction is unknown. It should be pointed out that in addition to deep focussed pressure at myofascial trigger-point sites, the massage procedure used in this study did additionally contain general effleurage strokes. Previously it has been shown that these less complicated massage procedures alone can be effective in lowering blood pressure in normal subjects (Cady & Jones 1997). Music also reduced SBP ($P = 0.01$) but not DBP.

The results when taken as a whole indicate that MTPT and to a lesser degree music are effective in producing a relaxation effect and a reduction in pain in subjects with painful diabetic neuropathy. This is associated with an increase in parasympathetic activity and a reduction in sympathetic drive, but exact mechanisms leading to improvements in pain are still unclear. With the exception of one male patient who found the massage to be uncomfortable because of increased contact sensitivity, most of the subjects enjoyed both the massage and music interventions and wanted further sessions. MTPT is a relatively simple technique to learn and under correct instruction and circumstances could be taught to the partners or spouses of patients who could benefit from massage therapy. It may be useful to help treat neuropathic pain in diabetic subjects. Further studies are now indicated to assess whether MTPT and

music result in sustained symptomatic improvement in diabetic neuropathy and whether the effects of MTPT and music have an additive effect.

The present study indicates that MTPT effectively reduces pain, muscle tension and emotional tension in patients with painful diabetic neuropathy whereas music therapy is only effective at reducing emotional tension. These changes are associated with a cardiovascular relaxation response. It is possible that MTPT administered at home might be a useful adjunct to other modalities for the treatment of painful diabetic neuropathy.

5.3 Acute Effects of Sympathetic Nerve Blockade on the Time and Frequency Domains of Heart Rate Variability in Patients with Chronic Refractory Angina.

Abstract

Blockade of the sympathetic nervous system is a commonly used technique for pain relief in many disease states. Usually, patient's subjective evaluation of pain and the observation of various clinical signs determine the success of blockade. Time and frequency domain analysis of heart rate variability (HRV) is a simple, non-invasive measure of cardiac sympathetic and parasympathetic nervous system activity. The purpose of this study was to use analysis of HRV to measure the effects of various nerve blocks on cardiac autonomic tone in patients with chronic refractory angina. Nineteen subjects (14M, 5F, age 59.7 ± 7.1) took part in the study. Twelve received left-sided stellate ganglion blockade, five received left suprascapular block and tworeceived paravertebral nerve blockade. In the group who received stellate ganglion blockade, there were no significant differences observed for any time and frequency domain variables of HRV when compared to baseline although there was an overall significant reduction in heart rate. This was demonstrated by an increase in mean cardiac interbeat (R-R) interval following treatment ($P < 0.01$). In the subjects who received suprascapular and paravertebral blockade the results were variable.

INTRODUCTION

Chronic refractory angina is a painful and debilitating disease, which causes considerable stress and can have profoundly damaging effects on the patient's quality of life (Chester *et al.* 2000). Pain and similar stressful behavioural states are characterised by organised neural responses of the somatomotor, somatosensory (analgesia), autonomic and neuroendocrine systems (Janig 1995). The pathogenesis of anginal pain involves activation of the afferent sympathetic nervous system (SNS) pathway and a frequent consequence of pain, especially when severe, is the activation of the 'fight or flight' response through SNS efferent activity. Therefore angina can be considered as the sensory component of a positive feedback loop. Blockade of sympathetic nerve conduction aims at permanent or temporary elimination of pain pathways conducted by the SNS (Weissenberg 1987). In this manner the angina relieving effects of sympathetic blockade might be due to interference with this maladaptive loop (Hammond *et al.* 2000a).

In two thirds of patients, cardiac sympathetic nerves relay at the stellate ganglion, and local anaesthetic injection at this level can alleviate angina (Hammond *et al.* 1999). In the remainder, the connections are mostly at a lower thoracic level and in these patients paravertebral blockade is considered appropriate (Hammond *et al.* 2000b). Blockade at the stellate ganglion is an established and highly effective diagnostic and therapeutic procedure for management of certain acute and chronic pain syndromes. Positive clinical signs such as changes in skin coloration or temperature, Horner's phenomenon (ptosis, miosis and enopthalmosis) or Guttman's sign (engorgement of the nasal mucosa) usually determine its efficacy. These

signs alone do not necessarily indicate complete blockade (Ackerman & Ahmed 2000).

The purpose of this study was to determine the effects of various sympathetic nerve blocks on cardiac autonomic tone as measured by analysis of HRV.

METHOD

Participants

Twenty-one patients (16M, 5F, age 59.7 ± 7.1, mean ± SD) with chronic refractory angina took part in the study. On the morning of the study they were asked to have a light, early breakfast and then to remain fasted until they had been treated. Written informed consent was obtained prior to treatment.

Protocol

The stellate ganglion procedure was performed with the patients reclined to 20° – 30° on an examination couch with a pillow behind the head in the central 'sniff the morning air" position. A peripheral cannula was sited to ensure intravenous access. The mouth was slightly open to prevent swallowing and possible oesophageal or pharyngeal trauma. The transverse process of C6 was identified and a standard long bevelled 21G needle, isolated by a piece of manometer tube was advanced to the bone. Following negative aspiration, 15ml of plain 0.5% bupivicaine were injected with repeated check aspirations every three to four ml. During the procedure the patient was fitted with a pulse oximeter and a Polar HR monitor to collect data for HRV analysis (see Section 2.2.3). A full resuscitation trolley and two

fully qualified medical practitioners, trained in advanced cardiac life support were on hand at all times.

After the equipment was fitted the patient was allowed to rest quietly for a five-minute period of readjustment. Following this a five-minute baseline R-R interval recording was taken immediately prior to the treatment and then as soon as treatment had finished. Also following treatment for 10 minutes, any signs of a Horner's syndrome along with Guttman's sign were noted. The study also investigated the effects of left-sided suprascapular block on five patients who had previously had unsuccessful stellate ganglion and a further two patients who received paravertebral nerve blockade. Pain relief was determined from patients self-report on their next visit to clinic.

Statistical Analyses

Data are given as mean ± standard error. All variables were normally distributed as determined using the Kolmogorov-Smirnoff test. A repeated measures t-test was used to compare pre- and post-treatment results. A two-tailed probability of $P < 0.05$ was considered statistically significant.

RESULTS

To ensure a clean signal, a visual inspection of the R-R interval tachogram from each patient was carried out and also in this way any change in R-R interval variability following treatment could be observed. Tables 5.3.1 and 5.3.2, report the means, standard errors and comparisons of means for all HRV variables patients who received stellate ganglion blockade and the suprascapular and paravertebral blocks. In the group of patients who received

left-sided stellate ganglion blockade a significant difference in heart rate (HR) as demonstrated by an increase in mean R-R interval length was observed following treatment ($p < 0.1$). No significant differences from baseline were observed for any other variables in both groups. Table 5.3.3 identifies the individual responses to selected nerve blocks.

DISCUSSION

Angina is a clinical syndrome characterised by discomfort in the chest, neck, jaw, shoulder or arm (Gibbons *et al.* 1999). The pain of angina is thought to be caused by stimulation of afferent sympathetic nerve fibres, however exact mechanisms still remain unclear. Blockade of sympathetic nervous system (SNS) conduction aims at permanent or temporary elimination of pain pathways conducted by the SNS (Weissenberg 1987). Evidence of complete blockade is considered to be essential for the efficient management of the patient with angina (Malmqvist *et al.* 1992) and clinical investigation alone is not thought to be reliable in the assessment of stellate ganglion blockade (SGB) (Schurmann *et al.* 2001). The main purpose of this study was to determine the efficacy of anaesthetic blockade of the SNS by investigating changes in sympathovagal status using time and frequency domain analysis of HRV. Furthermore, because the injection sites used in this study were similar to the treatment areas used for the myofascial trigger-point massage therapy (MTPT) investigations of Sections 5.1 and 5.2, the study was also conducted to investigate the likelihood of similar mechanisms of SNS reduction being responsible for the results. Sympathetic blockade has previously been shown

TABLE 5.3.1

Means, standard errors and comparison of means for all variables.

Variable	Units	Before treatment		Following treatment		
		M	SE	M	SE	P-value
Mean R-R interval	ms	979	57	1017	65	0.05
SDNN	ms	53	9.2	55	10.1	NS
RMSSD	ms	36	7.9	40	8.8	NS
pNN50	%	7.5	2.4	8.6	3.1	NS
Total power	ms^2	3498	1014	3820	1263	NS
Very low frequency power	ms^2	2116	506	2432	857	NS
Low frequency power	ms^2	833	330	887	341	NS
High frequency power	ms^2	557	273	500	171	NS
Normalised LF power	N.U.	65	5.2	57	4.9	NS
Normalised HF power	N.U.	35	5.2	43	4.9	NS
LF/HF ratio	~	3.1	0.9	1.7	0.4	NS

N.U. = normalised units, LF = low frequency, HF = high frequency.

TABLE 5.3.2

Means, standard errors and comparison of means for all variables.

Variable	Units	Before treatment		Following treatment		
		M	SE	M	SE	P-value
Mean R-R interval	ms	891	90	867	95	NS
SDNN	ms	36	7.1	34	6.5	NS
RMSSD	ms	17.6	4.5	13.9	3.8	NS
pNN50	%	1.3	1.1	0.3	0.3	NS
Total power	ms^2	2255	890	1611	643	NS
Low frequency power	ms^2	422	177	326	157	NS
High frequency power	ms^2	137	65	78	41	NS
Normalised LF power	N.U.	74	10.2	74	9.3	NS
Normalised HF power	N.U.	26	10.2	26	9.3	NS
LF/HF ratio	~	5.8	1.7	5.0	1.2	NS

N.U. = normalised units, LF = low frequency, HF = high frequency.

Table 5.3.3

Individual responses to autonomic nerve blockade.

No	Subject ID	Gender	Age	Nerve block	HR decrease	SDNN increase	RMSSD increase	TP increase	LF/HF decrease	Horners present	Guttmans present	Pain relief (weeks)
1	HD	M	65	L.Stellate	X	X	X	X	✔	✔	X	✔ 4
2	RT	F	72	L.Stellate	✔	X	✔	X	✔	✔	✔	✔ 4
3	GH	M	59	L.Stellate	✔	✔	✔	✔	✔	✔	✔	✔ 1
4	WL	M	67	L.Stellate	X	X	X	X	X	✔	X	X
5	CR	F	56	L.Stellate	✔	X	X	✔	X	✔	✔	X
6	MF	F	54	L.Stellate	✔	X	X	X	✔	✔	✔	✔ 8
7	JP	M	67	L.Stellate	✔	✔	✔	✔	X	✔	X	X
8	DMW	M	66	L.Stellate	X	X	X	✔	✔	✔	X	X
9	GR	M	65	L.Stellate	✔	✔	✔	X	✔	X	X	X
10	AS	M	62	L.Stellate	X	✔	✔	✔	✔	X	X	✔ 2
11	JR	M	57	L.Stellate	✔	✔	✔	✔	✔	✔	✔	✔ 1
12	AW	M	61	L.Stellate	X	X	X	X	✔	X	X	X
No	**Subject ID**	**Gender**	**Age**	**Nerve block**								
13	BD	M	55	PV	X	X	X	X	X	X	X	X
14	KV	M	53	PV	✔	X	X	X	✔	✔	X	X
15	MF	F	54	L. Suprascap	X	X	X	X	X	✔	✔	X
16	HL	F	52	L. Suprascap	X	✔	X	X	X	✔	✔	✔ 1
17	JP2	M	67	L. Suprascap	X	✔	X	X	X	X	X	X
18	RB	M	68	L. Suprascap	X	X	X	X	✔	✔	X	X
19	JWP	M	66	L. Suprascap	✔	X	X	X	X	~	~	~

L. stellate = Left stellate ganglion nerve blockade, PV = paravertebral blockade and L. suprascap. = Left suprascapular nerve blockade. X = no change or negative response. ✔ = positive response.

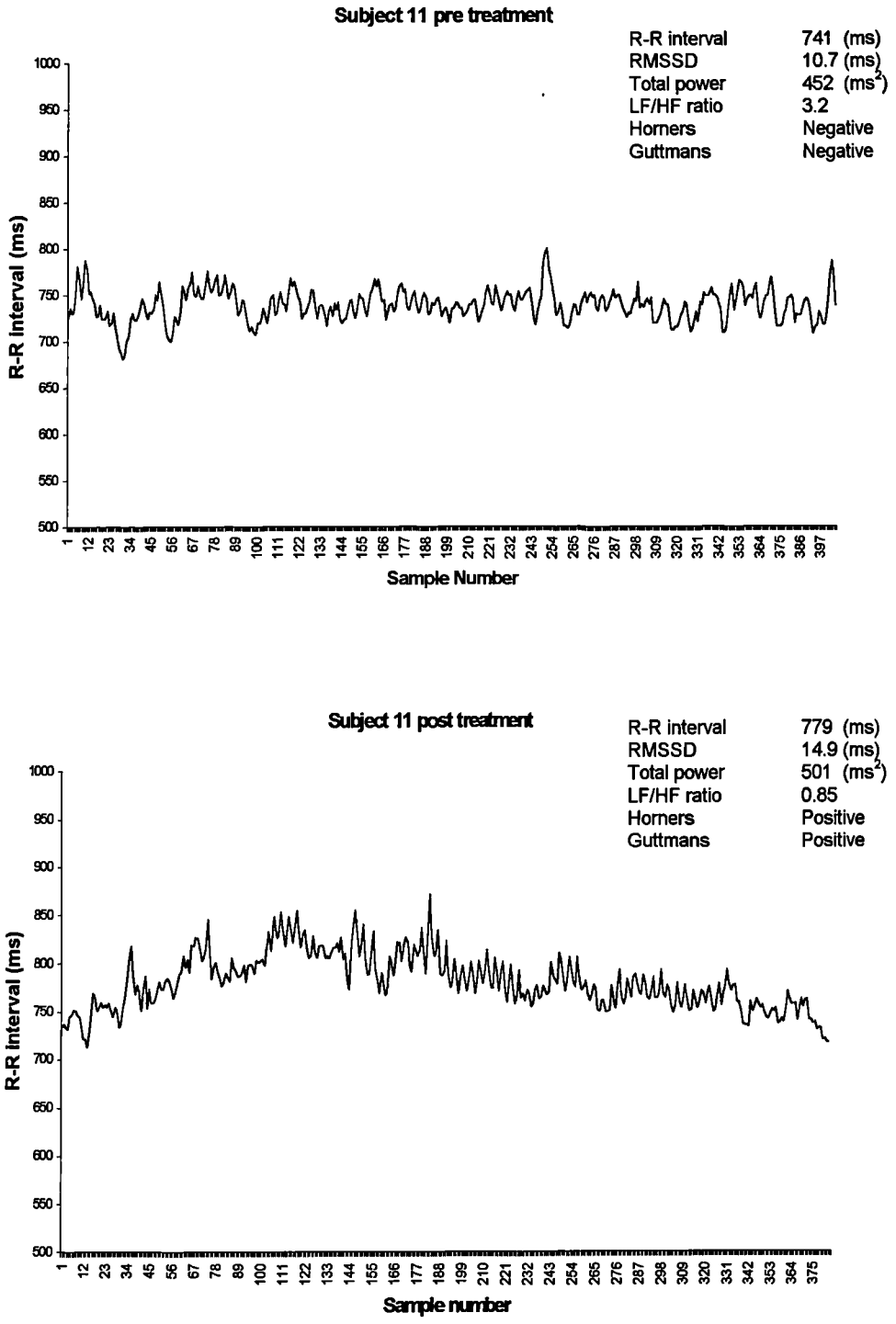


Figure 5.3 R-R interval tachograms before and 5-min immediately following left-sided stellate ganglion (cervicothoracic) blockade. Note the increased high frequency variability post-treatment, which along with the positive clinical signs (Horner's phenomenon and Guttman's sign) indicates complete sympathetic nervous system blockade.

to markedly reduce the number and intensity of myofascial trigger and tender points in patients with primary fibromyalgia (Bengtsson & Bengtsson 1988) therefore HRV analysis following sympathetic nerve block may provide further information on the mechanisms involved in MTPT.

To help the reader more fully appreciate this area of research a brief description of the sites of injection follows:

Stellate ganglion

The stellate ganglion is formed by the fusion of the inferior cervical and first thoracic ganglion and lies on the neck of the first rib extending to the transverse process of C7. The structures anterior to the ganglion include the skin and subcutaneous tissue, the carotid sheath and the sternocleidomastoid muscle (SCM). SCM often contains activated myofascial trigger-points (MTrp) and the pain and autonomic components, such as dizziness and visual disturbances (excessive lacrimation, ptosis and vascular engorgement), are widely recognised in the medical and particularly within the dental profession as a significant component of myofascial pain syndrome (Travell and Simons p203).

Suprascapular nerve

The suprascapular nerve is derived from the upper trunk of the brachial plexus and typically receives fibres from C5 and C6. It contains a high proportion of sympathetic nerve fibres which extend upwards to innervate the levator scapula and downwards and laterally to innervate the trapezius, supraspinatus and infraspinatus muscles. Suprascapular nerve block is commonly used in

the treatment of 'frozen shoulder' and is performed by needle insertion behind the lateral end of the clavicle at its junction with the insertion of the trapezius muscle. Ischaemic compression of MTrP in these areas is often used in MTPT to relieve shoulder pain and chronic muscle tension (see Sections 5.1 and 5.2 and Travell & Simons pp184-186 and p335).

Paravertebral nerve

Paravertebral somatic nerve blockade (PVB) is an old technique that was initially used as an alternative to spinal anaesthesia (Chan 1993). PVB are particularly advocated for unilateral surgical procedures and also provide excellent analgesia for rib trauma. In chronic pain management, they are used to treat benign or malignant neuralgia, in the management of complex regional pain syndromes with a sympathetic component and in the therapeutic control of hyperhydrosis (Richardson & Lonnqvist 1998).

The paravertebral space is a triangular area which contains the intercostal nerve (and its dorsal ramus), the rami communicantes and the sympathetic chain. Posteriorly is the costotransverse ligament, anteriorly the parietal pleura, medially the postero-lateral aspect of the vertebra and laterally the posterior intercostal membrane (Hammond *et al.* 2000b). Local anaesthetic injection into this space produces both a somatic and sympathetic block over several dermatomes (Cheema *et al.* 1995). In this study injection of 15 ml of 0.5% local anaesthetic was applied in the area of the transverse processes of T4 and T5. Active MTrP are often found in this and surrounding areas and are associated with the iliocostalis thoracis, mulitifidi and rotatores muscles.

There have been relatively few studies that have examined the effects of stellate ganglion blockade (SGB) on autonomic tone and of those that have investigated HRV the results have been inconsistent. In a study exploring the effects of right and left-sided SGB in young healthy volunteers, Fujiki *et al.* (1999) using 8 ml of mepivicaine during supine rest, showed that right sided SGB decreased both the LF and HF spectral components of HRV. The results indicate a reduction in both sympathetic and parasympathetic activity. In contrast left-sided SGB produced no significant effect on either LF or HF power. Neither technique produced any significant change in heart rate. In another study of 20 healthy male volunteers, Ikeda *et al.* (1996) injected 7 ml of mepivicaine into the left stellate ganglion and produced a significant *increase* in HR following anaesthetic injection. This was not observed in the control group who received saline-only injection into the left SGB. The results suggest that either sympathetic activity has increased or more likely, a reduction in parasympathetic activity has occurred causing the increased HR, presumably as the result of blockade of the cardiac vagal nerve.

In the present study 15ml of bipuvicaine were injected into the left stellate ganglion of the chronic refractory angina patients. This caused a significant *reduction* in HR as shown by a longer mean R-R interval ($P < 0.01$). This result is completely opposite to that seen in the study by Ikeda *et al.* (1996) described above. When the results of the present study are further broken down into time and frequency domain components although no significant changes were observed for any of the HRV variables there was a noticeable trend indicating a shift from sympathetic to parasympathetic predominance. This was demonstrated by a 45% reduction in LF/HF ratio,

which is an indicator of sympathovagal balance and by reductions in both absolute and normalised LF power and increases in absolute and normalised HF power. It is possible that larger subject numbers may have improved the statistical power of these results. The reason for the differences in results between the studies is not clear. The larger quantity of injectate used in this study may have produced a different autonomic effect and it also may be possible that there were neuro-anatomical differences in the angina patients compared with normal subjects. Further studies are needed to attempt to explain these differences.

Several of the other subjects involved in the study had previously received stellate ganglion blockade without success. They therefore received further nerve blocks in an attempt to improve their condition. Five received left suprascapular nerve block and two received paravertebral block. HRV and clinical signs were again monitored after injection. Three patients showed positive Guttman's and Horner's signs and of these only one patient reported any pain relief. The HRV results from this group were unremarkable and therefore no insight was gained with reference to autonomic effects and possible trigger-point mechanisms operating in these areas.

There are certain results that would be expected as the result of a complete sympathetic blockade. A successful treatment would cause increased parasympathetic activity which would be demonstrated by a reduction in HR, increased SDNN, RMSSD, TP (all measures of HRV associated with parasympathetic activity; see Section 1.6) decreased LF/HF ratio and positive Horner's phenomenon and Guttman's sign and reduction in pain. Figure 5.1 shows R-R interval tachograms from Subject 11,

immediately before and in the 5 minutes following injection. It will be observed that this patient achieved all results associated with a positive response and the change in R-R interval variation following SGB visually confirms these findings. Based on these variables a chart was constructed (Table 5.3.3) that shows the response to treatment for all patients.

From an observer's point of view it is important to mention that it was very noticeable that the techniques used in this study, especially stellate ganglion injection, appeared to be extremely uncomfortable and painful for the patient. This in itself would probably have caused the activation of the stress response resulting in increased sympathetic nervous system tone. When seen in this light, the overall reduction in HR and shift towards parasympathetic predominance is still more impressive.

In conclusion it can be said that a crude analysis of results revealed that there was a large variability in the response to these apparently stressful techniques. In general the HRV results demonstrate an overall reduction of sympathetic activity leading to a relative increase in cardiac vagal tone. It is also likely that a similar mechanism is operating and may be partly responsible for the positive effects of MTPT found in Sections 5.1 and 5.2.

CHAPTER SIX

CARDIAC REHABILITATION

General Overview of Chapter Six

The main purpose of the research of this chapter was to investigate the effects of an exercise-based, cardiac rehabilitation programme on cardiac autonomic tone. The effects of orthostatic stress were also explored, along with a comparison of aspects of HRV and functional measures during an exercise tolerance test. The Varia – Pulse TF 4 system, which uses a coarse-graining spectral analysis approach was used for the analysis of HRV to assess the sympathovagal profiles in patients at various stages of rehabilitation. The research was carried out at the Wirral Heart Support Centre (WHSC) and a brief description of this facility along with a description of the phases of cardiac rehabilitation is given below.

Wirral Heart Support Centre

The Wirral Cardiac Rehabilitation Service operates within Wirral Heart Support Centre at St Catherine's Hospital, Birkenhead, Merseyside. This establishment, which has strong research links with the University of Liverpool, specifically with the Departments of Medicine, Primary Care and Psychology, falls under the umbrella of the Wirral and West Cheshire Community Healthcare Trust (Odley 1997).

The unit accepts any patient who is suffering/has suffered from: uncomplicated myocardial infarction, recent cardiac surgery e.g. coronary artery bypass graft (CABG) or valve replacement; angina, hypertension, cardiomyopathy, stable heart failure or a significantly raised heart disease risk factor profile. Patients are referred to the service via one of five main routes:

- Wirral Hospital Trust (acute service)
- General Practitioners
- Regional Cardiothoracic Centre
- Health promotion/any other outside agencies
- Self-referral

Following an initial consultation where patients are fully informed on all aspects of the service, they are invited to take part in an initial five-week rehabilitation programme. This involves the patient attending the unit for one three-hour session a week for the five-week period. Each session incorporates four main components:

1. Pulse/blood pressure measurement and general patient monitoring.
2. Graded exercise – incorporating moderate aerobic exercise.
3. Health Education – topics covered include:
    i) Dietary advice
    ii) Stress management
    iii) Advice on medications
    iv) Healthy heart (what is a myocardial infarction, CHD etc. also information on investigations, surgery, research etc.)
    v) Sexual guidance
    vi) General risk factor discussion

It is a rolling programme so patients may join at any week from one to five and continue through until all topics are covered.

4) Relaxation – each week different techniques are taught.

On completion of the initial programme numerous additional groups, activities and opportunities are made available to patients. Complementary

therapies including Aromatherapy, Indian Head Massage and Reflexology, Meditation and Yoga therapy are all also available if the patient chooses to use them. The primary option at this stage is an exercise-based rehabilitation programme and further details are given below. To give the reader a fuller appreciation of the research of this chapter a brief description of the four phases of rehabilitation follows:-

THE FOUR PHASES OF CARDIAC REHABILITATION

Phase I

Phase I of cardiac rehabilitation normally occurs during the inpatient stage. Medical evaluation, reassurance and education (In Wirral Hospital Trust, an information pack containing advice on physical activity, diet and sexual guidance is given to each patient while they are still in hospital), correction of cardiac misconceptions, risk factor assessment, mobilisation and discharge planning are all key elements (Thompson 1989).

Phase II

This is the early post discharge period. It is recognised as a time when many patients feel isolated and insecure (SIGN 2002). Phase II can be accessed from any route of referral and generally lasts for about six weeks It normally includes three components, exercise, education, and relaxation. At WHSC, as previously mentioned, patients are invited along for an initial assessment. Risk factors are discussed and baseline measures established for blood pressure, cholesterol, weight, and BMI Clinical information is also gathered and a detailed patient history taken. At this stage patients may be triaged to

more appropriate care, or additional modules such as health psychology and dietetics may be offered. It was at the Phase I/Phase II interface that patients were recruited for the studies in this chapter.

Phase III

Historically this stage takes the form of a structured exercise programme in a hospital setting with educational and psychological support and further advice on risk factors. Prior to commencing the formal exercise programme, (Phase III) all patients complete a graded exercise test as detailed in Section 2.6.

Phase IV

Phase IV cardiac rehabilitation involves the long-term maintenance of physical activity and lifestyle change. Evidence suggests that both these components must be sustained for cardiac benefits to continue (Cupples & McKnight 1999, Schonhr *et al.* 2000). The research of this chapter did not explore the Phase IV stage of cardiac rehabilitation.

6.1 HEART RATE VARIABILITY DIFFERENCES BETWEEN CHD AND NORMAL SUBJECTS

ABSTRACT

The purpose of this study was to demonstrate the differences, a) between two groups of subjects (normals and rehabilitation patients) and b) as a result of an orthostatic test. Reduced heart rate variability (HRV) is consistently observed and interpreted as a result of predominantly sympathetic and reduced vagal modulation of the sinus node in patients with cardiac dysfunction. As these subjects are either uncomplicated post MI or post CABG patients, the study provides comparative information, which will help demonstrate the validity of HRV. The normal group were 16 healthy males (aged 43.2 ± 16.4 years; mean ± SD) and the rehabilitation group were 18 males (64.2 ± 8.2 years; mean ± SD) comprising 14 post MI, and four CABG patients. HRV was recorded by radio transmission from chest electrodes to a receiver (VariaPulse TF4 system, Advanced Medical Diagnostics Ltd, Leeds, UK) interfaced with a standard laptop computer. Data collection, filtering and analysis was provided by the VariaPulse TF4 software which provided a set of results corresponding to the mean RR interval time, total power and the key power frequencies. The orthostatic test consisted of three consecutive examination positions: supine 1 – standing – supine 2 with each position lasting five minutes. There was no statistical difference between the two groups at rest for any of the variables measured. As a consequence of the orthostatic test, the normal subjects showed significant reductions in RR interval ($P < 0.0001$), in very low frequency power ($P < 0.04$), in high frequency power ($P <$

0.01) and normalised high frequency power ($P < 0.004$). Increases were observed in normalised low frequency power ($P < 0.004$) and in low frequency to high frequency ratio ($P < 0.004$). The rehabilitation patients only showed a significant reduction in RR interval ($P < 0.001$). However, high frequency power reduced in this group by 63%, its lack of significance presumably caused by high variances. The low frequency power *increased* in normal subjects, yet *decreased* in rehabilitation subjects indicating a distinctive sympathetic drive mechanism in response to the orthostatic test. The normalised values *do not change in the rehabilitation patients, yet change* significantly in the normal subjects. As these values were very similar at rest between the two groups, they alone provide excellent means of measuring autonomic reactivity. It can thus be concluded that normalised power is approximately 50%, irrespective of cardiac status, but that the autonomic response to standing distinguishes the two groups. The results from this procedure should provide further evidence for the effectiveness of a cardiac rehabilitation programme.

INTRODUCTION

Autonomic nervous system activity contributes to the regulation of cardiac output during rest, exercise and cardiovascular disease (Rosenwinkel *et al.* 2001). Neural control of heart rate is achieved by membrane processes at the sino-atrial (SA) node, which is the dominant pacemaker of the heart (Task Force 1996). Both sympathetic and parasympathetic nerves innervate the SA-node and in the absence of any sympathetic, parasympathetic or hormonal input to the sinus node, it fires at its intrinsic rate, usually about 100 to 120 beats per minute (McCraty & Watkins 1996). In a healthy individual, the HR at any given time represents the net affect of the cardiac parasympathetic and sympathetic nerves. When vagal effects predominate, the HR is less than the intrinsic rate; when sympathetic effects predominate, the HR is greater than the intrinsic rate (Goldberger 1999).

The Schellong orthostatic test is a commonly used method for testing autonomic nervous system function (Nozawa *et al.* 1997). It comprises three phases i.e. lying for five minutes, standing for five minutes and a further five minute period of lying. The test is used to gauge both cardiac sympathetic and parasympathetic function.

Heart rate variability (HRV), which reflects the activity of the sympathetic and parasympathetic branches of the cardiac autonomic nervous system and analysis of HRV by power spectral analysis is used to assess cardiac autonomic status. Following myocardial infarction (MI) cardiac sympathetic and parasympathetic activity becomes disordered. This often results in loss of vagal reflexes leading to increased sympathetic activity (Casolo *et al.* 1992). Furthermore, in CHD and following MI cardiac

autonomic activity is often reduced. Increased mortality risk is associated with cardiovascular autonomic neuropathy following MI and in coronary artery disease (Kleiger *et al* 1987, Hayano *et al* 1990, Dreifus *et al* 1993, Bigger *et al* 1993).

The purpose of this study was to demonstrate, as a result of an orthostatic test, the differences in cardiac autonomic profiles between normal subjects and cardiac rehabilitation subjects using analysis of HRV to assess sympathovagal balance.

METHOD

Participants

The normal group consisted of 16 healthy males (aged 43.2 ± 16.4 years; mean ± SD) who were recruited via e-mail bulletin boards and from verbal requests for volunteers. Physical activity profiles were normal for the age group with most subjects engaging in modest physical activity weekly. None were involved in regular, high-intensity physical activity. Informed consent was obtained prior to the study. The rehabilitation group were 18, consecutively recruited male, cardiac patients (64.2 ± 8.2 years; mean ± SD) comprising 14 post MI and four CABG patients. Thirteen patients were taking beta-blocker medication and five were taking aspirin.

HRV data acquisition and analysis

Prior to data acquisition subjects were asked to lie down for ten minutes to exclude relevant emotional or external influence on the autonomic nervous system. After this resting phase HRV data acquisition, using the Varia-Pulse

TF4 system (see 2.2.4) was started. Data were collected for five-minutes in three positions of the orthostatic test (supine1 – standing –supine 2). In the present study data from lying to standing (i.e. supine1 – standing) were analysed.

Statistical analyses

Except where otherwise stated data are presented as mean ± standard error (SE). Prior to statistical analysis, all variables were tested for normality using the Shapiro-Wilk test. Unpaired t-tests and Mann-Whitney tests were used to compare baseline variables between groups and to compare test variables in both groups. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Except for a difference in age i.e. normals (aged 43.2 ± 16.4 years; mean ± SD) and rehabilitation patients (64.2 ± 8.2 years; mean ± SD) ($P < 0.0001$), there were no significant differences for all test variables at baseline (Phase 1, resting). Tables 6.1.1 and 6.1.2 show means, standard errors, change, percentage change and P-values for all variables.

TABLE 6.1.1

Means, standard errors and comparison of means for all variables.

Variable	Units	**Normal Subjects** (n = 16)				
		Phase One (lying)		Phase two (standing)		
		M	SE	M	SE	P-value
Mean R-R interval	ms	922	34	747	28	0.0001
Total power	ms^2	1625	275	1381	545	NS
Very low frequency power	ms^2	331	118	130	28	0.04
Low frequency power	ms^2	646	160	968	466	NS
High frequency power	ms^2	648	150	283	102	0.01
Normalised LF power	N.U.	50.8	5.4	73.2	5.0	0.004
Normalised HF power	N.U.	49.2	5.4	26.8	5.0	0.004
LF HF ratio	~	1.0	0.4	2.7	1.2	0.004

N.U. = normalised units, LF HF = low frequency to high frequency ratio.

TABLE 6.1.2

Means, standard errors, comparison of means for all variables.

Variable	Units	**Cardiac Rehabilitation Patients** (n = 18)				
		Phase One (lying)		Phase two (standing)		
		M	SE	M	SE	P-value
Mean R-R interval	ms	996	43.2	922	43.6	0.001
Total power	ms^2	1197	520	625	209	NS
Very low frequency power	ms^2	155	35	155	45	NS
Low frequency power	ms^2	375	127	221	70	NS
High frequency power	ms^2	666	415	249	117	NS
Normalised LF power	N.U.	52.7	5.0	53.9	4.5	NS
Normalised HF power	N.U.	47.3	5.0	46.7	4.5	NS
LF/HF ratio	~	1.1	0.34	1.2	0.9	NS

N.U. = normalised units, LF/HF = low frequency to high frequency ratio.

DISCUSSION

The main purpose of this study was to demonstrate the validity of HRV as a measure of the balance of the sympathetic and parasympathetic components of the cardiac autonomic system. The autonomic nervous system is a complex neural network maintaining internal physiological homeostatic mechanisms (Ravits 1997). Cardiovascular readjustment to orthostatic stress is one such important function. The simple change of posture that occurs in standing from a resting state, puts a significant strain on the cardiovascular system which is designed to ensure that the brain continues to receive sufficient blood, despite the sudden pull of gravity on the blood in the abdomen and legs. To prevent fainting or other symptoms that result from a reduction in blood flow to the brain, blood pressure, heart rate and other critical functions have to readjust almost instantaneously. These rapid adjustments are largely accomplished by the autonomic nervous system (ANS). In CHD autonomic deconditioning can occur, and following MI, ANS function may become disordered (Casolo *et al.* 1992). This may lead to an inadequate response to standing. The Schellong orthostatic test is a frequently used method of assessing autonomic function and in this study HRV response to standing was measured during the first and second phases of the Schellong test in a group of normal healthy male subjects and a group of male cardiac rehabilitation patients.

At baseline there were no significant differences for any HRV variables between groups. During the standing phase of the test, autonomic profiles for the groups showed significant differences. In the time domain of HRV in normal subjects, a significant increase in heart rate as represented by

a 19% reduction in mean R-R interval length ($P < 0.0001$) was observed during standing. A reduced effect to standing was observed in the rehabilitation group when compared with normals, with mean R-R interval significantly decreasing by 7% ($P < 0.001$). Within the frequency domain, power spectral analysis showed that upon standing there was a 61 % reduction in very low frequency power (VLF). This was not at all evident in the rehabilitation group, in fact as can be seen from the results (Table 6.1.2) there was no change at all in VLF power. The VLF range lies between 0 to 0.04 Hz and the exact mechanisms underlying VLF oscillations remain uncertain (Cerruti *et al.* 1995, Task Force 1996). They are thought to be associated mainly with thermoregulatory cycles (Sayers 1973, Kitney 1975, Fleisher *et al.* 1996) and with fluctuations of renin activity on arterial pressure. Although VLF oscillations are influenced by the renin-angiotensin system as low and high frequency R-R intervals, Taylor *et al.* (1998) suggested that VLF rhythms depend primarily on parasympathetic outflow. They further proposed that the prognostic value of VLF oscillations derive from the fundamental importance of parasympathetic mechanisms in cardiovascular health. Another important point that needs to be considered is that in the present study the recording time for the individual phases was only five minutes. Although the system in this present study used coarse-graining spectral analysis procedure, which is thought to be a more accurate measure of VLF rhythms (see 1.6.9.3), a longer recording period may be required in the investigation of these slow fluctuations (Task Force 1996).

Also in the frequency domain, absolute units of low frequency power (LF) *increased* in normal subjects yet were *decreased* in rehabilitation

patients. LF power in absolute terms is generally regarded as a measure of cardiac sympathetic activity (Ori 1992). The results therefore indicate a distinctive sympathetic drive mechanism, which is reduced in the cardiac patients. These results may in part be due to the fact that 13 of the 18 patients in the cardiac rehabilitation group were taking beta-blocker medication. An additional study was therefore conducted to further elucidate the effect of beta-blockade on the orthostatic mechanism and the results can be found in Section 6.2.

In terms of absolute high frequency (HF) power, as the result of the orthostatic test, there was a 56% significant reduction in HF power in the normal subjects and a similar 63% non-significant reduction in HF power in the cardiac patients. This lack of significance was presumably caused by high variances. The HF component is generally considered to be a measure of cardiac parasympathetic activity (see 1.6.10.1). The results appear to suggest that the vagal component of both normal and rehabilitation subjects is functioning similarly.

To attempt to further clarify this situation, low frequency and high frequency values were also reported in normalised units. The representation of LF and HF in normalised units emphasises the controlled and balanced behaviour of the two branches of the ANS (Task Force 1996). Moreover, normalisation minimises the effect on the values of LF and HF components of the changes in total power (Pagani *et al.* 1986, Malliani *et al.* 1991). Task Force recommendations suggest for this very reason that absolute and normalised units should always be quoted together to describe the distribution of power within the power spectrum (Task Force 1996). The normalised

values do not change in the rehabilitation patients, yet change significantly in the normal subjects. As these values were very similar at rest between the two groups, they alone provide excellent means of measuring autonomic reactivity. It can thus be concluded that normalised power is approximately 50%, irrespective of cardiac status, but that the autonomic response to standing distinguishes the two groups.

In addition to the use of normalised units, the ratio of low frequency power and high frequency power (LF/HF ratio) is also commonly used to describe the balance between the sympathetic and parasympathetic components of the cardiac autonomic system. There was a significant reduction in LF/HF ratio in the normals following standing ($P < 0.004$) indicating a shift towards sympathetic predominance but this was not evident in the cardiac rehabilitation group perhaps suggesting a derangement in autonomic function.

Overall, the results of the study demonstrate that short-term PSA of HRV is a valid measure of cardiac autonomic function and is of significant diagnostic value in terms of assessing sympathovagal status in normal and patients suffering from cardiac disease. The study also demonstrates that analysis of HRV, when combined with the orthostatic test as used in this study may prove a useful and practical tool for screening purposes in large population studies.

6.2 Heart Rate Variability Changes during an Orthostatic Test in Cardiac Rehabilitation Patients with and without Beta Blockade

Abstract

Power spectral analysis (PSA) of heart rate variability is a non-invasive method commonly used to evaluate cardiac autonomic activity. It offers the possibility of examining the function of parasympathetic and sympathetic pathways by analysing the various components of the frequency domain. An active and reverse orthostatic test is a commonly used procedure to examine changes in HRV reactivity. The purpose of this study was to examine the HRV response during the orthostatic test in a group of patients undergoing cardiac rehabilitation to provide further information on the underlying physiological mechanisms. The subjects consisted of 39 male, consecutively recruited cardiac rehabilitation patients (aged 61 ± 7.8 years; mean ± SD). The orthostatic test consisted of three consecutive examination positions: supine 1 – standing – supine 2 with each position lasting five minutes. Data collection was provided by the Varia - Pulse TF4 software, which provided a set of results corresponding to the mean RR interval time, total power and the key power frequencies. The patients were divided into those with beta blockade (N = 23, aged 60 ± 8.2 years; mean ± SD) and those without beta blockade (N=16, aged 62 ± 7.8 years; mean ± SD). A comparison between lying supine and standing showed a significant change in the beta blockade patients in RR interval ($P < 0.0006$), in high frequency power ($P < 0.01$) and in both normalised powers ($P < 0.03$). However, in the non beta-blockade

patients the only change as a result of standing was in the RR interval, which went from 806ms to 739ms ($P < 0.0001$). This study shows that in spite of the bradycardic effect of beta blockade there is a clear sympathovagal response during the orthostatic test. This is particularly evident in the high frequency power, which corresponds to parasympathetic withdrawal and in normalised low frequency power, which represents sympathetic predominance. The non beta-blockade patients only showed a statistically significant change in the reduced RR interval but the high percentage changes (e.g. 63% decrease in high frequency power), does suggest a similar reduction in parasympathetic control. It is possible that the larger distribution of all values in the non beta-blockade patients prevented statistical significance being achieved. This lack of significance is, however, reinforced by the absence of percentage change in both normalised values, thus supporting the recommendation to report results in absolute and normalised terms. This study has demonstrated that despite the known cardiological benefits of beta blockade, the autonomic reactivity to a simple change in posture is not diminished.

INTRODUCTION

Following on from the previous section, this study was designed to test the effects of beta-blockade on the cardiac autonomic response to orthostatic stress in cardiac rehabilitation patients. Beta-blockers are widely used in the treatment of coronary artery disease and considered the most important drugs for lowering mortality in post MI patients (Yusuf *et al.* 1985). They act as competitive antagonists at adrenergic beta-receptors causing decreased myocardial adrenergic activity, modifying autonomic nervous system activity and leading to restoration of sympathovagal balance. (Wikstrand & Kendall 1992, Mortara *et al.* 2000). Following myocardial infarction they have been shown to increase heart rate variability and improve survival (Haberthur *et al.* 1999).

Beta-blockers also have an anti-ischaemic effect and decrease myocardial oxygen consumption by reducing heart rate (HR), blood pressure (BP) and myocardial contractility (Pavlovic 1992). Additionally, by reducing surges of arterial BP and turbulent blood flow patterns, endothelial shear forces are decreased making coronary atherosclerotic plaque rupture less likely and therefore preventing the development of acute coronary syndrome (Cruickshank 1995).

The reduction in HR caused by beta-blockers also prolongs diastole, enabling improved perfusion of the jeopardised subendocardial myocardium (Opie 1996). Beta-blockers are considered the treatment of choice for sympathetically mediated rhythm disorders such as arrhythmias especially during exercise or conditions of emotional excitement (Opie 1996).

METHODS

Participants

Thirty-nine male subjects (aged 61 ± 7.8 years; mean ± SD) consecutively recruited cardiac rehabilitation patients took part in the study and were sequentially subdivided into those taking beta-blockade (N=23) and those without (N=16). Ethical committee agreement and informed consent was obtained prior to testing. The beta-blockade group (aged 60 ± 8.2 years; mean ± SD) consisted of 17 post MI patients, four coronary artery bypass graft (CABG) patients one angina patient and one patient suffering from cardiomyopathy. In addition to the beta blocker medication, 17 patients were taking aspirin, 13 were on statins and 5 took calcium channel blockers. In the group of patients not taking beta-blockers (aged 62 ± 7.1 years; mean ± SD) there were five post MI patients, 10 CABG patients and one angina patient. In this group, nine patients were taking aspirin, three were taking calcium channel blockers, two took ace-inhibitors, one was on digitalis and one was not taking medication.

HRV data acquisition and analysis

Prior to data acquisition subjects were asked to lie down for ten minutes to exclude relevant emotional or external influence on the autonomic nervous system. After this resting phase HRV data acquisition, using the Varia-Pulse TF4 system (see Section 2.2.4) was started. Data were collected for five-minutes in three positions of the orthostatic test (supine1 – standing –supine 2). In the present study data from lying to standing (i.e. supine1 – standing) were analysed.

Statistical analyses

Except where otherwise stated data are presented as mean ± standard error (SE). Prior to statistical analysis, all variables were tested for normality using the Shapiro-Wilk test. Unpaired t-tests and Mann-Whitney tests were used to compare baseline variables between groups and to compare test variables. A value of $P < 0.05$ was considered statistically significant.

RESULTS

At baseline there were no significant differences between groups for age, BMI and HRV variables with the exception of a longer R-R interval (1048 ms vs 806 ms, $P < 0.0001$). Tables 6.2.1 and 6.2.2 show means, standard errors, change, percentage change and P-values for all variables.

DISCUSSION

In Section 6.1, HRV responses to standing were measured in a mixed group of cardiac rehabilitation patients and compared to normal subjects. To further investigate the effects of the orthostatic test on HRV, this study was designed to measure the effects of beta-blockade on HRV responses to standing and compare results from cardiac patients who were not taking beta-blockers. A comparison between lying supine and standing revealed significantly different autonomic responses between the groups.

In the time domain of HRV in beta-blockade subjects, a significant increase in HR as represented by a 5.4% reduction in mean R-R interval length ($P < 0.0006$) was observed during standing. A more pronounced effect

TABLE 6.2.1

Means, standard errors, comparison of means for all variables.

Variable	Units	Beta-blockade subjects (n = 23)				
		Phase One (lying)		Phase two (standing)		
		M	SE	M	SE	P-value
Mean R-R interval	ms	1048	26	991	27	0.0006
Total power	ms^2	605	106	431	55	0.45
Very low frequency power	ms^2	115	24	161	34	0.32
Low frequency power	ms^2	186	44	150	17	0.33
High frequency power	ms^2	304	77	120	19	0.01
Normalised LF power	N.U.	41	5.2	57	3.7	0.003
Normalised HF power	N.U.	59	5.2	43	3.7	0.003
LF HF ratio	~	0.61	0.5	1.25	0.9	0 005

N.U. = normalised units, LF HF = low frequency to high frequency ratio.

TABLE 6.2.2

Means, standard errors and comparison of means for all variables.

Variable	Units	**Non-blockade subjects** (n = 16)				
		Phase One (lying)		Phase two (standing)		
		M	SE	M	SE	P-value
Mean R-R interval	ms	806	42	739	39	0.0001
Total power	ms^2	793	577	422	227	0.69
Very low frequency power	ms^2	64	17	80	29	0.94
Low frequency power	ms^2	201	99	148	74	0.73
High frequency power	ms^2	528	470	194	133	0.5
Normalised LF power	N.U.	53	5.8	52	5.9	0.95
Normalised HF power	N.U.	47	5.8	48	5.9	0.9
LF HF ratio	~	0.4	0.5	0.8	0.9	0.9

N.U. = normalised units, LF/HF = low frequency to high frequency ratio.

to standing was observed in the non-blockade group, with mean R-R interval significantly decreasing by 8.3% ($P < 0.0001$). This difference is probably due to the reduced adrenergic effect of beta blockade leading to reduced sympathetic drive and subsequent decreased response to standing.

In the frequency domain of HRV, in terms of total power, an overall measure of HRV, both groups showed non-significant reductions on standing, the beta-blockade group reducing by 29% and the non-blockade group by 47%. The lack of significance was probably due to high variances. There were no significant differences observed in very low frequency power for both groups. However once again as demonstrated in 6.1 both groups of cardiac patients showed reductions in low frequency (LF) power on standing whereas the expected result would be reversed if the ANS was intact (Section 6.1). LF power is generally regarded as a measure of sympathetic nervous system activity and the results suggest that there is reduced sympathetic responsiveness in both groups. In the beta-blockade group it is likely that the medication is causing a blunting of sympathetic drive as it is designed to, but this does not explain the reduced activity in the non-beta blockade group. Syncope following MI is a common clinical feature and according to Wasek *et al.* 2000, it is possible that remodelling and neurohormonal changes following MI may predispose to neurally mediated syncope probably more specifically due to sympathetic withdrawal. This may partly explain the results in terms of LF power.

High frequency power which is representative of cardiac vagal tone both reduced by the same amount on standing in both groups. In the beta-blockade group there was a significant 61% reduction in HF power ($P < 0.01$)

and in the non-blockade group a non-significant 63% decrease. Once again it is likely that large variances have caused the lack of statistical significance. Interestingly when both LF and HF power are normalised for the reasons stated in section 6.1, the results show significant changes in normalised values in the beta-blockade group and no change in the non blockade patients. In the beta-blocker group there is a 39% increase in LF norm ($P < 0.003$) and a similar decrease in HF norm ($P < 0.003$). This shift towards sympathetic predominance is further demonstrated with the significant increase in LF/HF ratio ($P < 0.005$) and is not evident in the non beta-blocked patients. The results support the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996) to report HRV results in both absolute and normalised terms to give a clearer understanding of the sympathovagal interaction. The study also shows that despite the known cardiological benefits of beta blockade, the autonomic reactivity to a simple change in posture in not diminished. Additionally, this provides further evidence for the validity of HRV as a sensitive measure of cardiac autonomic activity.

6.3 The Relationship between Heart Rate Variability during an Orthostatic test and Functional Measures during a Graded Exercise Test

Abstract

The purpose of this study was to select those parameters of heart rate variability (HRV) within its short-term power spectrum that indicate sympathovagal status and to compare these to functional measures acquired during a graded exercise treadmill test. This may provide evidence for HRV, which is a non-intrusive procedure, as a predictor of cardiovascular function and thus assist in anticipating how patients may respond to a graded exercise test. Thirty-nine subjects (aged 61 ± 7.8 years; mean ± SD) who were receiving cardiac rehabilitation took part in the study and were subdivided into those taking beta-blockade (N = 23) and those without (N = 16). The standard five minute lying – standing – lying orthostatic test was adopted with HRV recorded continuously using a VariaCardio TF4 ECF transmission system (Advanced Medical Diagnostics Ltd, Leeds, UK). All subjects also undertook an incremental exercise test on a motorised treadmill (modified Bruce protocol) when a 12-lead ECG (Centra, Marquette) was monitored continuously. At three-minute intervals, ratings of perceived exertion, dyspnoea and angina were also recorded, as was blood pressure. Peak ST segment depression, maximum rate pressure product (RPP max), one minute heart rate recovery from peak and exercise time were the main variables correlated with HRV. Besides total power (TP) and high frequency power (HF) at rest correlating with one minute heart rate recovery from peak (r

0.35, P = 0.03) and (r = 0.31, P = 0.05) respectively, there were relatively few significant correlations. Those that did achieve significance distinguished between beta-blockade and non beta-blockade groups. Peak ST segment depression correlated with the change in low frequency power from lying to standing (r = –0.56, P = 0.02) and from standing to lying (r = 0.53, P = 0.03) in non beta-blockade patients. RPP max correlated with the change in very low frequency power from lying to standing (r = –0.43, P = 0.04) and standing to lying (r = 0.57, P = 0.005) in beta-blockade. Exercise time correlated with changes in both low frequency power (r = 0.43, P = 0.04) and normalised low frequency power (r = 0.50, P = 0.02) from standing to lying in beta-blockade. It can be concluded that generally HRV is not a good predictor of functional exercise measurements in cardiac rehabilitation patients. However, in non beta-blockade patients the increased cardiac anoxia as determined by increased ST depression is related to an increased sympathetic drive. This is reversed when the subjects lie down after standing. As this is not evident in beta-blockade patients, it suggests that the medication is providing a protective effect on the sympathetic mechanism.

INTRODUCTION

Coronary heart disease (CHD) is the leading cause of morbidity and mortality in Britain and is responsible for almost 50% of all deaths (BHF 2001). It manifests clinically as stable angina, unstable angina, myocardial infarction (MI), silent ischaemia and sudden death. In England alone, more than 1.4 million people suffer from angina, 300,000 have heart attacks and over 110,000 die of heart-related problems every year *(National Service* Framework for Coronary Heart Disease 2000).

The exercise stress test remains the most widely used method of testing for heart disease (Task Force on Assessment of Cardiovascular Procedures 1986). It is indicated in select patients to rule out coronary artery disease and to determine a patient's cardiovascular functional capacity (Gibbons 1997). It has been used in clinical practice for many years, and its use has contributed significantly to the management of many patients. In its current form, clinical exercise testing most often consists of the continuous monitoring of an ECG with frequent recordings of 12-lead tracings. Additional tracings are taken according to clinical circumstances. Frequent blood pressure determinations are made before, during, and after exercise of progressively increasing intensity to any of a number of test end points.

Because exercise testing entails a very small but definite risk, and data confirm that up to one MI or death per 2500 tests occurs (Stuart & Ellestad 1980), it must be performed under the supervision of a trained physician.

HRV analysis is a sensitive, non-invasive technique, which can be used to identify cardiac autonomic disturbances. It is commonly used as a prognostic marker following MI (Kleiger *et al.* 1987) and a reduced HRV is

associated with an increased risk of CHD (Liao *et al.* 1997), sudden cardiac death (Singer *et al.* 1988) and all-cause mortality (Tsuji *et al.* 1994). HRV from short-term recordings has also been proposed as an indicator of compromised health in the general population (Dekker *et al.* 1997).

The purpose of this study was to select those parameters of heart rate variability (HRV) within its short-term power spectrum that indicate sympathovagal status and to compare these to functional measures (exercise time, peak ST-segment depression, maximum rate pressure product, one minute heart rate recovery from peak) acquired during a graded exercise treadmill test.

METHODS

Participants

Thirty-nine male subjects (aged 61 ± 7.8 years; mean ± SD) consecutively recruited cardiac rehabilitation patients took part in the study and were sequentially subdivided into those taking beta-blockade (N=23) and those without (N=16). Ethical committee agreement and informed consent was obtained prior to testing. The beta-blockade group (aged 60 ± 8.2 years; mean ± SD) consisted of 17 post MI patients, four coronary artery bypass graft (CABG) patients one angina patient and one patient suffering from cardiomyopathy. In addition to the beta blocker medication, 17 patients were taking aspirin, 13 were on statins and 5 took calcium channel blockers. In the group of patients not taking beta-blockers (aged 62 ± 7.1 years; mean ± SD) there were five post MI patients, 10 CABG patients and one with angina. In this group nine patients were taking aspirin, three were taking calcium

channel blockers, two took ace-inhibitors, one was on digitalis and one was not taking any medication.

Protocol

The graded exercise treadmill test (ETT) was performed using the modified Bruce protocol (Appendix 3) and further information on the procedure can be found at Section 2.6. The main variables examined from the ETT were:

Exercise time

This was the total time taken from the start of the test, excluding a short habituation period (not functionally stressing i.e. 1mph at 1% gradient), to peak exercise time. The test was stopped if the patient became too tired to continue (volitional cessation) or because the termination criteria were reached (e.g. a maximum ST-segment depression of 2mm).

Peak ST-segment depression

The ST-segment is the segment between the end of the QRS complex and the beginning of the T wave. It is normally isoelectric or on the same level as the baseline as represented by the line between the P wave and the QRS. ST segment depression demonstrates myocardial subendocardial injury and during an exercise treadmill test, ST-segment depression of 1mm or more is the most significant criterion for an exercise stress test, positive for ischaemia. Continued down-sloping or horizontal ST-segment depression 0.08sec or more is highly specific (Goldman 1982).

Maximum rate pressure product (RPPmax)

Rate-pressure product (RPP), also known as the Robinson Index (systolic blood pressure x heart rate/100) is an indicator of cardiac oxygen demand.

One-minute heart rate recovery from peak (1-min HR rec)

The rate of recovery immediately following peak exercise is considered to be an indication of the re-emergence of cardiac parasympathetic activity (Cole *et al.* 1999).

HRV data acquisition

Subjects rested for ten minutes prior to HRV testing to exclude relevant emotional or external influence on the autonomic nervous system. After this time data were collected for five-minutes during each phase of the lying-standing-lying test (see 2.4.6). Following HRV data acquisition the patient immediately continued on to the ETT.

Statistical analyses

Unless otherwise stated data are given mean ± SE. All variables were tested for normality using the Shapiro-Wilk test. A Mann-Whitney test or an unpaired t-test was used to compare the test and control groups for all variables at baseline. Simple linear regression and a Pearson correlation coefficient were used to compare normally distributed variables and a Spearman's rank correlation coefficient was used to compare non-normally distributed parameters. A two-tailed probability of $P < 0.05$ was considered statistically significant.

RESULTS

The patient population used in this study was the same as those reported in section 6.2. In summary, with the exception of a longer R-R interval for those patients taking beta-blockers (1048 ms vs 806 ms, $P < 0.001$) there were no significant differences observed at baseline for any other variables.

Besides total power (TP) and high frequency power (HF) at rest correlating with one-minute heart rate recovery from peak ($r = 0.35$, $P = 0.03$) and ($r = 0.31$, $P = 0.05$) respectively, there were relatively few significant correlations. Those that did achieve significance distinguished between beta-blockade and non beta-blockade groups. Peak-ST segment depression correlated with the change in low frequency power from lying to standing ($r = -0.56$, $P = 0.02$) and from standing to lying ($r = 0.53$, $P = 0.03$) in non beta-blockade patients. RPP max correlated with the change in very low frequency power from lying to standing ($r = -0.43$, $P = 0.04$) and standing to lying ($r = 0.57$, $P = 0.005$) in beta-blockade. Exercise time correlated with changes in both low frequency power ($r = 0.43$, $P = 0.04$) and normalised low frequency power ($r = 0.50$, $P = 0.02$) from standing to lying in beta-blockade patients. Tables 6.3.1, 6.3.2 and 6.3.3 show the HRV results for the three phases of the orthostatic test for the combined group and both the beta and non beta-blockade groups.

TABLE 6.3.1

Means and standard errors for all variables during the three phases of the orthostatic test.

Variable	Units	Combined Patients (n = 39)					
		Lying 1		Standing		Lying 2	
		M	SE	M	SE	M	SE
Mean R-R interval	ms	949	29.8	887**	29.9	981††	31.4
Total power	ms^2	682	241	428	97	885	278
Very low frequency power	ms^2	94.3	16	127	24	109	17
Low frequency power	ms^2	192	48	150	32	218	58
High frequency power	ms^2	396	195	150	55	558†	227
Normalised LF power	N.U.	46	3.9	55	3.6	44†	3.6
Normalised HF power	N.U.	54	3.9	45	3.6	56†	3.6
LF/HF ratio	~	0.5	0.35	1.0	0.93	0.4†	0.3

LF = low frequency, HF = high frequency, N.U. = normalised units. * = significant difference from lying 1, (P < 0.05), ** = (P < 0.01).
† = significant difference from standing, (P < 0.05), †† = (P < 0.01).

TABLE 6.3.2

Means and standard errors for all variables during the three phases of the orthostatic test.

Variable	Units	Beta-blockade subjects (n = 23)					
		Lying 1		Standing		Lying 2	
		M	SE	M	SE	M	SE
Mean R-R interval	ms	1048	26	991**	27	1086**	28
Total power	ms^2	605	106	431	55	931	234
Very low frequency power	ms^2	115	24	161	34	139	24
Low frequency power	ms^2	186	44	150	17	245	75
High frequency power	ms^2	304	77	120**	19	547††	179
Normalised LF power	N.U.	41	5.2	57*	3.7	37††	4.4
Normalised HF power	N.U.	59	5.2	43*	3.7	63††	4.4
LF/HF ratio	~	0.6	0.5	1.3**	0.9	0.4††	0.3

LF = low frequency, HF = high frequency, N.U. = normalised units. * = significant difference from lying 1, ($P < 0.05$), ** – ($P < 0.01$).
† = significant difference from standing, ($P < 0.05$), †† = ($P < 0.01$).

TABLE 6.3.3

Means and standard errors for all variables during the three phases of the orthostatic test.

Variable	Units	Non-blockade subjects (n = 16)					
		Lying 1		Standing		Lying 2	
		M	SE	M	SE	M	SE
Mean R-R interval	ms	806	42	739**	39	830††	43
Total power	ms^2	793	577	422	227	818	603
Very low frequency power	ms^2	64	17	80	29	67	16
Low frequency power	ms^2	201	99	148	74	179	93
High frequency power	ms^2	528	470	194	133	573	499
Normalised LF power	N.U.	53	5.8	52	5.9	54	5.2
Normalised HF power	N.U.	47	5.8	48	5.9	46	5.2
LF HF ratio	~	0.4	0.5	0.8	0.9	0.3	0.6

LF = low frequency, HF = high frequency, N.U. = normalised units. * = significant difference from lying 1, ($P < 0.05$), ** = ($P < 0.01$).
† = significant difference from standing, ($P < 0.05$), †† = ($P < 0.01$).

DISCUSSION

In cardiac rehabilitation, exercise tolerance testing is routinely carried out to determine a patient's cardiovascular functional capacity. An exercise treadmill test (ETT) was the method used in this study to establish the patient's suitability for the Phase III, 12-week moderate intensity exercise programme and to set the exercise prescription for the individual (for further information see section 6.4).

The major haemodynamic consequence of coronary artery disease (CAD) is decreased cardiac output resulting in reduced exercise capacity. During exercise, acute reduction of left ventricular function leading to reduced heart rate (HR) and stroke volume and increasing pulmonary artery pressure appears to be the mechanism limiting cardiac output. The interpretation of the ETT involves analysis of the clinical response of the patient, the exercise capacity, and haemodynamic and ECG responses. Chest pain consistent with angina is important, particularly if it terminates the test and becomes more predictive of CAD if it is associated with ST-segment depression. Signs of poor perfusion, such as a drop of skin temperature or peripheral cyanosis and symptoms of light-headedness or vertigo may also indicate inadequate cardiac output.

Power spectral analysis (PSA) of heart rate variability (HRV) is a non-invasive method commonly used to evaluate cardiac autonomic activity. It offers the possibility of examining the function of parasympathetic and sympathetic pathways by analysing the various components of the frequency domain. The purpose of this study was to select those parameters of HRV within its short-term power spectrum, that indicate sympathovagal status and

to compare these to functional measures acquired during a graded exercise treadmill test.

One-minute heart rate recovery from peak exercise and HRV

Increased HR during exercise is considered to be due to a combination of increased cardiac sympathetic activity and withdrawal of cardiac vagal tone (Arai *et al.* 1989). The reduction in HR immediately following exercise (i.e. the difference in heart rate between peak exercise and one minute later) is considered to reflect the reactivation of the parasympathetic nervous system (Imai *et al.* 1994). A reduced value for one-minute heart rate recovery from peak exercise (1-min HR rec.) is associated with decreased vagal tone and has been shown to be a powerful and independent predictor of the risk of death (Cole *et al.* 1999). In the present study, in the combined group of patients ($N = 39$), there were significant correlations for both total power (TP) ($r = 0.35$, $P < 0.03$) and high frequency power (HF) ($r = 0.31$, $P < 0.05$) when compared with 1-min HR rec. Both TP and HF are considered to reflect short-term cardiac parasympathetic activity and therefore the results of this study tend to confirm the suggestion that 1-min HR rec. is associated with resurgence of vagal activity Cole *et al.* 1999).

Peak ST-segment depression and low frequency changes

Exercise ischaemia is best represented by variations in the ST-segment. The probability and severity of CAD is related directly to the amount of depression and down-sloping of the ST-segment. Severity of disease and

prognosis is correlated with the lower workload at which ST-segment depression occurs.

ETT results are centred on the ST-segment response, with a ST-segment depression greater than or equal to 1mm signifying a positive test result. Several studies have previously compared HRV parameters with ST-segment characteristics and in general have concluded that reduced parasympathetic activity leading to an increase in sympathetic drive is the underlying mechanism that leads to episodes of ischaemia as demonstrated by ST-segment depression.

Lanza *et al.* (1997) showed that transient ischaemia on Holter monitoring is a powerful predictor of cardiac events in unstable angina and using HRV analysis demonstrated that an imbalance in cardiac autonomic tone towards a prevalence of sympathetic activity was associated with increased risk of events. Dilaveris *et al.* (1996) have also shown HRV to be reduced in the 5-minute period immediately prior to ST-segment depression and to be inversely related with the magnitude and duration of the ST episodes. Furthermore, Ponikowski *et al.* (1996) have suggested that increased sympathetic drive also plays a role in the pathogenesis of coronary syndrome X (angina pectoris, positive exercise test and angiographically normal coronary arteries). Using HRV data from 24-hour Holter monitors they showed that in patients with syndrome X as the result of sympathetic predominance due to vagal withdrawal an imbalance in sympathovagal status occurs that precedes episodes of ST-segment depression. Another study using fast-Fourier transforms of 24-hour Holter HRV data, sympathetic predominance as the result of parasympathetic withdrawal has also been

shown to be the major occurrence preceding episodes of nocturnal ischaemia (Vardas *et al.* 1996).

Results from the present study show that peak ST segment depression correlated with the change in low frequency power from lying to standing ($r = -0.56$, $P = 0.02$) and from standing to lying ($r = 0.53$, $P = 0.03$) in non beta-blockade patients. This effect was not seen in those patients taking beta-blockers (i.e. from lying to standing $r = 0.24$, $P < 0.2$ and from standing to lying $r = 0.25$, $P < 0.25$). The results confirm the findings of the previously mentioned studies and indicate an abnormality in sympathovagal interaction in patients not taking beta-blockers when compared with those on beta-blocker medication.

Exercise Time and low frequency changes

Strong prognostic markers identified in exercise testing are exercise capacity and exercise-induced ischaemia. Maximum exercise capacity is at least partly affected by left ventricular dysfunction, which can be evaluated by looking at maximal exercise duration, maximum MET level achieved, maximum workload achieved, maximum heart rate, or the maximum exercise double product (RPPmax). In the present study, exercise time correlated with changes in both low frequency power ($r = 0.43$, $P = 0.04$) and normalised low frequency power ($r = 0.50$, $P = 0.02$) from standing to lying in beta-blockade patients. This was not seen in the patients not taking beta-blockers and this again suggests that the medication is beneficially modifying the interaction between the sympathetic and parasympathetic components of the cardiac ANS in favour of improving cardiovascular responses to exercise.

RPPmax and VLF power changes

RPPmax reflects both the HR and systolic blood pressure at peak exercise and therefore factors that affect cardiac ANS balance and blood pressure regulatory mechanisms will alter RPPmax. In the present study RPPmax correlated with the change in very low frequency (VLF) power from lying to standing ($r = -0.43$, $P = 0.04$) and standing to lying ($r = 0.57$, $P = 0.005$) in beta-blockade. This relationship was not evident in those patients not taking beta-blockers i.e. from lying to standing ($r = 0.02$, $P = 0.93$) and standing to lying ($r = 0.12$, $P = 0.66$).

A major proportion of RR interval variability is due to VLF (0.003 to 0.04 Hz) fluctuations. Survival of post-MI infarction patients is related inversely to their levels of VLF R-R interval variability. The physiological basis for such oscillations is unclear. Although VLF heart period rhythms are influenced by the renin-angiotensin-aldosterone system, as low and respiratory frequency RR-interval rhythms as mentioned previously (see Section 1.6.10.3), they depend primarily on the presence of parasympathetic outflow. Therefore the prognostic value of VLF heart period oscillations may derive from the fundamental importance of parasympathetic mechanisms in cardiovascular health (Taylor *et al.* 1998). VLF R-R interval variability is also influenced by physical activity (Bernardi *et al.* 1996) and therefore it is possible that this may have influenced the results in some manner although the exact mechanisms still remain unclear. Further studies with larger subject numbers and longer recording times for more precise determination of VLF responses may elucidate this area of research.

From the results of the study it can be concluded that in general, HRV is not a good predictor of functional exercise measurements in cardiac rehabilitation patients. However, in non beta-blockade patients the increased cardiac anoxia as determined by increased ST depression appears to be related to an increased sympathetic drive. This is reversed when the subjects lie down after standing. As this is not evident in beta-blockade patients, it suggests that the medication is providing a protective effect on the sympathetic mechanism.

6.4 The Effects of Cardiac Rehabilitation on Heart Rate Variability in Patients with Coronary Heart Disease

Abstract

Heart rate variability (HRV) reflects the activity of the sympathetic and parasympathetic branches of the cardiac autonomic nervous system. It is reduced in coronary heart disease and following myocardial infarction and is associated with a poor prognosis. Exercise has the potential to increase HRV and forms a major part of many cardiac rehabilitation programmes. The purpose of this study was to test the effects of a 25.1 ± 0.73 weeks (mean ± SE), moderate intensity, aerobic exercise-based cardiac rehabilitation (CR) intervention on cardiac autonomic tone using coarse-graining, power spectral analysis of heart rate variability to assess cardiac sympathovagal balance. Forty-eight consecutively recruited male cardiac rehabilitation subjects took part in the study. The main findings of the study showed that following the first three months of the programme (i.e. Phase II CR), the high frequency (HF) component of HRV, a frequency domain measure of cardiac vagal tone, was significantly increased (133 ± 29 to 279 ± 70 ms^2, mean ± SE, $P < 0.01$) and there were significant changes in normalised units of high frequency and low frequency power (measures of cardiac parasympathetic and sympathetic activity respectively (both $P < 0.05$). These findings were maintained over the 2nd three-month period (Phase III, CR). The results of the study demonstrate that exercise-based CR is effective in enhancing cardiac autonomic activity, principally as the result of increased cardiac vagal tone. This may confer important cardio-protective benefits to the rehabilitation patient

INTRODUCTION

According to the British Heart Foundation (BHF 2001), coronary heart disease (CHD) is the most common cause of death in the United Kingdom. Over 270,000 heart attacks occur each year, and of these patients, about 43% die within twenty-eight days of their heart attack. Physical inactivity is considered a major risk factor for heart disease with seven out of 10 adults not taking enough regular physical exercise. Even though physical inactivity is so common eight out of 10 adults still believe that they are physically fit (BHF 2001).

During the last decade, the provision of exercise-based cardiac rehabilitation in the UK has increased considerably (SIGN 2002). This is due in part to the increasing realisation that people who are physically active live longer (Sherman *et al.* 1999). Recently the National Service Framework for Coronary Heart Disease (NSF 2000) has been published highlighting the importance of the cardiac rehabilitation (CR) process. Within the NSF are recommendations and service models for the provision of CR within the UK.

Many definitions of CR exist (Feigenbaum & Carter 1998, WHO 1993), but one which is appropriate to the theme of this research is promoted by the Scottish Intercollegiate Guidelines Network (2002). It defines cardiac rehabilitation as 'a process by which patients with cardiac disease, in partnership with a multi-disciplinary team of health professionals, are encouraged and supported to achieve and maintain optimal physical and psychosocial health'. This framework is in place at the Wirral Heart Support Centre (WHSC) and has been described in detail previously (see Section 6.4.1).

Structured exercise, as a therapeutic intervention is central to cardiac rehabilitation (Coates *et al.* 1995, Goble & Worcester 1999, AACPR 1995). The exercise component of CR has evolved from the recognition that physical de-conditioning occurs in CHD and post-MI, and the knowledge that regular exercise protects against cardiovascular disease (NIH 1996). The link between cardiovascular health and exercise training has long been recognised. Over 25 years ago, in a seminal study by Paffenbarger *et al.* (1978) an association between past levels of exercise participation, current levels of physical activity and the risk of CHD was established.

Following myocardial infarction (MI) cardiac sympathetic and parasympathetic activity becomes disordered. This often results in loss of vagal reflexes leading to increased sympathetic activity (Casolo *et al.* 1992). These effects occur during the period when the risk of arrhythmic events is at its highest. Sympathetic hyperactivity has been shown to predispose towards ventricular fibrillation in animal models (De Ferrari *et al.* 1991) while vagal reflexes are considered to have a cardio-protective effect (Task Force 1996).

Heart rate variability (HRV) reflects the activity of the sympathetic and parasympathetic branches of the cardiac autonomic nervous system and is a characteristic that is potentially increased by physical activity (Schuit *et al.* 1999). The purpose of this study was to determine the effects of an exercise-based cardiac rehabilitation programme over a six-month period (25 weeks ± 0.73 SE) on cardiac autonomic tone using power spectral analysis of HRV to determine sympathovagal status.

METHOD

Participants

Forty-eight male, consecutively recruited CR patients were initially enlisted to take part in the study (63.9 ± 8.8 years; mean ± standard deviation). Data from eighteen subjects were excluded for the following reasons: one patient died, four had further MI's, four underwent coronary artery bypass graft (CABG) surgery and data from nine patients were excluded because they contained too many frequent ectopic or aberrant beats.

The selection of a non-exercise control group from a similar population was not possible for two reasons. Firstly, WHSC has a 'no wait' policy for enrolment onto the exercise programme. Selection of a non-exercise control group made from a delayed waiting list was therefore not possible. Secondly, CR is a core therapy currently available through the Wirral & West Cheshire Community NHS Trust. It has been demonstrated that patients who access this service rapidly, (i.e. four to five weeks post MI), show a swifter return to pre-infarction levels of quality of life and functional capacity (Kelly 2001). Therefore the withdrawal of this service to individuals to provide an appropriate control group proved to be an insurmountable ethical issue for Wirral & West Cheshire Community NHS Trust. For the above reasons, a 10-subject 'control' group (66.6 ± 10.8 years; mean ± standard deviation) was retrospectively assembled. The group consisted of two patients who decided not to continue with treatment after three weeks of Phase II exercises and eight patients who for various logistical reasons following graduation from Phase II refused further input. These subjects were

left to their own devices but contacted towards the end of the study and agreed to return for a final testing session.

Therefore only 20 patients remained in the experimental group and of these 14, were post-MI, four were post-CABG, one had a calcified valve and one had undergone heart-valve replacement surgery. Twelve were on beta-blocker therapy, four received aspirin alone, one was on Warfarin, one was taking Vioxx, one on Ramipril and one patient was taking Nicarandil. The demographics of the control group were similar with six patients post-MI and taking beta-blockers and four patients post-CABG on aspirin alone.

EXERCISE PROTOCOLS

Phase II Rehabilitation Sessions

The Phase II sessions took place at WHSC and commenced with a brief individual interview with each patient. The interview process is considered to be useful for initiating lifestyle change, monitoring patient care and to establish suitability for exercise (Kelly 2001). Indications and contra-indications to exercise follow the ACSM's (2000) guidelines for exercise testing and prescription and can be found at Appendices 7 & 8. Outside of the programme, patients were encouraged to increase their levels of physical activity, usually by walking. Patients were advised to increase walking from 10 minutes per day up to 20 minutes per day by their fifth week. Blood pressure (BP), resting heart rate (HR) and rhythm were recorded and marked on the patient record. At the first session patients also received a booklet containing details of a home-based aerobic circuit. They were encouraged to engage in this home-circuit on a daily basis. Members of staff, who were

regularly trained in the use of semi-automatic defribillators and advanced life support techniques, supervised all exercise sessions carried out at the centre.

The exercise component consisted of 30 minutes moderate intensity exercise (see below) using aerobic circuit training techniques. Details of the circuit are given at Appendix 9. The session included a warm-up period, aerobic circuit, cool-down and flexibility. The warm-up and cool-down periods lasted for approximately six minutes and consisted of dynamic large muscle exercises, such as marching on the spot and side stepping (Appendix 10). Incorporated within these periods were flexibility exercises covering the major muscle groups. This allowed 15 to 20 minutes for completion of the circuit. An exercise physiologist or cardiac rehabilitation nurse with an instructor ratio of 1:10 supervised the classes. Patients were classified by risk and the circuit session was structured accordingly.

Phase II Exercise intensity, Monitoring and Progression.

Intensity for Phase II exercises was set using subjective ratings. Moderate intensity exercise based on a figure of 10 on the Rating of Perceived Exertion Scale, (Borg, 1985) and roughly equivalent to 4 METS (i.e. multiples of resting metabolic rate) was described to the patients prior to commencing exercise. It was explained that they should feel warm, slightly sweaty and slightly out of breath but that they should still be able to talk to other members of the group. Observation took place continuously, and staff members looked for signs of over-exertion, poor perfusion, angina and/or general distress. Initially 30 seconds were completed on each base of the circuit for patients on their 1st 2nd or 3rd weeks. Patients who were on their 4th week exercised for 45

seconds and patients completing the 5-week course exercised for one-minute on each base. The exercises continued without any breaks and patients who were not exercising for a full minute continued to march on the spot until the groups moved onto the next piece of apparatus. On cessation of the exercise, radial pulse was palpated by a member of staff and recorded on the patient record card.

On completion of Phase II patients could then choose to continue onto Phase III. If they agreed to proceed they were invited to attend a graduation (GRADS) class where they received further instruction on the cardiac rehabilitation process (see Appendix 11).

Enrolment onto Phase III and 'LINK' session

At Wirral Heart Support Centre, while patients waited for their exercise tolerance test appointment, they attended a 'LINK' class, which occurred at the Phase II/Phase III interface. This consisted of a weekly one-hour supervised session where patients engaged in a 10-minute warm up and stretching session followed by 30-minutes of continuous aerobic exercise. The exercises were basically similar to those of Phase II but the exercise intensity was increased slightly. The exercises were 'stepped-up' from the Phase II level of approximately RPE 10, (4 METS) to an approximate level of RPE 12, (six METS). This was then followed by a 20-minute cool-down and relaxation session. Patients continued with these sessions until they were recruited onto the Phase III, exercise-training programme.

Phase III Exercise Frequency

Patients attended WHSC twice per week for a total of 12 weeks. Guidelines from ACSM (2000) suggest that health gains may plateau between 3 - 5 days of training per week, therefore all patients were also encouraged to complete at least one additional session in their own time. There was no necessity for these sessions to be carried out in a formal setting such as a fitness suite. Thirty minutes of brisk walking was used as a benchmark at an RPE of approximately 11 – 15 (five to seven METS). No record of these home sessions was recorded.

Exercise Prescription

The prescription of exercise in the cardiac population is carried out for several reasons. These include, the need to increase physical activity (which is associated with a decreased risk of mortality and further cardiac event (ACSM, 2000)), to raise the ischaemic threshold, increase functional capacity and to increase strength. Exercise may also improve psychological status and mood (Kelly 2001). Considerable experience is required in exercise prescription to achieve increases in health, (cardio-respiratory fitness) whilst minimising risk. The prescription of exercise for patients on Phase III at WHSC began with the interpretation of the graded exercise test (ETT).

Exercise Intensity

Three methods for prescription of exercise intensity were used:

1. Percentage of Heart Rate Max, (% HR_{max})

This is probably the oldest scientific method of exercise prescription and has been used in general and diseased populations (Kelly 2001). Seventy per cent of HR_{max} is normally used and approximates to 55% VO_{2max}. According to ACSM (2000), this provides the necessary stimulus to improve or maintain aerobic fitness and is the method most frequently used for patients who have had an uncomplicated recovery from MI/CABG who are not taking beta-blockers.

2. Heart rate (HR) plotted against ETT.

This method uses the HR achieved at the penultimate stage of the ETT, as the target heart rate. This is used for de-conditioned patients and for those who are currently on beta-blockade therapy.

3. Ratings of Perceived Exertion

The Borg 6-20 RPE scale (1985) is used as an adjunct to setting target heart rate. It provides additional information to the patient on recommended levels of exercise. Patients are instructed to exercise between 11 and 13 (5 to 7 METS), or fairly light to somewhat hard. This is considered sufficient to achieve physiological adaptation (Kelly 2001). The RPE scale was used for all patients.

Duration of Phase III Exercise Sessions

All patients exercised continuously for a 20-minute period excluding warm-up and cool-down phases. The 20 minutes of exercise were split between four pieces of equipment and employed common forms of ergometery including, walking, cycling, rowing, stepping and arm ergometery. The warm-up lasted for between five and 10-minutes and depended on the patient's diagnosis. A

longer warm up of 10 minutes was used for angina patients as suggested in ACSM (2000) guidelines. During the cool-down session, light resistance training was used as a substitute for an aerobic cool-down. This helps to increase functional upper body strength. Total time for each session was therefore 35 to 40 minutes. Flexibility training was carried out as part of the warm up and following the cool down and all major muscle groups were included in this phase. No relaxation training was employed in the Phase III sessions.

Safety, Monitoring and Progression of Phase III exercises

Prior to commencing any exercise session in the fitness suite a brief patient history was taken. Blood pressure (BP), resting heart rate (HR) and rhythm were recorded along with details of the patient's general health and suitability for exercise. Provided there were no contra-indications they were allowed to continue. Throughout the session, staff monitored exercise HR and BP measurements at random periods. More formal procedures were in place for individuals considered to be at high risk of event, such as those with cardiomyopathy. Patients were instructed in the use of the RPE scale. Staff continued surveillance throughout the session observing for signs of over exertion, poor perfusion and general distress. On completion of the exercise session BP and HR were again recorded.

Progression on the 12-week session was carried out on an individual basis. The first four weeks of the session was considered as an initial conditioning phase consequently no increase in duration or intensity of exercise occurred within this period. If however the patient felt that the

programme was too difficult then the exercise physiologist altered the programme accordingly. After the 4th week a short consultation between physiologist and patient took place and if the patient agreed and felt comfortable then an increase in duration and intensity of exercise was fixed. This process was repeated following the 8th week.

HRV data acquisition and analysis

For test subjects, HRV data were collected at three time periods: 1) T1 (baseline), on the first week of Phase II, 2) T2, on the day of their exercise treadmill test and 3) T3 at the end of the Phase III exercise sessions. HRV data for the control group was collected at T1 and T3 only.

Prior to data acquisition subjects were asked to lie down for ten minutes to exclude relevant emotional or external influence on the autonomic nervous system. After this resting phase the HRV data acquisition was started. Data were collected for five-minutes in three positions (supine1 – standing –supine 2). In the present study HRV data from the first period (i.e. supine 1) was used for analysis and comparison.

Statistical analyses

Except where otherwise stated data are presented as mean ± standard error (SE). Prior to statistical analysis, all variables were tested for normality using the Shapiro-Wilk test. Unpaired t-tests and Mann-Whitney tests were used to compare baseline values for frequency domain variables between experimental and control groups. In experimental and control conditions, a two-way ANOVA followed by Bonferroni-adjusted t-tests were used to

explore differences between normally distributed parameters and a Friedman test with pairwise comparisons (Conover 1999) for non-normally distributed variables. A value of $P < 0.05$ was considered statistically significant.

Results

Time duration for T1 to T2 was 12.89 weeks ± 0.8: mean ± SE. T2 to T3 was 12.2 weeks ± 0.27: mean ± SE. The total time T1 to T3 for test subjects was 25.1 ± 0.73 weeks. *For the controls the period between T1 and T3 was 24.4 ±* 0.5 weeks.

Baseline HRV parameters were comparable in both groups with no significant differences observed for all variables. Tables 6.4.1 and 6.4.2 show the mean R-R interval and power spectral analysis results for test and control subjects.

DISCUSSION

This longitudinal study was designed to investigate, using HRV analysis, the effects of a 6-month (i.e. 25-week) cardiac rehabilitation programme on cardiac sympathetic and parasympathetic tone.

Chronic aerobic exercise elicits important cardio-protective adaptations that have been linked to reduced all-cause mortality (Blair *et al.* 1989, Cooke 1998). Effects such as increased aerobic capacity (consequent to decreased peripheral vascular resistance and increased cardiac output and arteriovenous oxygen difference) are well-documented (Blomqvist & Saltin 1983, Charlton & Crawford 1997) and characterise the physiological adaptation to endurance training. Despite the important implications for

TABLE 6.4.1

Means, standard errors, change, percentage change and P-values for all variables.

Variable	Units	Cardiac rehabilitation patients (n = 20)									
		T1		T2				T3			
		M	SE	M	SE	Change	† Diff	M	SE	Change	† Diff
Mean interbeat interval	ms	988	39.7	1036	34.0	48	4.9	1034	35.3	46	4.6
Total power	ms^2	395	63	676	158	281	71	721	142	326	83
Very low frequency power	ms^2	127	23	196	64	69	54	183	68	56	44
Low frequency power	ms^2	135	24	200	46	65	48	202	40	67	50
High frequency power	ms^2	133	29	279	70	146	109**	336	77	203	153**
Normalised LF power	N.U.	53	4.3	42	4.0	11	21*	45	5.1	8	15
Normalised HF power	N.U.	47	4.3	58	4.0	11	23*	55	5.0	8	17
LF HF ratio	~	1.0	0.3	0.72	0.3	0.3	33	0.6	0.3	0.4	40

*p<0.05. **p<0.01. †% of baseline. N.U. = normalised units, LF = low frequency, HF = high frequency.

TABLE 6.4.2

Means, standard errors, change, percentage change and P-values for all variables.

Variable	Units	Control subjects (n = 10)						
		T1		T3				
		M	SE	M	SE	Change	† Diff	P-value
R-R interval	ms	959	57	1004	71	45	4.7	0.31
Total power	ms^2	261	87	242	71	19	7	0.95
Very low frequency power	ms^2	78	24	59	26	19	24	0.36
Low frequency power	ms^2	102	53	83	36	19	19	0.93
High frequency power	ms^2	81	32	98	30	17	21	0.47
Normalised LF power	N.U.	50	8.0	41	7.1	9	18	0.18
Normalised HF power	N.U.	50	8.0	59	7.1	9	18	0.18
LF HF ratio	~	1.3	0.6	0.9	1.0	0.4	31	0.62

†% of baseline. N.U. = normalised units, LF = low frequency, HF = high frequency.

cardiovascular health, the effects of aerobic exercise on autonomic cardiovascular regulation have received comparatively little attention (Dixon *et al.* 1992, Smith *et al.* 1989). Effects such as resting sinus bradycardia and increased heart rate variability are thought to be mediated through adaptations in autonomic cardiovascular control (Kenney 1985).

Analysis of HRV provides important information on autonomic cardiovascular mechanisms by assessing the interaction of cardiac sympathetic and parasympathetic branches of the autonomic nervous system (ANS). In general most reports have shown that HRV increases following exercise training (Somers *et al.* 1991) but some have reported no significant changes (Bouthcher & Stein 1995). These conflicting results may be due in part to differences in methodology and types of training programme used or also to the ages of subjects studied.

Exercise is considered to improve cardiovascular outcomes partially by increasing vagal activity and attenuating sympathetic hyperactivity. High HRV is associated with increased parasympathetic cardiac control and reduced HRV is associated with decreased cardiac parasympathetic control. (Hayano *et al.* 1990). HRV is significantly higher in physically active subjects when compared with non-physically active healthy controls (Dixon et al. 1992, Kenney 1985).

In CHD and following MI there is an imbalance in ANS function (Casolo *et al.* 1992, Kleiger et al 1987). Chronic imbalance of the ANS is a prevalent and potent risk factor for adverse cardiovascular events, including mortality. Therefore any factor that leads to inappropriate activation of the sympathetic nervous system can be expected to have adverse effects on HRV

and thus on patient outcomes, while any factor that augments vagal tone tends to improve outcomes.

Exercise training is the major component of many cardiac rehabilitation (CR) programmes and at the start of this work the number of studies reporting the effects of exercise-based CR on HRV was small. Although study numbers remain limited, analysis of HRV has yielded positive information on the role of the ANS in the cardiac recovery process. In an early study using time and frequency domain measures of HRV, Malfatto *et al.* (1996) demonstrated an increase in parasympathetic tone following an eight-week exercise programme in uncomplicated MI patients. The same authors reported on the combined effects of beta-blocker and exercise therapy in 53 patients also following a first uncomplicated MI. They showed that the effects of exercise rehabilitation and beta-blockers are complementary to each other and that their association induces a more favourable sympathovagal balance, accelerating the recovery of a normal profile (Malfatto *et al.* 1998). Recently, Pardo *et al.* (2000) using 24-hour Holter monitoring and time and frequency domain analysis of HRV demonstrated that exercise conditioning improves HRV in cardiac patients on a Phase II, exercise-based cardiac rehabilitation programme who achieved at least 1.5 training METS increase over a 12-week period improves HRV. In the study 75% of patients demonstrated significantly increased total and high frequency power and also significant increases in normalised HF power. The authors suggested that the results were supportive of the concept that exercise training lowers the risk of sudden cardiac death via increased vagal tone, which likely beneficially alters ventricular fibrillatory and ischaemic thresholds. Using PSA of HRV a further

recent study by Carunchio *et al.* (2000) has reported similar findings on the effects of an eight-week exercise-training programme in patients recovering from a recent uncomplicated MI.

In comparison to the studies described above the present study examined the effects of a longer period of exercise-based cardiac rehabilitation and to the best of the author's knowledge, unlike any other study to date, used coarse-graining spectral analysis (CGSA) of HRV to measure the cardiac autonomic effects. CGSA as a method of spectral analysis is considered to be more suitable than fast Fourier transform alone in that it is able to separate harmonic and non-harmonic components of the power spectrum. Consequently the fractal component of the signal, which is considered to contribute to non-physiological 'noise' can be removed and a cleaner signal is obtained. This is considered to give a clearer estimate, particularly of the VLF and LF components of the power spectrum, and reflects more accurately the physiological processes that drive the cardiac autonomic nervous system (for further information refer to section 1.6.9.3).

Heart rate (HR) is modulated by the synergistic action of the sympathetic and parasympathetic branches of the cardiac ANS. In the present study similar non-significant decreases in HR were observed for both the control and experimental groups after the six-month period (T1 to T3) as demonstrated by an increase in mean R-R interval length. This reduction, although statistically non-significant, suggests a slight recovery of sympathovagal balance over time and is possibly the result of a healing or remodelling effect on the cardiac ANS.

When the results are further analysed within the frequency domain, different power spectral profiles between the groups become evident. In the control group there were no notable differences from baseline for total power (TP), very low frequency power VLF, low frequency (LF) and high frequency power. There was however an 18% non-significant decrease in normalised LF power and a similar increase in normalised HF power. This indicates a trend towards cardiac parasympathetic predominance and as previously suggested could represent improved recovery of the cardiac ANS over time. It is also possible however that non-autonomic factors are contributing to this effect and further studies are needed to further explore this hypothesis.

Within the frequency domain in the experimental group a different picture emerges. From baseline to the end of 6 months CR (T1 to T3) there was a non-significant, 83% increase of total power (TP). TP is a frequency domain measure of overall HRV and the lack of statistical significance is presumably caused by large variances. Similarly within the frequency domain, VLF power increased by 44% and LF power, which is generally considered to be a measure of cardiac sympathetic activity also increased by 50%. Both of which were statistically non-significant. The most important finding was observed in the high frequency (HF) component of HRV. The HF region between 0.15 to 0.4 Hz of the power spectrum is generally regarded as a measure of cardiac vagal activity (Task Force 1996). There was a significant 153% increase in HF power from baseline to the end of the six months rehabilitation period ($P < 0.01$).

When the results from the experimental group are subdivided into two 12-week blocks of exercise and analysed, further important information arises.

From the results (Table 6.4.1) it can be seen that in the first period of exercise i.e. from baseline (T1) to the end of 12 weeks rehabilitation (T2), non-significant increases were observed for TP, VLF and LF power and a 146% significant increase in HF power was observed ($P < 0.01$). There was also a significant decrease in normalised LF and a significant increase in normalised HF power (both $P < 0.05$). As previously described the representation of LF and HF in normalised units emphasises the controlled and balanced behaviour of the two branches of the ANS (Task Force 1996). Therefore the results when taken together strongly suggest an increase in cardiac vagal activity. From T2 to T3 the results are less impressive with no remarkable change in any variable besides a further small non-significant increase in total power and a non-significant 20% rise in HF power. The overall results demonstrate an initial rapid recovery of cardiac autonomic activity within the first 12-week period of rehabilitation, followed by a 'plateau' effect where the results are sustained but not improved upon further with the exception of non-significant increase in HF power. This is despite the fact that both exercise frequency and intensity are increased at Phase III i.e. in the second 12 weeks of exercise.

Following discussion of the results with the staff at WHSC, a possible explanation has been proposed for the initial increase and then apparent plateau effect on HRV. It is considered that this effect may in part be due to a difference in exercise methods. During the first 12 weeks of CR in this study, the exercise sessions consisted of continuous i.e. non-stop routines. In these sessions patients moved from one component to the next without a break. If they were not at a particular exercise station then they continued to march on the spot to keep the exercise intensity at a moderate level. During the second

block of 12-week exercise sessions at Phase III, although the patients were monitored continually they were allowed a certain amount of flexibility of choice. They were free to stop and chat etc. between different stages of the exercise session. It is thought that this may have caused a lessening of the exercise intensity and therefore inadequate maintenance of the stimulus necessary for continued physiological adaptation. Further research on this subject is therefore necessary to test this hypothesis.

Although the averaged HRV results of the study indicate a plateau effect after the first 12 weeks of exercise, this did not occur in all patients as can be seen in Figure 6.4, which shows a progressive improvement across all three stages of CR for one individual patient (DD).

In conclusion, most of the previous studies that have investigated the effect of exercise-based CR on cardiac autonomic tone have in general highlighted its favourable effects. They demonstrate that exercise-based cardiac rehabilitation facilitates a move towards increased cardiac parasympathetic activity leading to a relative reduction in sympathetic tone (Malfatto *et al.* 1996 and 1998, Pardo *et al.* 2000, Carunchio *et al.* 2000). The findings of the present study confirm these results and demonstrate that initially both sympathetic and parasympathetic components of the cardiac ANS are restored following a 6-month CR process but that the increase in vagal activity is more prevalent.

Limitations of the study

There are two main limitations of the present study. Firstly as previously described, although the rehabilitation programme that takes place at WHSC is

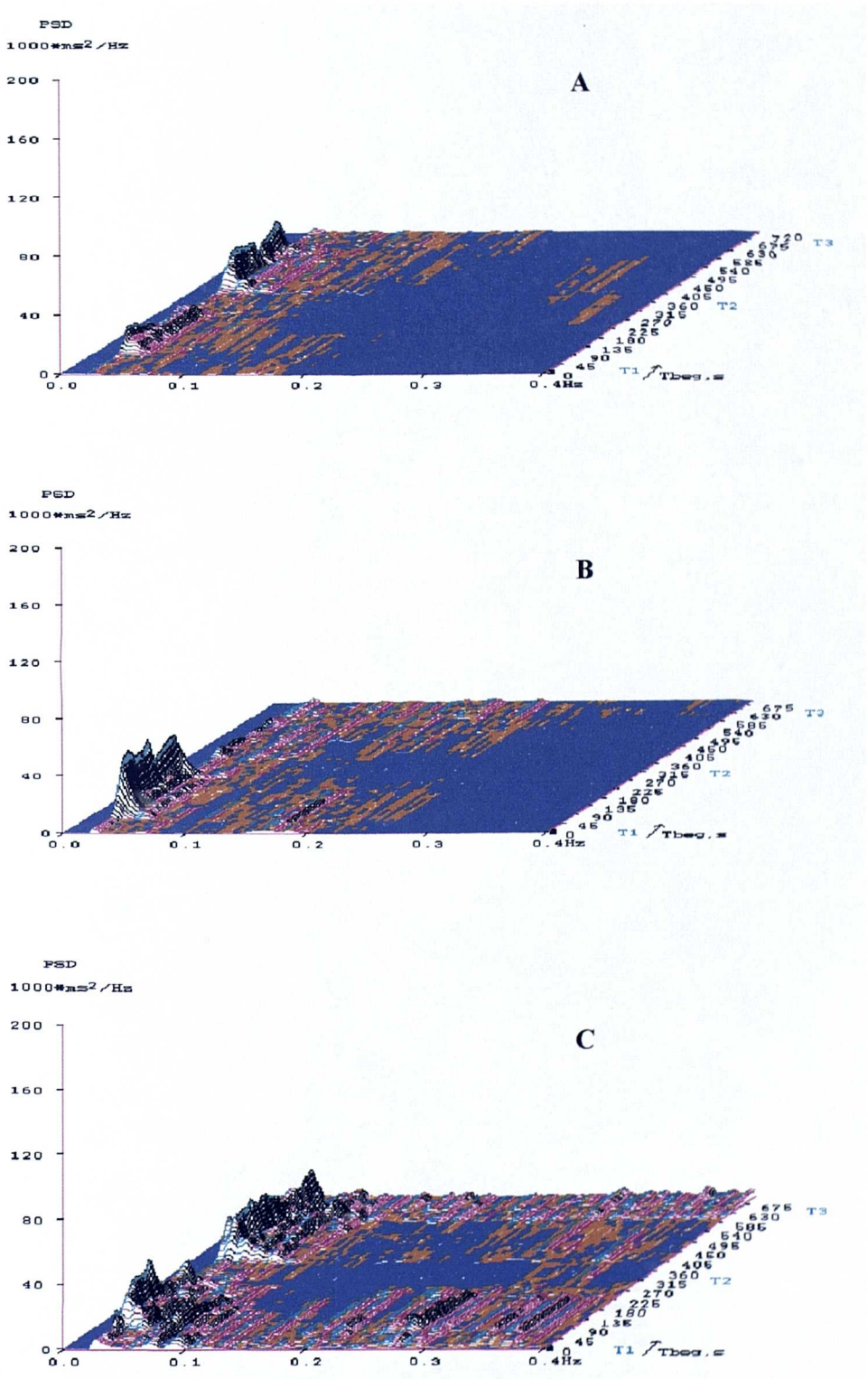


Figure 6.4 HRV power spectral graphs of the lying-standing-lying test demonstrating a progressive improvement in autonomic tone at three stages of cardiac rehabilitation (CR). (A) baseline (B) following 12-weeks and (C) after a total of 25-weeks CR.

predominantly an exercise-based system, other (both formal and informal) non-exercise components were on offer to patients. Therefore this precludes the possibility of reaching any definitive conclusion about the effects of exercise alone. Secondly perhaps the major concern of the study involves the inclusion of the so-called 'control group'. For the reasons stated previously because of ethical restraints it was not possible to recruit a control group proper. Therefore the author felt that the inclusion of an 'ecologically valid' control would add more real-world credibility to the study. Nevertheless the study has added further evidence for the positive effect of cardiac rehabilitation on improvement of cardiac vagal tone and has also provided further evidence for the validity of HRV as a measure of sympathovagal interaction.

CHAPTER SEVEN

BREATHING, HEART RATE VARIABILITY AND BAROREFLEX SENSITIVITY

7.1 THE EFFECTS OF BREATHING METHOD AND FREQUENCY ON HEART RATE VARIABILITY AND BAROREFLEX SENSITIVITY IN HEALTHY SUBJECTS

Abstract

Breathing exercises comprise a major part of many stress management interventions. Slow, rhythmical, deep breathing is commonly promoted as a method to facilitate relaxation. This study investigated the effect of different breathing rates on cardiac autonomic tone and blood pressure control. The influence of nose and mouth-only breathing was also assessed. Sixteen healthy subjects (8M, 8F aged 33.9 ± 2.5yrs, mean ± S.E.M.) breathed spontaneously for 5-minutes and then randomly at 6, 9 and 12 cycles per minute (cpm) whilst having continuous measures of heart rate (MP100, BIOPAC Systems Inc.-USA) and blood pressure (Portapres, TNO-Netherlands) performed. Cardiac autonomic tone was assessed by heart rate variability (HRV) in the time domain and by power spectral analysis (PSA) in the frequency domain. Blood pressure control was evaluated by baroreflex sensitivity (BRS) derived from a transfer function analysis of the PSA data. ANOVA and Bonferroni-adjusted t-tests were performed. Data are given as mean ± S.E.M. Time domain measures showed that compared to spontaneous breathing SDNN (ms) 81.5 ± 9.3 v 52.2 ± 5.2 (a primary index of HRV), RMSSD (ms) 51.2 ± 6.5 v 36.3 ± 4.7 and pNN50 (%) 17.0 ± 3.8 v 9.8 ± 3.0 (both measures of parasympathetic activity) were all significantly increased at 6 cpm ($p<0.01$), and SDNN (ms) 63.4 ± 7.3 v 52.2 ± 5.2 and pNN50 (%) 14.0 ± 4.1 v 9.8 ± 3.0 at 9 cpm ($p<0.05$). Total power (ms^2) (a frequency domain

measure of HRV) was increased at 6 cpm 7813.0 ± 1959.0 v 3045.0 ± 591.0 as was BRS (ms/mmHg) 10.6 ± 1.1 v 8.7 ± 1.0 ($p<0.05$). Compared with baseline, nose-only breathing demonstrated a decrease in LF/HF ratio (a measure of sympathovagal balance) 0.7 ± 0.3 v 3.1 ± 2.0 ($p<0.01$), normalised low frequency power (nLF-an index of sympathetic activity) 42.0 ± 5.0 v 62.0 ± 4.6 ($p<0.05$) and an increase in normalised high frequency power (nHF-a measure of parasympathetic activity) 58.0 ± 5.0 v 38.0 ± 4.6 ($p<0.05$). Compared with mouth breathing, nose-only breathing decreased nLF 42.0 ± 5.0 v 50.0 ± 5.0 and increased nHF 58.0 ± 5.0 v 50.0 ± 5.0 ($p<0.05$). These data suggest that reduced breathing frequency (particularly 6cpm) is associated with increased parasympathetic activity, cardiac autonomic tone and blood pressure control, and that nose only breathing is associated with altered sympathovagal balance.

INTRODUCTION

The achievement of certain breathing styles, especially within the discipline of yoga, is considered an essential prerequisite before relaxation training becomes effective for managing stress (Sovik, 2000). In the yogic model, breathing functions as an intermediary between mind and body. Preliminary techniques of breath control called 'pranayama', which include the slowing of breathing rates, are a commonly suggested means of reducing arousal, promoting relaxation and improving concentration (Pratap *et al.* 1978). The underlying premise of using breathing exercises in stress management is that since breathing is a behaviour that is under both voluntary and reflex control, it can be modified according to the principles of operant and classical Pavlovian conditioning (Ley, 1999).

An intricate relationship exists between breathing, heart rate (HR) and the control of blood pressure. Under resting conditions the electrocardiogram of healthy subjects exhibits periodic variation in the interval between heartbeats. This variability is partly due to fluctuations in parasympathetic (vagal) tone reflexly mediated by the different phases of breathing and results in acceleration of heart rate when breathing in and slowing of the heart rate when breathing out (Hirsch & Bishop 1981, Section 1.6.2). This is generally referred to as respiratory sinus arrhythmia.

Additionally, because the cardiovascular system is a 'pressure' controlled system, factors that alter blood pressure will also govern fluctuations in HR. Several biological sensors including mechanoreceptors in the atria, ventricle and lung and baroreceptors in the carotid sinus and aortic arch respond to perturbations in blood pressure and/or volume. These

biological sensors act as servo loops to oppose these changes by altering HR, often on a beat to beat basis (La Rovere 1995). The baroreceptor HR reflex or baroreflex, is considered to be the most rapid blood pressure buffering mechanism (Gerritsen *et al.* 2000). Baroreflex control of HR can be quantified by baroreflex sensitivity (BRS), which represents the amount of heart rate variability (HRV) attributable to changes in systolic blood pressure.

Heart rate variability is of increasing interest to clinicians after the demonstration that a reduction in HRV is associated with an increased risk of coronary heart disease (Liao *et al.* 1997), cardiac sudden death (Singer *et al.* 1988) and all-cause mortality (Tsuji *et al.* 1994). More recently, the prospective study Autonomic Tone and Reflexes after Myocardial Infarction (ATRAMI), has further demonstrated that markers of reduced vagal activity such as BRS and HRV are strong predictors of cardiac mortality after myocardial infarction (La Rovere *et al.* 2001).

Several studies have demonstrated the favourable effects of slower, deeper breathing on psychological variables such as cognitive anxiety, mental alertness, enthusiasm and subjective perceptions of energy levels (Wood 1993, Vedanthan *et al.* 1998). Additionally, using spectral analysis of HRV to determine cardiac autonomic tone, slowing of breathing rate was shown by Sakakibara & Hayano (1996) to reduce the cardiac parasympathetic withdrawal response to threat. They postulated that the results provided a rationale for the therapeutic use of the slowed respiration manoeuvre in attenuating cardiovascular reactivity in patients with anxiety disorder. Other studies have also reported on the effects of different breathing rates on cardiac autonomic tone as measured by HRV analysis but most have studied breathing

frequencies above 9 cpm or used only frequency domain analysis of HRV (Hirsch & Bishop 1981, Brown *et al.* 1993, Sanderson *et al.* 1996, Bernardi *et al.* 2000, Bloomfield *et al.* 2001). The purpose of this present study was to explore the effects of spontaneous breathing and controlled breathing at 6, 9 and 12 cpm on cardiovascular function using analysis of HRV both in the time and frequency domains and also to assess BRS by spectral analysis. Furthermore, the study was also designed to compare the effects of mouth and nose-only breathing on the same parameters.

METHODS

Participants

Sixteen, normal healthy volunteers (8M, 8F aged 33.9 ± 10.0 yr., mean ± SD) were recruited via e-mail bulletin boards and from verbal requests for volunteers. They comprised 12 members of the University Hospital staff and four friends who were not part of the University. Most of the subjects engaged in a modest amount of physical activity weekly. None were involved in regular, high intensity physical activity. Ethical committee agreement and informed consent was obtained prior to testing.

All subjects were in good general health with no medical conditions known to affect HRV or blood pressure control. No subject was taking any prescription drugs known to affect the cardiovascular system.

Data acquisition

Studies were carried out in the late afternoon (4 – 6 pm) in a warm, temperature-controlled environment (22°C). Subjects were asked to refrain

from smoking and drinking alcohol or any caffeine-containing beverages for at least eight hours prior to the study. They did not engage in any strenuous physical activity within the same time-period. They were allowed a light snack at least two hours before testing.

After arriving at the testing laboratory subjects sat for 10 minutes to return to a baseline resting state. During this time they were fitted with a Pneumotrace respiration transducer (World Precision Instruments Ltd, Aston, UK) to confirm breathing rate. Five-minute periods of continuous BP and ECG data were recorded into an AcqKnowledge software package (World Precision Instruments Ltd, Aston, UK). A Physiocal-controlled Portapres Model II (TNO, Amsterdam, Netherlands) via a finger cuff calibrated to the level of the heart was used and an MP100 ECG acquisition module (BIOPAC Systems Inc., Santa Barbara, CA, USA) via 3 ECG limb leads (Leong *et al.* 2000).

HRV and blood pressure analysis

Spectral analysis of the continuous BP and ECG data was performed in PowerMedic (Okiimura Taiwan CO., Ltd, Taiwan) using a fast Fourier transformation (FFT). Power spectral measurements were expressed as absolute units (ms^2) and normalised units (N.U.), an expression of the absolute units as a percentage of total power (see 1.6.8)

Baroreflex Sensitivity

BRS (ms/mmHg) was determined from the continuous BP and ECG data by the transfer function analysis using the CARSPAN program (Pro GAMMA,

Groningen, Netherlands) (Saul *et al.* 1991). The program performed a discrete Fourier transformation (DFT) of blood pressure and R-R intervals. The analysed time series was then corrected for artifacts and checked for stationarity and coherence. BRS was calculated from a period of 300 seconds as the mean modulus between spectral values of BP variability and heart rate variability (HRV) in the mid frequency band (0.07-0.15 HZ) with a coherence of 0.30.

Breathing protocol

To control for an order effect the breathing sessions were conducted in a randomised sequence. Subjects picked from a set of identical cards containing coded information about breathing method and frequency. Throughout the testing procedure subjects sat upright in a comfortable high-backed chair. Following fitting of the equipment, a five-minute baseline recording was taken with subjects breathing normally (spontaneous breathing). For the remaining tests subjects followed a visual guide on the computer screen corresponding to a particular breathing frequency. This was repeated on five separate occasions. On one occasion the subject wore a nose-clip and on another, breathed through the nose with lips sealed.

Statistical analyses

Except where otherwise stated data are presented as mean ± standard error (SE). All variables were tested for normality using the Shapiro-Wilk test. A two-way ANOVA followed by Bonferroni-adjusted t-tests were used to explore differences between normally distributed parameters and a Friedman

test with pairwise comparisons (Conover 1999) for non-normally distributed variables. Spearman's rank correlation coefficient (Rho) was used to compare RMSSD and pNN50 with spectral HF power and TP with SDNN. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Eight male and eight female subjects took part in the study. Compared with the males, the females were slightly older (34.9 ± 3.5 years *vs* 32.9 ± 3.8 years; P = 0.72 mean ± standard error). At baseline there were no significant differences between groups for any variables both in the time and frequency domains of HRV or for BRS. Spontaneous breathing rate at rest (baseline) ranged from 6 to 17 breaths per minute (12.8 ± 0.9: mean ± SE). Tables 7.1.1. summarises the time, frequency domain and baroreflex (BRS) results for all variables and indicates the significant differences from baseline. It also includes mouth and nose-only breathing comparisons. Table 7.1.2 summarises the results for all time and frequency domain and BRS variables at the three different breathing rates 6, 9 and 12 cpm). It shows comparisons between the groups and highlights the significant differences. Significant correlations were observed at baseline for SDNN and Total Power ($r = 0.94$, $P < 0.0001$) HF and RMSSD ($r = 0.92$, $P < 0.0001$) and HF at rest with pNN50 ($r = 0.87$, $P < 0.0001$). There were also a significant relationship between BRS and HF power at baseline ($r = 0.83$, $P < 0.0001$).

TABLE 7.1.1

Means and standard errors and P-values for all variables.

Variable	Units	Baseline		6 breaths/min		9 breaths/min		12 breaths/min		Mouth-only		Nose-only	
		M	SE	M	SE	M	SE	M	SE	M	SE	M	SE
Mean R-R interval	ms	868	32	880	34	856	28	880	36	890	36	860§	34
SDNN	ms	52.2	5.2	81.5**	9.3	63.4*	7.3	59.3	6.5	57.5	7.6	55.7	7.7
RMSSD	ms	36.3	4.7	51.2**	6.5	41	6.5	40.4	5.0	41.9	6.0	41.8	6.2
pNN50	ms	9.8	3.0	17.0**	3.8	14.0**	4.1	13.7	3.3	14.0	3.8	16.3	4.2
Total power	ms^2	3045	591	7813**	1959	4815*	1216	3567	814	3742	1016	3537	999
Very low frequency power	ms^2	996	195	1993	741	1748	432	1501	379	1700	526	1390	511
Low frequency power	ms^2	1358	359	5174**	1390	1544	493	1018	393	1004	361	855*	358
High frequency power	ms^2	691	174	647	151	1524**	600	1048	221	1040	270	1292*	467
LF/HF ratio	~	2.0	1.0	8.0**	1.4	1.0	0.40	1.0**	0.4	1.0**	0.3	0.7**§§	0.3
Normalised LF power	N.U.	62	4.6	89**	1.4	55	4	45**	5	50**	5	42**§	5
Normalised HF power	N.U.	38	4.6	11**	1.4	45	4	55**	5	50**	5	58**§	5
Baroreflex sensitivity	ms mm/Hg	8.7	1.0	10.6*	1.1	8.9	1.0	8.0	1.1	9.8	1.3	8.2	0.9

*$p<0.05$. **$p<0.01$, difference from baseline. § $p<0.05$, §§ $p<0.01$ nose versus mouth comparisons N.U. = normalised units.LF = low frequency, HF = high frequency.

TABLE 7.1.2

Means, standard errors and P-values for all variables.

Variable	Units	6 breaths/min		9 breaths/min		12 breaths/min	
		M	SE	M	SE	M	SE
Mean R-R interval	ms	880	34	856	28	880	35
SDNN	ms	81.5	9.3	63.4**	7.3	59.3**	6.5
RMSSD	ms	51.2	6.5	41**	6.5	40.4**	5.0
pNN50	ms	17.0	3.8	14.0**	4.1	13.7*	3.3
Total power	ms^2	7813	1959	4815**	1216	3567**	814
Very low frequency power	ms^2	1993	741	1749	432	1501	379
Low frequency power	ms^2	5174	1390	1544**	493	1018**	393
High frequency power	ms^2	647	151	1524**	600	1048**	221
LF/HF ratio	~	8.0	1.4	1.0**	0.4	1.0**§	0.4
Normalised LF power	N.U.	89	1.4	55**	4	45**§	5
Normalised HF power	N.U.	11	1.4	45**	4	55**§	5
Baroreflex sensitivity	ms/mm/Hg	10.6	1.1	8.9**	1.0	8.0**	1.1

*$p<0.05$. **$p<0.01$. Difference from 6 breaths/min. § $p<0.05$. Difference from 9 breaths/min. LF = low frequency, HF = high frequency.

DISCUSSION

The purpose of this study was to investigate the relationship between the method and frequency of breathing and cardiovascular control using heart rate variability (HRV) and baroreflex sensitivity (BRS) analysis.

HRV represents the variation of the cardiac R-R interval and this variability is modulated by the interplay of the cardiac sympathetic and parasympathetic nerves. Slow, deep breathing (6cpm) has been shown to have generally favourable effects on cardiovascular and respiratory function. Bernardi *et al.* (2001b) showed that slow breathing increases respiratory sinus arrhythmia and reduces the chemoreflex response to both hypoxia and hypercapnia. They suggested that enhanced baroreflex sensitivity might be one factor inhibiting the chemoreflex during slower breathing. Previously the same authors demonstrated increases in oxygenation of the blood and improved exercise tolerance in response to slow breathing (Bernardi 1998). In patients with chronic heart failure slow breathing has also been shown to reduce the exaggerated sensitivity of the respiratory chemoreflex and improve regular breathing (Friedman *et al.* 2000). It has also been suggested that slow deep breathing may reduce the deleterious effects of myocardial ischaemia and additionally increase calmness and wellbeing (Pratap *et al.* 1978, Friedman *et al.* 2000). These effects are considered to result in part from a synchronisation of respiratory and cardiovascular central rhythms. In the human there exists a 10-second cycle in blood pressure that is related to both vagal and sympathetic activity that was initially described over a century ago (Mayer 1876). These 0.1 Hz fluctuations, also known as Mayer waves, are thought to be generated either by a central nervous system oscillator in the

medulla oblongata or by the imperfect feedback control caused by one or other or both of two reflexes – the relatively slow baroreflex sympathetic response time and the faster vagal response to respiratory changes in blood pressure (De Boer *et al.* 1985, Sleight *et al.* 1995, Pieopoli *et al.* 1997 Bernardi *et al.* 2001a)

A reduction in breathing rate to approximately 6 cpm should therefore coincide with and augment the 10-second (0.1Hz) Mayer waves (Bernardi *et al.* 2001a). In this study this phenomenon can be effectively demonstrated by observing the R-R interval tachogram and power spectral graphs. During resting conditions of spontaneous breathing in normal, healthy subjects the effects of slow breathing on the R-R interval tachogram and power spectrum displays a fairly random, incoherent pattern (Figure 7.1.1). During slower breathing at 6 cpm a synchronising effect can be seen which demonstrates a more coherent form in the R-R interval tachogram (Figure 8.1.2). In the power spectral graph this translates into a significant 'entrainment' effect as synchronisation with the inherent cardiovascular rhythms (Mayer waves) occurs.

Because these favourable effects of slow breathing are mediated at least in part by a modulation of autonomic activity at both central and peripheral i.e. baroreflex levels (Bernardi *et al.* 2001a) they should be demonstrable by HRV and BRS analysis techniques.

The effect of changes in breathing rate on HRV

Within the time domain of HRV, the standard deviation of inter-beat intervals (SDNN) is generally regarded as the primary index of HRV. In the present

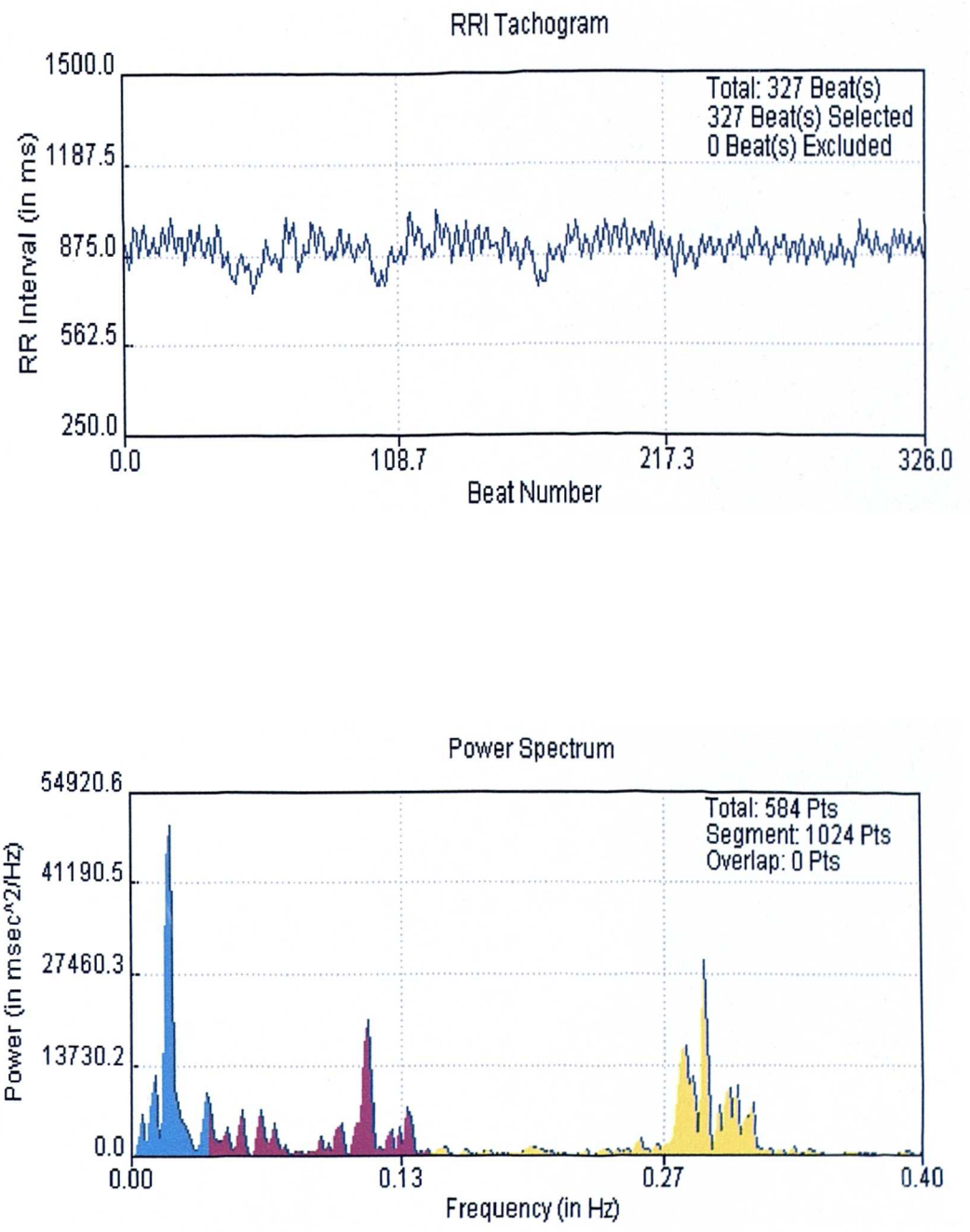


Figure 7.1.1 An R-R interval tachogram (**top**) and HRV power spectral graph (**bottom**) from patient KS at baseline (spontaneous breathing).

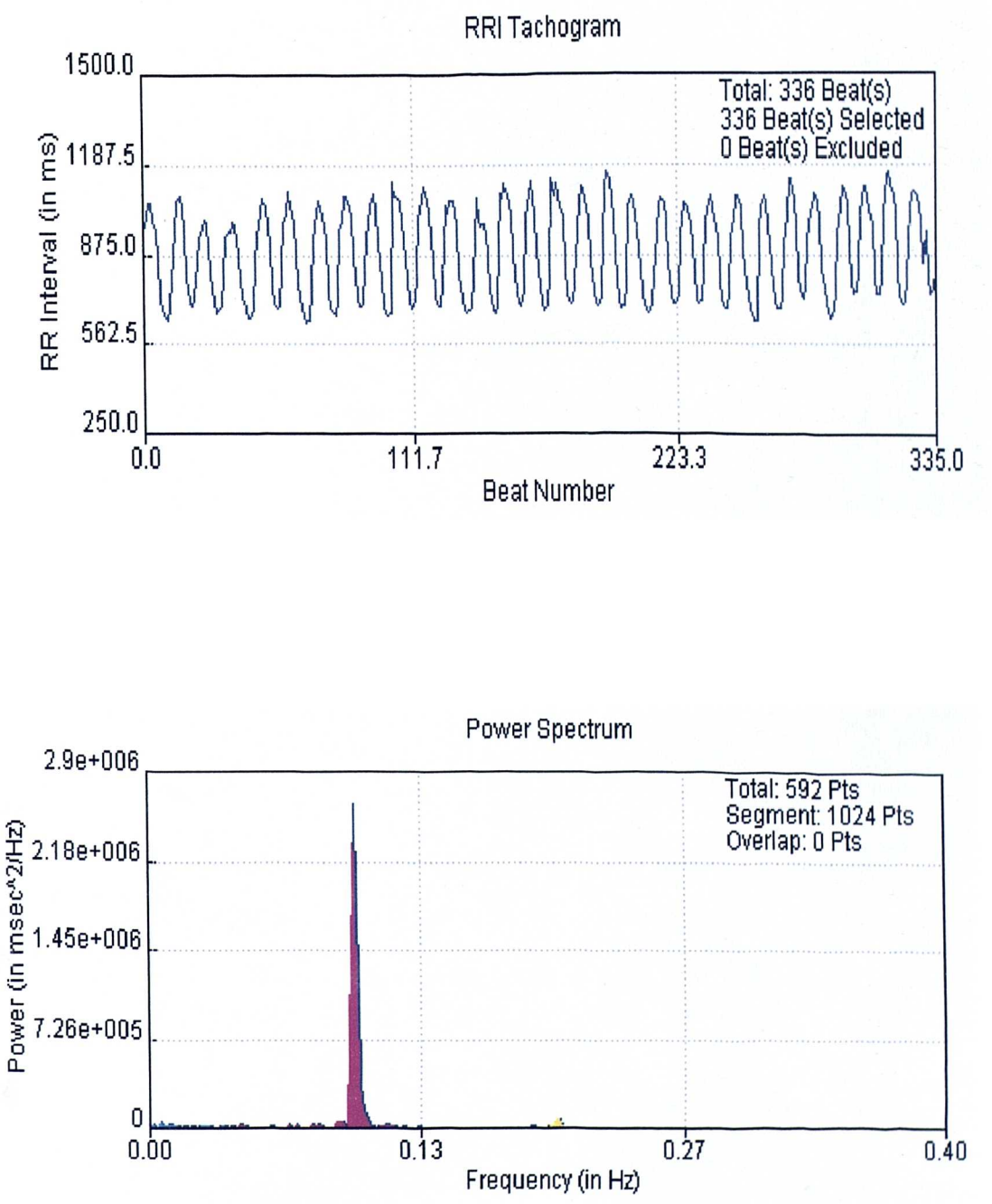


Figure 7.1.2 An R-R interval tachogram (**top**) and HRV power spectral graph (**bottom**) from patient KS during controlled breathing at six breaths/min.

study, in comparison to spontaneous baseline levels, breathing at 6 cpm was shown to have the most significant effect on SDNN increasing by 56.1% ($P < 0.01$). Breathing at 9 cpm showed a lesser but nonetheless significant increase of 21% ($P < 0.05$). Additionally within the time domain, root mean square of successive differences showed a significant 41% increase from baseline at 6 cpm ($P < 0.01$) and furthermore pNN50 was shown to be significantly greater at both 6 and 9 cpm (both $P < 0.01$). These short-term changes in HRV reflect the rapid alterations characteristic of the parasympathetic nervous system and contrast with the more gradual changes normally seen in the sympathetic nervous system.

In the frequency domain the increased ANS activity at 6 and 9 cpm was shown by a significant increase in total power (TP) as represented by the sum of all power frequencies ($P < 0.01$ and 0.05 respectively). This was not seen at 12 cpm as shown below in Figure 8.1.3. TP is considered to be equivalent to the SDNN of the time domain and at baseline these variables showed significant correlations ($r = 0.94$, $P < 0.0001$)

The very low frequency range (VLF), which falls below 0.04 Hz, is considered to reflect the action of long-term regulatory mechanisms related to thermoregulation and to the renin-angiotensin system, which regulates peripheral vascular resistance (Ori *et al.* 1992). In this study there were no significant differences found in VLF power across the entire breathing range This therefore suggests that breathing at different frequencies does not influence these peripheral mechanisms.

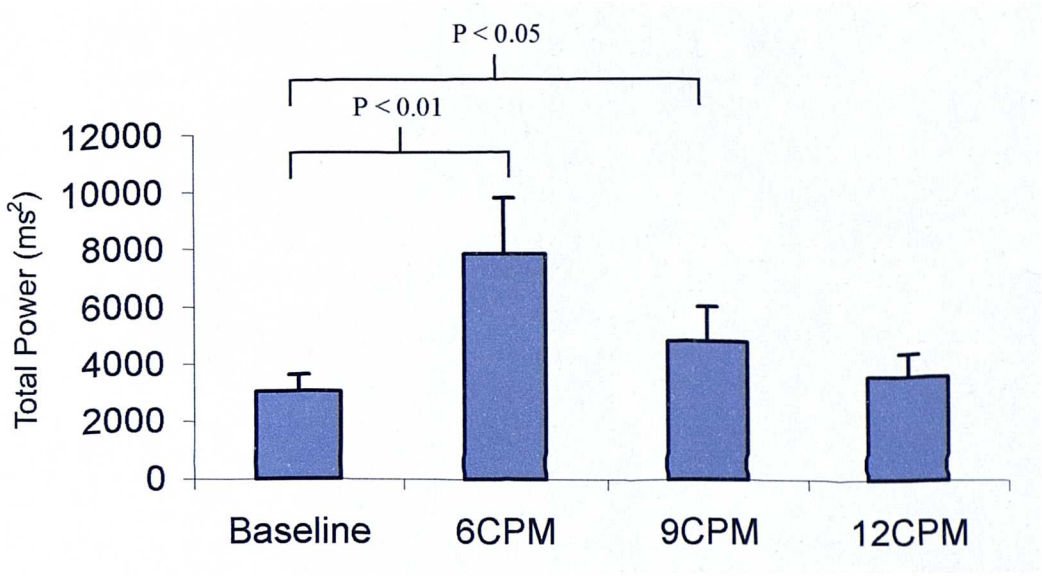


Figure 7.1.3 Differences from baseline and significance values for total power of heart rate variability at breathing frequencies of 6, 9 and 12 cycles per minute (CPM).

Significant variations were also identified in the low frequency (LF) and high frequency (HF) power spectral components although care needs to be taken in the interpretation of these data. As previously mentioned in Section 4.3, there is still much debate regarding the interpretation of these frequency domain components (Goldberger *et al.* 1999, Eckberg 2000). LF variations in the range 0.04 to 0.15 Hz of the power spectrum are generally considered to reflect cardiac sympathetic activity and in the range 0.15 to 0.40 Hz, high frequency oscillations are linked to respiratory sinus arrhythmia. These are often referred to as the 'respiratory frequency' and considered to reflect cardiac parasympathetic activity (Ori 1992). The term respiratory frequency can be misleading and some workers have suggested that if breathing frequency falls below 9 cycles per minute (0.15 Hz) then the respiratory frequency will be reflected by an increase in LF power (Coker *et al.* 1984,

Malliani *et al.* 1991, Ori *et al.* 1992). If therefore the results are taken in isolation, it would appear based on the view that the LF range reflects sympathetic activity that a large increase in sympathetic activity has occurred. In fact because RSA is vagally mediated, the increase observed during controlled breathing below 9 cpm (0.15 Hz) would actually represent increased parasympathetic tone. Therefore great care needs to be taken in the interpretation of results, particularly in absolute LF power and normalised values. HF power is also said to be highly correlated with the time domain variables of root mean square successive difference and pNN50. (Kleiger *et al.* 1987). The present study yielded significant correlations between both these variables at baseline. The correlation between baseline high frequency power with root mean square successive difference was 0.92, $P < 0.0001$ and with pNN50 was 0.87, $P < 0.0001$. Reporting time domain parameters alongside frequency domain results can also assist interpretation of this complex area of research.

The powerful effect of breathing at 6cpm was further highlighted when compared with breathing rates of 9 and 12 cpm. With the exception of VLF at both 9cpm and 12 cpm, all HRV variables both in the time and frequency domain were significantly different from breathing at 6 cpm. Significant differences were also seen in LFnorm and HF norm and LF/HF ratio between breathing at 9cpm and 12 cpm. BRS was also found to be significantly different at 9 and 12 cpm (both $P < 0.01$) when compared to 6 cpm. This again highlights the powerful effect of a simple change in breathing frequency particularly at 6 cpm.

The effect of changes in breathing rate on baroreflex sensitivity

In terms of BRS there was a 22% significant increase at 6cpm when compared with baseline ($P < 0.01$). No significant changes were seen at other breathing rates. BRS is generally considered to be mediated by the parasympathetic nervous system and this result when compared to the HRV results tends to confirm this suggestion.

Mouth v Nose breathing

Although in recent years investigations into the effects of changing breathing patterns on HRV has expanded considerably, to the best of the author's knowledge there are no studies that have compared the effects of mouth-only and nose-only breathing on HRV and BRS. In this study subjects breathed at 12 cpm by nose-only and mouth-only and the results on HRV and BRS were compared. Breathing at 12 cpm (0.2 Hz) was carried out to minimise the effects of 'spillover' of the respiratory component into the LF range as described above. In general the results demonstrate that in comparison to mouth-only breathing, nose-only breathing tended to increase those parameters of HRV that reflect increased cardiac parasympathetic tone i.e. reducing LFnorm, increased Hfnorm and a shift in LF/HF ratio indicating a shift towards parasympathetic predominance. Paradoxically there was a significant increase in HR as represented by a decrease in mean R-R interval ($P < 0.05$). This phenomenon is not readily explained and again highlights the complex nature of this area of research. It is possible that non-neural changes on intrinsic cardiac mechanisms are affected possibly as the result of sinus node modifications (Sleight 1998). The results are further confounded by the

fact that there was a non-significant decrease in BRS in the nose-only breathing condition. BRS is generally considered to be parasympathetically mediated and therefore the results suggest that the cardiac sympathetic system may also have a role in short-term blood pressure control. Further studies with larger subject numbers may help clarify this area of research.

There are several important conclusions that can be drawn from this present study:-

- To fully appreciate the effects of any intervention on cardiac autonomic tone it is important to consider both time and frequency domain variables in assessing and interpreting results.
- Visual inspection of both R-R interval tachogram and power spectral graphs is also desirable and considerably enhances the interpretation of results.
- When assessing cardiac autonomic tone using HRV analysis it is essential to control for, or at least recognise the important effect of breathing rate on HRV parameters. Controlled breathing should be performed above a rate of 9 cpm (0.15Hz) thus ensuring that the influence of RSA remains in the high frequency range. In this way the HF range can be reliably be referred to as the 'respiratory frequency' and any non-respiratory increases in HRV variables can be more accurately quantified.
- Slowing of breathing rate, particularly at 6cpm has a powerful effect on both the time and frequency domains of HRV and BRS and when taken as a whole the results indicate increased activity of the parasympathetic nervous system.

Therefore in the context of the research of this thesis this study has demonstrated that as a stress management intervention, a conscious effort to reduce breathing rate to around 6 cpm can have a powerful effect on cardiovascular parameters. Considering the poor prognosis of reduced HRV and BRS in many conditions a simple breathing re-training programme particularly including slow, deep breathing at 6 cpm may be effective in improving sympathovagal balance.

CHAPTER EIGHT

GENERAL DISCUSSION

8.0 GENERAL DISCUSSION

Chronic imbalance of the autonomic nervous system (ANS) is a prevalent and potent risk factor for adverse cardiovascular events, including mortality. Any factor that leads to inappropriate activation of the sympathetic nervous system (SNS) can be expected to have adverse effects on cardiovascular measures, while any factor that augments parasympathetic nervous system (PNS) tone tends to improve outcomes (Curtis & O'Keefe 2002). Prolonged psychological stress, overwork fatigue and negative psychosocial factors all have the potential to affect autonomic function adversely and thus cardiovascular prognosis.

Stress management in its various forms is aimed at reducing SNS activity, increasing PNS tone or a combination of both and the main purpose of this thesis was to investigate the physiological and some of the psychological outcomes of several techniques popularly used to alleviate the effects of stress. To put into context the effects of the various stress management interventions, the effects of the stress response on the physiological and psychological markers used in the subsequent studies were investigated.

In the early stages of the research, following an unsuccessful attempt to use plasma and salivary beta-endorphins as stress markers, attention was focussed on short-term analysis of HRV to measure the effects of stress and relaxation. HRV analysis is a non-invasive measure of cardiac sympathetic and parasympathetic activity and after a slow start in finding a suitable system; several different commercial systems became available. They were the Polar NV-Advantage, Biopac/Okimura and VariaPulse TF4 systems. The validation

studies in Chapter Three showed that in resting conditions with healthy individuals, FFT and autoregressive modelling (AR) were interchangeable as methods PSA of HRV. When these methods were compared to coarse-graining spectral analysis (CGSA), significantly reduced values as expected were observed in the VLF and LF regions. This highlights the need for caution when comparing the results of studies using different HRV systems but would be of less importance when the patient is his/her own control.

Using a three-phase orthostatic test, the Polar NV-Advantage and VariaPulse TF4 systems also proved useful in determining autonomic profiles for normal and cardiac rehabilitation subjects. This provided further evidence for the reliability and validity of these methods. Although there were considerable differences in cost for the three systems, the sampling methodologies were identical. The Polar NV-Advantage system is at least ten times less expensive than the other two systems and this is an important factor in the context of health resourcing. In the opinion of the author, it represents an extremely cost effective, easy-to-use method for the measurement of cardiac sympathovagal tone and would probably prove most useful as a screening tool in large population studies.

The Polar NV-Advantage system was successfully used in Chapter Four, to investigate the short-term effects of mental stress and relaxation on cardiac ANS tone. Using a modified version of the Stroop Word Colour Conflict Test in healthy subjects, changes indicating increased sympathetic activity were evident across all time and frequency domain variables of HRV. Significant increases in HR, muscle and emotional tension were also seen and the results were

characteristic of a classical defence/arousal response. This further demonstrated that this simple, cost-effective method of analysing HRV was suitable for the detection of short- term changes in sympathovagal balance.

Section 4.2 demonstrated the effects of a 5-minute guided imagery (GI) relaxation session on cardiac ANS function again using the Polar HRV system. Although no significant changes were observed for any HRV variables, there was a significant reduction in HR and improvement in emotional state. These changes were consistent with a mild relaxation effect and were not evident in the control group. The results of this study are quite promising considering that the subjects had no previous experience of GI as a relaxation method. It is possible that with sufficient practice, this simple method of inducing relaxation may prove useful for reducing HR and improving HRV in a variety of conditions. The study also highlighted the potentially important effect of breathing rate on HRV and the research was directed to explore this topic in more detail (see Chapter Seven).

In Chapter Five, the Polar NV-Advantage system was again used to assess HRV following myofascial trigger-point massage therapy (MTPT) to the head, neck and shoulder areas in both healthy and type-2 diabetic subjects with painful neuropathy. The chapter also reported on the effects of various sympathetic nerve blocks on HRV.

Myofascial trigger-points (MTrP) are small discrete painful areas of tension that are often present in muscles as a result of stressful conditions such as overwork fatigue and emotional distress. From experience the author has noted that MTrP are present in the majority of people and most report that they feel

physically and psychologically more relaxed following massage. To the best of the author's knowledge these studies were the first to explore the effect of therapeutic massage on HRV and the study was an attempt to give 'real science' to these techniques thus giving credibility to the anecdotal reports.

MTPT was found to be effective in improving HRV and increasing factors associated with relaxation in both groups of subjects. It also significantly improved pain scores in the diabetic population. An important finding was that despite the significant attenuation in cardiac autonomic tone (i.e. reduced HRV) seen in the type-2 diabetic subjects at baseline compared to normal subjects, there were still remarkably similar increases in total power of HRV following massage. These results are very positive and suggest that MPTP may represent a useful adjunct to more orthodox methods for the treatment of painful neuropathy. In the same study music therapy was also shown to induce a relaxation effect although to a lesser extent than the massage. The combination of music and massage may further enhance the relaxation response and further studies with larger subject numbers are needed to confirm this hypothesis.

Because MTPT is a relatively straightforward technique for the removal of active MTrP, it could be taught to the partners or friends of patients to help relieve pain and tension. A further feature of active MTrp is that they very often mimic the effects of certain heart conditions and therefore MTPT may also have applications in the field of cardiac rehabilitation for the reduction of pain and chronic muscle tension following MI (Delaney 1997). In the book 'Myofascial Pain and Dysfunction: The Trigger Point Manual (1983), Janet Travell, a leading

authority on muscle and soft tissue research suggests that hidden MTrP may be activated by a variety of conditions associated with stress, poor posture and heavy lifting. She further suggests that chest pain that persists following an acute MI is often due to MTrP in the pectoral muscles and that the removal of these trigger-points by whatever method can remove all symptoms. To quote from the manual: '*Corrective actions must include convincing the patient (when true) that the myofascial chest pain is treatable pain due to skeletal muscle rather than cardiac origin. Correction of poor standing and sitting posture and avoidance of mechanical overload insure continued freedom from pain*'

Patients suffering from refractory angina often suffer from severe; debilitating pain (Chester *et al.* 2000) and Chapter Five additionally explored the effects of sympathetic nerve blockade at various sites in a group of refractory angina patients. In the patients who received left-sided stellate ganglion blockade there were no significant differences observed for any HRV variables compared to baseline following treatment. There was however a significant reduction in HR. This suggested that the treatment, which was extremely painful and uncomfortable for the patients, was reducing sympathetic activity causing a relative increase in cardiac vagal tone. From the results seen in the previous studies (Sections 5.1 and 5.2) it is possible that MTPT may represent a less stressful alternative to pharmacological blockade for treating angina patients. Also the results of the study suggest that MTPT may be working by a similar mechanism to pharmacological blockade i.e. by temporarily reducing SNS activity and increasing parasympathetic tone. In the subjects who received

suprascapular and paravertebral blockade the results on HRV were variable and success for the treatment of pain was limited.

Exercise is considered to improve cardiovascular outcomes partially by increasing vagal activity and attenuating sympathetic hyperactivity. Chapter Six focussed mainly on the effects of a six-month exercise-based, cardiac rehabilitation programme on sympathovagal balance. Using the VariaPulse TF4 system it was shown by CGSA of HRV that patients receiving exercise rehabilitation had significantly improved parasympathetic tone after three months of rehabilitation. This appeared to reach a 'plateau' during the second, three-month phase. In order to maintain improvement, it is suggested that exercise intensity during the second 12-week period should be kept at a level high enough to continually promote physiological adaptation. Perhaps if less time were allowed for patients to rest or chat between using individual pieces of exercise apparatus then an adequate stimulus for change would be maintained.

Chapter Six also highlighted the favourable effects of beta-blocker therapy and showed that despite the bradycardic effect of beta blockade, there was still a clear sympathovagal response during the orthostatic test suggesting that the autonomic reactivity to a simple change in posture was not diminished. In Section 6.3, the beneficial effects of beta blockade therapy were further demonstrated when it was shown that patients not receiving medication had increased cardiac anoxia as determined by increased ST depression. This appeared to be associated with increased sympathetic drive. As this was not

evident in beta-blockade patients, it suggests that the medication provides a protective effect on the sympathetic mechanism.

In Chapter Seven the Biopac/Okimura system was used to examine the effects of breathing rate and method on HRV and baroreflex sensitivity. Often 'the aspects of things that are most important to us are hidden because of their simplicity and familiarity' (Wittgenstein 1878). Perhaps this is indeed the case when the results from this study are examined. Impressive increases in HRV and BRS were demonstrated when breathing frequency was reduced from the normal spontaneous breathing rate (12.8 ± 0.9 mean ± SEM) to breathing rates of 6 and 9cpm. Optimal increases were seen when breathing rate was reduced to 6 cpm but even a small reduction to 9 cpm showed significantly enhanced HRV. The study also examined the effects of nose-only breathing compared to mouth-only breathing and showed that nose-only breathing induced significant changes in HRV measures consistent with increased parasympathetic activity. There was however a paradoxical increase in HR, which still remains difficult to explain and may possibly be elucidated with further studies in this area.

The important message from this study is that perhaps a simple technique exists to enhance autonomic function and improve blood pressure control. This may indicate the use of a simple breathing re-training programme in combination with more orthodox treatments. Slow, deep breathing training particularly at 6 cpm could be applied using audiocassette tapes, or by watching a visual guide on a computer screen or could also be used as part of biofeedback training. It is hoped that future studies will further explore this interesting area of research.

In conclusion the studies in this thesis indicate that the analysis of HRV by various methods is a valid and reproducible technique for the evaluation of stress and relaxation in health and disease. However not all methods are comparable and cross-study comparisons need to recognise the impact of different approaches to the same measurement. When examining the effect of a variety of relaxation techniques on HRV, slow, deep breathing and therapeutic massage were found to be the most efficient methods for increasing short-term HRV. Furthermore, music and guided imagery also improved HRV but to a lesser extent. Exercise as part of a six-month cardiac rehabilitation programme was shown to be effective in increasing HRV probably as the result of increased cardiac parasympathetic tone. Whether improvements in HRV persist in the longer-term or can be maintained through reinforcement remains to be determined by further studies with larger subject populations.

PUBLICATIONS DERIVED FROM WORK PRESENTED IN THIS THESIS

FULL JOURNAL ARTICLES

Delaney,J.P.A. (1997) Massage as a treatment for cardiac rehabilitation: an initial theoretical justification. *Journal of the British Association for Cardiac Rehabilitation*. 7, 22 – 28.

Delaney,J.P & Brodie, D.A. (2000) Effects of short-term psychological stress on the time and frequency domains of heart rate variability *Percept.Mot.Skills*, **91**, 515-524.

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Delaney J, Leong K, Woodward A, McNulty S, MacFarlane I, Brodie D, Wilding J. (2002) The acute effects of myofascial trigger-point massage therapy on heart rate variability and blood pressure in patients with painful diabetic neuropathy. *Pain* (in submission).

JOURNAL ABSTRACTS

Brodie, D.A., Delaney, J.P.A., Drysdale, I., Williams, D. (1999) A low-cost, heart rate variability analysis system *The Journal of Physiology* **518P**

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CONFERENCE PRESENTATIONS\INVITED LECTURES

Delaney J P A. Pain relief through relaxation therapy. Invited Lecture *National Back Pain Association,* Merseyside Branch – September 1996.

The following four communications were presented together as a 10-minute oral communication and also presented as posters at the Annual Conference of the *British Association for Cardiac Rehabilitation.* September 2000.

1. Delaney J P A, Brodie D A. Heart rate variability: A measure of sympathovagal tone.
2. Brodie D A, Delaney J P A. Heart Rate Variability Differences between CHD and Normal Subjects.
3. Delaney J P A, Brodie D A. Heart rate variability changes during an orthostatic test in cardiac rehabilitation patients.
4. Houghton A, Kelly J, Delaney J P A, Bundred P Brodie D A. The relationship between heart rate variability at rest and functional measures during a graded exercise test.

GLOSSARY OF TERMS

ANGINA: pain in chest, neck, arm or jaw produced by lack of oxygen to the heart muscle (myocardium), not resulting in permanent damage.

ATTENUATE: reduce the amplitude of a signal or current.

AUTOGENIC TRAINING: a course of instruction during which subjects learn a series of simple exercises in body awareness and relaxation designed to switch off the stress-related "fight and flight" system of the body and switch on the "rest, relaxation and recreation" system.

BAROREFLEX SENSITIVITY: a phenomenon by which receptors located along the walls of blood vessels respond to changes in blood pressure. These receptors are connected to the heart by nerves, which carry the message to pump faster or slower in response to pressure changes.

BODY MASS INDEX (BMI): a classification of weight, calculated by weight (kg) divided by height (m^2).

BORG SCALE: a scale for rating perceived exertion in which the number 6 is associated with no exertion and the number 20 with maximal exertion. For practical purposes, ratings of perceived exertion measured with the Borg scale are considered reliable and valid estimates of effort.

CARDIAC REHABILITATION: a multi-factorial, multi-professional service designed to cater for the needs of patients with coronary heart disease (and their families with the objective of restoring them to as normal a life as possible.

COHERENCE: the property of waves to have a constant phase relationship.

DEPRESSION: a mood disorder whose main features are sadness and dejection, decreased motivation and interest in life, negative thoughts (such as feeling hopeless or low in self-esteem) and physical symptomatology (such as disturbed sleep, chronic fatigue, and loss of appetite and energy.

EFFLEURAGE: Gentle stroking hand movements along the length of a muscle.

ENTRAINMENT: the tendency for two oscillating bodies to lock into phase so they vibrate in harmony. It is also defined as a synchronisation of two or more rhythmic cycles.

FREQUENCY DOMAIN: a signal displayed in the frequency domain shows the amplitude or power of the signal as a function of frequency. Transforming a time-domain signal usually provides frequency representation.

GUIDED IMAGERY: a 'mind-body' intervention aimed at helping the individual through words (narration) and often music to calm the mind and relieve stress and assist the body to heal.

HACKING: light slaps or 'karate chops' along the long axis of tissue using the ulnar border of the hand.

HEART FAILURE: syndrome in which reduced pumping capacity of the heart leads to shortness of breath, fatigue or oedema, at rest or on exertion.

KNEADING: squeezing across the width of a muscle or slow circular compression of soft tissues against underlying bone.

METS: (metabolic equivalents). A simplified system for classifying physical activities where one MET is equal to the resting oxygen consumption, which is approximately 3.5 ml of oxygen per kilogram of body weight per minute (3.5 ml/kg/min).

OPERANT CONDITIONING: based upon the ideas of a B. F. Skinner this is a form of learning, also known as instrumental conditioning that suggests that learning is a function of change in overt behaviour. Operant conditioning is often used in a variety of clinical setting for behaviour modification.

CLASSICAL CONDITIONING: a form of learning first described by Pavlov that involves the pairing of stimuli independent of an organism's behaviour.

PETRISSAGE: skin rolling or pressure applied across the width of a muscle useful for stretching contracted or adherent fibrous tissue and relieving muscle spasm.

PRANAYAMA: a set of breathing exercises developed in the discipline of yoga claimed to be effective in improving both physical and mental health.

PROGRESSIVE MUSCLE RELAXATION: a relaxation technique first described by Edmund Jacobsen, which involves the tightening and relaxation of specific muscle groups in a particular order. It commonly used to reduce symptoms of stress, anxiety, insomnia and certain types of chronic pain.

QUALITY OF LIFE: a concept encompassing the broad range of physical and psychological characteristics and limitations, which describe an individual's ability to function and derive satisfaction from doing so. Quality of life is now usually assessed from the perspective of the individual rather than as a rating by health or other professionals.

RATING OF PERCEIVED EXERTION: quantification of the subjective intensity of physical effort (see Borg *scale*).

RISK FACTOR: factor known to increase the likelihood of future cardiac morbidity or mortality.

R-R INTERVAL: the time duration between two consecutive R waves of the electrocardiogram.

STRESS: the interaction between person and environment where the individual perceives that demands being placed upon him or her exceed his/her available resources and therefore threaten his/her well-being. The term is also used in exercise testing, which is sometimes referred to as 'stress-testing', relating to the physiological stress or load, rather than the psychological perception of stress.

TACHOGRAM: time-series derived from the occurrence of the R-wave of the electrocardiogram.

TAPOTEMENT: vigorous, percussive massage techniques used to vibrate tissues, trigger cutaneous reflexes and cause vasodilation.

TENSION MYOSITIS SYNDROME: a soft tissue condition that often involves the muscles, ligaments and nerves of the back and neck. The pain is caused or worsened by tension and can be alleviated by a mental process that focuses on release of mental and emotional tension rather than physical symptoms.

TIME DOMAIN: a signal in the time-domain is a representation of amplitude as a function of time.

TRANSFER FUNCTION: a definition of the relationship between the inputs to a system and its outputs. The transfer function is typically used in the frequency domain.

YOGA: a discipline comprising several different aspects including the practice of certain postures, breathing training and meditative exercises to achieve a balance between the physical, mental and emotional principles of the human system.

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APPENDICES

APPENDIX 1

Physical Tension, Emotional State and Pain Questionnaire.

Name: ..... Date: .....

How would you rate yourself ***right now*** on the following measures?

1. **Physical Tension.** Place a mark across the line below to indicate how you feel **NOW** with reference to physical tension:

No muscle tension anywhere ——— **most muscle tension ever**

2. **Emotional State.** Place a mark across the line below to indicate how you feel **NOW** with reference to your emotional state:

Most calm and composed ever ——— **Most stressed ever**

3. **Pain.** Place a mark across the line below to indicate how you feel **NOW** with reference to your sensation of pain:

Free from pain ——— **Most pain ever**

APPENDIX 2

Contraindications to Exercise Treadmill Test

Absolute

- A recent significant change in the resting ECG suggesting significant ischaemia, recent myocardial infarction (within 2 days) or other acute coronary event.
- Unstable angina
- Uncontrolled cardiac arrhythmia causing symptoms or haemodynamic compromise
- Severe symptomatic aortic stenosis
- Uncontrolled symptomatic heart failure
- Acute pulmonary embolus or pulmonary infarction
- Acute myocarditis or pericarditis
- Suspected or known dissecting aneurysm
- Acute infections

Relative

- Left main coronary stenosis
- Moderate stenotic valvular heart disease
- Electrolyte abnormalities (e.g., hypokalaemia, hypomagnesaemia)
- Severe arterial hypertension (i.e., systolic BP of > 200mmHg and/or a diastolic BP of > 110mmHg) at rest
- Tachyarrhythmias or bradyarrhythmias
- Hypertrophic cardiomyopathy and other forms of outflow tract obstruction
- Neuromuscular, musculoskeletal, or rheumatoid disorders that are exacerbated by exercise
- High degree atrioventricular block
- Uncontrolled metabolic disorders (e.g., diabetes, thyrotoxicosis, or myxoedema)
- Chronic infectious disease (e.g., mononucleosis, hepatitis, AIDS)

APPENDIX 3

MODIFIED BRUCE PROTOCOL EXERCISE TREADMILL TEST

Modified Bruce Protocol			
Functional class	Stage	mph	% grade
Normal 1	VIII	5.5	20
	VII	5.0	18
	VI	4.2	16
	V	3.4	14
	IV	2.5	12
II	III	1.7	10
III	II	1.7	5
IV	I	1.7	0

APPENDIX 4

BORG SCALE

RATING OF PERCEIVED EXERTION

6	No exertion at all
7	Extremely light
8	
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard (heavy)
16	
17	Very hard
18	
19	Extremely hard
20	Maximal exertion

Patient Instructions:

This is a scale for rating perceived exertion. Perceived exertion is the overall effort or distress of your body during exercise. The number 6 represents no perceived exertion or leg discomfort and 20 represents the greatest amount of exertion that you have ever experienced. At various times during the exercise test you will be asked to select a number that indicates your rating of perceived exertion at the time. Do you have any questions?

APPENDIX 5

ANGINA SCALE

0	No pain or discomfort
1+	Light, barely noticeable
2+	Moderate, bothersome
3+	Severe, very uncomfortable
4+	Most severe pain experienced

DYSPNOEA SCALE

0	No pain or discomfort
1+	Mild, noticeable to patient
2+	Mild some difficulty, noticeable to observer
3+	Moderate difficulty, but can continue
4+	Severe difficulty, cannot continue

APPENDIX 6

INDICATIONS FOR TERMINATING EXERCISE TEST

Absolute Indications

- Drop in systolic blood pressure of more than 10 mmHg from baseline blood pressure despite an increase in workload, when accompanied by other evidence of ischaemia
- Moderate to severe angina or increasing nervous system symptoms (e.g. ataxia, dizziness, or near-syncope)
- Signs of poor perfusion (cyanosis or pallor)
- Technical difficulties monitoring the ECG or systolic blood pressure
- Subject's desire to stop
- Sustained ventricular tachycardia
- ST elevation (1.0mm) in leads without diagnostic Q-waves (other than VI or AVR)

Relative Indications

- Drop in systolic blood pressure of more than 10 mm Hg from baseline blood pressure despite an increase in workload, in the absence of other evidence of ischaemia ST or QRS changes such as excessive ST depression (2mm horizontal or down-sloping ST-segment depression) or marked axis shift
- Arrhythmias other than sustained ventricular tachycardia, including multifocal PVCs, triplets of PVCs, supraventricular tachycardia, heart block, or bradyarrhythmias
- Fatigue, shortness of breath, wheezing, leg cramps or claudication
- Development of bundle branch block or IVCD that cannot be distinguished from ventricular tachycardia
- Increasing chest pain
- Hypertensive response – Systolic blood pressure of 250 mmHg and/or a diastolic blood pressure of 115 mmHg

APPENDIX 7

CLINICAL INDICATIONS FOR OUTPATIENT CARDIAC REHABILITATION

Indications

- Medically stable post-myocardial infarction
- Stable angina
- Coronary artery bypass graft surgery
- Percutaneous transluminal coronary angioplasty
- Compensated congestive heart failure
- Cardiomyopathy
- Heart or other organ transplantation
- Other cardiac surgery including valvular and pacemaker insertion (including implantable cardioverter defibrillator)
- Peripheral vascular disease
- High-risk cardiovascular disease ineligible for surgical intervention
- Sudden cardiac death syndrome
- End-stage renal disease
- At risk for coronary artery disease, with diagnoses of diabetes mellitus, hyperlipidaemia, hypertension, etc.
- Other patients who may benefit from structured exercise and/or patient education (based on physician referral and consensus of the rehabilitation team)

APPENDIX 8

CLINICAL CONTRAINDICATIONS FOR OUTPATIENT CARDIAC REHBILITATION

- Unstable angina
- Resting systolic blood pressure of 200 mmHg or resting diastolic blood pressure of 110 mmHg should be evaluated on a case-by-case basis
- Orthostatic blood pressure drop of 20 mmHg with symptoms
- Critical aortic stenosis (peak systolic pressure gradient of 50 mmHg with an aortic valve orifice area of 0.75 cm^2 in an average size adult)
- Acute systemic illness or fever
- Uncontrolled atria or ventricular arrhythmias
- Uncontrolled sinus tachycardia (120 beats/min)
- Uncompensated congestive heart failure
- 3 AV block (without pacemaker)
- Active pericarditis or myocarditis
- Recent embolism
- Thrombophlebitis
- Resting ST segment displacement (2mm)
- Uncontrolled diabetes (resting blood glucose of 400 mg/dL)
- Severe orthopaedic conditions that would prohibit exercise
- Other metabolic conditions, such as acute thyroiditis, hypokalaemia or hyperkalaemia, hypovolaemia, etc.

APPENDIX 9

Phase II Circuit Training

Pulse taken here

Warm Up

Marching on the spot, side stepping, heel digs, knee raises, side shoulder raises, biceps curls, upright rowing.

Flexibility training

Triceps, shoulder girdle, latissimus dorsi, deltoids, quadriceps, hamstring, calf.

Circuit

Brisk walking
Biceps curls
Marching on the spot
Side shoulder raises
Stepping or toe touching
Side leg raises
Side stepping
Standing up/sitting down
Wall press-ups

Pulse taken here

Cool down

Marching on the spot, side stepping, heel digs, knee raises, side shoulder raises, biceps curls, upright rowing.

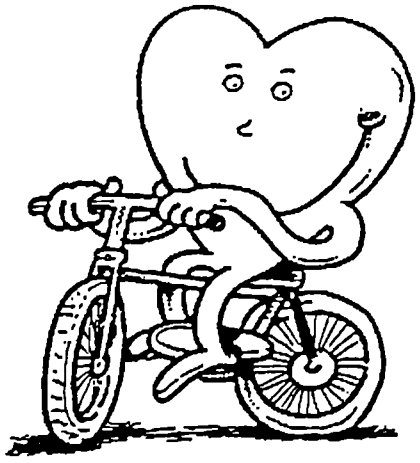
Flexibility training

Triceps, shoulder girdle, latissimus dorsi, deltoids, quadriceps, hamstring, calf.

APPENDIX 10A

WIRRAL CARDIAC REHABILITATION PROGRAMME

Cardiac Class Exercises

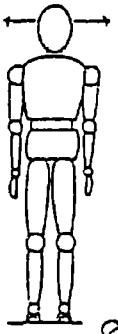


APPENDIX 10B

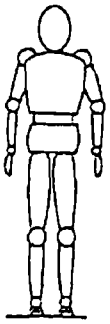
Warm up Exercises

These exercises should be done at a slow pace, as they have been designed to gradually warm up the body.

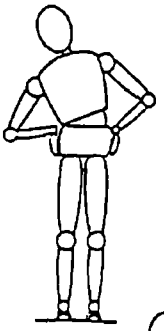
1. Turning head from side to side x 10



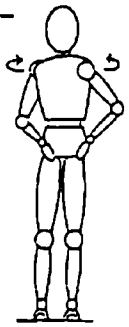
2. Shrugging shoulders x 10
   Circle arms also x 10



3. Side bends x 10

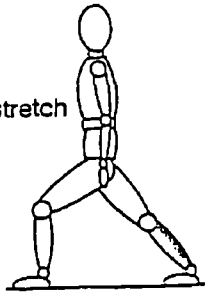


4. Side twists x 10

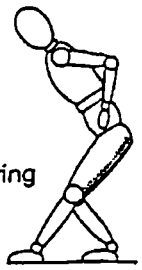


Short stretches - These exercises are designed to stretch the muscles we will be using in the main exercises in order to prevent injury. All exercises to hold approx 15 seconds.

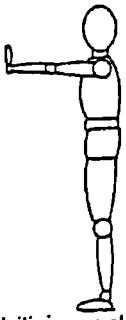
1. Calf stretch



2. Hamstring

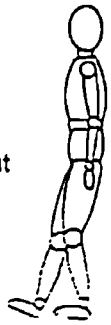


3. Back and arm stretch



4. Chest stretch

5. Mobilising ankle joint



APPENDIX 10C

Cardiovascular Exercises

If it is your 1st, 2nd, 3rd week only do these exercises for 30 seconds

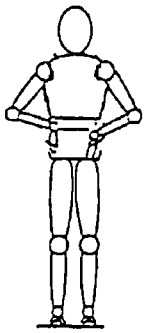
4th week	40 seconds
5th week	50 seconds
6th week	60 seconds

If you experience any pain or discomfort whilst doing these exercise please Stop only do what you can.

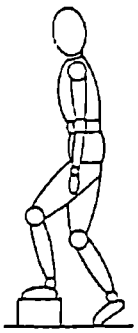
1. Bicep curls

2. Marching on the spot.

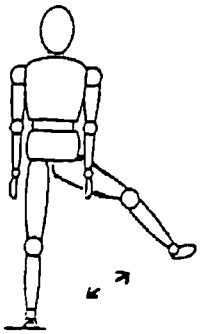
3. Upright rowing



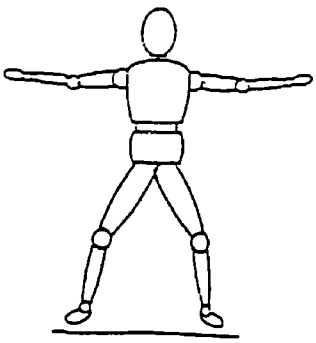
4. Stepping toe touching



5. Leg raises

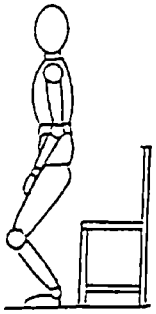


APPENDIX 10D

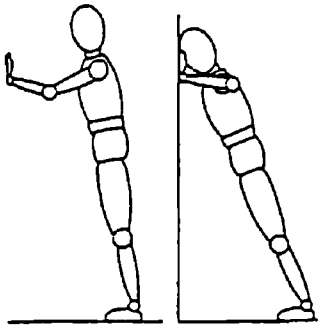


6. Side stepping

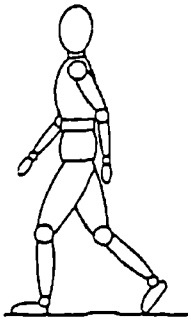
7. Standing up
Sitting down



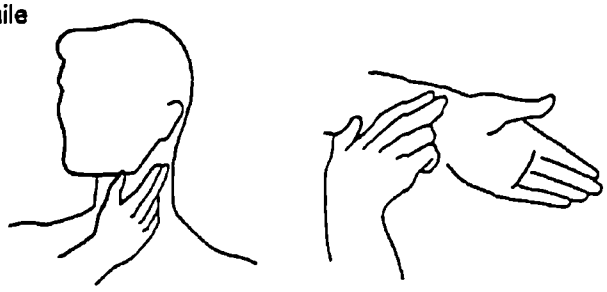
8. Wall press-ups



9. Walking up
and down



10. Gently march on the spot while
you take your pulse

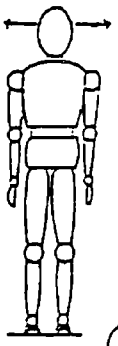


APPENDIX 10E

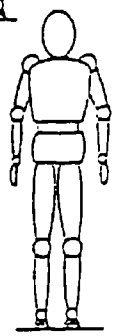
Cool down exercises

These exercises should be done at a slow pace, as they have been designed to gradually cool down the body.

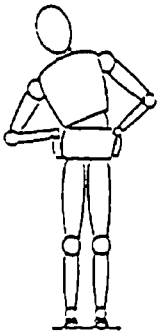
1. Turning head from side to side x 10



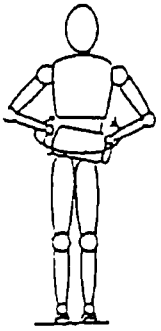
2. Shrugging shoulders x 10
   Circle arms also x 10



3. Side bends x 10

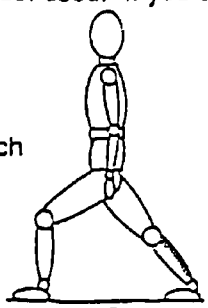


4. Side twists x 10



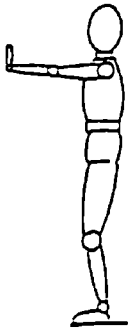
These exercises should be held for a longer period of time as we need to stretch the muscles we have just used. If you can hold these stretches for approx 20 seconds.

1. Calf stretch

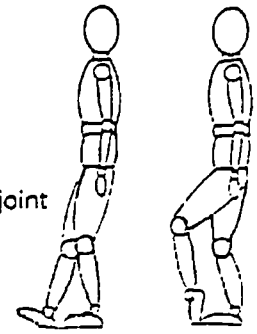


2. Hamstring

3. Back and arm stretch



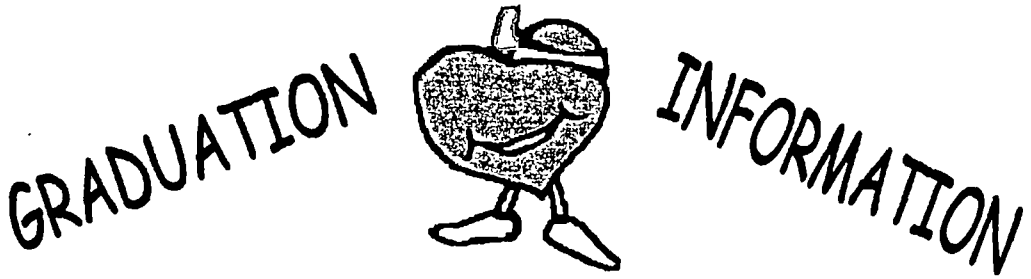
5. Mobilising ankle joint



4. Chest stretch

APPENDIX 11A

THE WIRRAL CARDIAC REHABILTATION PROGRAMME



WE OFFER A NUMBER OF SERVICES AND ACTIVITIES TO HELP YOU ON YOUR ROAD TO RECOVERY.

WE HAVE PUT TOGETHER THIS BOOKLET AS A GUIDE TO WHAT IS AVAILABLE TO YOU.

PLEASE CONTACT US IF YOU WOULD LIKE FURTHER INFORMATION ON THE ENCLOSED ACTIVITIES.

WIRRAL HEART SUPPORT CENTRE
ST CATHERINE'S HOSPITAL
CHURCH ROAD
BIRKENHEAD

TEL: (0151) 604 7307

January 2002

APPENDIX 11B

THE WIRRAL HEART BEAT APPEAL

BEAT HEART DISEASE IN WIRRAL

'WIRRAL HEART BEAT' IS A LOCAL REGISTERED CHARITY ESTABLISHED IN 1990 AND FOUNDED BY FORMER PATIENTS AND THEIR FAMILIES.

'WIRRAL HEART BEAT' WAS CREATED TO SUPPORT THE CARDIAC REHABILITATION PROGRAMME AND TO RAISE FUNDE FOR THE BENEFIT OF PRESENT AND FUTURE PATIENTS.

'WIRRAL HEART BEAT' IS ALSO COMMITTED TO:

- ADVANCING THE EDUCATION OF ALL IN THE KNOWLEDGE OF CARDIOVASCULAR DISEASE.
- PROMOTING RESEARCH INTO THE CAUSE, PREVENTION AND MANAGEMENT OF CARDIOVASCULAR DISEASE.

PLEASE HELP US!
ONE DAY WE MAY NEED TO HELP YOU!!

*DONATIONS
*FUND RAISING
*EVENTS
*LEGACIES
*SUPPORT

VOLUNTEERS ARE ALSO MUCH NEEDED AND MOST WELCOME.
FOR FURTHER INFORMATION PLEASE CONTACT:

WIRRAL HEART BEAT
WIRRAL HEART SUPPORT CENTRE
ST CATHERINE'S HOSPITAL
CHURCH ROAD
BIRKENHEAD
TEL/FAX: (0151) 604 7307

APPENDIX 11C

HEALTHY HEART CLASS

..... A NEW HEALTHIER AND FITTER YOU .....

ONE AND A HALF-HOURS PER WEEK FOR 7 WEEKS AND YOU COULD BE ON THE ROAD TO A HEALTHIER, FITTER AND MORE CONFIDENT LIFESTYLE.
EACH WEEK WILL CONSIST OF 45 MINUTES EXERCISE, 30 MINUTES OF A HEALTH TOPIC, PLUS RELAXATION.

SESSIONS: TUESDAY 10:15 - 11:45 A.M

HEALTH TOPICS:
FOOD LABELLING
WEIGHT MANAGEMENT
PHYSICAL ACTIVITY
ALCOHOL
FLEXIBILITY/MOBILITY

THIS IS A NON-COMPETATIVE PROGRAMME AND EVERYONE WORKS AT THEIR OWN LEVEL OF FITNESS.
..... PARTNERS WELCOME .....

GYM

HAVE YOU COMPLETED YOUR 5 WEEK CARDIAC REHABILITATION PROGRAMME AND/OR HEALTHY HEART CLASS?

WOULD YOU LIKE TO HAVE AN EXERCISE TOLERANCE TEST AND DO SUPERVISED GYM ACTIVITY?

COME AND USE THE EXCELLENT FACILITIES IN OUR EXERCISE SUITE.
SESSIONS: TUESDAY/FRIDAY A.M
MONDAY/WEDNESDAY A.M
TUESDAY/THURSDAY P.M

APPENDIX 11D

CHAMPISSAGE

(INDIAN HEAD MASSAGE)

A RELAXING MASSAGE THAT WILL HELP RELIEVE HEADACHES, EYESTRAIN AND STRESS RELATED PROBLEMS, THUS IMPROVING CONCENTRATION AND LEAVING YOU FEELING RELAXED, AND YET ALERT.

YOU REMAIN FULLY CLOTHED AND SEATED IN A CHAIR FOR THIS 30-MINUTE MASSAGE. THE AREAS OF THE SHOULDERS, UPPER ARMS, NECK, SCALP AND FACE ARE GENTLY, FIRMLY AND RHYTHMICALLY MASSAGED.

AROMATHERAPY AND MASSAGE

AROMATHERAPY USES ESSENTIAL OILS TO PROMOTE AND MAINTAIN HEALTH AND VITALITY. ESSENTIAL OILS DILUTED WITH A BASE OIL ARE USED TO MASSAGE THE BACK AND SHOULDERS, WHICH RELIEVE STRESS AND PROMOTE RELAXATION.

REIKI

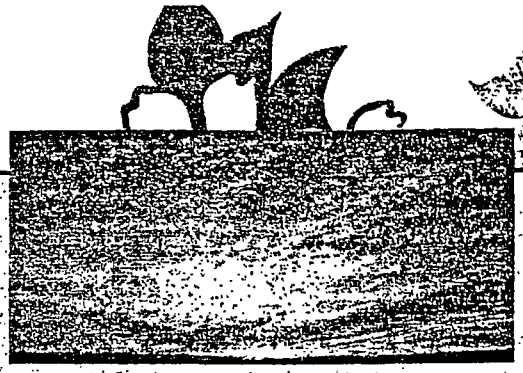
REIKI (PRONOUNCED RAY-KEY) IS A HOLISTIC TREATMENT LASTING 1HOUR. THE TREATMENT INVOLVES THE HANDS OF THE PRACTITIONER BEING PLACED GENTLY ON THE BODY. THE POSITION OF THE HANDS IS MOVED EVERY 3 MINUTES. REIKI IS NOT A FORM OF MASSAGE AND THE HANDS REMAIN STILL.

IT IS A VERY RELAXING AND SOOTHING EXPERIENCE AND THE PERSON RECEIVING REIKI REMAINS FULLY CLOTHED.

THE ABOVE METHODS ARE ALL ADMINISTERED BY:
CLINICAL PRACTITIONER
SUE LAWTON, BM DIP A, MTSPA

WANT TO KNOW MORE? PLEASE PICK UP A LEAFLET FROM THE WAITING AREA OR ASK SUE LAWTON.

APPENDIX 11E



REFLEXOLOGY

Reflexology is a complimentary therapy involving the treatment of various disorders by gently working the reflexes of the feet. It can also be used preventatively to keep the body in good working order. Following illness, stress, injury, or disease, the body is in a state of "imbalance", and vital energy pathways are blocked, preventing the body from functioning effectively. Reflexology can be used to restore the body's natural equilibrium and encourage the body's own natural ability to heal.

General benefits can include:
Stress relief Deep Relaxation Increased Energy Pain relief

Relief from

Insomnia
Menstrual problems Skin problems Migraine
Poor circulation Digestive disorders.
Arthritis
And others

~~~

THERAPIST : Bernadette Williams. IIHT. FHT.

If you would like more information, please take a leaflet from the waiting area, or call on 0151 604 7307
~~~

APPENDIX 11F

CARDIAC LINK UP

FRIDAY'S

(1st Class) 1:00PM - 2:00PM

& (2nd Class) 2:00PM - 3:00PM

FOLLOWING THE GRADUATION CLASS, IT IS OFTEN A NUMBER OF WEEKS BEFORE A PLACE IS AVAILABLE FOR YOU ON EITHER A HEALTHY HEART COURSE, OR IN THE EXERCISE SUITE.

WHILST YOU ARE WAITING, YOU HAVE THE OPPOURTUNITY EVERY FRIDAY TO CONTINUE YOUR EXERCISEES UNDER SUPERVISION AND FURTHER YOUR RELAXATION SKILLS.

..... EXERCISE .....

..... TEA BAR .....

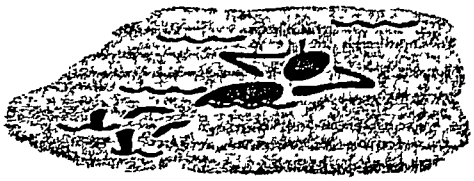
..... RELAXATION .....

WE SEE THIS AS AN EXTENSION OF THE 5 WEEK COURSE YOU HAVE JUST COMPLETED, SO JUST TURN UP NEXT FRIDAY FOR EITHER THE 1ST OR THE 2ND CLASS!!

PARTNERS WELCOME!

AQUAEROBICS

A FUN WAY TO DO GENTLE EXERCISE WITH THE SUPPORT OF WATER, WHICH HELPS PREVENT ACHES AND PAINS.



AT THE **EUROPA POOL**, CONWAY PARK, BIRKENHEAD.

40 MINUTES EXERCISE AND THEN 20 MINUTES FOR A RELAXING SWIM

EVERY FRIDAY 9:30 A.M - 10:30 A.M

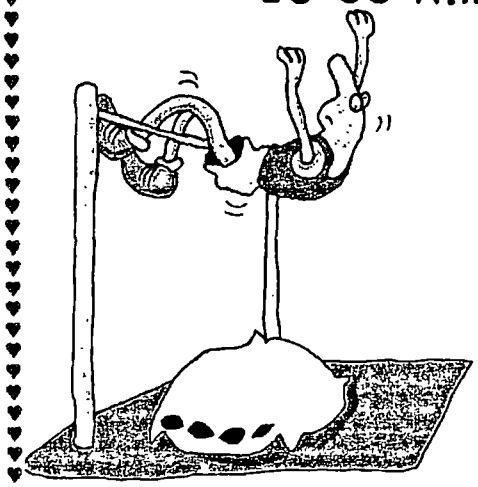
COST £2.00 (DISCOUNT AVAILABLE WITH WIRRAL LEISURE CARD.)

APPENDIX 11G

DROP-IN

OPEN MONDAY AND FRIDAY MORNINGS

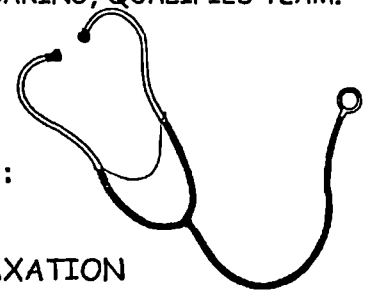
10:00 A.M - 11:30 A.M



IF YOU, A MEMBER OF YOUR FAMILY OR A FRIEND HAS SUFFERED OR IS PRESENTLY SUFFERING FROM A HEART PROBLEM.

PLEASE CALL IN AND SEE US.

HELP AND SUPPORT FROM A CARING, QUALIFIED TEAM.

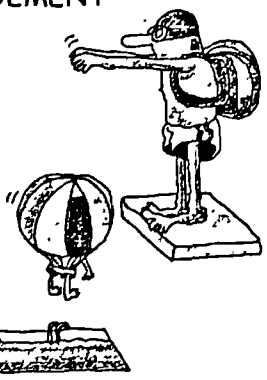


ADVICE GIVEN ON:

DIET - EXERCISE - RELAXATION

KEEPING FIT

STOPPING SMOKING - STRESS MANAGEMENT



APPOINTMENTS NOT NECESSARY!

APPENDIX 11H

Community Keep-Fit

ELAINE CORLETT

MONDAY: 10am - 12 noon
St John's Ambulance HQ
1 Mather Road
Oxton

MONDAY: 12 noon - 1pm
St John's Ambulance HQ
1 Mather Road
Oxton

BERYL WITHY

MONDAY: 1.30pm - 4pm
Exercise and Relaxation
The Oval
Bebington
Wirral

THURSDAY: 1.30pm - 4pm
Exercise/Fitness Suite, Swimming
The Oval
Bebington
Wirral

RUTH MULLINS

TUESDAY: 10am - 12 noon
Field Road Health Centre
Wallasey

WEDNESDAY: 1.30pm - 3.30pm
The Chapel Hall
Old Maryland Lane
Moreton

TUESDAY: 1.30PM - 3.30PM
WOODCHURCH COMMUNITY CENTRE
(NEAR LEISURE CENTE ALONGISIDE
SPORTS BARN)

WEDNESDAY: 10AM - 12 NOON
ST STEPHENS CHURCH HALL
PRENTON

SUE SMETHURST

FRIDAY: 10am - 11.30am
Christchurch Church Hall
Port Sunlight

FOR MORE INFORMATION CALL HEALTHWISE FREE ON 0800 66 55 44

OTHER COMMUNITY BASED ACTIVITIES

APPENDIX 111

RESUSCITATION

WOULD YOU LIKE TO LEARN HOW YOU COULD HELP TO:

SAVE A LIFE?

RESUSCITATION SKILLS

..... WATCH NOTICEBOARDS FOR NEXT SESSION .....

NOTES