THE BAROREFLEX CONTRIBUTION TO HUMAN CARDIOVASCULAR CONTROL: INSIGHT FROM PASSIVE EXERCISE STUDIES.

A thesis submitted for the degree of Doctor of Philosophy

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ABSTRACT

The present thesis examined the affect of passive exercise on spontaneous baroreflex sensitivity (BRS) and cardiac sympathovagal balance. Other cardiovascular variables such heart rate (HR) and blood pressure (BP) were also assessed.

Study 1 revealed that during passive exercise spontaneous BRS is decreased, the cardiac sympathovagal balance is shifted as a result a vagal withdrawal, and HR and BP increase in parallel. Study 2 investigated the interaction between postural shift and passive exercise on baroreflex control and HR. At rest, the postural shift from upright to supine resulted increased BRS and elicited bradycardia, while during both upright and supine passive exercise decreased BRS and elicited tachycardia. Study 3 showed that after passive exercise the cardiac vagal traffic was increased and HR was attenuated compared with pre-exercise. While, total peripheral resistance (TPR) increased, resulting in BP elevation. Study 4 showed that during passive exercise the local muscle tissue oxygenation increases despite the augmentation in oxygen uptake.

In conclusion, the overall findings demonstrate that during passive exercise spontaneous BRS is decreased and the cardiac sympathovagal balance is shifted due to vagal withdrawal. The effects of passive exercise on BRS and HR override those of postural shift. After passive exercise cardiac vagal activity is enhanced and HR is reduced, while TPR and BP are elevated, presumably caused by increased vasoconstriction, as Q did not change. Also during passive exercise both muscle oxygenation and oxygen uptake increase.

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I would to thank my family and my mother for the support and encouragement.

This thesis is dedicated to my family.

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List of abbreviations

Abbreviation	Term
ANS	Autonomic nervous system
BP	Blood pressure
BRS	Baroreflex sensitivity
CBV	Central blood volume
DBP	Diastolic blood pressure
DMNV	Dorsal motor nucleus of vagus
EMG	Electromyography
HF	High frequency
HR	Heart rate
HRV	Heart rate variability
LF	Low frequency
LBNP	Lower body negative pressure
LBPP	Lower body positive pressure
MAP	Mean arterial pressure
MSNA	Muscle sympathetic nerve activity
NA	Nucleus ambiguus
n.u.	Normalised units
NTS	Nucleus tractus solitaii
PEH	Post-exercise hypotension
PI	Pulse interval
PNS	Parasympathetic nervous system
Q	Cardiac output

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Definitions of terms

Arterial baroreceptors: Stretch receptors located in the tunica externa of the carotid sinus and the aortic arch, responding to changes in transmural pressure within the arterial walls.

Arterial baroreflex: A feedback mechanism that controls beat-by-beat short-term blood pressure, minimising blood pressure oscillations and stabilising perfusion pressure in the face of disturbance to circulatory homeostasis.

Autonomic nervous system: It comprises the sympathetic and parasympathetic nervous system representing the efferent branch of the baroreflex, and regulating cardiac activity and vascular tone.

Cardiac output: The volume of blood ejected by the left ventricle in a minute, expressed in litres.

Cardiopulmonary baroreceptors: Stretch receptors located at the junction of the great veins and atrial, ventricular myocardium, and pulmonary arterial walls, responding to changes in central blood volume.

Central command: A feed forward mechanism arising from higher brain centres that activate in parallel the locomotor and cardiovascular centres.

Exercise pressor reflex: The combined actions of the mechanoreflex and the metaboreflex.

High frequency power: Portion of the heart rate variability total power comprising the frequency between 0.15 and 0.4 Hz, mainly related to cardiac vagal influence.

Low frequency power: Portion of the heart rate variability total power comprising the frequency between 0.04 and 0.15 Hz, mainly related to cardiac sympathetic traffic, also comprising some vagal and baroreflex influences.

Mechanoreceptors: Group III muscle afferents thin fibre sensory nerves, exhibiting unencapsulated nerve endings without a perineal sheath surrounding their receptive areas, and responding to mechanical stimuli.

Metaboreceptors: Group IV muscle afferents thin sensory fibres, located close to the blood vessels, responding to metabolic stimuli.

Mechanoreflex: A feedback mechanism that contributes to cardiovascular adjustments is response to muscular contraction and/or stretch.

Metaboreflex: A feedback mechanism that contributes to cardiovascular adjustments is response to metabolite accumulation.

Nucleus ambiguus: A region of histologically disparate cells located just dorsal (posterior) to the inferior olivary nucleus in the lateral portion of the upper (rostral) medulla. It gives rise to the efferent motor fibers of the vagus nerve terminating in the

laryngeal and pharyngeal muscles, as well as to the efferent motor fibers of the glossopharyngeal nerve terminating in the stylopharyngeus.

Nucleus tractus solitarius: Neurones located in the medulla oblongata that plays a major role in the regulation and integration of visceral systems, including baroreflex function.

Passive exercise: Passive movements of limbs or other body parts in absence of central command activation and muscular contraction.

Post-exercise hypotension: A clinically significant reduction in blood pressure below pre-exercise levels.

Sinus node: A small mass of specialised cardiac cells located in the posterior wall of the right atrium that acts as pacemaker by generating at regular interval the electric impulses of the heartbeat.

Spontaneous baroreflex sensitivity or gain: The rapidity and magnitude of baroreflex-induced pulse interval change in response to spontaneous blood pressure deviation from the baroreflex's operating point.

Stroke volume: The volume of blood ejected by ventricular contraction in a single heartbeat, expressed in millilitres.

Spectral analysis of heart rate variability: Beat-by-beat cardiovascular variability analysis using Fast Furier Transform that provides quantitative indices of autonomic neural control of the sinus node.

Ventrolateral medulla: The neural area located in the medulla oblongata representing the major site of preganglionic sympathetic neurones.

Chapter 1

Introduction

Cardiovascular system and baroreflex control

1.1 Introduction

The cardiovascular system, consisting of the heart and the blood vessels, plays a critical role in the maintenance of homeostasis (Rowell et al., 1986, Blomqvist and Saltin, 1983). The primary function of the cardiovascular system is to supply the various body tissues with adequate quantity of oxygen and nutrients, and remove carbon dioxide and other waste products of metabolism (Scheuer and Tipton, 1977, McMurray and Hackney, 2005). In addition, the cardiovascular system transports hormones to the target organs that play important role in the regulation of the body's functions (Deuster et al., 2000). The requirements of different tissues for oxygen and nutrients vary according to the level of activity, e.g. during exercise the skeletal muscle metabolic rate increases progressively with intensity (Raven et al., 2006). Furthermore, the circulatory homeostasis is profoundly affected by stressors such as orthostasis and exercise (Booth, 1988, Westerhof et al., 2006). It is therefore critical that the cardiovascular system is regulated on a moment-to-moment basis.

The arterial baroreflex is a feedback mechanism that plays a vital role in the maintenance of circulatory homeostasis, i.e., adequate perfusion pressure, by regulating arterial blood pressure (BP) on a beat-by-beat basis, via changes in autonomic outflow (Raven et al., 2006). The regulation of BP is accomplished by alterations in cardiac output (Q), mainly via changes in heart rate (HR); and by alterations in the diameter of blood vessels that in turn affect total peripheral resistance (TPR, Fadel et al., 2003a). These baroreflex-mediated changes in the cardiovascular system are achieved by a fine-tuned regulation of sympathetic and

parasympathetic nerve activity on the heart and vasculature (Fadel et al., 2001, Ogoh et al., 2003).

The purposes of this chapter are threefold; a) to describe succinctly the anatomy and function of the heart and blood vessels; b) to illustrated the baroreflex anatomical organization and function, and the control of the circulation during postural charges and exercise; c) and describe post exercise hypotension.

The heart

The heart that acts as a "pump", consisting of two atria and two ventricles, is divided into a left and a right side by a septum that runs along its longitudinal axis (Noble, 2004, Anderson et al., 2004). The main function of the atria is to optimise ventricular filling, while that of the ventricles is to generate sufficient force to overcome the vascular resistance and propel blood in a pulsatile manner (Ten Tusscher et al., 2006). The right side of the heart propels blood around the pulmonary circulation, while the left side propels blood to the systemic circulation (Noble, 2006). The contractions (systole) and relaxations (diastole) of the cardiac muscle (the myocardium) occur in a coordinated and rhythmical fashion, allowing an efficient and constant blood delivery around the body (Noble, 2001, Anderson et al., 2004). The HR is dictated by the depolarization of cells in the sinus node (Mazurov, 2006, Zhang et al., 2002). The sinus node is constantly under the influence of cardiac vagal and sympathetic traffic that regulate cardiac activity, even though the sinus node cells may undergo self-depolarisation, termed intrinsic HR (Levy, 1997).

The blood vessels

Blood flows through a network of specialized vessels that can be broadly categorized in arteries, capillaries, and veins. The walls of arteries and veins contain three layers, the tunica externa, tunica media, and tunica interna (Noble, 2001). The tunica externa forms a connective tissue sheath that stabilizes the position of the vessel. The tunica media contains smooth muscle and connective tissue fibres such as elastin (Nitenberg, 1983). The tunica interna includes the endothelium and its underlying elastic membranes (Escourrou, 1991).

The arterial system includes elastic arteries, muscular arteries, and arterioles. Close to the heart the arteries are large, while towards the periphery the diameter of the vessels decreases and their walls become relatively thin as their number increases (Escourrou, 1991).

Capillaries are the smallest blood vessels, measuring 5-10 μm, which connect arterioles and venules, and are the main sites of substance exchange between blood and tissue cells. Diffusion across capillary walls depends on the organization of the endothelium, the size of the diffusing molecule, and its lipid solubility (Nitenberg, 1983). Individual capillaries are usually part of an organized capillary plexus, or capillary bed. Pre-capillary sphincters determine the relative volume of flow through each of the capillaries. Blood flow through a capillary plexus changes as vasomotion occurs (Escourrou, 1991). The entire network may be bypassed by blood flow through arteriovenous anastomoses or via preferred channels within the capillary plexus (Nitenberg, 1983).

Venules are small veins that collect the blood leaving a capillary network. They merge into medium-sized veins; these convey the blood to large veins including the superior and inferior vena cavae that empty in the heart (Escourrou, 1991). The arterial BP is highest in the aorta, and it decreases progressively in smaller arteries, reaching the lowest values in the large veins (Noble, 2006). Given the low BP in the veins, special valves are necessary to prevent the backflow of blood (Nitenberg, 1983). Furthermore, dynamic muscular contractions (the muscle pump) rhythmically compress the blood vessels and contribute significantly to venous return to the heart (Delp and Laughlin, 1998). In addition, the pressure changes in the pleural cavity associated with breathing also assist in moving blood towards the heart (Rowell, 1988, Saltin et al., 1998).

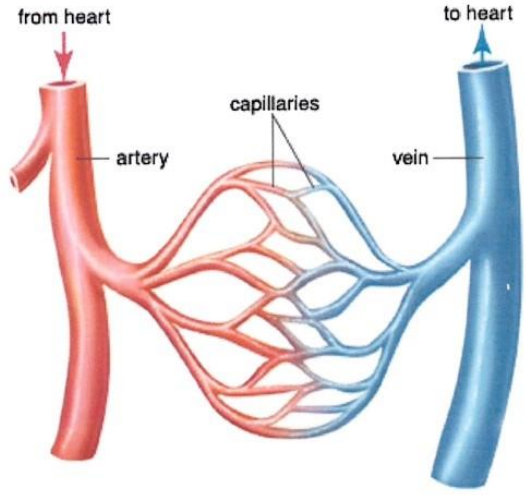

Fig. 1.1: Illustration of arterioles, venules and capillaries

The baroreflex

The baroreflex consists of the afferent branch, represented by the arterial and cardiopulmonary baroreceptors; the central neural circuits; and the efferent branch,

represented by the sympathetic and parasympathetic nervous system (Dampney and Horiuchi, 2003).

The arterial and cardiopulmonary baroreceptors

The arterial baroreceptors are stretch receptors located in the carotid sinus and aortic arch (Kirchheim, 1976). An elevation in arterial BP increases the diameter of the arterial vessels and mechanically distorts the arterial baroreceptors that increase their firing rate (Cohen and Taylor, 2002). This afferent neural activity is transmitted to the cardiovascular centres in the brain stem where it is processed (Raven et al., 2006).

The cardiopulmonary baroreceptors located in the heart and great veins (Desai et al., 1997) respond to changes in central blood volume (CBV) and their afferent activity to the brain stem also contributes to BP regulation (Roddie et al., 1957).

The autonomic nervous system

The cardiovascular activity is profoundly affected by autonomic traffic (Levy et al., 1970). The nucleus ambiguous (NA) is the main site of preganglionic neurones of the parasympathetic system (PNS, Gunn et al., 1968). The postganglionic neurons of the PNS innervate the heart via the vagus nerve (Furnival et al., 1973b). The pre- and postganglionic parasympathetic neurotransmitter is acetylcholine (ACh, Vanhoutte and Levy, 1980). Stimulation of the vagus nerve causes ACh release in the heart (Levy et al., 1970). The cardiac effects of ACh are a rapid cardiodeceleration and a decrease in myocardial contractility (O'Leary, 1996). Furthermore, when vagal stimulation ceases, these cardiac effects dissipate rapidly, as ACh reuptake is fast (Guyenet and Koshiya, 1995).

The ventrolateral medulla (VLM) is the main cite of preganglioninc neurons of the sympathetic nervous system (SNS, Reis and Cuenod, 1965, Willette et al., 1984b). The preganglionic sympathetic neurotransmitter is ACh (Feldberg and Gaddum, 1934), while the postganglionic neurotransmitter is noradrenalin (Bolme and Fuxe, 1970). Cardiac sympathoexcitation is provoked by noradrenalin release, and is manifested as cardioacceleration and increased myocardial contractility (Bolme and Fuxe, 1970). The cardiac effects of noradrenalin occur and dissipate more slowly compared with those of ACh (Levy, 1984, Irisawa et al., 1993). Furthermore, comparatively small quantity of ACh is sufficient to counteract the effects of noradrenalin (Giles and Shimoni, 1989). Cardiac activity is determined by the sympathovagal balance, and the vagal activity is more dominant, especially at rest, presumably due to the action characteristics of ACh (Levy, 1984).

Peripheral sympathoexcitation, manifested as noradrenalin release in the vasculature, provokes contraction of smooth muscle within the blood vessel and in turn increases TPR (Raven et al., 2006). However, especially during exercise, vascular conductance is determined by the interaction between adrenergic vasoconstriction and metabolite-induced vasodilatation (Remensnyder et al., 1962) .

Baroreflex central circuits

The nucleus tractus solitarious (NTS) is situated in the medulla oblongata, and is considered the main site for baroreflex control (Seller and Illert, 1969, Andresen and Kunze, 1994). Any deviation in BP from the baroreflex's setpoint is detected by the baroreceptors, which change their firing rate (Cohen and Taylor, 2002). This carotid

and aortic baroreceptors's afferent activity is transmitted to the NTS, where it is processed, resulting in appropriate changes in cardiac and peripheral autonomic outflow that aim to restore BP to the reflex's setpoint (Potts, 2006, Raven et al., 2006).

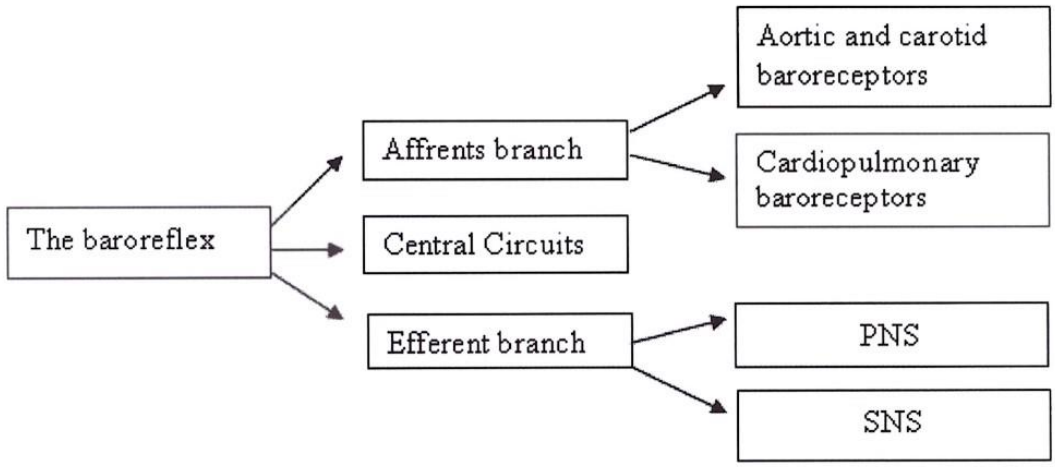

Fig. 1.2: Schematic representation of the different components of the arterial baroreflex

Baroreflex control of circulation during postural shift and exercise

Postural shift from upright to supine causes the redistribution of blood from the pelvis and lower limbs to the thorax, increasing CBV and loading the cardiopulmonary baroreceptors, while it also obliterates the pressure difference between carotid and aortic baroreceptors (Pump et al., 1999, Pump et al., 1997). The consequent increase in CBV, and arterial and cardiopumanary baroreceptors loading, elicits reflexogenic responses that enhance cardiac vagal traffic and inhibit peripheral sympathetic activity (Ogoh et al., 2006a).

Exercise is one of the greatest challenges for circulatory homeostasis, requiring profound changes in cardiovascular activity to meet the new metabolic demand (Raven et al., 2006, Bangsbo et al., 1992). Circulatory control during exercise is more complex compared to rest as other important reflexogenic areas that influence the cardiovascular system are also activated. At the onset of exercise neural impulses arising from higher brain centres (central command, Gallagher et al., 2006), and the afferent activity of stretch and contraction responsive mechanoreceptors, located within the musculature (muscle mechanoreflex, Smith et al., 2006), evoke a rapid increase in HR, Q, and BP (Hayes et al., 2005, Kaufman and Hayes, 2002). Furthermore, the concomitant actions of central command and muscle mechanoreflex relocate the baroreflex's operating point to higher BP, facilitating in this way the cardiovascular response to exercise (Raven et al., 2006). As the exercise progresses, especially at higher intensity, the accumulation of metabolites activates the muscle metaboreflex, which also contributes to the baroreflex's upward resetting and to the cardiovascular response to exercise (Kaufman and Hayes, 2002). The collective influences of central command, mechanoreflex and metaboreflex on the function of the arterial baroreflex result in the finely-tuned regulation of the cardiovascular system during exercise (Gallagher et al., 2006, Smith et al., 2003, Ogoh et al., 2002, Iellamo, 2001b).

Post exercise hypotension

Following exercise there is a clinically significant reduction in BP termed post exercise hypotension (PEH, Kenney and Seals, 1993). Studies on rodents have shown that after exercise there is a significant decrease in BP (Yao et al., 1982b).

Furthermore, in humans, PEH has been observed in normotensive (Kaufman et al., 1987) and hypertensive subjects (Legramante et al., 2002). However PEH does not always occur, as studies reported no significant change in PB in normotensive humans after exercise (Cleroux et al., 1992b, Cleroux et al., 1992a, Pescatello et al., 1991). In addition, following exercise in normotesive rabbits a higher BP compared with pre-exercise levels has been found (Howard et al., 2000). The explanation of these contrasting results is not readily apparent, as the interaction between the factors that determine PEH have not been fully elucidated and are still under investigation. However, there is evidence suggesting that the change in vascular conductance plays a major role in the establishment of PEH (Halliwill, 2001). After exercise vascular conductance is determined by the balance between the vasoconstricting effect of peripheral adrenergic traffic and the vasodilating effect of the exercise-borne substances (Legramante et al., 2002, Remensnyder et al., 1962). Nonetheless, the exercise-borne vasodilating substances may increase the vascular conductance that in turn reduces TPR and BP in normotensive and hypertensive humans, even in the presence of sympathoexcitation (functional sympatholysis, Legramante et al., 2002, Piepoli et al., 1993, Remensnyder et al., 1962).

1.2 Thesis overview

The aim of the present thesis is to further the understanding of the cardiovascular responses observed during passive exercise. The specific objectives of the thesis include examination of: 1) baroreflex control by evaluating the spontaneous BRS; assessment of the cardiac sympathovagal balance by evaluating spectral analysis of heart rate variability (HRV); 3) the effects and interaction between postural changes and passive exercise on spontaneous BRS and HR; 4) baroreflex control and HRV following passive exercise; 5) the aftereffects of passive exercise on post-exercise haemodynamics; 6) regional muscle tissue oxygenation at rest, during passive exercise and recovery.

An extensive review of the literature, together with aims and hypotheses will be presented in chapter (2). Chapter (3) comprises the general methods common to all empirical studies, which are reported in chapter (4-7). Finally chapter (8) contains the general discussion and directions to future research, as well as considerations of the original hypothesis.

Chapter 2

Literature review

2.1. Introduction

The purpose of this chapter is to review the current literature regarding the baroreflex and the control of the circulation. The first part of this review will describe the baroreflex anatomy and baroreflex function at rest, as well as the methods for baroreflex sensitivity assessment. Also will be provided an insight into the reflexogenic areas activated during exercise, namely central command, the metaboreflex and mechareflex, as well as the methods of assessment and their influence on baroreflex function. The subsequent sections of this review will describe the fluctuations of the cardiac rhythm and heart rate variability assessment. Also, in this chapter will be described the baroreflex control of the circulation during postural shift at rest and during exercise, as well as post exercise hypotension. Finally, the remainder of this chapter will provide a summary of the review, highlighting the areas that require further investigation, and clarify the aims and hypotheses of the present thesis.

2.2. Baroreflex afferent branch

Arterial Baroreceptors

Baroreceptor reflexes, unlike most somatic reflexes, are constantly engaged on a second to second basis. Even under "resting" conditions including sleep, baroreceptors are cyclically active with bursts of action potentials during each cardiac cycle (Thoren and Jones, 1977). The arterial and cardiopulmonary baroreceptors represent the afferent branch of the baroreflex.

The arterial baroreceptors are stretch receptors located in the tunica externa of the carotid sinus (right and left bifurcation) and the aortic arch (Kirchheim, 1976, Brown et al., 1976, Cohen and Taylor, 2002). The axon terminals of the baroreceptors are

enveloped with an elastic layer that is closely opposed to deformable elements of the vascular wall including elastic fibres, smooth muscles, and collagen bundles. This elastic layer plays a critical role in the transfer of force from the vascular wall to the sensory nerve terminals (Rees, 1967). Baroreceptors are characterized by densely packed mitochondria, which reflect the high metabolic rate of these stretch-sensitive organs that fire rapidly during every cardiac cycle (Rees, 1967).

An elevation in BP increases the transmural pressure of arterial walls and mechanically distorts the baroreceptors that increase their firing rate (Hay et al., 2001) (Costantinos et al., 2002). The impulse firing rate of the baroreceptors represents a precise image of the transmural pressure changes within the blood vessels, as the firing rate increases during cardiac systole and decreases during cardiac diastole, but the mean impulse rate mainly depends on MAP (Rees, 1967). Furthermore, the faster the rate of pressure changes the greater the baroreceptors' firing (Schreihofer and Guyenet, 2002, Dampney et al., 2003). In addition, the baroreceptors' responses are larger during pressure elevations than reductions at the same absolute pressure and, therefore, show substantial hysteresis, or directional sensitivity (Brunner et al., 1982). However, at systolic blood pressure (SBP) below 40-50 mmHg the baroreceptors are silent, while at SBP above 160-200 mmHg the baroreceptors become saturated, i.e., constant impulse rate (Kirchheim, 1976, Donald and Shepherd, 1980). Nevertheless, the firing characteristics (threshold and saturation) of a single baroreceptor may vary significantly (Brown et al., 1976).

Cardiopulmonary baroreceptors

The cardiopulmonary baroreceptors are "low pressure" baroreceptors and are located at the junction of the great veins and atria, the ventricular myocardium, and

pulmonary arterial walls (Desai et al., 1997). The afferent nerves of the cardiopulmonary baroreceptors travel to the central nervous system over diverse pathways, which include the vagus nerves and the spinal cord, and terminate in the NTS (Malliani, 1982, Longhurst, 1984). The discharge pattern of the cardiopulmonary baroreceptors is related to the change in CBV (Raymundo et al., 1989, Desai et al., 1997, Ferguson and Hayes, 1989). Animal studies in dogs and monkeys showed that the discharge rate of atrial baroreceptors is linearly related to atrial pressure (Gilmore et al., 1979). Nonetheless, the sensitivity of the cardiopulmonary baroreceptors varies between animal species, for instance, the sensitivity of cardiopulmonary baroreceptors in monkeys is less than that in dogs, possibly due to differences in body posture (Gilmore et al., 1979). In humans, the function of the cardiopulmonary baroreceptors can be investigated by posture changes (Donald and Shepherd, 1980), or lower body negate/positive pressure, which manipulate CBV and central venous pressure (Shepherd, 1981). Elevation of the lower limbs, which increases CBV and loads the cardiopulmonary baroreceptors, has been shown to induce reflex forearm vasodilatation (Roddie et al., 1956, Roddie et al., 1957). These findings exemplify the negative linear correlation between muscle sympathetic nerve activity (MNSA) and CBV (Ferguson and Hayes 1989).

2.3. Baroreflex efferent branch: the autonomic nervous system

The autonomic nervous system (ANS) represents the efferent branch of the baroreflex. The ANS contributes to the maintenance of circulatory homeostasis by regulating the functions of the heart, smooth muscle in the blood vessels, and hormone secretion (Ravits, 1997). The ANS consists of two different functional and anatomical divisions, the PNS and the SNS (Shields, 1993).

Parasympathetic nervous system

The PNS consists of relatively long preganglionic cell bodies, located principally in the nucleus ambiguus (NA, Gunn et al., 1968) and dorsal motor nucleus of vagus (DMNV, McAllen and Spyer, 1976). The populations of the efferent preganglionic PNS (X nerve) neurons are situated in the medulla oblongata (Wang et al., 2003b), and project their axons via the vagi to intrinsic cardiac parasympathetic efferent postganglionic neurons. In turn, the postganglionic neurons innervate the sinus node, the atrioventricular conduction pathway and the atrial myocardium (Furnival et al., 1973a, Hainsworth, 1995, McAllen and Spyer, 1978), while there is increasing evidence for the existence of ventricular vagal innervations as well (Standish et al., 1994, Johnson et al., 2004). Canine studies indicate that the intrinsic cardiac nerves of the ventricles consist primarily of postganglionic parasympathetic axons, which arise from supraventricular ganglia and cross the atrioventricular groove (Blomquist et al., 1987). The NA is very important for the control of circulation, as destruction of the NA causes degeneration of cardiac vagal fibres (Szentagothai, 1964) and abolishes baroreceptor-cardiac responses (Chen et al., 1972).

Stimulation of the preganglionic parasympathetic nerve releases the neurotransmitter ACh at the ganglion, which acts on nicotinic receptors of the postganglionic nerve (Vanhoutte and Levy, 1980). The short postganglionic nerve endings then release ACh to stimulate the muscarinic receptors of the target organ (Levy et al., 1970, Calaresu et al., 1975). The cardiac parasympathetic effect occurs principally through the binding of ACh to the postganglionic M2 muscarinic receptors of the cardiac sinoatrial and atrioventricular node. Subsequently, a rapid (within 100 ms) membrane

hyperpolarisation and attenuation of both the conduction velocity of the atrioventricular node (AV node) and the contractility of cardiac muscle, induce cardiodeceleration and decrease Q within 0.4 s (O'Leary, 1996). Following the cessation of vagal nerves discharge, the effect dissipates rapidly as ACh is quickly hydrolysed (Guyenet and Koshiya, 1995).

The cardiac vagal activity is an important indicator of health and fitness, as it is diminished and unresponsive in many disease states, while restoration of parasympathetic activity to the heart lessens ischemia and arrhythmias and decreases the risk of sudden death (Wang et al., 2003a, Wang et al., 2003b). Furthermore, delayed decrease in the HR during the first minute after graded exercise, which may be a reflection of decreased cardiac vagal activity, is a powerful predictor of overall mortality, independent of workload, the presence or absence of myocardial perfusion defects, and changes in HR during exercise (Cole et al., 1999). In addition, cardiac vagal activity is capable of preventing ventricular arrhythmias by maintaining cardiac electrostability during high cardiac sympathetic outflow, often observed in patients with cardiovascular disease (Billman, 2002).

Sympathetic nervous system

Neurons in the caudal and rostral ventrolateral medulla (VLM) synapse with sympathetic preganglionic neurones in the intermediolateral nucleus of the spinal cord (Barman and Gebber, 1985), and are important sites for the control of sympathetic outflow (Reis and Cuenod, 1965, Willette et al., 1984b, Ciriello et al., 1986), and thus the baroreflex control of circulation (Bauer et al., 1989, Guyenet and Koshiya, 1995). Electrical stimulation of the VLM provokes large increases in BP and HR (Dampney and Moon, 1980, Ross, 1983) while destruction of this area, or injection of inhibitory

aminoacids, leads to profound hypotension (Dampney and Moon, 1980, Ross et al., 1984). The VLM units display two types of discharge patterns in response to contraction; a rapid onset response occurring within 3-5 s and a delayed onset response occurring within 10-20 s (Bauer et al., 1989). Additionally, 14 of 28 VLM units tested had a cardiac-related rhythm and 10 of those 14 also responded to muscular contraction (Bauer et al., 1989). Furthermore, muscular contraction has no effect on the discharge patterns of most neurons located outside the VLM (Bauer et al., 1989). Collectively, these studies provide evidence of the important role of VLM in the control of circulation.

All preganglionic neurons of the SNS are located in the spinal cord. The majority of cardiovascular sympathetic nuclei are situated in the lateral horn of the gray matter at the T1-L4 of the spinal cord called intermediolateral cell column (Calaresu et al., 1975). The sympathetic preganglionic neurones are relatively short, exhibiting myelinated axons, and synapse with the paravertebral ganglia located laterally to the spinal cord and form the truncus sympathicus (Barman and Wurster, 1975). These sympathetic pregaglionic fibres then leave the spinal nerve trunk and travel to the ganglia of the sympathetic chain, particularly to the stellate ganglia, where they synapse with the post ganglionic fibres. The sympathetic axons of the postganglionic neurons are relatively long and unmyelinated, and travel to the target organs (Gebber et al., 1997). From the target organs axons travel back to the spinal cord and part of them travel on to the skin and muscles through the spinal nerves (Barman and Wurster, 1975). Sympathetic innervation of the heart arises from the cervical and upper thoracic (stellate) ganglia. In general, excitatory (e.g. L-glutamate) and inhibitory (e.g. GABA) substances mediate rapid communication within the central autonomic circuits e.g. baroreflex pathways (Sun and Guyenet, 1985).

The cardiac sympathetic fibres are distributed to all parts of the heart with higher number in the ventricles (Dampney, 1994). The principal neurotransmitter for preganglionic sympathetic neurones is ACh (Feldberg and Gaddum, 1934), while the principal post ganglionic neurotransmitter is noradrenalin (Bolme and Fuxe, 1970). The sympathetic control of blood vessels diameter occurs via binding of noradrenalin and adrenaline to postganglionic α- and β-adrenoreceptors; while cardioacceleration as well as the increase in contractility occurs mainly via the catecholamine induced stimulation of the cardiac β_1-adrenoreceptors (Bolme and Fuxe, 1970). Cardiac responses to sympathetic stimulation arise relatively slowly (2-5 s, Levy, 1984). This is caused by the slow dispersion of noradrenalin following its release at sympathetic nerve endings; nonetheless, within about 30 s steady state is reached (Levy, 1971). The effect of sympathetic stimulation dissipates more gradually than the onset phase, due to a slow noradrenalin reuptake by sympathetic nerve terminals, and slow rate of noradrenalin metabolism by the cardiac tissue (Irisawa et al., 1993).

Sympathetic and parasympathetic interaction in the sinoatrial node

The heart is constantly under autonomic control. Vagal stimulation tends to decrease cardiac contractility and HR, while sympathoexcitation tends to increase these cardiac indexes. Interaction between the SNS and PNS in HR regulation occurs through prejunctional and postjunctianal mechanisms (Rosemblueth and Simeone, 1934). In the postjunctional mechanism, ACh is released from vagal nerve terminals causing an outward K^+-current in the sinoatrial (SA) node cells, which may reduce the depolarization rate of the cells, and thus the discharge rate (Osterrieder et al., 1980, Sakmann et al., 1983). Additionally, ACh decreases the Ca^{++} current and this affects the rate of depolarization as well (Sunagawa et al., 1998). In contrast, noradrenalin

has opposite effect, as it augments both the Ca^{++} current and depolarization rate. However, this effect is inhibited by ACh in low concentrations (50-100 fold lower for direct K^{+}, or Ca^{++} current effect, Giles and Shimoni, 1989), via attenuation in the rise of intracellular ions concentrations (Rosemblueth and Simeone, 1934). In the sympathovagal prejunctional interactions, ACh released by vagal stimulation inhibits the release of noradrenalin by acting on the receptors of the sympathetic nerve terminals (Levy and Zieske, 1969, Levy, 1984).

On the other hand, sympathetic stimulation inhibits ACh release by acting on the receptors of the parasympathetic nerve terminals (Sunagawa et al., 1998). However, these cardiac sympathovagal interactions are more complex and not simply mutually inhibitory. This view is supported by Levy, (1984) who reported that the level of vagal activity exerts a more prominent effect in the presence of substantial sympathetic activity than vagal activity alone. This is consistent with a previous study (Levy, 1971) where concurrent sympathetic activation exaggerated the effect of cardiac vagal stimulation, due, at least in part, to cAMP accumulation (Sunagawa et al., 1998). This phenomenon is termed accentuated antagonism, implying that the effects of sympathovagal stimulation on HR are not simply additive. Furthermore, studies in rabbits indicate that the cardioacceleration due to adrenaline is suppressed by ACh, and the cardiodeceleration due to ACh is enhanced by adrenaline (Mackaay et al., 1980). Therefore, this functional inhomogeneity of the sinus node explains the predominant effect of ACh over that of adrenaline (Mackaay et al., 1980). In addition, changes in vagal impulse frequency affects HR about 5-10 times faster than changes in sympathetic frequency (Levy, 1971). This is due to a faster vagal pathway transmission, and more rapid synaptic ACh release and re-uptake than noradrenaline (Warner and Cox, 1962, Borst and Karemaker, 1983). Taken together these studies

clearly indicate that the cardiac sympathovagal interactions are rather complex, and that the vagal activity exhibits a more predominant and rapid action on HR, compared with sympathetic activity.

2.4. Baroreflex central neuronal circuits

The arterial and cardiopulmonary baroreceptors afferent neurones, the Hering's and vagus nerves, respectively, terminate in the NTS (Miura and Reis, 1969, Seller and Illert, 1969, Wallach and Loewy, 1980, Ciriello, 1983, Felder, 1986, Zhang and Mifflin, 2000), which extends over almost the entire length of the medulla oblongata (Andresen and Kunze, 1994). This complex structure, with bidirectional connections to medullary and forebrain nuclei, subserves autonomic functions, and plays a major role in the regulation and integration of visceral systems, including baroreflex function (Potts, 2006), and cardiovascular control mechanisms (Lohmeier, 2002, Stauss, 2002).

Neurones in the NTS subserving cardiovascular regulation occupy primarily the densely packed portion near the obex (Paton et al., 2001). The NTS is innervated by neurones from the hypothalamus through descending projections from higher brain structures such as the frontal cortex and amygdala (Willette et al., 1984a). In addition, the NTS synapses with the NA, and dorsal motor nucleus of vagus (DMNV), where parasympathetic preganglioninc neurones are situated (Morest, 1967, Norgren, 1978), and with the VLM where sympathetic preganglionic neurones are located (Willette et al., 1984b, Minson et al., 1997). Besides the innervations by the NTS, the NA, DMNV and VLM are innervated by the hypothalamus and higher brain centres (Spyer, 1981). Furthermore, skeletal muscle afferent neurones also synapse with the NTS (Janssen et al., 1993, Andresen et al., 2004).

The pivotal role of the NTS in the BP control is highlighted by a number of animal investigations, in which bilateral oblation of the NTS provokes hypertension in rats (Reis and Doba, 1973) and rabbits (Blessing et al., 1982), and labile hypertension in cats (Nathan and Reis, 1977). In contrast, electrical stimulation of parts of the NTS mimics effects of baroreceptors stimulation and provokes hypotension and bradycardia (Oberholzer, 1960). Furthermore, ablation of the NTS in humans may be followed by resting tachycardia, supine hypertension, orthostatic hypotension, and elevated plasma noradrenaline levels (Langford et al., 1986). In addition, some patients with medullary lesions exhibit severe hypertension (Pamphlett and Harper, 1985) and large BP lability (Magnus et al., 1977). Collectively, these studies illustrate the complex central circuits, and the dense neural network between the NTS and other areas responsible for the control of circulation.

2.5. Baroreflex function: Afferent activity, central integration and autonomic response

The arterial baroreflex is the main short-term BP controller on a moment-to-moment basis (Di Rienzo et al., 2001). In response to an elevation in arterial BP the afferent activity of the arterial baroreceptors increases. This activity is conveyed through the Hering's and afferent vagus nerves to the NTS (situated in the medulla oblongata), and excite a second-order of neurones via glumatergic synapses (Pilowsky and Goodchild, 2002, Dampney et al., 2003). These neurones within the NTS process this information before it is transmitted to the NA resulting in excitation of cardiac vagal motoneurones (Agarwal and Calaresu, 1992, Dampney, 1994). Furthermore, these NTS neurones conveying baroreceptors signals also project to and excite (via glutamate synapse) neurones within the caudal VLM. The latter neurones project to and inhibit (via GABAenergic synapse) sympathetic premotor neurones in the rostral

VLM, which in turn reduce the release of glutamate to the sympathetic preganglionic neurones located in the spinal cord and, thus, decrease sympathetic discharge (Minson et al., 1997, Liu et al., 2000). Thus, the activation of these central neural circuits induces a concomitant cardiac vagal excitation and cardiac and peripheral sympathoinhibition (Schreihofer and Guyenet, 2002) that decrease HR, Q and TPR and, ultimately, restore BP to the reflex's operating point (Convertino and Adams, 1991). Reversely, in response to a reduction in BP both Q and TPR are augmented by baroreflex-induced tachycardia and peripheral vasoconstriction (Cohen and Taylor, 2002).

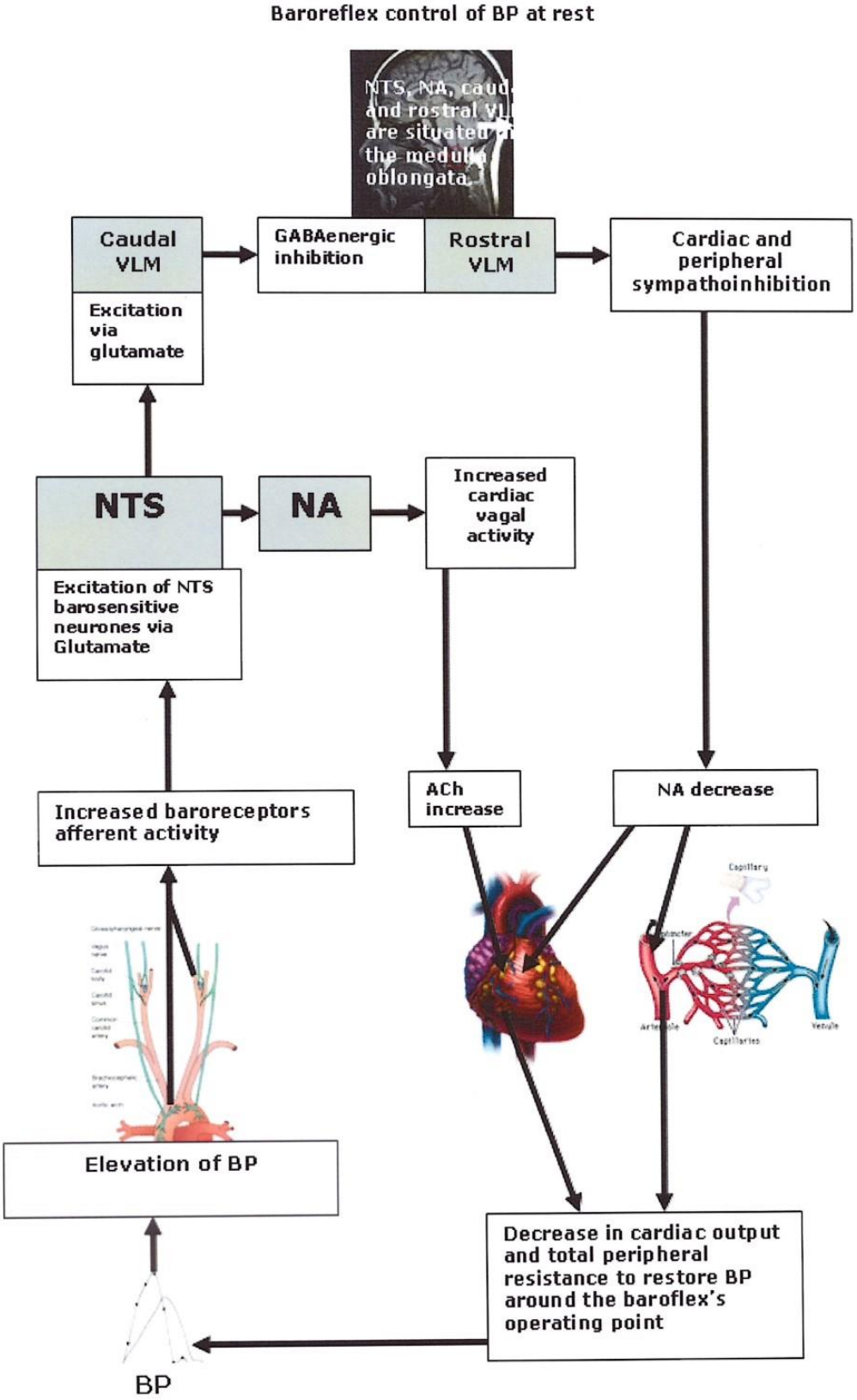

Fig. 1.3: Diagrammatical representation of the baroreflex-induced cardiovascular adjustments in response to blood pressure increase, including afferent activity, central integration, and autonomic response.

Indices of baroreflex function

Baroreflex sensitivity (BRS), or gain, a measure of the reflex's efficiency, refers to the rapidity of the baroreflex to induce bradycardia/tachycardia in response to increase/decrease in BP (Legramante et al., 2002) and together with the reflex's operating point are descriptors of baroreflex function (Fadel et al., 2003b). Abnormalities in arterial baroreflex function have been correlated with adverse cardiovascular outcomes (Farrell et al., 1992, Lanfranchi and Somers, 2002). Depression of BRS has been observed immediately after the onset of several cardiovascular pathologies (Barney et al., 1988, De Ferrari et al., 1992, Dibner-Dunlap and Thames, 1992, Airaksinen et al., 1994, Head, 1995). Specifically, BRS may have a diagnostic as well as prognostic value in several forms of disease including myocardial infarction and heart failure (Gulli et al., 2003). Various approaches have been developed to estimate BRS; some use a spontaneous BRS assessment, while others use more invasive techniques.

Methods, advantages and limitations of baroreflex assessment

Oxford method

The Oxford method of BRS assessment (Smyth et al., 1969) uses bolus injection of an alpha-adrenergic agonist (usually phenylephrine) to cause vasoconstriction and thus increase BP. In response, the baroreflex mediates an increase in cardiovagal traffic provoking R-R interval prolongation (i.e. bradycardia) to counteract the BP surge. The slope of the linear regression of the R-R against the preceding BP values provides an index of baroreflex sensitivity, or gain (Sagawa, 1978).

This pharmacological method allows for BRS assessment over a larger range of blood pressure changes (Pickering et al., 1972). However, the use of drugs interferes with the closed-loop nature of the reflex, through unnatural drug-induced BP increases (Casadei and Paterson, 2000). Furthermore, the use of drugs affects the baroceptors' activity (Peveler et al., 1983, Imaizumi et al., 1984), as well as the sinus node function (White et al., 1973).

The neck chamber method

The use of neck chamber permits the reconstruction of the baroreflex function curve (Raven et al., 2006). The neck chamber method is based on the principle that afferent carotid baroreceptors activity can be decreased/increased by applying pressure or suction on the neck (Ernisting and Parry, 1957). Positive or negative pressure of different magnitude, applied to a chamber fixed around the neck, is transmitted to the carotid arteries in human subjects and provokes a reduction or increase in the carotid artery diameter and thus unloading/loading of the carotid baroreceptors (Eckberg et al., 1976). The gain of the stimulus-response curve is derived from the first derivative of Kent's logistic function and the maximal gain is calculated as the gain at the centring point (Kent et al., 1972). Furthermore, the threshold is the point of the stimulus-response curve where no further increase is observed in the response variable e.g. HR, despite further reduction in carotid sinus pressure (CSP), while saturation is the point where no further decrease is observed in the response variable despite increase in CSP. The difference between threshold and saturation of the stimulus-response curve defines the operating range of the reflex (Fadel et al., 2003a). While, the operating point is defined as the prevailing BP at which the reflex operates, more specifically, it determines the steady-state relationship between baroreceptor

input and basal cardiovascular variables (i.e., HR and SNA, Potts, 2006). Under resting conditions, the baroreflex normally operates within the highest sensitivity region (Dorward et al., 1982). Furthermore, the resting values of HR and BP reflect the ongoing baroreflex actions on sympathovagal balance. In addition, these resting values indicate that BP excursions normally traverse the midpoint of the reflex function curve, often described as a sigmoid or logistic relation (Ricketts and Head, 1999). The baroreflex responses to neck chamber stimulation may be assessed by analysing changes in HR, muscle sympathetic nerve activity (MSNA), MAP, stroke volume (SV), or plasma neurotransmitter concentrations (Eckberg et al., 1976, Parati and Mancia, 1992, Ogoh et al., 2003).

The use of the neck chamber allows the assessment of the full baroreflex function curve (Raven et al., 2006). However, the responses to the application of the neck chamber do not include the input of the aortic baoreceptors (Parati et al., 2000). As the carotid baroreceptors are externally manipulated, by applying unnatural forces that are not of physiological magnitude, this method also interferes with the closed-loop nature of the reflex (Parati et al., 2000).

Spontaneous baroreflex assessment methods

Spontaneous BRS may be estimated from BP and R-R, or pulse internal (PI) fluctuations, and analysed in the frequency domain by Fourier analysis, at the frequency band between 0.05 and 0.15 Hz. The average spectral (transfer) ratio is then extracted to obtain a value in ms/mmHg (Sayers et al., 1982, Robbe et al., 1987). BRS estimates using the spectral method compare acceptably with the phenylephrine

(Oxford) test (Robbe et al., 1987). However, this method is not able to discern non-baroreflex fluctuations, i.e. when changes in R-R cause changes in BP.

Another method of estimating the BRS is the sequence method, where spontaneous HR changes expressed as R-R changes i.e. lengthening/shortening (milliseconds) are associated to BP changes (mmHg). The sequence method is largely used to evaluate the spontaneous BRS and is calculated as the slope of the linear relationship between changes in BP and changes in the same direction of R-R (Di Rienzo et al., 1985, Bertinieri et al., 1988, Legramante et al., 2002).

A modified approach of the sequence method is the cross-correlation function (xBRS) (Di Rienzo et al., 1985). In the cross-correlation function, BRS estimates are derived from changes in beat-to-beat systolic BP and PI, or R-R. These changes are observed by determining the best cross-correlation value, at optimum delay of changes in pulse interval (0-5 s) with respect to blood pressure, over running 10 s intervals (Borst and Karemaker, 1983, Westerhof et al., 2004).

The spontaneous BRS method permits the assessment of the cardiac baroreflex gain, relying on stimuli of physiological nature and magnitude (Iellamo, 2007). This non-invasive approach does not interfere with the closed-loop nature of the reflex as it does not require any pharmacological or mechanical disturbance external to the cardiovascular system, and has been validated against the pharmacological method (Parlow et al., 1995). Furthermore, the spontaneous BRS assessment includes both carotid and aortic baroreceptors inputs, and also comprising activation/deactivation i.e. hypertensive/hypotensive stimuli (Iellamo et al., 1997). In addition, this

spontaneous method allows for dynamic baroreflex assessment providing a greater number of rumps in comparison with other techniques, and this is especially important during short-lasting experimental conditions (Parati et al., 1988, Iellamo et al., 1994). However, the spontaneous BRS method furnishes estimates of the baroreflex gain at the prevailing BP only, and it is inadequate for assessment of the full baroreflex function curve (Raven et al., 2006).

Varsalva manoeuvre

The Valsalva manoeuvre is probably the most widely used test of human baroreflex function. It is a complex physiological perturbation that by straining against a closed glottis alters intracardiac and intravascular distending pressures (sometimes in opposite direction), afferent barosensory traffic, central modulation of autonomic traffic, BP and HR (Looga, 2005). The Valsalva manoeuvre is subdivided in four phases: 1) a brief augmentation in BP and decrease in HR immediately after the onset of straining; 2) a fall, and later partial or complete recovery, of BP to baseline levels, and cardioacceleration during the period of straining; 3) a sudden, very brief further reduction in BP and increase in HR immediately following the release of straining; 4) a terminal, sustained elevation in BP above control levels and concomitant cardiodeceleration (Hamilton et al., 1936). The cardiodeceleration occurring in phase 1 in response to elevation in BP is used to investigate the cardiac baroreflex responses (Wong et al., 2004).

The valsalva manoeuvre also contributes to the investigation of baroreflex function, however, the results are widely variable, presumably due in part, to the different techniques employed (Leon et al., 1970, Korner et al., 1976, Sharpey-Schafer, 1955).

Thus, each method of baroreflex assessment exhibits advantages and limitations. Nonetheless, the implementations of these methods permit the exploration of the baroreflex function from different but complementary perspectives.

Sympathovagal interaction and physiological mechanisms determining BRS

While higher BRS values are mainly determined by the efficiency of cardiac vagal tone activation (Smyth et al., 1969, Eckberg et al., 1971, Ogoh et al., 2005); nonetheless, normal sympathetic activity also contributes (La Rovere et al., 2001a). Conversely, lower BRS values are associated with shifting of the sympathovagal balance towards a sympathetic predominance (La Rovere et al., 2001b). The predominant role of vagal traffic on BRS is further supported by Levy et al., (1970) who observed that after a single vagal stimulation maximum response occurs within 400 ms, and its effect is noticeable (lengthening of RR) within the first or second beat (Levy et al., 1970). Additionally, after the end of vagal stimulation the RR rapidly returns to its previous length (Levy et al., 1970), while following the onset of sympathetic stimulation, there is a latency of up to 5 s followed by the RR shortening (Hainsworth, 1995). Although changes in sympathetic and parasympathetic activity occur virtually at the same time the end-organ responses to sympathetic activity are considerably delayed (Levy et al., 1970). Thus, the baroreflex-mediated changes in HR occur within 0.5 s (Eckberg et al., 1976, Borst and Karemaker, 1983), with the

maximum response within 1.5-2 s (Eckberg, 1980), while, the effect dissipates within 2 s (Eckberg and Eckberg, 1982). Therefore, BRS is considered to be mainly vagally mediated, as the effect of cardiac sympathetic traffic occurs and dissipates more slowly (Hainsworth, 1995). Additionally, BRS is also attenuated in rats by injection of domoic acid that causes lesions and significantly reduces the population of motor neurons in the NA, where preganglionic cardiac parasympathetic neurones are situated (Cheng et al., 2004). This finding further supports that cardiac parasympathetic activity plays a dominant role in the baroreflex control of HR, and the integrity of the NA is critically important for normal baroreflex control (Cheng et al., 2004).

However, normal baroreflex function requires both branches of the autonomic nervous system. This notion is readily apparent in the study of Chandler and DiCarlo, (1997), where both vagal and sympathetic blockade equally eliminated the HR reflex response to changes in BP. In addition, the effect of vagal stimulation is more prominent when the frequency of sympathetic stimulation is increased, while the effect of sympathetic stimulation is more prominent when vagal stimulation is minimal (Henning et al., 1990). Thus, the cardiac baroreflex response does not reflect the algebraic summation of sympathetic and parasympathetic tone; rather, it is the result of sympathetic activity modulating the cardiac vagal response to changes in BP (Chandler and DiCarlo, 1997).

2.6. Cardiovascular control and baroreflex function during exercise

The significant changes in cardiovascular activity that accompany the onset of exercise are mainly evoked by the action of central command, and the afferent activity of muscle mechanoreflex and chemoreflex (the exercise pressor reflex, Alam and Smirk, 1937, Iwamoto et al., 1985, Fadel et al., 2001, Iellamo, 2001a, Gallagher et al., 2001b). However, the respective roles and influences of muscle afferents on cardiovascular regulation remain to be established.

During exercise BP and HR move in the same direction. Since normal baroreflex function elicits bradycardia in response to hypertensive surges it was initially thought that during exercise the baroreflex either becomes inoperable, or that there is a change in baroreflex sensitivity that permits the parallel increase in HR and BP (Bristow et al., 1971, Mancia et al., 1978). However, more recent investigations suggest that during exercise the arterial baroreflex is functionally reset upwards and it remains an operative negative feedback controller of the prevailing exercise-induced BP (Melcher and Donald, 1981, Ebert, 1986, Potts et al., 1993, Papelier et al., 1994, Potts and Mitchell, 1998). Further support for this view is provided by a corollary study (Scherrer et al., 1990) where the BP elevation induced by exercise was opposed by nitroprusside infusion, and the baroreflex induced an increase in both muscle sympathetic nerve activity and HR by more than 300%. Furthermore, when the exercise-induced BP augmentation was accentuated by phenylephrine infusion, the baroreflex-mediated an attenuation in muscle sympathetic nerve activity and HR by more than 50% (Scherrer et al., 1990). These data clearly demonstrate that during exercise the baroreflex is still operative and able to induce both augmentation in sympathetic activity and vagal withdrawal. Additionally, Sheriff et al., (1990)

reported that in anaesthetized dogs the increase in BP during exercise-related muscle ischemia is much greater after than before sinoaortic denervation. Furthermore, denervation of the baroreceptors in anaesthetized cats resulted in attenuated exercise-induced pressor response (Waldrop and Mitchell, 1985). The importance of the baroreflex for the cardiovascular response to exercise is further highlighted by (Potts and Li, 1998) who observed that increasing the level of baroreceptors' input transforms the interaction between the baroreflex and the pressor reflex from facilitation to inhibition. In this context, at the onset of exercise, the rapid upward resetting of the baroreflex (which decreases the functional level of baroreceptors input to the central nervous system) facilitates the sympathoexcitatory responses evoked by the exercise pressor reflex, and in turn minimises the transient fall in BP and hypoperfusion of active skeletal muscle (Potts and Li, 1998). However, during moderate to severe exercise the magnitude of sympathoexcitation evoked by muscle afferents is attenuated by the baroreflex (Potts and Li, 1998).

Taken together, these studies indicate that the baroreflex plays a central role in the control of the cardiovascular response to exercise. This view is further supported by (Potts et al., 1993) who also provided evidence that the baroreflex function is maintained during exercise and the operating point is relocated upward and rightward on the stimulus-response function curve to higher operating pressures (classical resetting). Also, this study described a relocation of the operating point away from the centring point and closer to the threshold pressure region of the baroreflex function curve. In addition, Melcher and Donald (1981) suggested that the operating point of the baroreflex is relocated upward on the response arm of the baroreflex function curve in direct relation to the intensity of exercise, and thus permitting the baroreflex

control of the exercise-induced prevailing pressure (Potts and Mitchell, 1998). Presumably, the baroreflex upward resetting during exercise is mediated by the feedforward mechanism, i.e., central command, and the feedback mechanism, i.e., the exercise pressor reflex, that alter the activity of neurones within the NTS, while baroreflex function is preserved (Smith et al., 2003). This may be achieved via neural interconnection between the central cardiovascular circuits, the cerebral cortical and subcortical structures implicated in the origin of central command, and muscle afferents (Yasui et al., 1991).

During exercise, alterations in TPR are the primary means by which the arterial baroreflex regulates MAP (Ogoh et al., 2003). Adjustments in Q are accomplished mainly through changes in HR, while stroke volume has only a minor contribution (Ogoh et al., 2003).

Central command

Central command is a feed-forward mechanism and arises from higher centres in the brain including the mesencephalic locomotors region, and motor cortex, and acts in parallel with the motor signals directed to the exercising muscles as well as on the central motoneuron pool that integrates the baroreflex (somatomotor and cardiovascular responses, Krogh and Lindhard, 1913, Rowell and O'Leary, 1990, Iellamo, 2001a, Raven et al., 2006, Degtyarenko and Kaufman, 2006). Rowell and O'Leary (1990) proposed that central command is responsible for relocating the operating point of the carotid baroreflex to higher arterial blood pressure (rightward) during exercise. This permits the reflex to remain operational despite the increased blood pressure that occurs with exercise. This view is further supported by Gallagher

et al., (2001c) who reported that central command actively contributes to the resetting of the carotid baroreflex at the onset of static and dynamic exercise. Furthermore, (Gandevia et al., 1993) observed that under neuromuscular blockade the attempt to contract skeletal muscles increased HR and BP due to central command activation. Similar results were reproduced by Pawelczyk et al., (1997) who investigated the influence of central command on the cardiovascular response to contractions with weakened muscles following partial curarization. The authors reported an elevation in HR, MAP and plasma catecholamine as a result of central command activation. In addition, Goodwin et al., (1972) reported that the cardiorespiratory responses are in direct relation to changes in central command during exercise. Collectively, these studies provide evidence that central command plays an important role in the upward resetting of the baroreflex and the cardiovascular response to exercise.

Peripheral mechanisms contributing to the cardiovascular response to exercise

The mechanically (mechanoreflex) and chemically (metaboreflex) sensitive muscle afferents act as a modulator of the cardiovascular response to exercise (muscle pressor reflex) and contribute to the functional upward resetting of the baroreflex through negative feedback to the brainstem (Alam and Smirk, 1937, Coote et al., 1971, McCloskey and Mitchell, 1972, Kaufman et al., 1983, Gallagher et al., 2001a).

The mechanoreflex

Group III muscle afferents (mechanoreceptors) are thin fibre sensory nerves and have unencapsulated nerve endings without a perineal sheath surrounding their receptive areas (Hanna et al., 2002). These unencapsulated nerves contain mitochondria, and

are associated with collagen structures in skeletal muscle (Andres et al., 1985). The mechanoreceptors respond to mechanical perturbation and discharge immediately with the onset of contraction (Kaufman and Hayes, 2002), with the first discharge occurring within about 0.2 s after the start of contraction (Kaufman et al., 1983). Animal and human studies demonstrated that mechanoreceptors are particularly affected by stimuli such as stretch (Kaufman et al., 1983), or contraction (Kaufman et al., 1984b), resulting in cardiovascular changes that represent the mechanoreflex branch of the exercise pressor reflex. In addition, some of these muscle afferents are polymodal as they also respond to accumulation of metabolites (Kaufman and Hayes, 2002). However, only potassium (Rybicki et al., 1985) and lactic acid, in concentrations similar to those observed during moderate or heavy exercise, stimulate these mechanical muscle afferents (Thimm and Baum, 1987, Sinoway et al., 1993). The sensitivity to metabolites may explain why some mechanoreceptors exhibit a secondary response to static contraction when the working musculature is fatiguing (Kaufman et al., 1983).

Group III afferents increase their response as the tension developed within the muscle increases (Kaufman et al., 1983, Mense and Stahnke, 1983). The sensitivity of group III afferents to mechanical distortion may explain their frequent discharge in synchrony with the contraction phase of the step cycle during dynamic exercise (Adreani et al., 1997). In addition, the conduction velocities of the subtype afferents stimulated by stretch are on average significantly higher than those of the subtype afferents stimulated by static contraction (Hayes et al., 2005).

The contribution of the mechanoreflex to the cardiovascular response to exercise has been investigated with different experimental models such as active isometric and electrically stimulated muscular contractions, as well as passive stretch, or passive cycling that bypass the effect of central command (Kaufman and Hayes, 2002, Nobrega and Araujo, 1993, Iwamoto et al., 1985). Activation of the mechanoreflex with passive stretch has been employed in both animal (Wilson et al., 1994, Leshnower et al., 2001) and human studies (Gladwell and Coote, 2002). Passive stretch of triceps surae in anesthetised cats evokes an increase in HR and BP in proportion to the tension developed within the muscle (Iwamoto et al., 1985, Wilson et al., 1994, Leshnower et al., 2001). Furthermore, when the muscles are stretched passively in vitro to produce a pattern and amount of tension similar to that occurring during static hindlimb contraction, the increase in BP averages 51% of that established during voluntary contraction (Stebbins et al., 1988).

Similarly, stimulation of skeletal muscle mechanoreceptors by rhythmical compression (Nishiyasu et al., 2001), or application of lower body positive pressure in humans (LBPP, Gallagher et al., 2001a), both at rest and during exercise, increases BP. Such responses are dependent upon both the changes in intramuscular pressure and the quantity of muscle mass compressed, while they are eliminated by epidural blockade (Williamson et al., 1994). However, it should be considered that such forces are not present during actual exercise, where tension is developed actively, and its magnitude is generally greater than that produced in vivo during these experimental models.

Electrically stimulated muscular contractions are another experimental model employed to isolate the effect of pressor reflex from the effect of central command (Iellamo et al., 1997). Electrical stimulation of group III muscle afferents increases both HR, within 1s (Hollander and Bouman, 1975, Gelsema et al., 1985), and sympathetic activity to the vasculature (Victor et al., 1989). In similar studies where central command was bypassed by ventral root stimulation in cats (Kaufman et al., 1983), or by electrical stimulation in humans, group III muscle afferents have been shown to induce an abrupt BP elevation (Bull et al., 1989). In these conditions, stimulation of muscle mechanoreceptors was considered to be the major cause for the HR change since activation of the metaboreflex requires longer time, to allow for accumulation of metabolites (Kaufman and Hayes, 2002). Additionally, the magnitude of the reflexively evoked increase in BP is greater during static than rhythmic twitch contractions of the hindlimb muscles in anaesthetised cats, a difference that has been attributed to the discharge of group III afferents (Kaufman et al., 1984b).

Although the method of electrical stimulation has provided important information about the discharge properties of group III and IV muscle afferents, it should be considered that electrical stimulation of peripheral nerves, or ventral roots, recruits alpha-motoneurons first, whereas dynamic exercise recruits alpha-motoneurons last (Henneman et al., 1965). Furthermore, electrical stimulation involves synchronous motoneuron discharge, whereas during dynamic exercise motoneurons discharge asynchronously (Hoffer et al., 1987). Thus, the mechanical forces distorting the receptive fields of group III afferents during electrical stimulation may be different from those during dynamic exercise. Consequently, the responses to electrically

stimulated muscular contractions may be different than the responses to dynamic exercise (Adreani et al., 1997). Nevertheless, when the stimulation is applied in the mesencephalic locomotor region of the brain, the motor recruitment patterns are similar to those observed during dynamic exercise (Adreani et al., 1997).

The contribution of the mechanoreflex to the cardiovascular response to exercise is further highlighted by Williamson and et al., (1994), who reported that application of LBPP of 35 and 45 Torr during the early stages of exercise, before metabolites start to accumulate, selectively activates the muscle mechanoreflex and elevates BP. In addition, afferent input from the working skeletal muscles is requisite for the resetting of the baroreflex during exercise, as blockade of mechanosensitive channels attenuates the cardiovascular responses to both static contraction and tendon stretch (Hayes and Kaufman, 2001). Furthermore, the mechanoreflex is capable of inducing cardiac (Matsukawa et al., 1994) and renal sympathoexcitation (Matsukawa et al., 1990, Kim et al., 2007).

Passive cycling was used by Williamson et al., (1995) to activate the mechanoreflex and an increase in HR was observed during exercise. A plausible explanation for this observation is that passive cycling movements induced changes in myoelectric activity via a spinal reflex circuit associated with muscle stretch, which increased HR (Williamson et al., 1995). The discrete isolated involvement of the mechanoreflex in the observed responses was ensured by EMG recordings that did not show any muscular contraction, thus suggesting that central command was absent (Nobrega and Araujo, 1993). Furthermore, in similar studies, passive cycling increased both SV, BP and Q (Nurhayati and Boutcher, 1998, Nobrega et al., 1994).

The above studies suggest that the mechanoreflex is important for the cardiovascular regulation during exercise and validate passive cycling as a useful model for investigating the role of the mechanoreflex in autonomic cardiovascular regulation during exercise.

The metaboreflex

Group IV muscle afferents (metaboreceptors) are thin sensory fibres, located in proximity to the blood vessels (Proske et al., 2000). This group of afferents respond to products of metabolism, and tend to discharge approximately 15-20 s after the onset of muscle contraction and gradually increase their activity until the end of muscular activity (Alam and Smirk, 1937, Kaufman and Hayes, 2002).

During exercise the increased metabolic demand results in a rapid alteration of the chemical environment within the working musculature (Gandevia, 2001). By arresting the circulation after exercise, and thus trapping the metabolites, the BP remains elevated while the HR returns to resting levels (Alam and Smirk, 1937). The metabolites accumulated activate the metaboreflex branch of the exercise pressor reflex, which increases sympathetic activity and provokes a significant increase in BP (Iellamo et al., 1999b). Furthermore, administration of dichloroacetate decreases the production of some metabolites and attenuates the metaboreflex-induced sympathoexcitation (Ettinger et al., 1991). Papelier et al., (1997) observed that in human subjects activation of chemically sensitive receptors, by using post-exercise

circulatory occlusion, does not affect the sensitivity of the carotid-cardiac stimulus-response curve.

Integration of the metabo-and mechanical reflexes components: the exercise pressor reflex

Group III and IV muscle afferents comprise the afferent arm of the exercise pressor reflex arc (McCloskey and Mitchell, 1972). Electrophysiological studies have clearly demonstrated that somatosensory feedback excites both NTS and rostral VLM neurones (Person, 1989, Bauer et al., 1990, Bauer et al., 1992, Potts, 2002). Furthermore, within the NTS, rhythmic muscle contraction in anaesthetized cats also increases the discharge rate of NTS neurones and their excitation pattern is tightly coupled to the frequency of somatic activation (Potts et al., 1998). These muscle afferents reach the spinal cord via the dorsal roots and disseminate throughout the dorsal horn, making also connections with a group of spinal neurones in laminae I-V of the spinal cord, and the dorsal column nuclei (Kalia et al., 1981, Gao et al., 2005). These fibres synapse at the segmental level and through a second-order of fibres, and ascend the spinal cord via the lateral funiculus tract (Kozelka et al., 1987) and the spino-thalamic and spino-reticular tracts, and then project to the NTS and other areas of the brainstem (Potts, 2002, Degtyarenko and Kaufman, 2006). The putative neurotransmitters at the first synaptic relay point in the reflex arch include glutamate (fast acting, De Biasi and Rustioni, 1988), the substance P (slower) acting as neuromodulator, and somatostatin (Kaufman et al., 1988, McCoy et al., 1988), the release of which may be modulated by opiates acting at opiate receptor sites on the afferents nerves (Pomeroy et al., 1986). In addition, neural feedback from skeletal muscle promotes substance P release, which activate postsynaptic glutamate receptors

and neurokinin (NK1-Rs) expressed on second order barosensitive glutamatergic interneurons (Talman et al., 1980, Gordon, 1995, Andresen et al., 2004). This, in turn, directly activates a population of GABA neurones in the NTS that express NK1-Rs, which selectively targets and inhibits barosensitive NTS neurones (Potts, 2006). Ultimately, this may affect baroreflex function, as the inhibition in the NTS requires a greater degree of baroreceptor input to evoke a reflex response (bradycardia and hypotension) during exercise, resulting in a functional resetting of the arterial baroreflex, while overall sensitivity remains unchanged (Potts, 2006).

Contribution of the exercise pressor reflex to cardiovascular regulation during exercise

The exercise pressor reflex is evoked by both mechanical and metabolic reflexes, as the mechanoreflex provides the NTS with information about the magnitude of tension developed within the working musculature (Kaufman and Hayes, 2002), while, the metaboreflex provides information about the muscles' internal milieu (Degtyarenko and Kaufman, 2006). During exercise muscle afferent activity contributes to the baroreflex's fine-tuned control of circulation (Hayes and Kaufman, 2001), as demonstrated by the abolition of the pressor response following ablation of the dorsal roots (and thus muscle afferent activity, Kaufman et al., 1984a). Furthermore, partial blockade of skeletal muscle afferent nerve traffic reduces the magnitude of baroreflex resetting, while the magnitude of the resetting tends to be greater during static than dynamic exercise (Smith et al., 2003).

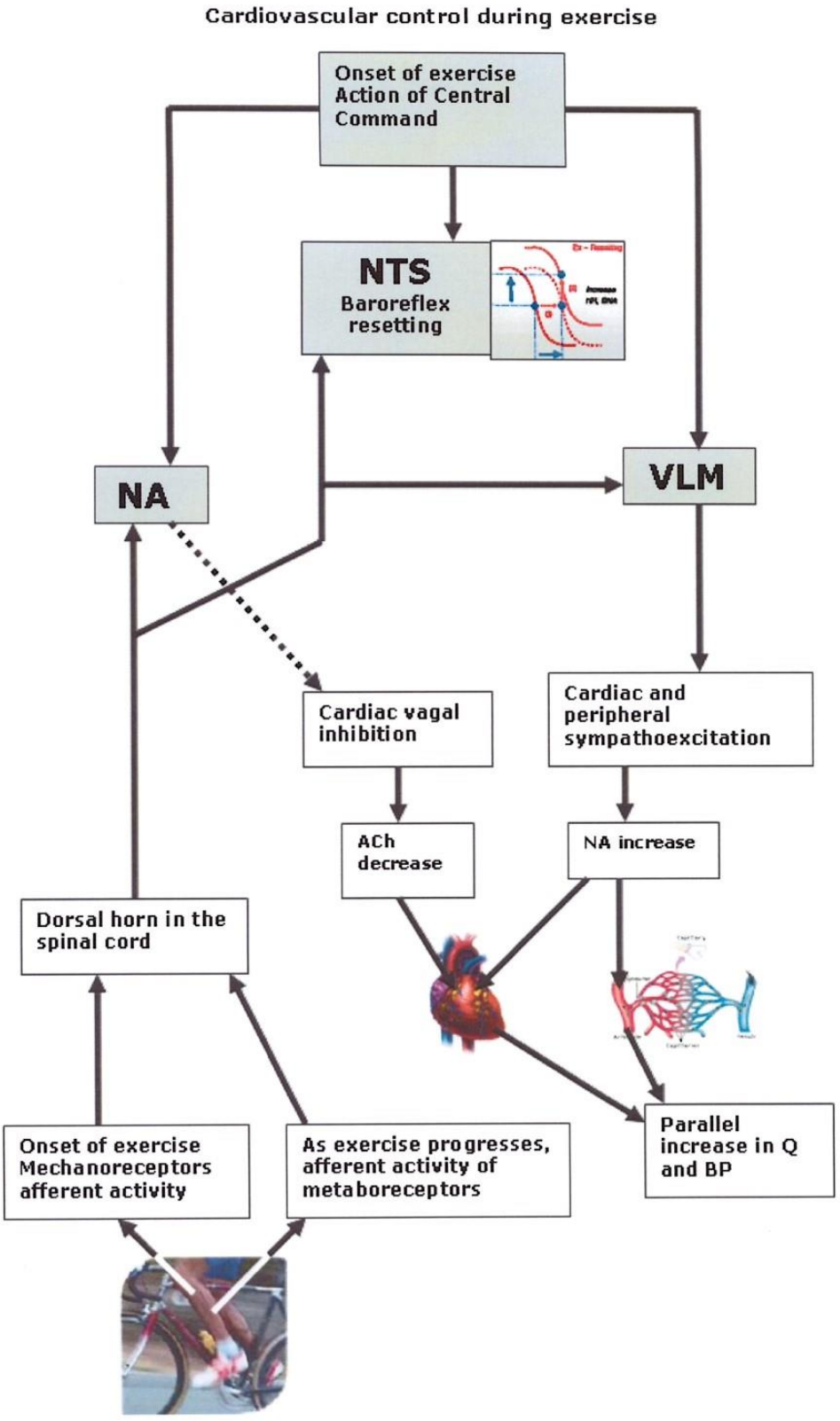

Fig. 1.4: Diagrammatical representation of the baroreflex control of blood pressure during exercise, including the contribution of central command and muscle afferents in mediating the cardiovascular responses to exercise, and the upward resetting of the baroreflex function curve.

2.7 Fluctuations in cardiac rhythm-Heart Rate Variability (HRV)

At rest, the HR fluctuates around its mean and these periodic fluctuations in HR were first observed and described by Hales (1735) and subsequently by von Haller (1778). More recently the measurements and interpretation of these fluctuations in HR, or heart rate variability (HRV) became an important issue in cardiology (Pagani et al., 1988). Originally, this method of cardiovascular assessment was promoted by clinicians and physiologists who reported that HRV may furnish insight into the cardiac sympathovagal modulation (Pagani et al., 1984, Lombardi et al., 1987, Saul et al., 1988). This approach was subsequently employed for the assessment of cardiac autonomic outflow during physical stress (Pagani et al., 1988), the diagnosis of autonomic neuropathy (Bernardi et al., 1992), and risk assessment after myocardial infraction (Kleiger et al., 1987). The principle of these investigations is that in these disease states the autonomic function, and thus HRV that reflects the influence of the sympathovagal activity on the sinus node, is altered. In addition, HRV is employed to assess the alterations in HR in response to ongoing physiological perturbations such as postural shift, or exercise (Levy et al., 1970).

Methods of heart rate variability analysis

Analysis of HRV consists of a series of measurements of RR interval (or PI) variations of sinus origin, providing information about the cardiac autonomic tone (Tsuji et al., 1996) and may be evaluated using different methods including time and frequency domain methods (Task Force, 1996). These HRV measurements may be performed on the basis of 24 hour Holter recording, or shorter recording ranging from 0.5 to 5 min (Task Force, 1996). The calculated time domain variables may be simple,

such as the mean RR interval, difference between day and night HR, or more complex based on statistical analysis (Kleiger et al., 1992). The time domain parameters may include the standard deviation of all normal to normal intervals (SDNN), which is a global index of HRV and reflects all the long-term components and circadian rhythms responsible for the variability of the recorded period (Sztajzel, 2004). The percentage difference between adjacent normal to normal intervals that are greater than 50 ms (pNN50) is an index of short-term HRV changes that is not dependent on day/night variations (Tsuji et al., 1996).

Spectral analysis of HRV is a method for quantification of cardiovascular rhythms on beat-by-beat basis that was introduced by Akselrod et al.,(1981). The analysis of cardiovascular variability derived from the HRV spectrum provides quantitative indices of neural control of the SA node (Pagani et al., 1986, Task Force, 1996). Since no microneurographic techniques are available for direct measurements of the actual cardiac autonomic nerve traffic, spectral analysis of HRV represents a non-invasive index of autonomic cardiovascular regulation (Pagani et al., 1986, Task Force, 1996). Analysis of the power density (variance) of the cardiotachogram provides information for the distribution of RR intervals as a function of frequency (Sayers, 1973, Akselrod et al., 1981). The HR signal is decomposed into its frequency components and quantified in terms of their relative intensity (power, Sayers, 1973). The power (i.e. the density of the beat-to-beat oscillation in the PI) of HRV in the high frequency (HF) band, between 0.15-0.4 Hz, is an index of cardiac vagal traffic (Task Force, 1996, Pagani et al., 1986), while the power in the low frequency (LF) band, between 0.04-0.15 Hz, is a more complex index as it includes contributions from cardiac sympathetic and vagal traffic (Berger et al., 1989, Saul et al., 1991), and

baroreflex actions (Julien et al., 2003, deBoer et al., 1987). The calculation of normalised units (n.u.) of HF and LF powers eliminates the noise and includes only the frequencies related to the cardiac sympathovagal traffic, thus increasing the reliability of HRV parameters in reflecting sympathetic cardiac modulation (Task Force, 1996) especially when cardiac sympathetic drive is increased (Berger et al., 1989, Parati et al., 1995, Saul et al., 1991). Alternatively, the LF/HF ratio represents the dual opposing effects of sympathetic and parasympathetic activity, and has been used to describe sympathovagal balance (Pagani et al., 1986). High values of HF component and total HRV power have been associated with physical fitness and health (Goldsmith et al., 1997). HRV has been employed to investigate cardiac sympathovagal balance during changes in body posture, valsalva manoeuvre, as well as during and post exercise (Task Force, 1996). Importantly, post-exercise HRV has provided evidence for the beneficial effect of exercise training on cardiac sympathovagal balance (Iellamo et al., 2000).

Other approaches for HRV analysis are the geometrical methods, which are derived and constructed from the conversion of sequences of normal to normal (NN) intervals (Sztajzel, 2004). Various geometrical forms allowing to assess HRV are available, including the 24 hour histogram, HRV triangular index and its modification, the triangular interpolation of NN interval, and the method based on Lontz, or Poincare, plots (Task Force, 1996, Cripps et al., 1991, Sztajzel, 2004). These geometrical methods are less affected by the quality of the recorded data and may provide an alternative to the less easily obtainable statistical parameters. However, the minimum recording required is 20 min, and thus geometric methods are inappropriate for short-term recordings (Sztajzel, 2004).

The effect of exercise on BRS, HRV and cardiovascular health

The arterial baroreflex is a requisite for the circulatory adjustments seen during exercise, as sinoaortic denervation results in abnormal response (Potts and Mitchell, 1998, Fadel et al., 2001). Several animal studies have indicated that a depressed BRS and a reduced HRV are the consequence of decreased reflex vagal control of the sinoatrial node (Barron and Lesh, 1996), and are associated with greater risk for ventricular fibrillation during transient ischemic episodes that occur after myocardial infarction (MI, Schwartz et al., 1988, Hull et al., 1990, Billman et al., 1982). Furthermore, a depressed BRS may play a role, even long after MI, in the occurrence of malignant arrhythmias (Hohnloser et al., 1994).

Reduced HRV may be predictive of a second MI and an independent predictor of risk for sudden death in asymptomatic individuals (Molgaard et al., 1991). Furthermore, low HRV has also been associated with insulin resistance (Pober et al., 2004), low cardiorespiratory fitness, and other risks factors of cardiovascular disease (CVD, Odemuyiwa et al., 1991).

Interventions that improve BRS and HRV may reduce the risk of cardiovascular events (Parati et al., 2000). Among these interventions, exercise training might be an effective non-pharmacological tool to improve BRS, HRV, cardiac vagal control in patients with coronary artery disease (Pagani et al., 1988, Somers et al., 1991b). Also exercise may improve cardiac electrical stability, and prevent ventricular fibrillation (Pober et al., 2004, Gulli et al., 2003, Billman et al., 1984, Hull et al., 1994, Ueno et al., 2002, Farrell et al., 1992), as well as having beneficial effects on BRS, in diabetic

subjects (Loimaala et al., 2003). Young and physically fit people exhibit higher values of BRS, while lower values are associated with low level of fitness and disease (Barney et al., 1988). Furthermore, these beneficial effects may be achieved by a single bout of exercise (Pober et al., 2004). Taken together, these studies demonstrate that BRS and HRV constitute important markers of health and fitness that may be improved with exercise training.

Summary

The NTS is considered the main central neural circuit of baroreflex, where afferent neural signals from baroreceptors and skeletal muscles integrate with the input of different brain centres (central command). The various neural inputs to the NTS play both independent and interactive roles in the functional resetting of the arterial baroreflex and the control of circulation during exercise. The baroreflex is a major circulatory controller at rest, while during exercise works in concert with the central command and the pressor reflex to provide the fine-tuning of cardiovascular control. Several studies clearly indicate that inputs from these three neural mechanisms, namely, central command, the exercise pressor reflex and the arterial baroreflex, are requisite for the normal physiological responses to exercise. Spontaneous BRS assessment furnishes estimates of the barorerflex's ability to induce rapid changes in HR in response to hypertensive/hypotensive stimuli Furthermore, BRS has been used to investigate the baroreflex control of the sinus node during homeostatic challenges such as exercise and orthostasis. Reduced BRS has been associated with cardiovascular disease. Spectral analysis of HRV is an index of the sympathovagal balance, and has been used in various settings. Decreased HF power with concomitant augmented LF power has also been associated with some disease

states. There is growing evidence suggesting that higher values of BRS and HRV are largely determined by the action of cardiac vagal traffic, while reduction of cardiac vagal tone is associated with depressed BRS and reduced HRV and may lead to adverse cardiovascular events. Exercise training may increase BRS and HRV, while physical inactivity may reduce BRS and HRV.

2.8. Cardiopulmonary baroreceptors, central blood volume and postural shift at rest and during exercise

Postural shift at rest

The cardiovascular responses to postural change reflect both the mechanical influence of gravity on the circulatory system and autonomic reflex responses (Toska and Walloe, 2002). During postural shift, from upright to supine, the redistribution of blood, away from the high capacitance veins in the pelvis and lower limbs to the thorax, loads the carotid and cardiopulmonary baroreceptors and increases venous return and SV (Miyamoto et al., 1982). The cardiopulmonary baroreceptors are loaded as a result of increased CBV, cardiac filling, and distension of the heart chambers (Pump et al., 2001). Also, the position of the aortic and carotid baroreceptors in relation to the heart changes (Toska and Walloe, 2002). As a result, the hydrostatic pressure acting on the carotid baroreceptors, that are located above heart level in the erect posture, is increased when supine where the carotid sinus is practically at heart level (Pump et al., 1997, Pump et al., 1999). The resulting afferent activity of arterial and cardiopulmonary baroreceptors to the medullary cardiovascular centres decrease HR (Floras, 1990) and sympathetic activity to the systemic vasculature aiming to counteract the increase in SV and Q (Jacobsen et al., 1993, McMahon et al., 1998, Ogoh et al., 2006a Johnson et al., 1974; Victor and Leimbach, 1987). Furthermore, this physiological perturbation shifts the cardiac sympathovagal balance towards a more vagal predominance and thus enhances BRS (Kardos et al., 1997). BRS increases linearly as the tilt angle decreases during postural shift (Cooke et al., 1999, Westerhof et al., 2006, O'Leary et al., 2003, Jasson et al., 1997, Bahjaoui-Bouhaddi et al., 1998). Nevertheless, in this experimental model BRS is not only affected by

changes in cardiac vagal traffic (Hughson et al., 1993), but also by the latency of the vagally mediated carotid baroreceptor-heart rate reflex (Keyl et al., 2001) that increases during postural stress (Westerhof et al., 2006). Taken together, these studies suggest that, at rest, postural shift from upright to supine enhances CBV and affects the sympathovagal balance that consequently enhances BRS.

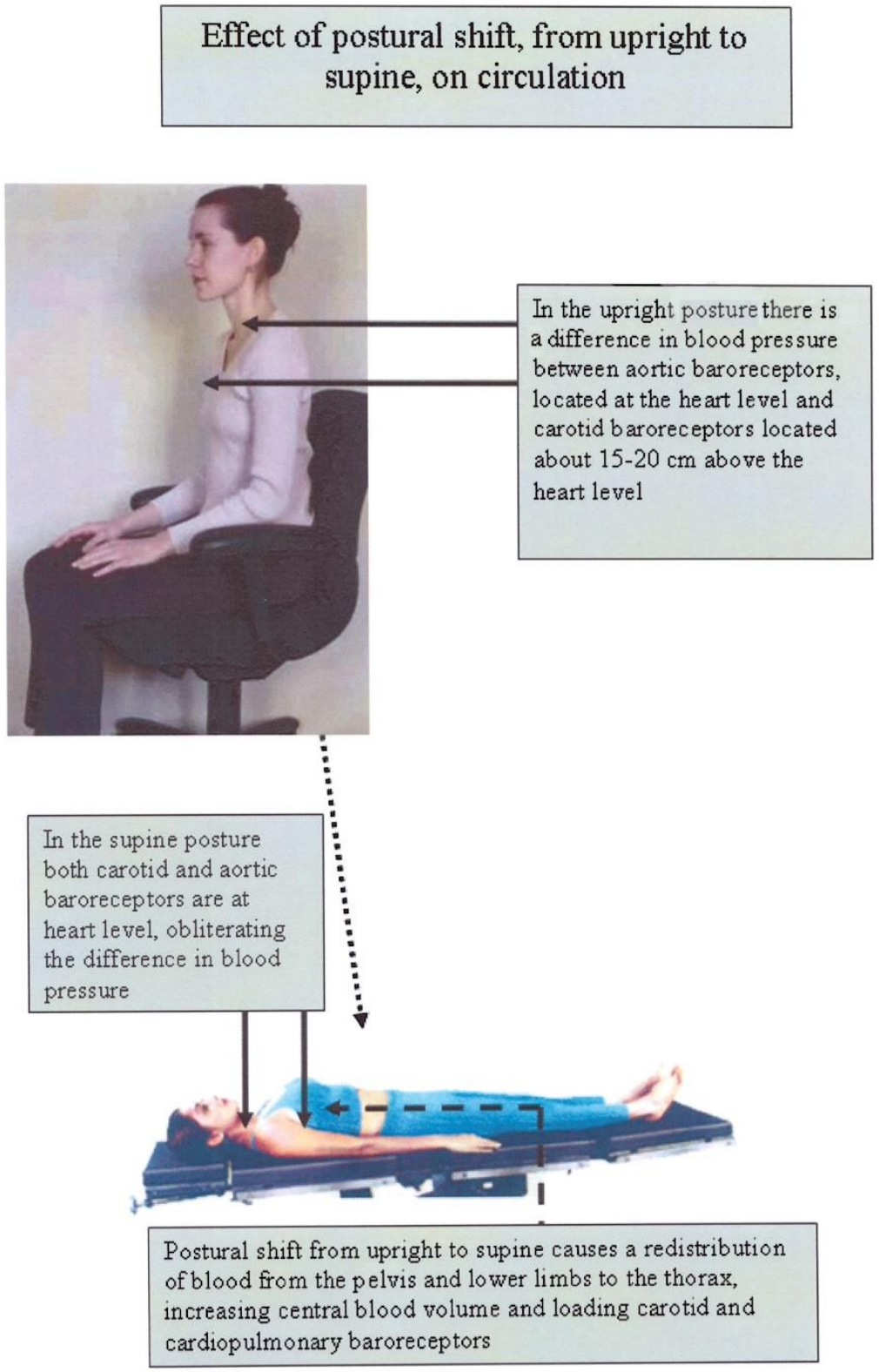

Fig. 1.5: Diagrammatical representation of the effect of postural shift, from upright to supine on blood redistribution, and the consequent loading of the arterial and cardiopulmonary baroreceptors.

Postural shift during exercise

The resetting of the arterial baroreflex during exercise may be also affected by inputs from cardiopulmonary baroreceptors (Ogoh et al., 2007). However, during exercise many reflexogenic areas are activated, making it difficult to determine their interactions and the findings of various studies present with seeming inconsistencies. For instance, in the transition from rest to heavy exercise the carotid-cardiac baroreflex function curve is relocated upward and rightward in a workload-dependent manner (Ogoh et al., 2003). In contrast, the addition of leg exercise to arm exercise relocates the carotid-vasomotor baroreflex function curve lower compared to arm exercise alone, despite employing a larger muscle mass and performing more absolute work (Volianitis et al., 2004). The muscle pump, employed by the addition of leg to arm exercise (Volianitis et al., 2004), increases venous return and CBV, and the consequent loading of the cardiopulmonary baroreceptors attenuates the BP response. Conversely, the increase in BP in relation to workload observed by Ogoh et al., (2003) occurs because the effectiveness of the muscle pump in increasing venous return tends to decrease at heavier workloads (Brechue et al., 1995) and this factor may have contributed to these seemingly contrasting results.

During one-legged upright exercise the muscle pump increases CBV and the consequent loading of the cardiopulmonary baroreceptors reflexively reduces sympathetic outflow (Ray et al., 1993). Nonetheless, this decrease in sympathetic traffic does not occur during supine exercise (Ray et al., 1993) presumably due to the fact that when supine the cardiopulmonary baroreceptors are already loaded and the employment of the muscle pump has no further effect (Ogoh et al., 2007). Alternatively, as suggested by Leyk et al., (1994) the muscle pump may be less

effective during supine exercise. In contrast with this view, the thoracic admittance, an accurate index of changes in CBV (Ebert et al., 1986), has been found to be higher during supine exercise compared to supine rest (Ogoh et al., 2007), suggesting that the muscle pump is still effective during supine exercise. Furthermore, atrial natriuretic peptide, which is released in response to increased CBV and atrial stretch (Stein and Levin, 1998), is higher during supine exercise compared with supine rest and upright exercise (Vogelsang et al., 2006). In addition, SV that is profoundly affected by venous return and CBV, increases progressively with intensity during both upright and supine exercise (Warburton et al., 1999). Taken together, these studies suggest that the muscle pump is still effective during supine exercise but possibly the effect of the cardiopulmonary baroreflex may have a ceiling, following saturation of the cardiopulmonary baroreceptors. Moreover, the interaction of different reflexogenic areas and their influence on autonomic circulatory control during exercise is not fully understood, and therefore requires further investigation.

2.9. Post-exercise hypotension

Following exercise there is often a clinically significant reduction in blood pressure below pre-exercise levels, termed post-exercise hypotension (PEH, Kenney and Seals, 1993), that can be observed even with a single bout of exercise (Thoren et al., 1990). Although PEH was first observed during 90 min following a 400 yards dash (Hill, 1897), it was only after (Fitzgerald, 1981) reported the effect of jogging on his own labile hypertension that the scientific community began to systematically examine this phenomenon.

There is evidence suggesting that the magnitude of reductions in BP following exercise is generally greater in hypertensive compared with normotensive subjects (Kenney and Seals, 1993). The peak in systolic and diastolic blood pressure (SBP, DBP) reductions may range between 18 to 28, and 7 to 9 mmHg, respectively, in hypertensive humans, and 8 to 10, and 3 to 5 mmHg, respectively, in mormotensive subjects (Bennett et al., 1984, Coats et al., 1989, Seals et al., 1988, Somers et al., 1991a, Kenney and Seals, 1993). PEH has been observed in response to different types of dynamic exercise including running, cycling and swimming (Coats et al., 1989, Pescatello et al., 1991, Kenney and Seals, 1993). In addition, rodents also develop PEH following treadmill running (Overton et al., 1988, Shyu and Thoren, 1986). In terms of exercise intensity, both in humans and rats, PEH was reported after exercise ranging from moderate to exhaustion (Coats et al., 1989, Seals et al., 1988, Somers et al., 1985, Somers et al., 1991a).

A significant reduction in BP was observed after an exercise bout lasting 10 min (MacDonald et al., 2000, Bennett et al., 1984), as well as after exercise lasting 170 min (Seals et al., 1988), although the majority of studies used exercise lasting between 20 and 60 min (Fitzgerald, 1981, Floras et al., 1989, Boone et al., 1992, Hara and Floras, 1995, Isea et al., 1994, Cleroux et al., 1992a, Hara and Floras, 1992, Halliwill et al., 1996a). PEH may occur within the initial minutes after the cessation of exercise (Piepoli et al., 1993, Piepoli et al., 1994, Boone et al., 1993), or between 30 min and 2 hours after exercise (Fitzgerald, 1981, Pescatello et al., 1991, Somers et al., 1991a, MacDonald et al., 2000, Coats et al., 1989, Kaufman et al., 1987). However, in normotensive humans PEH does not always occur, as several investigations did not observed changes in BP after exercise compared with pre-exercise levels (Cleroux et

al., 1992a, Franklin et al., 1993, Pescatello et al., 1991, Piepoli et al., 1994, Convertino and Adams, 1991). Furthermore, after exercise, both in humans (O'Connor et al., 1993) and in animals (Howard et al., 2000), BP may even increase. Collectively, these studies suggest that after exercise BP may be reduced, unchanged, or even increased. Given the complex nature of BP regulation that includes central and peripheral mechanisms, their respective role and contribution to PEH have not been conclusively determined.

Mechanisms: Sympathetic activity and PEH

An important determinant of PEH is TPR, as generally the reduction in BP is due to a persistent increase in vascular conductance that is not completely offset by augmentation in Q (Halliwill et al., 1996b, Halliwill, 2001). After exercise the two factors that regulate vascular conductance are the vasoconstricting sympathetic vasomotor tone and the vasodilating effect of exercise-borne substances (Halliwill et al., 1996a).

The after-effects of exercise on sympathetic activity are controversial. In humans, reductions in systolic BP and muscle sympathetic tone are observed in borderline hypertensive subjects after treadmill running (Floras et al., 1989). Furthermore, in mild hypertensive subjects, exercise decreases noradrenalin release, which also suggests a reduction in sympathetic traffic (Brown et al., 2002). In accordance with these findings, Meredith et al., (1991) reported a post-exercise decrease in noradrenalin spillover in humans. Additionally, in normotensive subjects, Halliwill et al., (1996a) found a decrease in baseline muscle sympathetic activity, associated with a downward shift in the relationship between sympathetic activity and BP.

In hypertensive rats BP decreased along with lumbar sympathetic tone after exercise (Kulics et al., 1999). However, other studies suggest a limited contribution of sympathoinhibition to PEH (Halliwill et al., 2000, Hara and Floras, 1995). Indeed, in normotensive humans a reduction in BP after exercise has been observed despite unchanged sympathetic traffic (Hara and Floras, 1992). Furthermore, following intensive exercise PEH was observed in normotensive (Piepoli et al., 1993) and hypertensive subjects (Legramante et al., 2002) even in the presence of increased sympathetic traffic. Presumably, in these studies the vasoconstricting sympathetic discharge was overridden by the vasodilating substance associated with exercise. Collectively, these studies indicate that PEH may develop independently from post-exercise sympathetic activity.

Contribution of exercise-borne vasodilating substance to PEH

Exercise causes the release of substances that impair the vasomotor efficiency of sympathetic activity. The relationship between sympathetic activity and vascular resistance is attenuated following exercise in humans (Halliwill et al., 1996a). Similarly, reduced vascular responsiveness to adrenergic receptors has been observed both in animals (Howard and DiCarlo, 1992) and in aortic tissue in vitro (Howard et al., 1992). Thus, decreased vascular responsiveness to sympathetic stimuli post exercise may cause reduction in BP *per se*, even in the presence of unchanged sympathetic discharge. Some exercise-borne substances may be responsible for this ineffective transduction of sympathetic activity into vascular resistance (Halliwill et al., 1996a). For instance, after a bout of exercise circulating opioids may be augmented (Schwarz and Kindermann, 1992), and this causes sympathoinhibition

(Reid and Rubin, 1987). The sympathetic nerve terminal possess presynaptic inhibitory opioid receptors (Wong-Dusting and Rand, 1989) that may be occupied after exercise, and thus reduce noradrenalin release (Halliwill et al., 1996a). Indeed, systemic opioids blockade with naloxone reverses PEH in animals (Shyu and Thoren, 1986) and humans (Boone et al., 1992), while administration of opioids provokes sympathoinhibition and hypotension (Holaday, 1983).

Another exercise-borne substance that may cause presynaptic sympathoinhibition is neuropeptide Y (Lundberg and Stjarne, 1984), which is co-released with noradrenalin during exercise (Pernow et al., 1986). After exercise, neuroptide Y may remain bound to presynaptic receptors, reducing noradrenalin release (Pernow et al., 1986). In addition, nitric oxide synthase blockade in rodents partially reverses the attenuated adrenergic responsiveness of smooth muscle post-exercise (Patil et al., 1993), strongly supporting a role for enhanced nitric activity in the development of PEH.

Muscular contractions mechanically compress the blood vessels and cause the release of endothelium-derived vasodilating substances (Niebauer and Cooke, 1996) causing vasodilatation and hyperemia during exercise (Moncada et al., 1991). These effects may persist after exercise contributing to decreasing TPR and thus PEH (Legramante et al., 2002, Kenney and Seals, 1993). Furthermore, exercise induces the release of prostaglandins that induce arterial and venous vasodilatation (Ward, 1999) and mediate a reduction in TPR post-exercise (Morganroth et al., 1977). In addition, during exercise the production of metabolites also provokes vasodilatation and may contribute to PEH (Kenney and Seals, 1993). The significant muscle hyperaemia occurring during exercise may persist after exercise (Gaesser and Brooks, 1984,

Hussain et al., 1996, Bahr et al., 1987) as a result of decreased oxygenation and pH in combination with increased metabolites, such as carbon dioxide, or adenosine (Hussain et al., 1996, Goonewardene and Karim, 1991). Taken together, these studies suggest that the exercise-borne vasodilating substance play a major role in PEH.

Other factors that may contribute to PEH

A decrease in HR and Q may potentially contribute to PEH (Hagberg et al., 1987). However, in humans post-exercise Q is generally increased through elevated HR (Coats et al., 1989, Piepoli et al., 1993, Isea et al., 1994), enlarged SV (Kulics et al., 1999), or both (Floras et al., 1989, Cleroux et al., 1992b). This suggests a limited contribution of decreased Q to PEH, as significant reductions in BP were observed post-exercise in the presence of increased HR and Q (Cleroux et al., 1992a, Coats et al., 1989, Hara and Floras, 1992).

During exercise the elevation in BP drives plasma into the interstitial space and, thus, reduces blood volume (MacDonald, 2002). After exercise, the cessation of muscle pump and the reduced blood volume may result in decreased venous return, SV and Q, which may contribute to PEH (MacDonald, 2002). However, several investigations reported decreased BP in the presence of unchanged blood volume (Cleroux et al., 1992b, Cleroux et al., 1992a, Hara and Floras, 1992, Kaufman et al., 1987), suggesting that reductions in blood volume do not contribute importantly to PEH.

The arterial baroreflex, muscle afferents, and PEH

It has been proposed that after exercise the loss of central command may result in downward resetting of the arterial baroreflex, thus contributing to PEH (Kenney and

Seals, 1993). However, direct stimulation of the hind limb muscle in rodents, a technique that does not activate central command, resulted in PEH (Hoffmann et al., 1990a, Hoffmann et al., 1990b, Hoffmann et al., 1990c), indicating a limited contribution of the loss of central command to the development of PEH.

On the other hand, PEH was observed in intact rats, but was absent in sinoaortic denervated rats, which impairs the arterial baroreflex function, and it was suggested that this feedback mechanism may contribute to PEH (Chandler and DiCarlo, 1997). In addition, a downward shift in the relationship between sympathetic nerve activity and arterial pressure was observed after exercise in humans, which also suggests that the baroreflex may contribute to PEH (Halliwill et al., 1996a). However, the involvement of the baroreflex has been implicated in the development of PEH even in the presence of increased sympathetic activity (Legramante et al., 2002, Piepoli et al., 1993), as it is suggested that the arterial baroreflex may mediate peripheral sympathoexcitation to counteract the effect of the exercise-borne vasodilating substances and prevent excessive BP falls (Legramante et al., 2002). Thus, the contribution of the arterial baroreflex to PEH is still controversial.

Somatic afferents may also be involved in the development of PEH, as it has been shown that sciatic nerve stimulation results in reduction in BP after the cessation of the stimulus (Kenney et al., 1991), an effect that appears to be mediated by activation of type III muscle mechanoreceptors (Yao et al., 1982a). This response is eliminated when the sciatic nerve is anesthetized prior to the stimulation (Hoffmann et al., 1990c), highlighting the neurogenic origin of this observation. Furthermore,

stimulation of mechanical responsive type III muscle fibres may contribute to opioids release and thus to PEH (Yao et al., 1982b).

However, the effect of exercise on post-exercise BP remains controversial. Several investigations in normotensive humans reported no changes in BP following exercise compared with pre-exercise (Cleroux et al., 1992a, Franklin et al., 1993, Pescatello et al., 1991, Piepoli et al., 1994, Convertino and Adams, 1991, Floras and Senn, 1991). Furthermore, it has also been reported that sympathetic activity and BP in normotensive rabbits (Howard et al., 2000) and in normotensive humans (O'Connor et al., 1993) were elevated following active exercise compared to pre-exercise. Collectively, these studies suggest that exercise may result in decreased, unchanged, or even increased BP compared with pre-exercise. Therefore, further investigations to elucidate the mechanisms determining BP levels after exercise are warranted.

Summary

Physical exercise may induce a clinically significant decrease in BP both in humans and animals. Furthermore, reductions in BP have been observed even after a single bout of exercise. Even though, significant reductions in BP after exercise have been associated with decreased sympathetic outflow; nevertheless, the contribution of exercise-born substances appears to be crucial. Furthermore, the aftereffects of exercise in BP is still controversial, as following exercise BP may remain unchanged, or even increase, compared with pre-exercise. The reasons for these contrasting reports remain to be elucidated.

2.10. Investigating the cardiovascular neural control during exercise *in vivo*, in human

The main aim of the studies contained in the present thesis is to investigate the baroreflex cardiovascular control and the cardiac autonomic outflow during passive exercise *in vivo*, in humans. It is important to consider that in humans, it is impossible to stimulate solely one reflexogenic area of cardiovascular control, as this would require very invasive techniques and thus inadequate in human investigations settings. Therefore, human investigation settings, the studies generally aimed to stimulate mainly one reflexogenic area involved in cardiovascular control, while limiting the contribution of other reflexogenic areas. Thus, in this context, in the studies contained in the present thesis, passive exercise will be used, assuming that passive limbs movements stimulate mainly the muscle mechanorereflex resulting in cardiovascular responses such as increase in HR and BP (Nobrega and Araujo, 1993). On the other hand, the metaboreflex also contributes to cardiovascular responses to exercise (Wyss et al., 1983). The following section will provide insight into the potential contributions of the mechano-and metabolic reflexes to cardiovascular responses to exercise. This section will also consider the potential contribution of these reflexes to the control of circulation during passive exercise.

The study by Alam and Smirk (1937) was the first to investigate the contribution of the metaboreflex cardiovascular control by applying a cuff around the thighs to arrest the circulation. This circulatory arrest, immediately after the cessation of exercise, when the metabolism is still high prevents the washout of metabolites, which accumulate in markedly and activating the muscle metaboreflex. This maintains the BP elevated, while HR returns to baseline values. However, it should be considered

that the application of the cuffs around the thighs exerts pressure in the muscle, and consequently this also stimulate the mechanoreceptors that respond to muscle compression (Nishiyasu et al., 2001, Gallagher et al., 2001a). This represents a classical example of the difficulty to isolate completely one reflexogenic area, *in vivo*, in humans. Despite this limitation, the work of Alam and Smirk (1937) is considered an important contribution to the understanding of the effect of the metaboreflex activation on control of the circulation. Wyss et al., (1983) used terminal aortic occlusion to induce graded decrease in hindlimb blood flow in dogs during dynamic exercise. The application of this technique during exercise at moderate-to-high workloads resulted in increased aortic pressure in response to reduction in muscle blood flow. It should be considered that this manoeuvre represents a potent metaboreceptors stimulus; since during exercise blood flow to active muscles increases markedly, while in the investigation by Wyss et al., (1983) blood flow was reduced. However, at low workloads, the cardiovascular responses to exercise were only affected by substantial reductions in hindlimb perfusion (Wyss et al., 1983). Therefore, the authors suggested Wyss et al., (1983) that signals other than feedback from metaboreceptors must be involved in the control of circulation during low intensity exercise.

Iellamo et al., (1997) used low-intensity electrically induced muscular contraction in humans to stimulate the contraction-responsive muscle mechanoreceptors, and found the typical responses seen during exercise, i.e. a parallel increase HR and BP. It should be noticed that during low-intensity electrically induced muscular contraction there is production of metabolites. This is another example of the difficulties to identify the mechanisms of cardiovascular control during neural investigation in

humans, *in vivo* settings. However, the authors Iellamo et al., (1997) reasoned that during low-intensity exercise the neural mechanism mainly activated is mechanical, because the stimulation of metabo-sensitive receptors would requires severe reduction in muscle blood flow (Wyss et al., 1983) or circulatory arrest that result in marked accumulation of metabolites within the active muscles (O'Leary, 1993). Thus, in this context Iellamo et al., (1997) also arrested the blood flow to the active muscle to provoke the accumulation of metabolites and activate the metaboreflex. In accordance with the above notion, previous studies also reported that during mild exercise the metaboreflex is activated only when the blood flow to active muscle is occluded (Victor and Seals, 1989, Victor et al., 1987). While several other studies reported that the muscle metaboreflex begins to be active from moderate-to high-intensity exercise levels during unrestricted flow dynamic exercise in humans (Rowell and O'Leary, 1990, Victor and Seals, 1989, Victor et al., 1987), Support for this notion is provided by corollary study Gallagher et al.,(2001a) that investigated the relative contribution of the mechanoreflex and the metaboreflex, during submaximal dynamic exercise. In that study, it was observed that at the same exercise intensity, the application of LBPP pressure, which stimulate the mechanoreceptor, resulted in BP elevation, while this BP response did not occur during the application of thigh cuffs that augments the accumulation of metabolites (Gallagher et al., 2001a). The authors concluded Gallagher et al., (2001a) that under normal conditions the mechanoreflex is tonically active and represents the primary mediator of the pressor reflex during submaximal dynamic exercise in humans. Thus, collectively all these studies clearly demonstrate that the during low-intensity dynamic exercise, the mechanoreflex contributes significantly to the cardiovascular response to exercise, while the metaboreflex comes

into play during severe reduction in blood flow to the active muscle, circulatory arrest, and high-intensity exercise.

Passive exercise has been used to study cardiovascular control, assuming a predominant mechanoreflex activation (Nobrega and Araujo, 1993). During passive exercise there is not voluntary muscle contraction as suggested by the EMG that did not change compared with rest (Nobrega and Araujo, 1993), and hence it may be considered as very light exercise. Therefore, it is reasonable to assume that during passive exercise the muscle mechanoreflex is mainly activated as a result of the passive limbs movements, while the muscle metaboreflex is involved to a lesser extent. As the latter is associated with severe reductions in blood flow to the active muscle (Wyss et al., 1983), circulatory arrest (Alam and Smirk, 1937) or high-intensity exercise (Gallagher et al., 2001a), all of which are absent during passive cycling.

Other methods aiming to investigate the contribution of the mechanoreflex to circulatory control includes passive stretch (Wilson et al., 1994, Leshnower et al., 2001), rhythmical compression of skeletal muscle (Nishiyasu et al., 2001) and LBPP (Gallagher et al., 2001a). All these studies showed that the mechanoreflex activation evokes the characteristic cardiovascular response, such increase in HR and BP, observed during active exercise, and thus contributed to the understanding the role of the mechanoreflex to circulatory control. However, passive exercise was used in the studies contained in the present thesis because is the model that more closely resembles to dynamic exercise.

Cardiovascular control during passive exercise

Previous studies demonstrated that during 5 min bout of passive exercise, there is an increase in HR and BP (Nobrega and Araujo, 1993). These findings of parallel increase in HR and BP were confirmed in a subsequent investigation also using passive exercise of similar duration, which also resulted in increased Q (Nurhayati and Boutcher, 1998). These studies demonstrated that passive limbs movements induce the characteristic cardiovascular responses seen during low-intensity active exercise, and the authors suggested that these responses resulted mainly from the mechanoreflex stimulation (Nobrega and Araujo, 1993, Nurhayati and Boutcher, 1998). However, the baroreflex control of the sinus node and the cardiac autonomic outflow during passive exercise remain to be elucidated.

During postural shift from upright to supine, the redistribution of blood away from the capacitance veins in the pelvis and lower limb to the thorax, increase CBV and SV (Miyamoto et al., 1982), and loads the carotid and cardiopulmonary baroreceptors (Pump et al., 1999) resulting in bradycardia (Floras, 1990) and increased BRS (Kardos et al., 1997), via changes in autonomic traffic (Raven et al., 2006). However, the interaction between postural shift and passive exercise, on BRS and cardiac autonomic outflow is not known.

Dynamic exercise may be followed by reduction in BP (Kenney and Seals, 1993), often resulting from decreased total peripheral resistance that is not offset by increased Q (Halliwill et al., 1996a). After exercise, the reduction in peripheral resistance may be determined by decreased sympathetic outflow, decreased vascular

responsivess to sympathetic stimuli, and the effect of the exercise-borne varodilating substances (Halliwill et al., 1996a, Kenney and Seals, 1993). A downward resetting of the baroreflex may result in decreased peripheral sympathetic outflow and reduction in BP (Halliwill et al., 1996a, Floras et al., 1989, Kulics et al., 1999). During exercise, the neurotransmitter substance P is released in the NTS (Potts et al., 1999), due to muscle afferent activation (Wilson et al., 1992, Kuraishi et al., 1989). It has been shown that substance P contribute to decreased central sympathetic outflow, and thus causing a reduction in BP (Chen et al., 2002), by augmenting the excitability of NTS neurones (Morin-Surun et al., 1984). However, it also been shown that the exercise-borne vasodilating substances are important contributors to decreased in BP following exercise (Legramante et al., 2002). Because during active exercise the muscle afferents are stimulated and the vasodilating substances are produced, it is therefore difficult to determine the respective roles.

2.11. Aims of the thesis

1. To investigate the baroreflex control during passive exercise, using the spontaneous baroreflex method.
2. To examine whether passive exercise modifies the cardiac sympathovagal balance, by evaluating spectral analysis of heart rate variability.
3. To investigate the effects and interaction between postural changes and passive exercise on haemodynamics, spontaneous baroreflex sensitivity and heart rate variability.
4. To assess the effect of passive exercise on post-exercise BP, HR and cardiovascular control.
5. To evaluate whether passive exercise modifies post-exercise cardiac baroreflex sensitivity and cardiac autonomic modulation.

6 To evaluate regional muscle tissue oxygenation during passive exercise.

Four studies will be conducted in order to address the aims of the present thesis. The relevant chapters of each study will provide more information regarding the specific aim and the methods used in the investigation.

2.12. Hypotheses

1. H_1: Passive exercise will decrease the cardiac baroreflex sensitivity.
2. H_1: Passive exercise will result in cardic vagal withdrawal causing a shift of the sympathovagal balance.
3. H_1: The affects of passive exercise on spontaneous baroreflex sensitivity and cardiac chronotropic state will override those caused by postural changes.
4. H_1: Passive exercise will provoke a reduction in post-exercise BP values.

5. H_1: Spontaneus baroreflex sensitivity will be increased following passive exercise.
6. H_1: After passive exercise the cardiac vagal modulation will be enhanced.

Chapter 3

General methods

General methods

The methods applied within the studies contained in the thesis are outlined in the following chapter. Any specific method employed in the individual studies is described in the relevant chapter. The general methods employed within this thesis may be categorised as subjects' anthropometric data, non-invasive assessment of cardiovascular activity, electromyography and expired gas analysis.

3.1 Preliminary information

All the studies presented in this thesis were performed following approval from the Ethics Committee of Brunel University. All subjects voluntarily participated in the studies following informed written consent. In number of subjects recruited for each study was: study 1 n = 15 (11 male and 4 female); study 2 n = 11 (8 male and 3 female); study 3, n = 14 (11 male and 3 female); Study 4 n = 6 (5 male and 1 female).

Anthropometry

In all studies subjects' stature (cm) and body weight (kg) were measured using standard procedures. Stature was assessed using a stadiometer (SECA 225, Germany) while body weight was assessed using a scale (SECA 335, Germany).

6.1.3 Cardiovascular variables

In each study continuous non-invasive blood pressure measurements from the finger, were performed using a haemodynamic monitoring system (Finometer PRO, Finapres Medical Systems, Amsterdam, Nederlands). This hemodynamic monitoring system measures BP continuously and non-invasively, and the method and principles of these

measurements, as well as those regarding electromyography and expired gas analysis are outlined in this chapter.

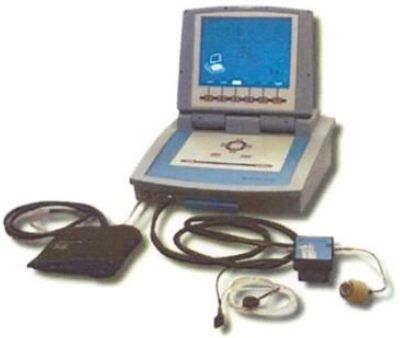

Fig 2.1: Finometer hemodynamics monitoring system

Continuous Blood pressure measurements using the Finometer hemodynamics monitoring system

The arterial pressure in the finger is measured making use of the volume-clamp method (Penaz, 1973). The method is based on the development of the dynamic pulsatile unloading of the finger arterial walls (Wesseling et al., 1995, Imholz et al., 1998). In this method the diameter of an artery under a cuff wrapped around the finger is kept constant (clamped) at a certain diameter, the 'set-point', in spite of the changes in arterial pressure during each cardiac cycle. Changes in diameter are detected by means of an infrared photo-plethysmograph built into the finger cuff. If during systole an increase in arterial diameter is detected the cuff pressure is immediately increased by a rapid servo-controller system to prevent diameter change. The collapse of the finger artery requires a cuff pressure larger than the finger intra-arterial pressure. At zero transmural pressure the artery is not collapsed (unstressed arteries still have ~1/3 or 1/2 of their original cross-sectional area and volume) but 'unloaded', that is, the

arterial walls are held at zero transmural pressure which corresponds with their unstressed diameter (Imholz et al., 1998, Wesseling et al., 1995). As a result, finger cuff pressure equals intra-arterial pressure when the volume-clamp method is active at the proper unloaded diameter of the finger artery. The unloaded diameter is close to the average diameter at a pressure where the amplitude of the pulsations in the plethysmogram is largest.

Changes in stress and tone of smooth muscle in the arterial wall affect the unloaded diameter. Therefore, the unloaded diameter is usually not constant during a measurement and is verified at intervals. This is achieved by the Finometer built-in system (Physiocal, Finometer Medical Systems, Amsterdam) consisting of a dynamic servo set-point adjuster that defines and maintains the diameter at which the finger artery is clamped (Wesseling et al., 1995). The Physiocal algorithm includes the search procedure and criterion for the automated determination and periodic adjustment of the arterial unloaded volume. It explores part of the pressure–diameter relation by analysing the plethysmogram at a number of steady pressure levels, and is able to track the unloaded diameter of a finger artery even if smooth muscle tone changes. To adjust the correct unloaded diameter of the finger artery based on the signal from the finger cuff plethysmograph, cuff pressure is kept constant at regular intervals. Consequently, the measurement of blood pressure is temporarily interrupted. The finger pressure tracks the intra-arterial pressure even though the pressure waves may differ systematically both in shape and magnitude (Imholz et al., 1991, Imholz et al., 1992, Bos et al., 1992).

Calculation of cardiovascular variables

The Modelflow method (Wesseling et al., 1993) as implemented in the Finometer hemodynamics monitoring system, computes an aortic flow waveform from either finger or intra-arterial pressure by simulating a non-linear three-element model of the aortic input impedance. The major determinants of systolic inflow are the aortic impedance and arterial compliance (Westerhof et al., 1971), which depend on the elastic properties of the aorta. Peripheral vascular resistance, as the third element of the model, is not a major determinant of systolic inflow (Wesseling et al., 1993) and is time-varying, expressed for each heart beat as the quotient of arterial pressure and modelled flow.

The aortic impedance relates pulsatile flow to pulsatile pressure at the entrance of the aorta. Left ventricular contraction ejects blood into the aorta, but as the aorta already contains blood, the existing aortic pressure opposes the left ventricular outflow. Aortic pressure increases in response to the accelerated inflow of blood. The magnitude of the augmentation in aortic pressure depends on instantaneous flow, the cross-sectional aortic area and compliance. Thus, aortic impedance represents aortic opposition to pulsatile inflow from the contracting left ventricle and has the dimension of pressure divided by flow (Bogert and van Lieshout, 2005). The arterial compliance describes the extent of aortic pressure augmentations for a certain quantity of blood. When a volume of blood is expelled into the aorta, it expands elastically and its pressure increases. The increased pressure opposes further inflow to the aorta until a further rise in left ventricular pressure. A compliant aortic wall expands easily producing only a small rise in aortic pressure (Windkessel function, Wesseling et al., 1993). The arterial compliance represents the aortic opposition to an increase in blood volume.

The dimension of compliance is a change in volume divided by a change in pressure while peripheral vascular resistance, the ratio of mean pressure to mean flow, is a measure for the ease of constant blood drainage from the compliant aorta into the peripheral vascular beds (Bogert and van Lieshout, 2005).

The Finometer software (BeatScope version 1.1; Finapres Medical System, Amsterdam, Nederlands) was used to compute cardiovascular variables. SV was computed using the pulse-contour model, by integrating the computed aortic flow waveform. Specifically, SV was computed as the true integrated mean of the simulated flow waveform between current upstroke and the dicrotic notch. HR was computed from PI, defined as the time (ms) between two adjacent upstrokes, and Q as the product of SV and HR. TPR was computed as the ratio between mean arterial pressure and Q. Systemic vascular conductance was calculated, Q dived by MAP, and arterial-venous difference as VO_2 dived by Q.

In each study, spontaneous baroreflex sensitivity and spectral analysis of heart rate variability were employed to assess the effect of mechanoreflex stimulation on baroreflex control of the sinus node and cardiac autonomic outflow.

Spontaneous baroreflex sensitivity using the cross-correlation (xBRS) method

Spontaneous baroreflex sensitivity (BRS) was calculated using a cross-correlation function (xBRS) described previously (Westerhof et al., 2004). In this method, changes in the same direction of SBP and PI were identified by specific software. The correlation between beat-to-beat SAP and PI, resampled at 1 Hz in a sliding 10 s window, with delays of 0-5 s for interval, was calculated (Borst and Karemaker,

1983).. The delay with the greatest positive correlation was selected and, when significant at $P = 0.01$, slope and delay were recorded as one xBRS value. The mean individual slope of the SAP-to-PI relationship, obtained by averaging all slopes within the data collecting period, was calculated and taken as a measure of spontaneous BRS for that period. The correlation of current SAP with later PI values allows sufficient time so that the effects of both vagal and sympathetically mediated reflexes on PI are considered (Westerhof et al., 2004). This approach removes uncertainty regarding the optimal number of beats delay to be implemented, since it may vary among subjects (Steptoe and Vogele, 1990) and body posture (Westerhof et al., 2004). Furthermore, in order to ensure that these changes were the result of baroreflex action, the accepted regression slope was divided by the correlation coefficient to obtain a slope fitting SAP and PI simultaneously (Snedecor and Cochran, 1967, Westerhof et al., 2004). This spontaneous BRS method allows the dynamic assessment of the integrated cardiac baroreflex control at the prevailing blood pressure (Iellamo et al., 1997, Westerhof et al., 2004) and provides values that correlate highly with those obtained with the pharmacological method (Parlow et al., 1995, Westerhof et al., 2004). Furthermore, spontaneous baoreflex methods provides good BRS reproducibility under various stimuli that affect the neural control of circulation differently (Iellamo et al., 1996).

Heart rate variability assessment using spectral analysis

Heart rate variability (HRV) data were derived from PI, and analysed in the frequency domain, using specifically designed software (Biomedical signal analysis, Kuopio, Finland). The Fast Fourier Transform (FFT) is a method largely used in the frequency domain and the spectrum is characterized by discrete peaks for several frequency

components (Task Force , 1996). The power spectrum consists of four main frequency bands: a high frequency (HF) 0.15-0.4 Hz, a low frequency (LF) 0.04-0.15 Hz, a very low frequency (VLF) 0.003-0.04 Hz and an ultra low frequency (ULF) < 0.003 (Task Force, 1996). Since the underlying physiological significance of VLF and ULF components is still unclear, generally HF and LF are the components mostly considered in HRV analysis. The total area under the power spectral curve represents total power.

HF fluctuations exhibit a periodicity of 2.5-7 s, and represent an index of vagal tone acting on the sinoatrial node, as seen in clinical observations, such as vagal stimulation, muscarinic receptor blockade and vagotomy (Task Force, 1996). The LF oscillations show a periodicity of 7-25 s and reflect the influence of sympathetic (Task Force 1996), as well as parasympathetic activity (Berger et al., 1989, Saul et al., 1991); and baroreflex contributions (Julien et al., 2003) on HR. In the studies contained in the present thesis the HF and LF power were normalised and thus, are expressed in normalises units (n.u.). The normalization procedure (the HF and LF powers after discarding VLF components) permits a better assessment of HF and LF power distribution, as it reduces inter-individual difference in total power and VLF noise that may be present a rest and during exercise (Pagani et al., 1997, Iellamo et al., 1999b). Furthermore, normalization of LF increases the reliability and validity of spectral parameters as a reflection of cardiac sympathetic modulation (Task Force, 1996), particularly when sympathetic traffic is augmented (Berger et al., 1989, Saul et al., 1991, Parati et al., 1995).

Spectral analysis of HRV provides noninvasive, reproducible information regarding the autonomic cardiac regulation (Sztajzel, 2004, Appel et al., 1989, Guijt et al., 2007) and it also been used in clinical settings (Maestri et al., 2006).

3.3 Surface electromyography

The surface electromyography (EMG) signal is an extracellular recording of propagated muscle fibres action potentials during muscular contractions (Ankrum, 2000). Surface EMG is widely used to evaluate muscular activity (Solomonow, 1999). In surface EMG, the electrodes are attached to the surface of the skin overlying the muscle and measure the amount of electricity that the muscle produces as the fibres contract. Surface EMG may determine which muscles are activated and their degree of activation compared to capacity. Furthermore, surface EMG may estimate muscle force (Arendt-Nielsen and Zwarts, 1989, Ankrum, 2000).

Fig 2.2: The Noraxons's TEleMyop 2004, surface EMG

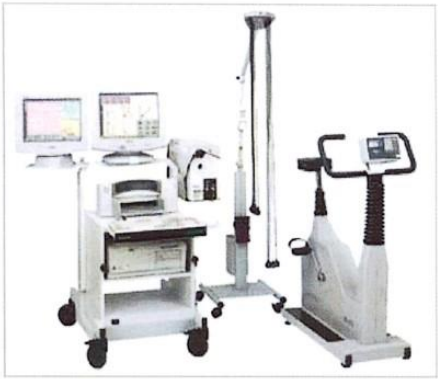

Fig 2.3: Gas analyser Oxycon Pro

3.4. Expired gas analysis using the Oxycon Pro

Pulmonary gas exchange was measured breath-by-breath using an online gas analysis system (Oxycon Pro, Jeager). Airflow was measured with a turbine transducer that has a low-mass helical impeller mounted upon jewelled bearings. The impeller is housed in a plastic support structure and inserted into a cylinder with pairs of light emitting diodes. As airflow spins the impeller's blade the light beams are interrupted and digital signals proportional to volume are sent to the processor. Bidirectional flow is sensed by changes in the direction of rotation of the impeller. The flow transducer was calibrated before every test by passing a known volume of air over the transducer using a 3 litres calibration syringe. Care was taken not to slam the piston into the end of the syringe cylinder as this would provide false volumes due to the potential for the rebound of the piston against the end of the cylinder adding an unknown quantity to the correct volume. Oxygen and carbon dioxide concentrations were measured using paramagnetic and infrared gas analysers, respectively. Before each test the analyser was calibrated with gases of known concentration over the expected range of measurement for exercise testing. Prior to data collection all subjects were fitted with mouthpiece and noseclip.

6.5 The Borg scale and rating of perceived exertion

The 6 to 20 Borg scale (Borg, 1970) for the rating of perceived exertion (RPE) during physical activity has been widely used in clinical and exercise setting. Subsequently, this scale was modified in an array of numbers ranging from 0 (no physical exertion at all) to 10 (maximal physical exertion; Fig. 7), and may be used as a valid measure of perceived exertion (Gearhart et al., 2001, Gearhart et al., 2002). This scale was used in all studies for the rating of perceived exertion during passive exercise. All subjects were familiarised with the Borg scale and care was taken to provide subjects with clear, specific, and consistent instructions.

0	Nothing at all
0.3	
0.5	Extremely weak
0.7	
1	Very weak
1.5	
2	Weak
2.5	
3	Moderate
4	
5	Strong
6	
7	Very strong
8	
9	Extremely strong
10	Maximal

Fig. 2.4: Borg Scale of
Rating of Perceived Exertion

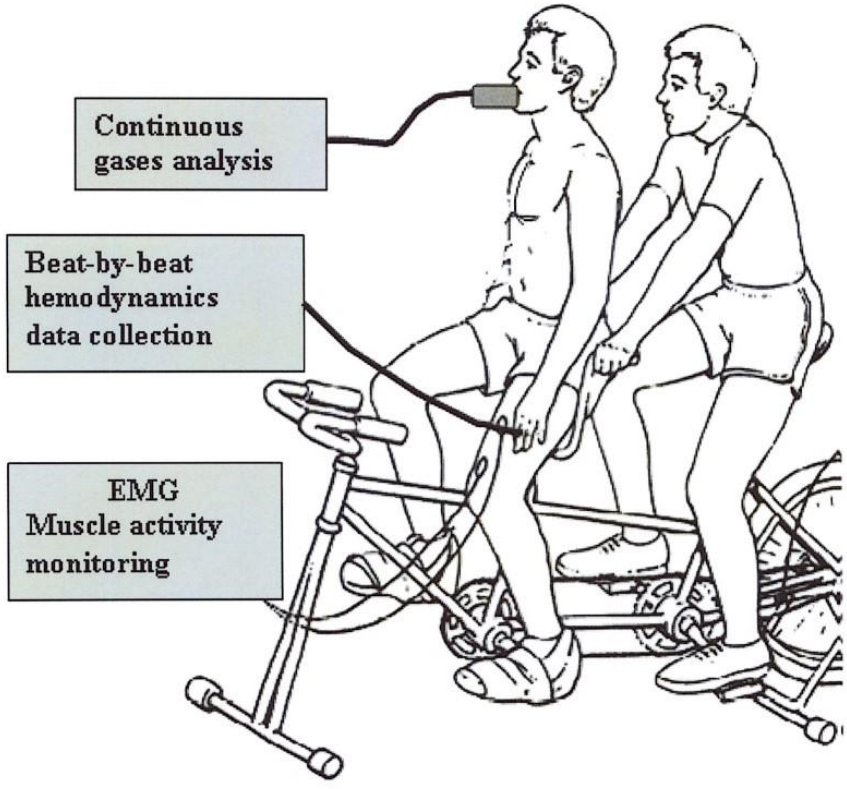

Fig. 2.5: Mechanoreflex activation by passive cycling

6.6 Mechanoreflex stimulation by passive exercise

In all studies, passive cycling was used to activate the to larger extent mechanoreflex, while trying to minimise the metaboreflex. This was achieved by strapping the subjects' feet on the pedals of the tandem bicycle, while a second rider preformed the cycling exercise. Prior to the experimental day, all subjects were familiarised with passive cycling during two sessions, and asked to relax and not to contribute to pedalling. During passive exercise the EMG and RPE were used to assess muscular activity and the individual's rating of exertion, respectively. This is important because

in absence of muscular contraction and volitional activity, the activation of central command is prevented.

Fig. 2.6: Diagrammatical representation of supine passive exercise

Measurements variability and reliability

The key outcome variables in the studies contained in the present thesis are spontaneous BRS and spectral analysis of HRV. All participants in the present thesis appeared to be healthy and free from cardiovascular disease, and therefore normal baroreflex and autonomic cardiac modulation were likely. The key outcome variables were measured to evaluate the variability and reproducibility of the methods. The result showed a variability of 2.5 - 3.4% for spontaneous BRS and 2.6 – 3.9% for HRV, respectively. Previous studies investigating the validity and reliability of spontaneous BRS and spectral analysis of HRV that have also shown that these methods of baroreflex control and cardiac sympathovagal balance assessment are valid and reliable (Iellamo et al., 1996, Parlow et al., 1995, Westerhof et al., 2004, Sztajzel, 2004, Appel et al., 1989, Guijt et al., 2007).

Statistical analyses

Prior to data collection, a power analysis was performed using the outcome variables to calculate the required sample size for achieving statistically significant result. The desired sample size was 10 subjects, which is comparable to the sample used in previous similar studies (Nobrega et al., 19994: n = 10; Nishiyasu et al., 1998: n = 8; Leshnover et al., 2001: n = 10 Gladwell and Coote, 2002: n = 6). All statistical analyses within the thesis were conducted using SPSS (SPSS v11.5 for Windows, SPSS Inc, IL, USA), Alpha set at 0.05. The specific statistical methods pertaining to each study are described in the individual method within the study chapters.

Chapter 4

Baroreflex control of sinus node during dynamic exercise in humans: effect of muscle mechanoreflex

4.1 Introduction

During exercise the concomitant increases in HR and BP are facilitated by the upward resetting of the arterial baroreflex (Ebert, 1986, Potts et al., 1993, Papelier et al., 1994, Iellamo et al., 1997, Potts and Mitchell, 1998). The resetting of the arterial baroreflex has been attributed to the same mechanisms that are responsible for the cardiovascular response to exercise, namely, the influences of central command (feedforward mechanism; (Gallagher et al., 2001c) and muscle afferents (feedback mechanism; Iellamo et al., 1997, Iellamo et al., 1999a, Gallagher et al., 2001a). Central command arises from higher centres in the brain and acts on the central motoneuron pool that integrates the baroreflex in parallel with the motor signals directed to the exercising muscles (Iellamo, 2001b). Group III and IV muscle afferents also contribute to the cardiovascular response to exercise (the exercise pressor reflex, Alam and Smirk, 1937, Coote et al., 1971) and the resetting of the arterial baroreflex (Gallagher et al., 2001a), via negative feedback to the brain stem (Coote et al., 1971, Kaufman et al., 1983). Group IV afferents are primarily responsive to the accumulation of metabolites (Kaufman and Hayes, 2002) and are known as metaboreceptors, while group III afferents, which are divided in three subtypes, respond to mechanical stimuli such as muscle stretch (Wilson et al., 1994), contraction (Kaufman et al., 1983), or both (Hayes et al., 2005) and are known as mechanoreceptors.

Stimulation of mechanoreceptors by passive stretch of the hind limb muscles in dogs (Potts and Mitchell, 1998) and cats (Stebbins et al., 1988, Wilson et al., 1994) evokes increases in HR and BP. Similarly, stimulation of mechanoreceptors with passive cycling in humans, induces increases in HR, BP (Nobrega and Araujo, 1993, Nurhayati and Boutcher, 1998) and SV, (Nobrega et al., 1994). Furthermore,

stimulation of contraction-responsive mechanoreceptors with electrically induced dynamic knee extension modifies the integrated arterial baroreflex control of sinus node function and reduces BRS (Iellamo et al., 1997). Considering that the mechanoreceptor subtypes have different conduction velocities (Hayes et al., 2005) and respond differently, either inhibiting or facilitating sympathetic discharge depending on the type of stimulation (Coote and Perez-Gonzalez, 1970), it is deduced that stimulation of stretch-responsive mechanoreceptors may affect the integrated arterial baroreflex control of the sinus node differently than stimulation of contraction-responsive mechanoreceptors. The effect of stretch-responsive mechanoreceptors stimulation on the integrated arterial baroreflex control of the sinus node is not known.

In order to investigate the effect of stretch-responsive mechanoreceptors stimulation on the integrated arterial baroreflex control of the sinus node we evaluated spontaneous BRS and HRV at rest and during passive cycling, where a second rider was moving the subject's limbs in a rhythmic "exercise-like" pattern. This model that closely resembles dynamic exercise enables the study of cardiovascular responses to stimulation of primarily stretch-responsive mechanoreceptors (Hayes et al., 2005) without the influences of central command, i.e., volitional control, or other muscle afferents (Kaufman et al., 1983, Kaufman et al., 1984b, Leshnower et al., 2001). Also, the passive nature of the movements ensures minimal stimulation of contraction-responsive mechanoreceptors (Hayes et al., 2005) and prevents any possible contraction-associated metabolites that in turn enhance the sensitivity of group III afferents to mechanical stimuli (Rotto et al., 1990, Sinoway et al., 1993).

4.2 Methods

Fifteen subjects (eleven male and four female) mean age ± S.D., 31.6 ± 5.9 yr, height 1.76 ± 0.9 m, body mass 70 ± 15.5 kg, participated in the study following written informed consent, approved by the institutional Ethics committee. All participants were free from known cardiovascular and respiratory diseases, based on medical history, not taking any prescribed medication, and were requested to abstain from exercise and beverage containing caffeine for at least 12 hours before the experiment.

Procedure

All participants were familiarized with passive exercise prior to data collection. Subjects sat on an adapted tandem bicycle for 15 min, in order to attain a stable circulatory state. To accomplish passive exercise a second rider cycled the tandem bicycle, while the subjects' feet were strapped to the pedals. Subjects were instructed to remain relaxed and not to contribute to pedalling. A blood pressure cuff was placed in the middle phalanx of the middle finger for beat-to-beat non-invasive systolic (SAP) and mean arterial pressure (MAP) measurements, using a haemodynamic monitoring system (Finometer PRO, Finapres Medical Systems, Amsterdam, Nederlands). Prior to data collection, the Finometer was calibrated using a conventional arm cuff, and the difference in hydrostatic pressure between arm and finger cuffs was corrected by a finometer built-in devise. Surface electromyography (EMG) on the right vastus lateralis and vastus medialis muscles, with a Noraxon Telemetry EMG system (Scottsdal, USA), was used to monitor the muscular activity, while the Borg Scale was used to assess perceived exertion. In nine of the fifteen subjects expired gases were measured breath-by-breath using an Oxycon analyser (Oxycon Pro, Jaeger, Haechberg, Germany). All data were collected for 5 min at rest

and during passive exercise. All the variables including HR, SV, Q, MAP, TPR, and expired gases values presented are the averaged data during rest and the exercise period. All values are expressed as mean ± SD. Comparisons between resting and passive exercise conditions were made with paired t-test and differences were considered significant at $P < 0.05$. Calculation of the cardiovascular variables and data analysis are described in chapter 3.

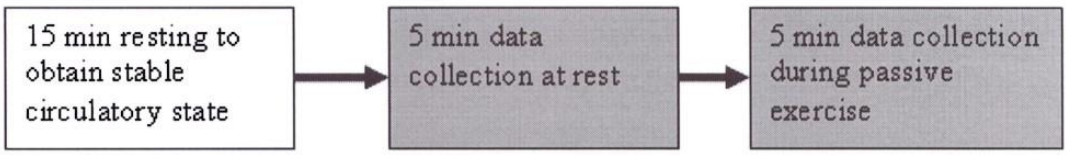

Fig. 3.1. Diagrammatical representation of the experimental protocol

4.3. Results

Both HR and SV increased during passive exercise ($P < 0.01$, Table 1) and these changes were reflected in the ~13% increase in Q compared to rest ($P < 0.01$, Table 1; Fig. 2). MAP also increased, in parallel with Q, by ~9% ($P < 0.01$, Table 1; Fig. 2), resulting in unchanged TPR during passive exercise compared to rest (Table 1).

BRS decreased during passive exercise compared to rest ($P < 0.01$, Table 1, Fig. 1) and there was a rightward and downward shift of the regression line relating SAP with PI, which may indicate an upward resetting of the baroreflex's operating point to higher BP. During passive exercise the LF power of HRV was enhanced, while the HF power was attenuated compared to rest ($P < 0.05$; Table 1). An increase in oxygen uptake was also observed (~ 44 %) during passive exercise ($P < 0.01$, Table 1), while there was no significant difference in breathing frequency between rest and passive exercise (14 ± 3 and 18 ± 4, respectively). Also, there was no change in EMG

activity, and none of the subjects reported any significant sensation of effort compared to rest.

Table 1. *Haemodynamic, autonomic and metabolic variables at rest and during passive exercise*

	Rest	Passive Exercise	% Change
MAP, mmHg	87 ± 8	95 ± 7*	9
PI, ms	890 ± 165	850 ± 167 *	4
HR, beats/min	67 ± 12.3	70 ± 13.8*	4
SV, ml	85.1 ± 27.8	91.7 ± 22.6*	8
Q, L/min	5.6 ± 1.6	6.3 ± 1.3*	13
TPR, mmHg/L/min	16.8 ± 4.8	15.9 ± 3.8	-5
SVC ml/min/mmHg	64 ± 20	66 ± 19	3
BRS, ms/mmHg	13.1 ± 7.2	10.5 ± 6.8#	-20
LF, n.u.	56.7 ± 13.5	62.7 ± 18.7#	11
HF, n.u.	43.2 ± 13.4	36.9 ± 19.1#	-15
$\dot{V}O_2$, ml/min	270 ± 105	390 ± 90*	270
a-vO_2diff ml/l	48 ± 14	62 ± 18	29
VL, rms-EMG, μV	0.8 ± 0.1	0.8 ± 0.1	0
VM, rms-EMG, μV	0.9 ± 0.1	0.9 ± 0.1	0
RPE	0	0	0

Values are means ± SD; $n = 15$ except for $\dot{V}O_2$, where $n = 9$. MAP, mean arterial pressure; PI, pulse interval; SV, stroke volume; Q, cardiac output; TPR, total peripheral resistance; SVC, systemic vascular conductance; BRS, baroreflex sensitivity; LF, power in the low frequency band; HF, power in the high frequency band; VO_2, oxygen uptake; a-v-O_2diff; arterial-venous O_2 difference; RPE, rating of pieceved exertion vastus lateralis (VL), rms-EMGμV, electromyography root mean square; vastus medialis (VM). Different from rest, * $P < 0.01$; # $P < 0.05$.

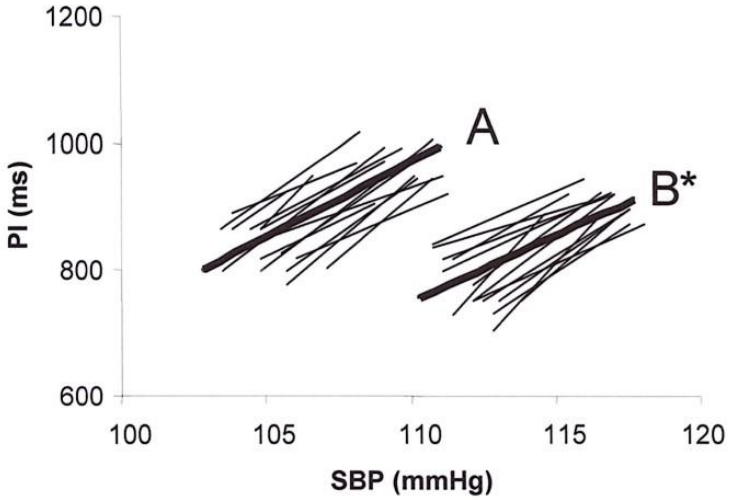

Fig 3.2: Mean spontaneous BRS estimates, n = 15 derived from changes in systolic blood pressure (SBP) and pulse interval (PI) at rest (A) and passive exercise (B). * Significant difference between conditions, $P < 0.05$.

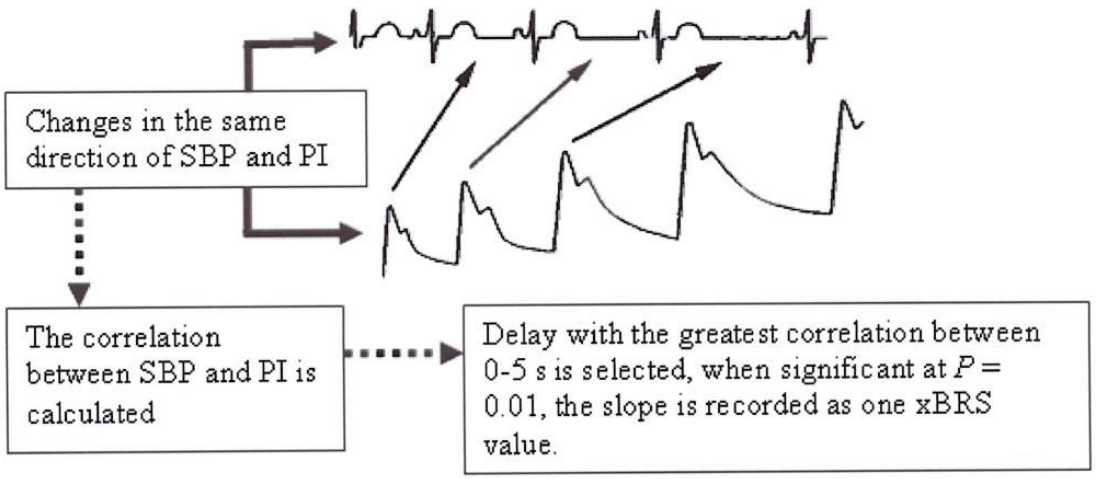

Fig. 3.3: Diagrammatical representation of the cross correlation method for estimation of BRS. The mean BRS estimation was obtained by averaging all the slopes computed within 5 min at rest and during passive exercise.

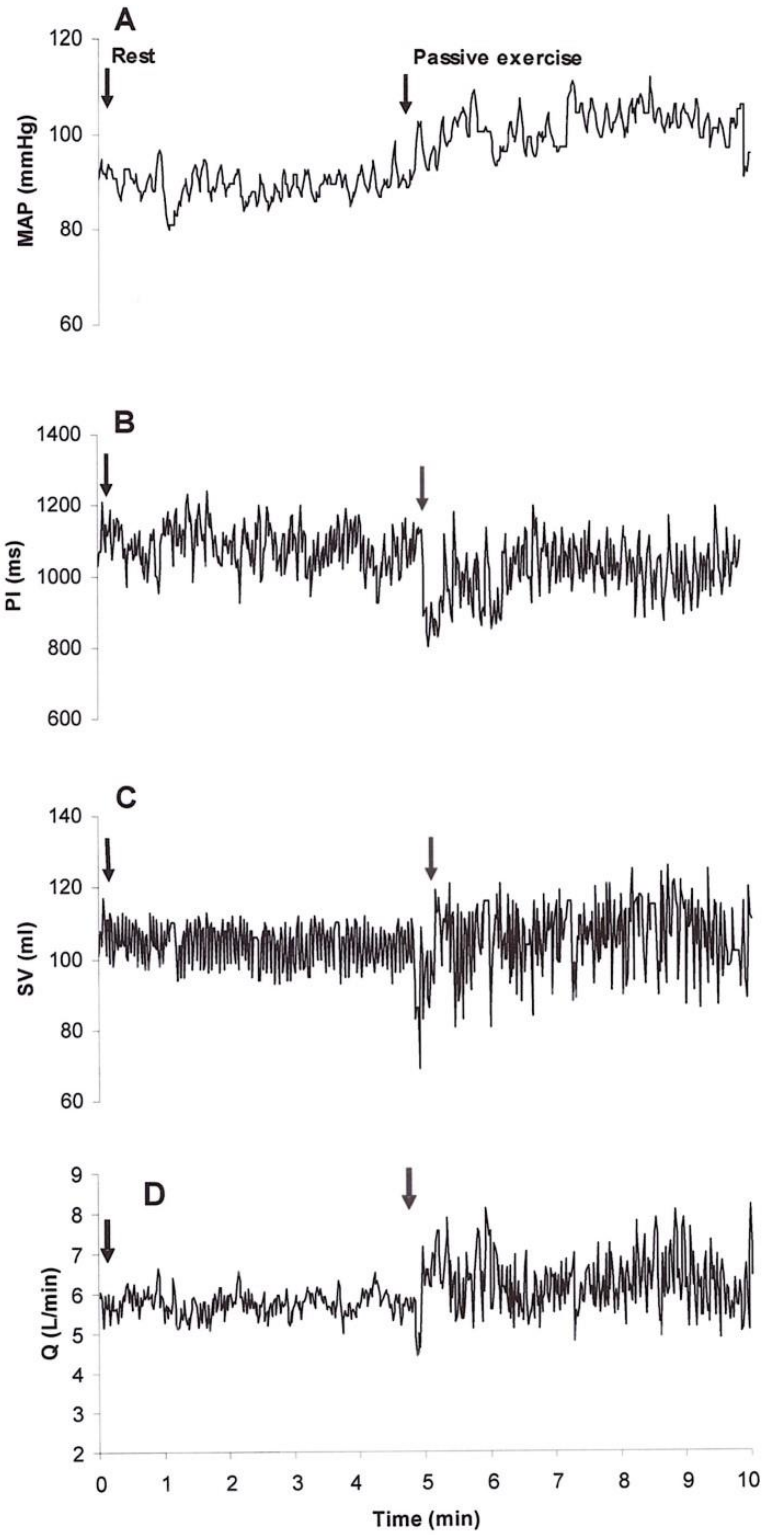

Fig 3.4: Original recording from 1 subject showing beat-by-beat values. A, mean arterial pressure (MAP); B, pulse interval (PI); C, stroke volume (SV); D, cardiac output (Q). Arrows (left to right) indicate the beginning of resting and passive exercise periods.

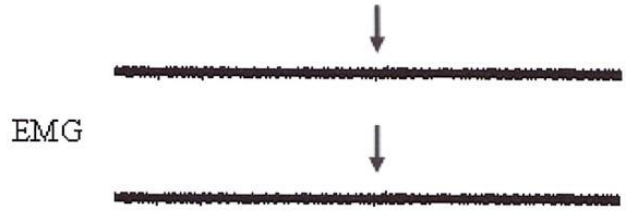

Fig 3.5: Electromyographic output of vastus lateralis (upper tracing) and vastus medialis muscles (lower tracing) of the right leg of one subject. The arrows indicate the onset of passive exercise

Note on electromyography

The electromyography (EMG) was used in all studies, and it did not change during passive exercise compared with resting. Thus, in subsequent studies figures regarding EMG are not reported.

4.4. Discussion

The major finding of this investigation is that stimulation of stretch-responsive mechanoreceptors with passive exercise decreases BRS. A second novel finding is that during passive exercise the sympathovagal balance shifted towards sympathetic predominance. These findings are suggestive of a significant contribution of the stretch-responsive mechanoreceptors to the function of the arterial baroreflex during dynamic exercise.

The mechanoreflex was activated by passive cycling, a model that is more representative of dynamic exercise than electrically induced movements used previously (Iellamo et al., 1997). This exercise model did not involve muscle contractions, as confirmed by the EMG signal that did not change compared to rest. Considering that there are three different mechanoreceptors subtypes, some responsive to muscle contraction, some to stretch, and some to both mechanical stimuli (Hayes et al., 2005), it is assumed that the passive limb movements stimulated mainly stretch-responsive mechanoreceptors.

Iellamo et al., (1997) also reported a decrease in baroreflex gain during low intensity electrically stimulated dynamic contractions, which were assumed to activate the muscle mechanoreflex. However, considering the response characteristics of the different mechanoreceptors subtypes (Hayes et al., 2005) the technique employed by (Iellamo et al., 1997) activates mainly contraction-responsive mechanoreceptors. According to (Stebbins et al., 1988) and (Leshnower et al., 2001) muscle mechanoreceptors may respond during contraction differently than stretch. Importantly, the present study confirms that independently of the mechanoreceptors

subtype stimulated, their activation evokes invariably the same response, i.e., a decrease in BRS with a rightward shift in the baroreflex function curve.

It is unlikely that the BRS changes we observed could be explained by changes in breathing frequency that remained unchanged during passive exercise compared to rest. Nonetheless, considering that during spontaneous baroreflex assessment it is not possible to evaluate the full baroreflex function curve, the decrease in BRS observed in the present study may not be a true decrease but only reflecting a shift of the operating point away from the centring point of the reflex to a locus of lesser gain (Raven et al., 2006).

During passive exercise the LF power of the HRV increased, while the HF power decreased. This sympathovagal shift suggests a reduction in cardiac vagal traffic and augmentation of the cardiac sympathetic drive (Pagani et al., 1986, Task Force, 1996). Activation of the mechanoreflex mediates cardio-acceleration by reducing the excitability of cardiac vagal motoneuron pool (McWilliam and Yang, 1991, Gladwell and Coote, 2002, Murata and Matsukawa, 2001). Furthermore, electrically evoked static contraction and passive stretch mechanically distort type III muscle afferents, and reflexively reset upwards the baroreflex neural arc to higher sympathetic nerve activity (Yamamoto et al., 2004) resulting in increased cardiac (McWilliam and Yang, 1991) and renal (Matsukawa et al., 1990) sympathetic traffic before the metaboreflex is activated (Kaufman and Hayes, 2002). Thus, activation of muscle mechanoreflex can mediate vagal inhibition and sympathoexcitation in absence of central command and muscle metaboreflex. This shifting of the sympathovagal balance is not counteracted by the baroreflex because the neural input from the muscle

mechanoreflex resets the baroreflex operating point to a higher operating pressure (Potts and Mitchell, 1998, Yamamoto et al., 2004), in a manner similar to that of central command (DiCarlo and Bishop, 2001). This functional resetting allows the baroreflex to operate at the prevailing pressure evoked by exercise (Raven et al., 2006).

The increases in MAP and HR observed during passive exercise are in agreement with previous studies (Nobrega et al., 1994, Nurhayati and Boutcher, 1998, Nobrega and Araujo, 1993). The enhanced SV and Q, in agreement with (Nurhayati and Boutcher, 1998), are probably a consequence of increased venous return resulting from the lower limbs being moved passively and/or mechanoreflex-evoked increased myocardial contractility (Nobrega et al., 1994). Furthermore, in agreement with (Nobrega et al., 1994), TPR was not different compared to rest suggesting that during passive exercise the increase in MAP is mainly, if not solely, due to the increase in Q.

Even though during passive exercise there is no voluntary muscle contraction, nevertheless, the muscle sarcomeres shorten and lengthen while the limbs are moving passively, and this may contribute to the increased oxygen uptake observed. Even though it is unclear whether and how this change in muscle length affects the actomyosin interaction, ATPase activity, ATP hydrolysis, and in turn the oxygen demand, we speculate that the increase in oxygen uptake observed during passive exercise reflects the contribution of the stretch response (Feng, 1932). When isolated muscle is stretched its metabolic rate increases, a phenomenon known as the stretch response (Feng, 1932). Thus, a stretch-induced increase in muscle metabolism may occur in absence of muscle contraction (Clinch, 1968, Euler, 1935).

Spontaneous BRS assessment methods have the advantage that they do not perturb the reflex they measure, as they do not involve vasoactive drugs, or unnatural mechanical manipulation of the baroreceptors to provoke changes in BP. Furthermore, spontaneous BRS allows estimation of baroreflex function under natural conditions, where changes in BP are counteracted by bradycardia/tachycardia, which in turn affects BP, without interfering with the closed-loop nature of the reflex. However, the limitation of such approaches is that the BRS is assessed over smaller changes in BP, and further, the whole baroreflex function curve cannot be estimated.

Nevertheless, the present experimental design permits the evaluation of the stretch-mechanoreflex while stimuli to other reflexogenic areas are held constant. This is of functional significance as it provides information about the effect of stretch responsive mechanoreceptors stimulation on the cardiac baroreflex control, at the prevailing BP.

Conclusions

Stimulation of stretch-responsive mechanoreceptors by passive exercise induces a decrease in BRS, and shifts the sympathovagal balance towards a more sympathetic predominance. Furthermore, the concomitant increases in HR, Q and MAP suggest that these muscle afferents also contribute to the functional resetting of the arterial baroreflex to higher operating pressure, and to the cardiovascular responses to exercise.

Chapter 5

The interaction of cardiac and muscle mechanical afferents on baroreflex control of the sinus node during dynamic exercise

5.1 Introduction

During exercise the arterial baroreflex is reset in direct relation to work intensity (Raven et al., 2006) and operates around the elevated prevailing arterial blood pressure (BP; Potts et al., 1993, Norton et al., 1999, Fadel et al., 2001, Ogoh et al., 2003, Ogoh et al., 2005). The resetting of the arterial baroreflex has been attributed to the influences of central command, a feedforward mechanism that acts in parallel with the motor signals directed to the exercising muscles (Gallagher et al., 2001c), and muscle afferents that convey negative feedback to the brain stem (Gallagher et al., 2001b, Smith et al., 2003). Group III muscle afferents are divided in three subtypes that respond to mechanical stimuli such as muscle stretch (Wilson et al., 1994), contraction (Kaufman et al., 1983), or both (Hayes et al., 2005) and are known as mechanoreceptors. Stimulation of mechanoreceptors by passive stretch of the hind limb muscles in dogs (Potts and Mitchell, 1998) and cats (Stebbins et al., 1988, Wilson et al., 1994) evokes parallel increases in HR and BP. Similarly, stimulation of mechanoreceptors in humans with passive cycling (Nobrega and Araujo, 1993, Nurhayati and Boutcher, 1998) and low-intensity electrically induced muscular contractions (Iellamo et al., 1997) also induces increases in HR and BP, while it attenuates cardiac BRS (Iellamo et al., 1997). Furthermore, passive cycling increases SV (Nobrega et al., 1994) and, presumably, CBV.

Recent findings suggest that the amount of CBV also provides modulatory neural information to the arterial baroreflex function during exercise. Reduction of CBV either with application of low body negative pressure (Ogoh et al., 2006b) or by postural shift (Ogoh et al., 2007, Volianitis et al., 2004) resets the arterial baroreflex to a lower operating arterial BP and enhances the sensitivity of the reflex both at rest

and during exercise. Postural shift from upright to supine enhances CBV as blood accumulated in the high capacitance veins of the pelvis and the lower limbs returns to the thorax (Harms et al., 2003). The CBV enhancement is associated with increases in cardiac filling pressure, SV and, ultimately, cardiac output (Q; Matzen et al., 1991, Harms et al., 2003, Bergenwald et al., 1977). The loading of the cardiopulmonary and arterial baroreceptors, associated with the supine posture, modulates the reflexogenic afferent input to the brainstem and elicits an increase in cardiac vagal tone and a concomitant decrease in cardiac and peripheral sympathetic activity (Jacobsen et al., 1993, Berry et al., 2006). Furthermore, the posture-induced augmentation in cardiac vagal tone and sympathoinhibition, enhances BRS (Kardos et al., 1997).

Taken together, the above studies demonstrate that stimulation of both the cardiopulmonary baroreceptors and muscle mechanical afferents are capable of modifying the integrated cardiac baroreflex control. However, the interaction between these two reflexogenic areas on BRS during exercise has not been investigated. In order to assess the interaction between the cardiopulmonary baroreceptors and the muscle mechanical afferents on integrated cardiac baroreflex control, we evaluated BRS during upright and supine passive exercise, two conditions where CBV is modified and the mechanoreflex is activated.

5.2. Methods

Eleven subjects (8 male and 3 female) mean age ± S.D., 32 ± 6.5 years, height 1.72 ± 0.9 m, body weight 69 ± 11.7 kg, participated in the study approved by the institutional Ethics committee. All the subjects gave consent to participate in the study

after being informed about the experimental protocol. They were all asymptomatic from cardiovascular and respiratory disease; not taking any prescribed medication, and requested to abstain from exercise and beverage containing caffeine, or alcohol, for at least 12 hours before the experiment.

8.1.2 Procedure

Prior to the study all subjects were familiarized with the experimental protocol that consisted of supine and upright passive cycling exercise performed in randomized order. In each posture the subjects rested for $\geq$ 15 min, in order to attain a stable circulatory state, before collecting baseline resting data. In the supine posture the subjects laid on a mat with their arms relaxed on the side of the body, while their feet were strapped to the pedals of an adapted tandem bicycle. Passive exercise was accomplished with the assistance of a second rider that cycled the tandem bicycle, while subjects were instructed to remain relaxed and not to contribute to pedalling. In the upright posture, subjects sat on an adapted tandem bicycle and their feet were strapped on the pedals. Passive exercise was accomplished as described for the supine posture.

A blood pressure cuff (plethysmographic method) was placed on the middle phalanx of the middle finger for beat-to-beat non-invasive systolic (SAP) and mean arterial pressure (MAP) measurements, using a haemodynamic monitoring system (Finometer PRO, Finapres Medical Systems, Amsterdam, Nederlands). Prior to data collection, the Finometer was calibrated using a conventional arm cuff, and the difference in hydrostatic pressure between arm and finger cuffs was corrected by a finometer built-in devise. The Borg Scale was used to obtain individual ratings of perceived exertion

while surface EMG on the right vastus lateralis and vastus medialis muscles, using a Noraxon Telemetry EMG system (Scottsdal, US), monitored the muscular activity. In eight of the eleven subjects respiratory gases were measured breath-by-breath using an Oxycon analyser (Oxycon Pro Jaeger, Haechberg, Germany). Data were collected for 5 min at rest and during passive exercise in both postures. All the variable including HR, SV, Q, MAP, TPR, BRS, HRV and respiratory gases data at rest and during supine and upright passive exercise were compared using two-way ANOVA repeated-measures test. A Student-Newman-Keuls test was employed *post hoc* when interactions were significant. All values are expressed as mean ± SD. Differences were considered significant at $P < 0.05$. Calculation of the cardiovascular variables and data analysis are described in chapter 3.

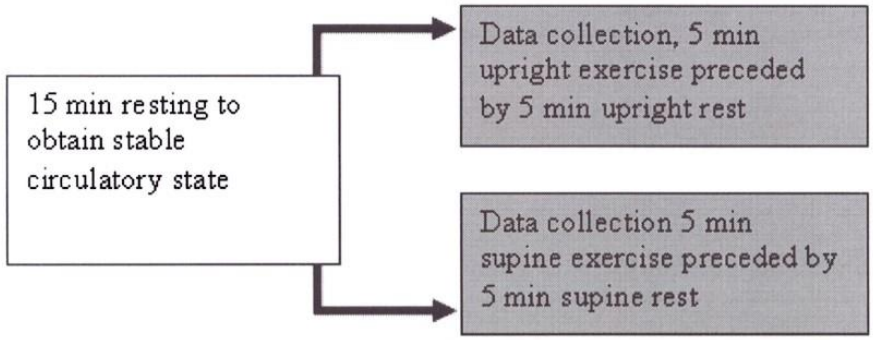

Fig. 4.1: Diagrammatical representation of the experimental protocol

5.3. Results

MAP increased during both upright (~7 mmHg) and supine passive exercise (~4 mmHg, $P < 0.05$, Table1) compared to rest, while there was no difference between the two postures either at rest or during passive exercise. Similarly, HR increased during both upright and supine exercise ($P < 0.05$, Table1) and the magnitude of this increase

was not different between the two postures. However, at rest, the postural shift from upright to supine induced a significant cardio-deceleration ($P < 0.05$, Table 1).
At rest the postural shift from upright to supine augmented significantly SV ($P < 0.05$; Table 1), while there was no further increase during supine exercise. Upright and supine exercise evoked a similar augmentation in Q compared with rest ($P < 0.01$).

In the supine posture TPR decreased during exercise compared with rest ($P < 0.01$), while it was not different between the two conditions in the upright posture. Similarly, TPR was not different at rest in the two postures.

BRS decreased during both upright ($P < 0.05$) and supine passive exercise ($P < 0.01$) compared to rest, and the respective regression lines relating SAP with PI shifted rightward and downward. In contrast, BRS was higher at supine compared with upright rest ($P = 0.05$), while it was not different between upright and supine exercise.

During upright and supine exercise the LF power of the HRV spectrum was enhanced, while the HF power was attenuated, compared to rest, ($P < 0.05$). Postural shift at rest, from upright to supine resulted in decreased LF power and increased HF power, while there was no difference in LF and HF values between postures during exercise.

Oxygen uptake increased during both upright ($P < 0.05$) and supine passive exercise ($P < 0.01$, Table 1), while there was no difference between postures either at rest or during exercise. Also, there was no significant difference in breathing frequency between rest and passive exercise either in the upright (14 ± 3 and 16 ± 5 breaths/min), respectively, or in the supine postures (17 ± 6 and 19 ± 6 breaths/min),

respectively. There was no change in EMG activity during supine or upright exercise compared to rest and none of the subjects reported any significant sensation of effort.

Table 2. *Haemodynamic, autonomic and metabolic variables at upright rest, upright passive exercise, supine rest, and supine passive exercise.*

	Upright		% Change	Supine		% Change
	Resting	Passive exercise		Resting	Passive exercise	
SBP, mmHg	121 ± 9	127 ± 11*	5	124 ± 8	131 ± 9*	5
DBP, mmHg	74 ± 6	77 ± 6*	4	73 ± 4	76 ± 5*	4
MAP, mmHg	90 ± 9	97 ± 7 *	7	92 ± 4	96 ± 6 *	4
PI, ms	959 ± 252	901 ± 215*	-6	1075 ± 242#	881 ± 219*	-22
HR, beats/min	67 ± 16	71 ± 17 *	6	59 ± 13#	73 ± 18 *	19
SV, ml	84.2 ± 25	91.9 ± 21*	8	95.7 ± 23#	95.6 ± 22	0
Q, L/min	5.4 ± 1.7	6.3 ± 1.5**	14	5.6 ± 1.6	6.8 ± 1.8 **	18
TPR, mmHg/L/min	18 ± 5.7	16.7 ± 4.4	-8	17.7 ± 4.8	15.1 ± 4.2**	-17
SVC ml/min/mmHg	60 ± 21	67 ± 16	10	60 ± 18	70 ± 20	14

Values are means ± SD; SBP, systolic blood pressure; DBP diastolic blood pressure; MAP, mean arterial pressure; PI, pulse interval; SV, stroke volume; Q, cardiac output; TPR, total peripheral resistance, SVC, systemic vascular conductance. Passive exercise different from rest: $*P < 0.05$; ** $P < 0.01$; upright rest different from supine rest: $\#P < 0.05$.

Table 3. *Haemodynamic, autonomic and metabolic variables at upright rest, upright passive exercise, supine rest, and supine passive exercise.*

	Upright		% Change	Supine		% Change
	Resting	Passive exercise		Resting	Passive exercise	
BRS, ms/mmHg	16.4 ± 12.1	12.5 ± 9*	-30	23.4 ± 12.9#	10 ± 8**	134
LF, n.u.	51.1 ± 18.6	58.8 ± 21.2*	14	44.9 ± 14.7#	58.5 ± 12.7*	23
HF, n.u.	48.9 ± 18.6	41.1 ± 21.2*	-19	55.1 ± 14.7#	41.5 ± 12.7 *	-33
$\dot{V}O_2$, ml/min	301 ± 90	425 ± 92**	29	310 ± 138	394 ± 93*	21
a-vO2diff, ml/l	56 ± 16	67 ± 19	16	55 ± 15	58 ± 16	5
RPE	0	0	0	0	0	0
VL, rms-EMG, µV	0.8 ± 0.1	0.8 ± 0.1	0	0.8 ± 0.1	0.8 ± 0.1	0
VM, rms-EMG, µV	0.9 ± 0.1	0.9 ± 0.1	0	0.9 ± 0.1	0.9 ± 0.1	0

Values are means ± SD; $n = 11$ except for LF and HF where $n = 10$ and for $\dot{V}O_2$, where $n = 8$. BRS, baroreflex sensitivity; LF, power in the low frequency band; HF, power in the high frequency band; VO_2, oxygen uptake; a-vO_2diff aterial-vanous O2 difference; RPE, rating of pieceved exertion; vastus lateralis (VL), rms-EMGµV, electromyography root mean square; vastus medialis (VM). Passive exercise different from rest: $*P < 0.05$; ** $P < 0.01$; upright rest different from supine rest: $\#P < 0.05$.

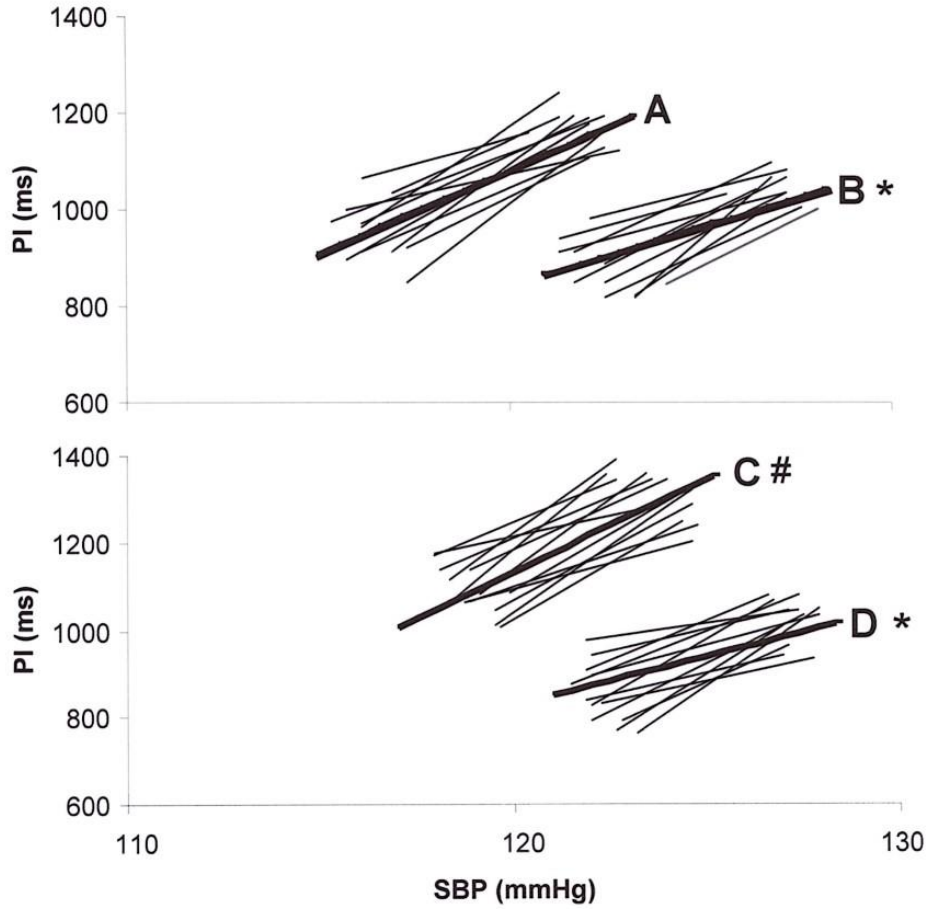

Fig 4.2: Mean spontaneous BRS estimates, n = 11 derived from changes in systolic blood pressure (SBP) and pulse interval (PI) at upright rest (A) upright passive exercise (B), supine rest (C), and supine passive exercise (D) * Significant difference between rest and exercise conditions; # significant difference between upright rest and supine rest conditions, $P < 0.05$.

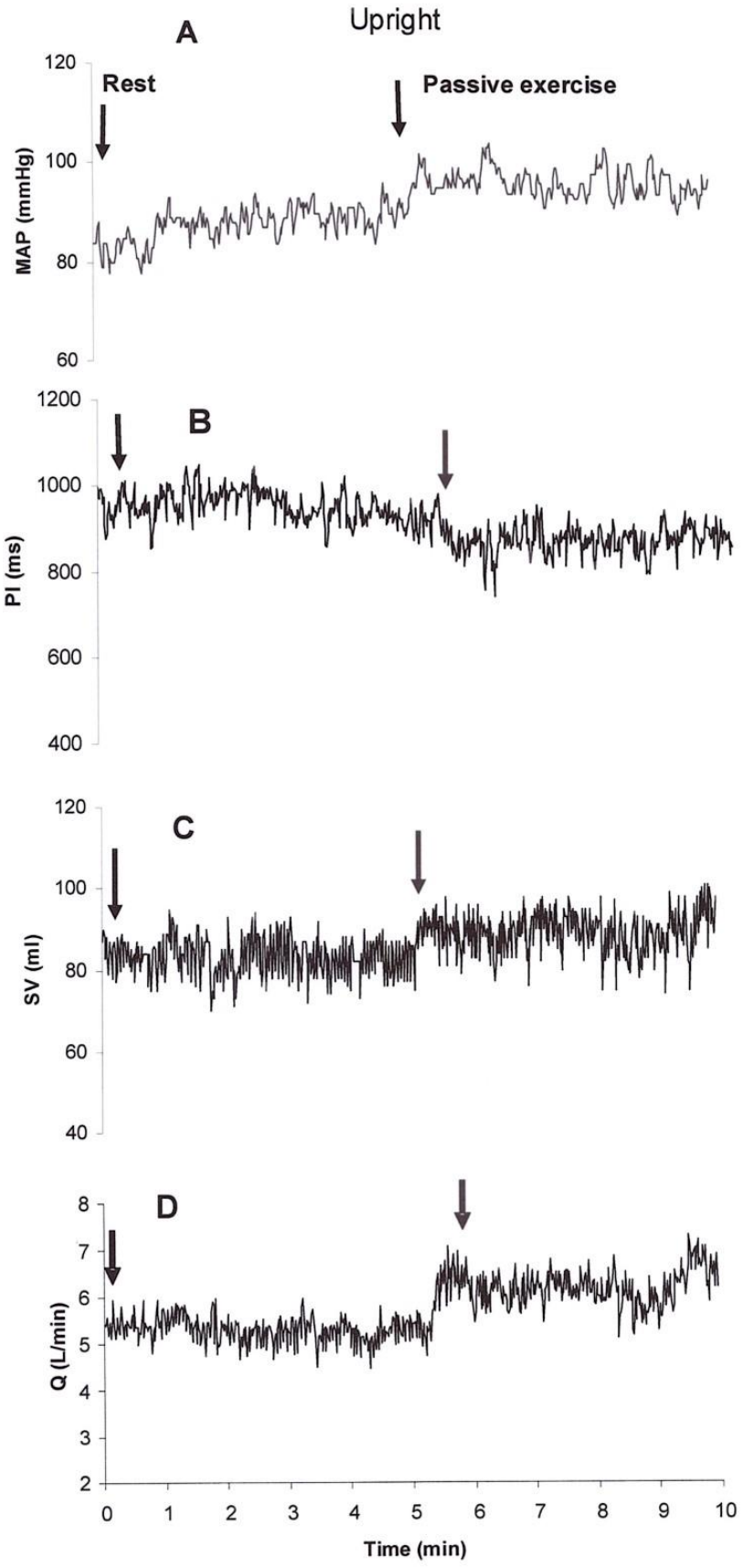

Fig. 4.3. Original recording from 1 subject showing beat-by-beat values. A, mean arterial pressure (MAP); B, pulse interval (PI); C, stroke volume (SV); D, cardiac output (Q). Arrows (left to right) indicate the beginning of upright resting and upright passive exercise periods.

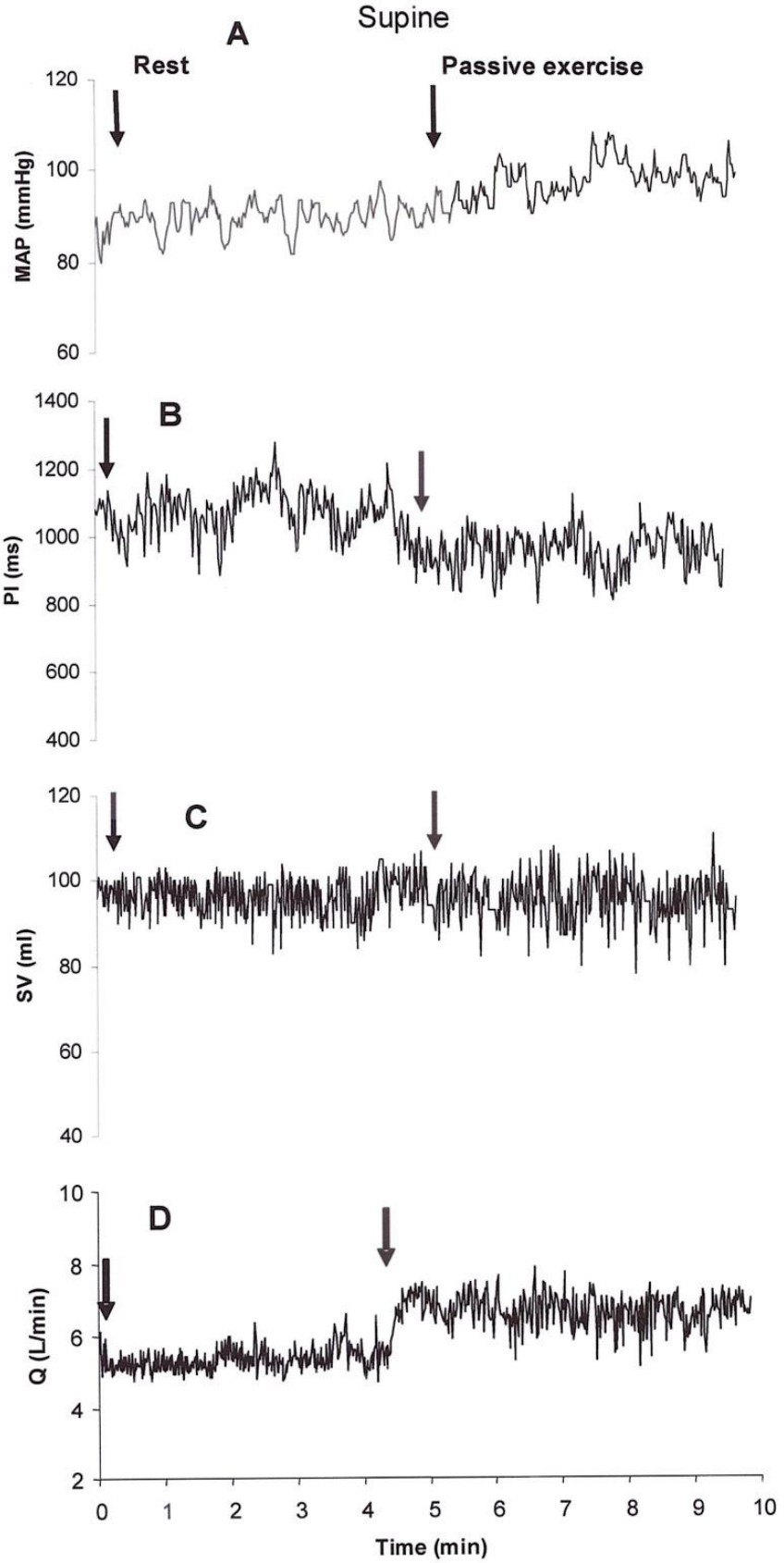

Fig 4.4: Original recording from 1 subject, showing beat-by-beat values. A, mean arterial pressure (MAP); B, pulse interval (PI); C, stroke volume (SV); D, cardiac output (Q). Arrows (left to right) indicate the beginning of supine resting and supine passive exercise periods.

5.4. Discussion

The main finding of the study is that activation of the mechanoreflex can override the effect of the cardiopulmonary baroreflex and attenuate BRS during dynamic exercise. Previously, it has been shown that stimulation of the muscle mechanoreflex in the upright posture decreases BRS (Iellamo et al., 1997). The present findings extend these observations by demonstrating that the mechanoreflex is capable of decreasing BRS also in the supine posture, thus overriding the influence of the cardiopulmonary baroreflex stimulation that increases BRS, as shown at rest. Passive exercise activates the mechanoreflex (Nobrega and Araujo, 1993, Nobrega et al., 1994, Nurhayati and Boutcher, 1998), as passive limb movements mechanically distort the receptor fields of type III muscle afferents (Kaufman and Hayes, 2002), and reflexively decreases the excitability of the cardiac vagal motoneuron pool (McWilliam and Yang, 1991). Considering that BRS is affected by vagal traffic (Parati et al., 2000) the reduction in baroreflex gain observed may reflect a mechanoreflex-induced cardiac vagal inhibition. Nonetheless, taking into consideration that the spontaneous baroreflex method does not assess the full baroreflex function curve (Iellamo et al., 1997), the observed reduction in BRS may not be a true decrease but only reflecting a shift of the baroreflex's operating point away from the centring point to locus of lesser gain (Raven et al., 2006). Indeed, during exercise vagal withdrawal has been shown to relocate the baroreflex's operating point to a locus of reduced gain (Ogoh et al., 2005). Therefore, during upright and supine passive exercise, the mechanoreflex-induced vagal inhibition (McWilliam and Yang, 1991) may have relocated the arterial baroreflex's operating point to a locus of lesser gain (Ogoh et al., 2005).

At rest the postural shift from upright to supine increased BRS. The mechanism responsible for this BRS modification may be attributed to the redistribution of blood, away from the high capacitance veins of the pelvis and lower limbs to the thorax, associated with the postural shift that enhances CVB (Matzen et al., 1991). The consequent cardiopulmonary and carotid baroreceptors' afferent activity to the central circuits results in compensatory sympathoinhibition and increased cardiac vagal traffic (Berry et al., 2006, Jacobsen et al., 1993, Westerhof et al., 2006) that may be reflected in the increased BRS at rest (Kardos et al., 1997, Westerhof et al., 2006). In contrast, BRS during both upright and supine passive exercise was equally attenuated compared to the respective resting values. This observation suggests that the sympathoinhibitory effect, associated with stimulation of the cardiopulmonary baroreceptors in the supine posture, was overridden by the vagal inhibition induced by the activation of the muscle mechanoreflex during passive exercise. A similar interaction between the cardiopulmonary baroreflex and the mechanoreflex may be reflected in the similar tachycardic HR response to passive exercise in both postures. The tachycardic response to passive exercise, induced by the mechanoreflex-mediated cardiac vagal inhibition (Gladwell and Coote, 2002, McWilliam and Yang, 1991), is in contrast with the bradycardic response observed during postural shift from upright to supine at rest, which is consistent with previous studies (Bahjaoui-Bouhaddi et al., 1998, Miyashita et al., 1995), These observations also suggest that the influence of passive exercise on the HR overrides that of the postural shift and indicates that the role of mechanoreflex predominates over that of the cardiopulmonary baroreflex.

During upright exercise SV increased compared to rest, indicative of increased venous return following the passive limbs movements and/or increased cardiac contractility

(Nobrega et al., 1994). In contrast, SV did not change further during supine exercise compared to supine rest, suggesting that passive limbs movements do not increase venous return any further than the increase induced by the postural shift (Harms et al., 2003, Matzen et al., 1991). During upright exercise, the concomitant increase of SV and HR augmented Q, which is in accordance with previous studies (Nurhayati and Boutcher, 1998, Nobrega et al., 1994). Furthermore, we observed that Q also increased during supine exercise but this increase was consequent to increased HR, while SV remained unchanged compared with supine rest.

During upright passive exercise MAP was elevated compared to rest, in agreement with previous investigations (Nobrega and Araujo, 1993, Nurhayati and Boutcher, 1998) that have shown a parallel increase in HR and BP associated with stimulation of the mechanoreflex. We also observed a parallel increase in MAP and HR during supine exercise compared with supine rest. This hypertensive stimulus is not counteracted by the baroreflex because the neural input from the muscle mechanoreflex resets the baroreflex's operating point to a higher BP (Potts and Mitchell, 1998). This functional resetting allows the baroreflex to operate at the prevailing pressure established during exercise (Raven et al., 2006). Thus, the mechanoreflex plays in important role in inducing the cardiovascular response to exercise. This view is further supported by (Yamamoto et al., 2005) who observed an interaction between baro/mechanical reflexes on sympathetic outflow and demonstrated that activation of the mechanoreflex is capable of resetting the baroreflex's neural arc to higher SNA, relocating the operating point to a higher BP (Yamamoto et al., 2004), and provoking cardiac, renal and peripheral

sympathoexcitation (Matsukawa et al., 1990, Matsukawa et al., 1994, Yamamoto et al., 2005).

The postural shift alone did not affect MAP, as comparisons of MAP between upright and supine rest, and between upright and supine exercise, showed modest, not significant differences. During upright and passive exercise the LF power of the HRV spectrum increased, while the HF power decreased compared to rest. These data provide further support to the notion that activation of the muscle mechanoreflex modifies cardiac autonomic outflow. These mechanoreflex-induced changes in cardiac autonomic outflow, are similar to those observed during low-intensity active exercise, and reflect mainly cardiac vagal withdrawal (Robinson et al., 1966). This decrease in vagal traffic shifts the cardiac sympathovagal balance towards sympathetic predominance (Pagani et al., 1986). In addition, autonomic ganglionic blockade resulted in the disappearance of HF and LF powers, further highlighting that they are mediated by the cardiac sympathovagal activity (Rimoldi et al., 1990). Thus spectral analysis of HRV enables the examination of autonomic cardiac regulation without artificially isolating the influence of either branches; as interference with the activity of one division of the autonomic nervous system might lead to compensatory changes in the other that could obscure the relative contribution of each of the two components (Iellamo et al., 1999b). In addition, we expressed the HF and LF data in n.u. as this technique eliminates the noise and enables a better assessment of power distribution in defined spectral components (Pagani et al., 1986, Montano et al., 1998). Postural shift at rest, from upright to supine resulted in reduced LF power and enhanced HF power, while there was no difference in LF and HF values between postures during exercise.

There was an increase in oxygen uptake during upright and supine exercise. Even though during passive exercise there are no muscle contractions, however, passive movements cause shortening and lengthening of muscle sarcomeres, and this may contribute to the increased oxygen uptake observed. Even though it is uncertain whether and how this may affect the actomyosin interaction, ATPase activity, ATP hydrolysis, and in turn the oxygen demand, we speculate that the increase in oxygen uptake observed during passive exercise reflects the contribution of the stretch response (Feng, 1932). When isolated muscle is stretched its metabolic rate increases, a phenomenon known as the stretch response (Feng, 1932). Thus, a stretch-induced increase in muscle metabolism may occur in absence of muscle contraction (Euler, 1935, Clinch, 1968).

The spontaneous baroreflex method does not require any pharmacological or mechanical perturbation external to the cardiovascular system (Parati et al., 2000) and permits the evaluation of cardiac baroreflex sensitivity under natural conditions without interfering with the closed-loop nature of the reflex that may alter baroreflex function (Rudas et al., 1999, Peveler et al., 1983, Casadei and Paterson, 2000, Parati et al., 2000)

Conclusions

Activation of the mechanoreflex by passive cycling, both in the upright and supine postures, modifies the integrated cardiac baroreflex control by decreasing BRS. These findings suggest that during passive exercise the effect of the mechanoreflex activation overrides that of the cardiopulmonary baroreceptors loading, which increases BRS at rest, resulting in attenuation of BRS.

Chapter 6

The effect of mechanoreflex stimulation on post-exercise BRS and autonomic cardiovascular control

6.1. Introduction

After a single bout of active dynamic exercise a significant reduction in arterial blood pressure (BP), known as post-exercise hypotension (PEH), is established and can persist for several hours (Kenney and Seals 1993). Even though the exact mechanism responsible for PEH is unclear it is recognised that the acute decrease in ABP is related to decreased peripheral resistance that is not completely offset by an increase in Q (Halliwill et al., 1996a, Halliwill et al., 1996b, Halliwill et al., 2000). Two mechanisms have been proposed to explain the decrease in peripheral resistance after exercise: sympathetic inhibition and altered vascular responsiveness.

Reductions in sympathetic outflow after exercise have been reported in both animals and humans (Floras et al., 1989, Halliwill et al., 1996a, Kulics et al., 1999), but the responsible mechanisms remain unclear. Studies using sinoaortic denervation (Chandler and DiCarlo, 1997) and cardiac afferent blockade (Collins and DiCarlo, 1993) in rats have implicated the arterial and cardiopulmonary baroreflexes in the sympathoinhibition observed post-exercise. Indeed, resetting of the operating point of the arterial baroreflex to a lower BP (Halliwill et al., 1996a) and concomitant increase in arterial baroreflex sensitivity (Silva et al., 1997) have been associated with PEH. However, the factors associated with dynamic exercise that contribute to the post-exercise modulation of BRS are not known. It has been suggested that stimulation of muscle afferents during exercise may directly alter the discharge properties of NTS neurons, resulting in an increased BRS in the post-exercise period (Minami et al., 2006). For example, Substance P, a neurotransmitter which is released during exercise from skeletal muscle group III (Wilson et al., 1992, Kuraishi et al., 1989) and IV afferent fibres (Kaufman et al., 1983) in the NTS (Potts et al., 1999), has been shown

to contribute to the decreased central sympathetic outflow, and hence PEH (Chen et al., 2002), by increasing the excitability of NTS neurons (Morin-Surun et al., 1984).

The reduced vascular responsiveness to α-adrenergic stimulation contributes to the decreased transduction of sympathetic outflow to vascular resistance observed during PEH (Halliwill et al., 1996a). During exercise, muscular contractions and augmented muscle blood flow provoke the production of metabolites (Halliwill et al., 1996a) and the release of endothelium-derived vasodilating substances (e.g., nitric oxide, Niebauer and Cooke, 1996) that persist after exercise and mediate vasodilatation and PEH.

In order to selectively evaluate the effect of muscle afferents on BRS post-exercise, we employed passive exercise that stimulates group III muscle afferents and evokes cardiovascular responses similar to those observed during active exercise, such as the parallel increase in HR and BP (Nobrega and Araujo, 1993, Nurhayati and Boutcher, 1998). Also, the use of the passive exercise model, where muscular contractions are prevented, enables the evaluation of the importance of contraction-related vasodilating substances for PEH.

6.2. Methods

Fourteen subjects, (11 male and 3 female, mean age ± S.D., 30.4 ± 5.7 yr, height 1.76 ± 0.09 m, body mass 71.0 ± 13.2 kg) volunteered to participate in this experiment following informed written consent approved by the institutional Ethics committee. All participants were normotensive (resting BP < 140/90 mmHg) and none reported any history of neurological or cardiovascular pathology. They were requested to

abstain from exercise and beverages containing caffeine, or alcohol, for ≥ 12 hours prior to the experiment, and were not taking any prescribed medication. All participants were familiarized with the experimental procedures before data collection.

Procedure

All subjects were required to remain relaxed for ≥ 10 min in order to attain a stable circulatory state, both in the supine and the upright seated position, before collecting baseline resting data for 5 min. A blood pressure cuff was placed in the middle phalanx of the middle finger for beat-to-beat non-invasive systolic (SBP) and diastolic blood pressure (DBP) measurements, using a haemodynamic monitoring system (Finometer PRO, Finapres Medical Systems, Amsterdam, Nederlands). Prior to data collection, the Finometer was calibrated using a conventional arm cuff, and the difference in hydrostatic pressure between arm and finger cuffs was corrected by a Finometer built-in devise. Subsequently, the subjects commenced a 20 min bout of passive exercise on an adapted tandem bicycle. Passive cycling at 75 revolutions per minute was accomplished by a second rider cycling the tandem bicycle, while the subjects' feet were strapped to the pedals. Subjects were instructed to remain relaxed and not to contribute to pedalling. Surface electromyography (EMG) on the right vastus lateralis and vastus medialis muscles, with a Noraxon Telemetry EMG system (Scottsdal, USA), was used to monitor the muscular activity, while the Borg Scale was used to assess perceived exertion. In nine of the fourteen subjects expired gases were measured breath-by-breath using an Oxycon analyser (Oxycon Pro, Jaeger, Haechberg, Germany). Because the magnitude of pressure change post-exercise may be different in the upright compared to supine posture (Kenney and Seals, 1993,

1992a, Coats et al., 1989, Hagberg et al., 1987, Halliwill, 2001) data were collected in both postures pre- and post-exercise. Post-exercise data were collected at 20 min post-exercise in the supine posture and at 30 min post-exercise in the upright seated posture for 5 min. Comparisons between pre-to post-exercise in the supine posture, and between pre-to post-exercise in the upright posture were made with paired t-test and were considered significant a $P < 0.05$. Calculation of the cardiovascular variables and data analysis are described in chapter 3.

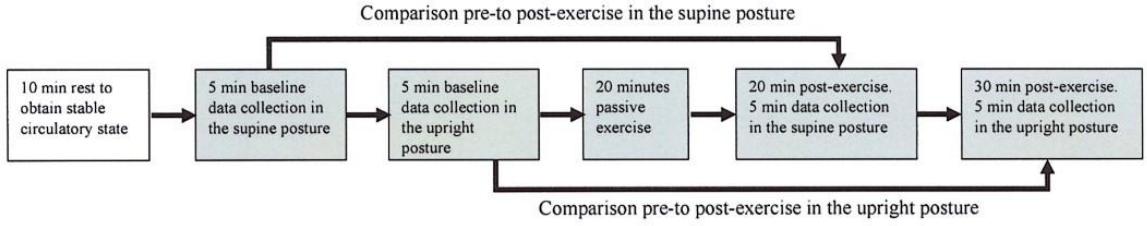

Fig. 5.1: Diagrammatical representation of the experimental protocol

6.3. Results

During passive exercise, SBP and DBP increased from 119 ± 8 and 72 ± 5 mmHg, respectively, at rest to 129 ± 8 and 78 ± 6 mmHg ($P < 0.05$), respectively. Similarly, HR and Q increased from 66 ± 13 bpm and 5.5 ±1.4 L/min, respectively, at rest, to 74 ± 14 bpm and 6.9 ± 1.4 L/min ($P < 0.05$), while BRS decreased during passive exercise compared to rest from 14.1 ± 8.1 to 8.0 ± 4.0, ms/mmHg ($P < 0.05$). There was no change in EMG activity during passive exercise, and none of the subjects reported any significant sensation of effort compared to rest.

Post-exercise SBP, DBP and MAP, both in the upright and supine posture were higher compared to rest (table 1; $P < 0.05$), while BRS was not different compared to rest. HR decreased significantly (table 1; $P < 0.05$) compared to rest both in the upright and supine posture. In contrast, SV, Q and oxygen consumption were not different pre

and post-exercise, either in the upright or supine posture. There was no significant difference in breathing frequency between rest and post-exercise, either in the upright (12 ± 2 and 12 ± 3), or in the supine posture (12 ± 3 and 12 ± 2), respectively. TPR increased significantly post-exercise compared with rest, both in the upright and supine posture (table 1; $P < 0.05$). LF power of the HRV spectrum decreased post-exercise, while HF power increased post-exercise compared to rest ($P < 0.05$; table 1) both in the upright and supine posture.

Table 4. *Haemodynamic, autonomic and metabolic variables at pre-exercise upright, post-exercise upright, pre-exercise supine, and post-exercise supine.*

	Upright		% Change	Supine		% Change
	Pre-exercise	Post-exercise		Pre-exercise	Post-exercise	
SBP, mmHg	119 ± 8	126 ± 7*	5	121 ± 8	127 ± 9*	5
DBP, mmHg	72 ± 5	76 ± 6 *	5	69 ± 5	72 ± 6 *	4
MAP, mmHg	88 ± 7	95 ± 7*	7	88 ± 7	92 ± 7	4
PI, ms	909 ± 186	967 ± 218*	6	1052 ± 179	1110 ±206*	5
HR, beats/min	66 ± 13	62 ± 14 *	-6	57 ± 11	54 ± 11 *	-6
SV, ml	86.1 ± 23	89.1 ± 21	3	98.1 ± 20	100.1 ± 21	2
Q, L/min	5.5 ± 1.4	5.3 ± 1.5	-3	5.5 ± 1.3	5.3 ± 1.6	-3
TPR, mmHg/L/min	16.9 ± 4.6	18.6 ± 4.6*	9	16.7 ± 3.6	18.1 ± 3.9*	8
SVC, ml/min/mmHg	63 ± 18	57 ± 13	-11	63 ± 14	58 ± 13*	-9

Values are means ± SD; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP mean arterial pressure; PI, pulse interval; SV, stroke volume; Q, cardiac output; TPR, total peripheral resistance, SVC, systemic vascular conductance. *, Post passive exercise different from pre passive exercise, $P < 0.05$.

Table 5. *Haemodynamic, autonomic and metabolic variables at pre-exercise upright, post-exercise upright, pre-exercise supine, and post-exercise supine.*

	Upright		% Change	Supine		% Change
	Pre-exercise	Post-exercise		Pre-exercise	Post-exercise	
BRS, ms/mmHg	14.1 ± 8.2	14.4 ± 8.3	0	23.5 ± 11.0	23.9 ± 11.3	0
LF, n.u.	58.3 ± 12.8	55.3 ± 15.5*	-5	49.4 ± 11.7	46.6 ± 12.1*	-6
HF, n.u.	41.7 ± 12.9	44.6 ± 15.5*	7	50.6 ± 11.7	53.4 ± 12.2*	5
$\dot{V}O_2$, ml/min	293 ± 108	262 ± 85	-11	316 ± 138	271 ± 114	-16
a-vO_2diff, ml/l	53 ± 15	49 ± 14	-8	57 ± 16	51 ± 15	-11
RPE	0	0	0	0	0	0
VL, rms-EMG, μV	0.8 ± 0.1	0.8 ± 0.1	0	0.8 ± 0.1	0.8 ± 0.1	0
VM, rms-EMG, μV	0.9 ± 0.1	0.9 ± 0.1	0	0.9 ± 0.1	0.9 ± 0.1	0

Values are means ± SD; $n = 14$ except for where $\dot{V}O_2$, $n = 8$. BRS, baroreflex sensitivity; LF, power in the low frequency band; HF, power in the high frequency band; VO_2, oxygen uptake; a-vO_2diff, arterial-venous O_2 difference; RPE, rating of perceived exertion; ; vastus lateralis (VL), rms-EMGμV, electromyography root mean square; vastus medialis (VM). *, Post passive exercise different from pre passive exercise, $P < 0.05$.

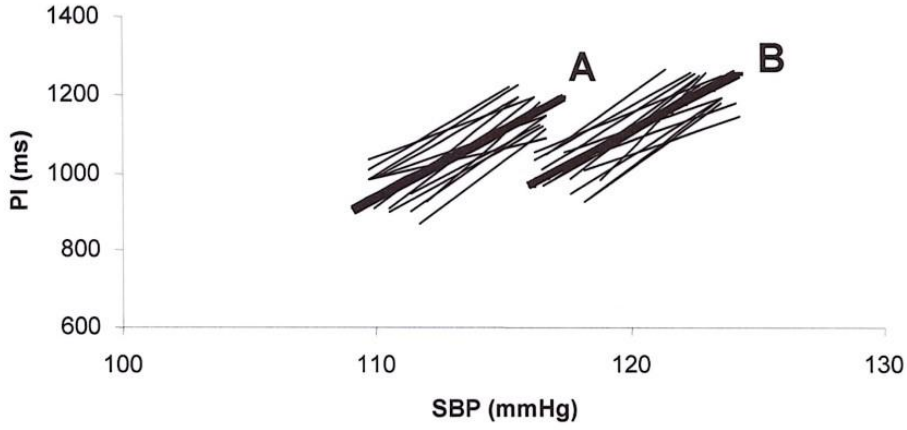

Fig 5.2: Mean spontaneous BRS estimates, n =14, derived from changes in systolic blood pressure (SBP) and pulse interval (PI) at pre-exercise (A) post-exercise (B).

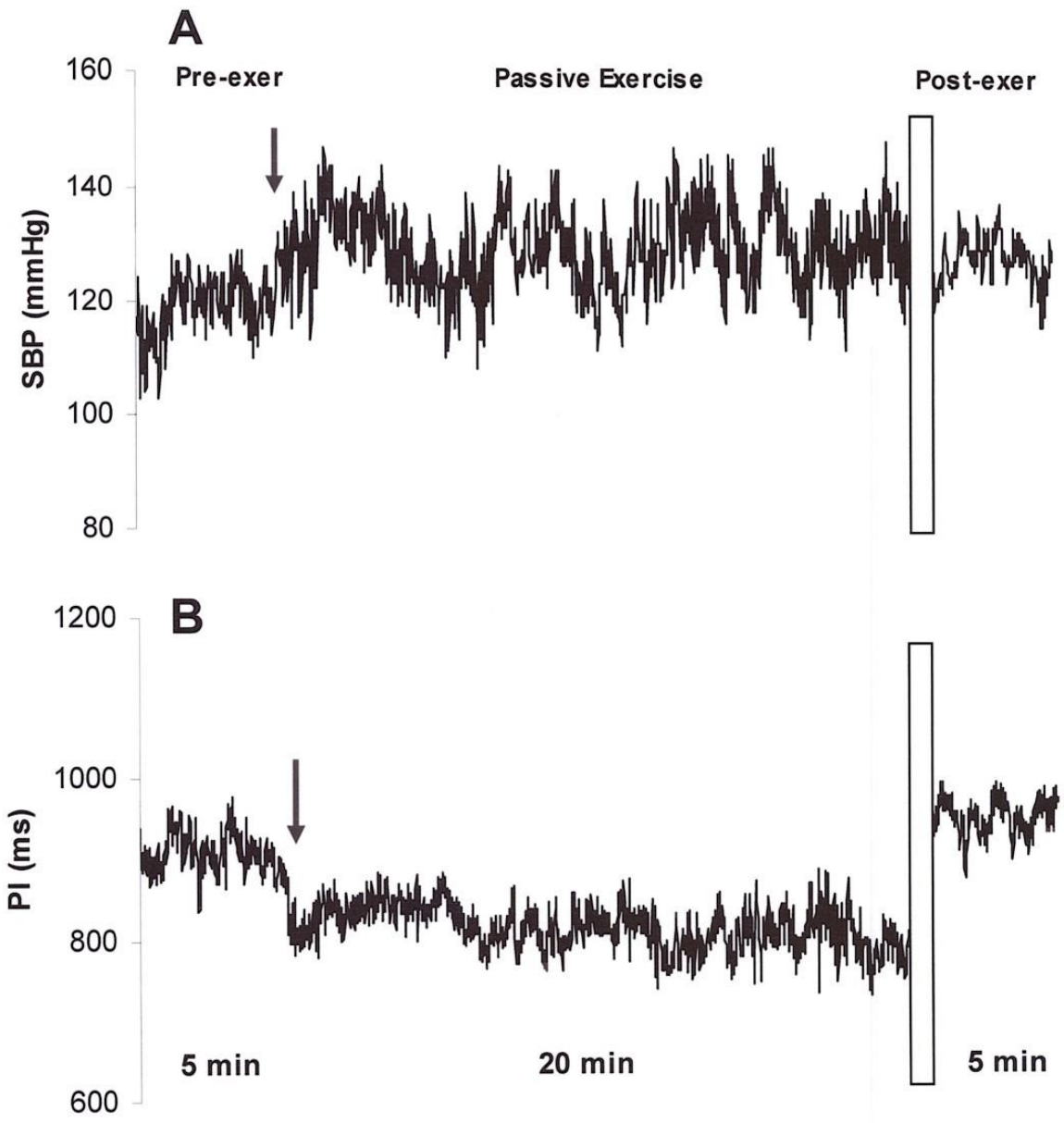

Fig. 5.3: Original recording from 1 subject, showing beat-by-beat values. A, systolic blood pressure (SBP); and B, pulse interval (PI). The arrow indicates the transition period between upright resting and exercise, and the open bar indicates the transition period between the cessation of exercise and 30 min post-exercise upright resting.

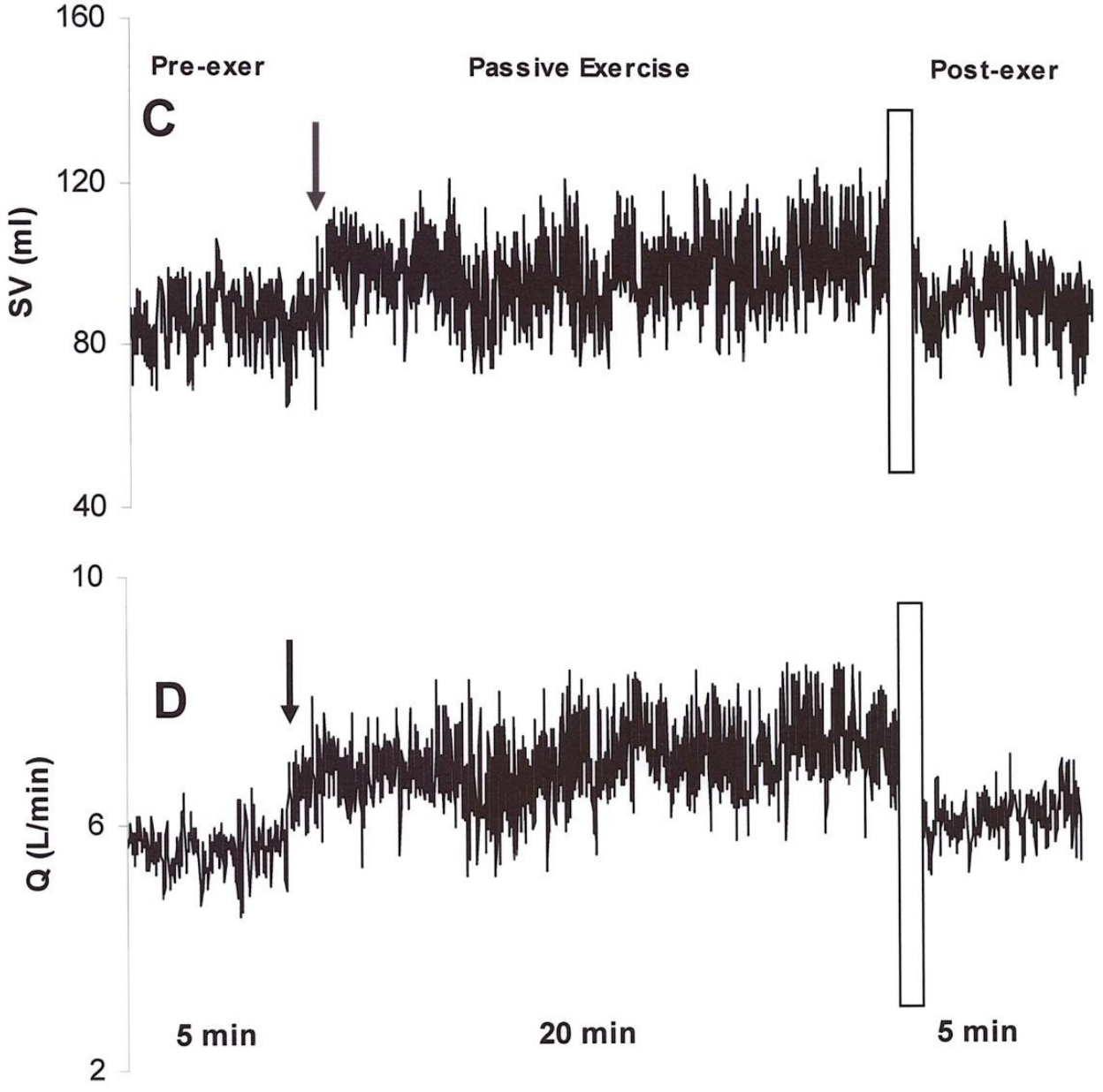

Fig. 5.4: Original recording from 1 subject, showing beat-by-beat values. C, Stroke volume (SV); and D, cardiac output (Q). The arrow indicates the transition period between upright resting and exercise, and the open bar indicates the transition period between the cessation of exercise and 30 min post-exercise upright resting.

6.4. Discussion

The main finding of the present study is that post-passive exercise BRS was not different from rest. Mechanoreflex activation with electrically-induced muscular contractions has been shown to modify the integrated baroreflex control of the sinus node (Iellamo et al., 1997). The present study demonstrates that mechanoreflex activation by passive exercise also decreases BRS, while post-exercise BRS returns to the resting value.

A second important finding is that SBP and DBP were elevated post-exercise compared to rest, both in the upright and supine posture. We assessed cardiovascular variables both in the upright and supine postures because after active exercise the magnitude of change in cardiovascular variables may be posture dependent (Kenney and Seals, 1993, Cleroux et al., 1992a, Coats et al., 1989, Hagberg et al., 1987, Halliwill, 2001). The results of the present study suggest that following mechanoreflex activation by passive exercise the magnitude of change in TPR and BP is similar in the upright and supine posture. We also observed a significant increase in TPR post-exercise compared with rest both in the upright and supine posture. Since Q was not different before and after exercise, the increased TPR was presumably responsible for the significant elevations in SBP and DBP. This finding provides further support to the view that the attenuation of TPR is essential for the development of PEH (Coats et al., 1989, Isea et al., 1994, Halliwill et al., 1996b). In the absence of voluntary muscular contractions during passive exercise, and thus contraction-related vasodilatating substances, such as nitric oxide (Patil et al., 1993), TPR post-exercise was determined solely by peripheral sympathetic traffic.

The findings of sympathoexcitation and pressure elevation following exercise are in agreement with previous studies suggesting that PEH does not always occur, especially in normotensive subjects, or that BP may even be increased both in animals and humans. Elevations in sympathetic activity and BP post-exercise have been found in normotensive rabbits (Howard et al., 2000) and humans (O'Connor et al., 1993), while several other investigations in normotensive humans reported no change in BP following exercise compared with rest (Cleroux et al., 1992a, Franklin et al., 1993, Pescatello et al., 1991, Piepoli et al., 1994, Convertino and Adams, 1991).

Another important finding of the present investigation is that a single bout of passive exercise induced a significant post-exercise bradycardia, both in the supine and upright posture. This cardiodeceleration is presumably the consequence of increased cardiac vagal traffic and decreased cardiac sympathetic activity as suggested by the HF and LF spectral data (Pagani et al., 1986, Task Force, 1996). The importance of vagal modulation in cardiac health has been demonstrated in clinical settings (Farrell et al., 1992). Furthermore, enhancing cardiac parasympathetic traffic, while concomitantly reducing sympathetic activity, is highly desirable because it may prevent adverse cardiac events (La Rovere et al., 1998). The beneficial effect of passive exercise on HRV were similar to those seen following active exercise (Pober et al., 2004).

Nevertheless, even though following passive exercise the cardiac sympathovagal balance is shifted toward vagal predominance, peripheral sympathetic traffic is increased as suggested by increased TPR in the face of unchanged Q. There was a modest increase in SV post exercise, and even though this increase did not reach

statistical significance, nonetheless, it was sufficient to maintain Q despite the significant reduction in HR.

Previous studies that activated the mechanoreflex through low intensity electrically-induced muscular contractions on spontaneous hypertensive rats showed a post-stimulation bradycardia and decreased BP (Yao et al., 1982b, Hoffmann and Thoren, 1986, Hoffmann and Thoren, 1988). In agreement with these studies we observed significant bradycardia after passive exercise. However, we found post-exercise BP elevation compared to rest. This disparity may be explained by the different mechanoreceptors stimulated in the respective studies. Indeed, some mechanoreceptors are responsive to stretch, some to contraction, and some to both mechanical stimuli (Hayes et al., 2005). Thus, in the present investigation stretch responsive mechanoreceptors were stimulated, as a result of passive limbs movements, while during electrically-induced muscular contractions mechanoreceptors responsive to contraction were stimulated. The different mechanoreceptors stimulated may have contributed to the difference in BP observed post exercise.

Furthermore, electrically-induced muscular contractions stimulate the release of endorphins that also contribute to TPR reduction, and thus PEH (Yao et al., 1982a). In addition, electrically-induced muscular contractions may induce the release of endothelium-derived vasodilating substances, via mechanical-induced sheer stress, and the production of metabolites. All these factors may counteract sympathoexcitation and reduce TPR and thus induce PEH (Halliwill et al., 1996a, Howard and DiCarlo, 1992, Howard et al., 1992, Niebauer and Cooke, 1996, Schwarz

and Kindermann, 1992). However, during passive exercise muscular contractions, and thus the exercise-borne vasodilating substances, are absent. Consequently, after passive exercise the vasoconstricting peripheral sympathetic activity was unopposed resulting in increased TPR and thus BP. Thus, the findings of the present study further highlight the importance of the exercise-born vasodilating substances to the reduction in TPR and PEH.

In the present study BP measurements were made 20 to 30 min post-exercise, as peak BP response occurs during this time (MacDonald et al., 1999, MacDonald et al., 2000). Furthermore, we measured post-exercise hemodynamics upright and supine, as they may be affected by body posture (Kenney and Seals, 1993).

Conclusions

After passive exercise there is a shifting of the cardiac sympathovagal balance toward vagal predominance associated with bradycardia, both in the upright and supine posture. Furthermore, after passive exercise, there is a BP elevation resulting from increased TPR, which may indicate an increased peripheral sympthoexcitation. This peripheral sympathoexcitation is not counteracted because all the vasodilator factors that could oppose and/or impair vasoconstriction are absent during passive exercise. Consequently, after passive exercise TPR and BP are increased despite the significant bradycardia.

Chapter 7

Regional muscle tissue oxygenation during passive exercise

7.1. Introduction

Near infrared spectroscopy (NIRS) is a non-invasive optical technique used to monitor cerebral and muscle regional oxygenation levels (Chance et al., 1992, Pereira et al., 2007). NIRS evaluates tissue oxygenation by estimating the oxygenated (HbO_2) and deoxygenated haemoglobin (Hb) content in mixed arterial venous blood, and most of the information comes from vessels smaller than 2 mm (Liu et al., 1995). This feature of NIRS favours evaluation of microcirculation of regional muscle tissue (Nioka et al., 2006). Muscle tissue oxygenation, measured with NIRS is highly related to venous oxygen saturation (Pereira et al., 2007). Furthermore, during exercise and electrically-induced muscular contraction, muscle tissue oxygenation decreases in parallel with HbO_2 (Hirata et al., 2006) and progressively with the increase in workload (Shibuya and Tanaka, 2003). Similarly, a reduction in muscle tissue oxygenation has also been reported immediately at the beginning of and during static exercise (Moalla et al., 2006). Collectively, these studies suggest that during electrically-induced muscular contraction, as well as during static and dynamic exercise muscle tissue oxygenation decreases, however, muscle tissue oxygenation during passive exercise remains to be elucidated. Thus, to evaluate muscle tissue oxygenation we used NIRS at rest, during passive exercise and during recovery.

7.2. Methods

Six subjects (five male and one female) mean age ± SE 32.8 ± 10.6 yr, height 1.69 ± 0.1 m, body mass 68 ± 9 kg, participated in the study following written informed consent, approved by the institutional Ethics committee. All participants were free from known cardiovascular and respiratory diseases, based on medical history, not

taking any prescribed medication, and were requested to abstain from exercise and beverage containing caffeine for at least 12 hours before the experiment.

Procedure

All participants were familiarized with passive exercise prior to data collection. Subjects sat on an adapted tandem bicycle for 15 min, in order to attain a stable circulatory state. To accomplish passive exercise a second rider cycled the tandem bicycle, while the subjects' feet were strapped to the pedals. Subjects were instructed to remain relaxed and not to contribute to pedalling. Muscle tissue oxygenation was measured using a Somanetics INVOS Cerebral Oximeter system (NIRS, Somanetic Corporation, Troy Michigan, US). A NIRS self-adhesive probe was placed on the belly of the vastus lateralis muscle, midway between the hip and the knee joints, and secured with self-adhesive tape. Expired gases were measured breath-by-breath using an Oxycon analyser (Oxycon Pro, Jaeger, Haechberg, Germany). Surface EMG on the right vastus lateralis and vastus medialis muscles, with a Noraxon Telemetry EMG system (Scottsdal, USA), was used to monitor muscular activity, while the Borg Scale was used to assess perceived exertion. All data were collected for 5 min at rest, during passive exercise and during recovery. Comparisons between resting, passive exercise and recovery conditions were made with one-way analysis of variance (ANOVA) for repeated measures and significant pair-wise differences were identified using Tukey's *post-hoc* test. Differences were considered significant at $P < 0.05$.

Measuring tissue oxygenation using NIRS

Somanetics INVOS Cerebral Oximeter system measures changes in regional haemoglobin oxygen saturation (rSO_2 index), by emitting near infrared light photons, which scatter in the underlying tissues while some of them return and exit the skin ("reflectance"). The spectral absorption of the underlying tissue is estimated by measuring the quantity of returning photons as a function of wavelength, which provide on estimation of the average tissue oxygenation (Liu et al., 1995). Human tissue is translucent to NIR photons with wavelengths between about 650 and 1100 nm. The chromophores with the highest absorption in body tissue are found in the haemoglobin molecules. The exact shade of red of each haemoglobin molecule depends on the amount of oxygen it is carrying, a property that enables the estimation of tissue oxygenation (Nioka et al., 2006). NIRS measurements are validated and are generally consistent with other methods (Van Beekvelt et al., 2001). The Oxycon analyser and the Noraxon Telemetry EMG system have been described in chapter 3.

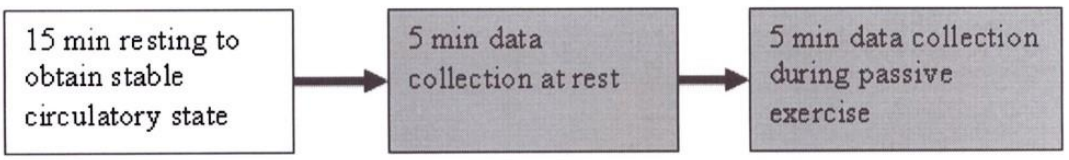

Fig. 6.1: Diagrammatical representation of the experimental protocol

7.3. Results

Muscle tissue oxygenation increased during passive exercise (~ 13%) compared to rest ($P < 0.01$, Table 1), while there was not significant difference between resting and recovery values. Also, an increase in oxygen uptake was observed during passive exercise ($P < 0.01$, Table 1), which returned to resting values during recovery. The

EMG activity of the vastus lateralis and vastus medialis muscles did not change during passive exercise compared with rest. Also, none of the subjects reported any significant sensation of effort during passive exercise.

7.4. Discussion

The major finding of the present study is that during passive exercise muscle tissue oxygenation increases, while it returns to baseline values during recovery. Oxygen uptake exhibits a similar patter as it increases during passive exercise and returns to resting values during recovery. Previously, we observed an average Q increase of 800 ml/min during passive exercise, while the average increase in $\dot{V}O_2$ was 120 ml/min (Vorluni and Volianitis, 2007). Considering that the average body mass of the participants was 70 kg, this represents an increase in relative $\dot{V}O_2$ of 1.7 ml/kg.

Thus, the increase in muscle tissue oxygenation during passive exercise may reflect the increase in Q, and presumably muscle blood flow, that offsets completely the increase in metabolic rate that would tend to reduce muscle tissue oxygenation. In support of this view is the fact that NIRS, used in the present investigation, computes tissue oxygenation by estimating the HbO_2 and Hb content on mixed arterial venous blood in vessels smaller than 2 mm (Liu et al., 1995). This feature of NIRS favours measurements of microvasculature of regional muscle tissue (Nioka et al., 2006). Furthermore, regional blood flow may be estimation from VO_2 and the HbO_2 and Hb content within the muscle tissue, as the amount of these two variables is determined by the relationship between change in blood flow and change in metabolic rate (Nioka et al., 2006). Therefore, the augmented muscle tissue oxygenation, observed in the present study, may suggests that during passive exercise the increase in oxygen delivery, presumably due to increase in blood flow, is greater that the increase in metabolic demand. Consequently, the relative muscle tissue O_2 saturation is increased. This provides support to the view that during passive exercise the main reflexogenic area activated, as a result of passive limbs movements, is the muscle

mechanorefex. Indeed, the muscle metaboreflex is only activated during conditions in which metabolites within the active muscle accumulated considerably i.e. restricted or arrested flow to the active muscles, or high-intensity exercise (Alam and Smirk, 1937; Wyss et al., 1983; Victor et al., 1987; Victor and Seals, 1989; O'Leary, 1993; Rowell and O'Leary, 1990; Iellamo et al., 1997; Gallagher et al., 2001).

Other investigations have shown that during active exercise and electrically-induced muscular contraction muscle tissue oxygenation decreases in parallel with decreased HbO_2 (Hirata et al., 2006). Along with these lines a decrease in muscle tissue oxygenation was also observed during static exercise, and this decrease was apparent immediately at the beginning of exercise (Moalla et al., 2006). Furthermore, Shibuya and Tanaka, (2003) reported that during exercise muscle tissue oxygenation decreases progressively with the increase in workload. Thus, the findings of the present add to the body of knowledge as they provide information about the muscle tissue oxygenation during passive exercise.

We have previously observed an increase in VO_2 during passive exercise (Vorluni and Volianitis, 2007), which is in agreement with the findings of the present investigation. Even though during passive exercise there is no voluntary muscle contraction, as suggested by the EMG activity that did not change compared to rest, nevertheless, the muscle sarcomeres shorten and lengthen while the limbs are moving passively, and this may contribute to the increased VO_2 observed. Even though it is unclear whether and how this change in muscle length affects the actomyosin interaction, ATPase activity, ATP hydrolysis, and in turn the oxygen demand, we speculate that the increase in VO_2 observed during passive exercise reflects the contribution of the

stretch response (Feng, 1932). When isolated muscle is stretched its metabolic rate increases, a phenomenon known as the stretch response (Feng, 1932). Thus, a stretch-induced increase in muscle metabolism may occur in absence of muscle contraction (Euler, 1935, Clinch, 1968).

In conclusion, during passive exercise muscle tissue oxygenation increases despite the augmentation in oxygen uptake. This may suggest that during passive exercise the increase in oxygen delivery is greater than the increase in metabolic demand.

Chapter 8

General discussion and future directions

8.1 General discussion

Overview of the study aim

The present thesis addressed a series of aims, involving the investigation of baroreflex control and cardiac sypathovagal balance during passive cycling; the effects and interaction between postural shift and passive exercise on spontaneous BRS and HR; as well as the effect of passive exercise on post-exercise BP and autonomic cardiac control, and tissue oxygenation during passive exercise and recovery.

Study one demonstrated that during passive exercise, a type of exercise where the stretch-responsive muscle mechanoreceptors are mainly stimulated, the spontaneous baroreflex gain is decreased. This finding confirms and extends previous investigation in which stimulation of contraction-responsive mechanoreceptors also reduced baroreflex gain (Iellamo et al., 1997). This suggests that the two mechanoreceptors subtypes, namely stretch-responsive and contraction responsive-mechanoreceptors decrease spontaneous BRS. Also, a rightward shift in the regression line relating SAP to PI, which may indicate a mechanoreflex-induced baroreflex resetting, was observed. Furthermore, passive exercise induced a decrease in cardiac vagal activity and, consequently, shifted the sympathovagal balance toward a more sympathetic predominance. In addition, the increases in BP, HR and Q suggest that mechanoreflex activation with passive exercise evokes cardiovascular responses similar to those observed during dynamic exercise. These results confirm and extend those of previous studies also using passive exercise.

The second study showed that the effects of passive cycling on BRS override those of postural changes. At rest, postural shift from upright to supine causes a redistribution

of blood away fro the high capacitance veins in the lower limb and pelvis to the thorax, which increase CBV, loading the carotid and cardiopulmonary baroreceptors, resulting increased BRS and bradycardia. While during both upright and supine passive exercise, the passive limbs movements activate the mechanoreflex resulting in decreased BRS and tachycardia. These results suggest that the effect of mechanoreflex stimulation overrides those of carotid and cardiopulmonary loading. This finding adds to the body of knowledge, as it provide insights into the interaction between two reflexogenic areas contributing to cardiovascular control during exercise. In addition, the findings of study two revealed that both upright and supine passive exercise evoke cardiac vagal withdrawal and increased BP, HR and Q.

Study three demonstrated that a single bout of passive exercise increased cardiac vagal activity and shifted symapathovagal balance toward more parasympathetic predominance. These changes in cardiac autonomic traffic are similar to those observed following a bout of active exercise. The augmented cardiac vagal activity is manifested in the significant bradycardia seen after passive exercise. The results of study three also suggest that during passive exercise spontaneous BRS decreases, and after the cessation of exercise BRS returns to pre-exercise levels. In addition, we observed that following passive exercise, there is an increase in TPR that resulted in elevation of SBP and DBP. Presumably, this resulted from augmented peripheral sympathetic tone, as Q did not change. This may highlight the predominant role of increased vascular conductance to PEH, because following passive exercise the exercise-borne vasodilating substances are absent. Thus, the present findings combined with those of previous investigations (Coats et al., 1989, Isea et al., 1994,

Halliwill et al., 1996b) suggest that reduction in TPR represents a major contributor to reduction in BP absorbed following exercise.

Reflexogenic area activated during passive exercise

The cardiovascular responses observed during passive exercise are mainly the result of muscle mechanoreflex activation; nonetheless, it should be considered that the muscle metaboreflex may also have contributed to a minor extent. However, this is unlikely as suggested by several investigations that showed that the muscle metaboreflex is only activated during conditions in which the metabolites within the active muscle accumulate markedly, including restricted and arrested blood flow to the active muscles, or during high-intensity exercise (Alam and Smirk, 1937, Wyss et al., 1983, Victor et al., 1987, Victor and Seals, 1989, O'Leary, 1993, Rowell and O'Leary, 1990, Iellamo et al., 1997, Gallagher et al., 2001a), and none of these conditions is present during passive cycling. This view is further supported by the findings of study four that demonstrated that during passive exercise the tissue oxygenation is increased despite the increased oxygen uptake. This suggest that during passive exercise the increase in oxygen delivery, that can be explained by an increase in blood flow, is greater that the increase in metabolic demand. Thus facilitating the washout of metabolites, and therefore removing the possibility of accumulation. Taken together, it appears that during passive exercise the muscle mechanoreflex is mainly activated.

Passive exercise and other methods employed to activate the muscle mechanoreflex

The mechanoreflex has also been investigated by passive stretch, rhythmical compression of skeletal muscle and LBP. The results from all these studies

demonstrated that the activation of the mechanoreflex evokes cardiovascular responses such increase in HR and BP. In the present study passive exercise was used as it resembles more closely to dynamic exercise. During passive exercise, the passive limbs movements activated the mechanoreflex, resulting in decreased BRS and shift that sympathovagl balance resulting from vagal withdrawal. The findings are similar to those seen during low-intensity active exercise. However, these results may be different than those observed during high-intensity exercise, especially considering that at high-intensity exercise there is both cardiac vagal withdrawal and increase in cardiac sympathetic traffic.

8.2. Functional implications

The findings from the present thesis suggest that mechanoreflex stimulation with passive exercise decreases cardiac BRS and HF power of HRV. This highlights the importance of parasympathetic activity to spontaneous baroreflex gain and to cardiac vagal modulation. In addition, the results from the present thesis indicate that during passive exercise the mechanoreflex induces a baroreflex resetting, as suggested by the rightward shift in the regression line relating SBP to PI (Iellamo et al., 1997). Furthermore, the present data provide information about the interaction of changes in CBV and mechanoreflex activation by passive exercise. We observed that postural shift from upright to supine at rest, a manoeuvre that increase CBV and loads the carotid and cardiopulmonary baroreceptors, resulted in increases BRS and bradycardia, due to augmented cardiac parasympathetic traffic (Jacobesen et al., 1993; Kardos et al., 1997). In contrast, muscle mechanoreflex stimulation during upright and supine passive exercise decreases BRS and induces tachycardia. These observations are of functional significance, as they suggest that the mechanoreflex

stimulation overrides the effect of increased CBV and carotid and cardiopulmonary baroreceptors loading on cardiac baroreflex control.

In addition the findings of the present thesis showed that following a single bout of passive exercise there is an increase in vagal cardiac control, which is reflected in the augmented HF power of HRV spectrum, associated with bradycardia. While, TPR increases resulting in elevated SBP and DBP indicating an increase in peripheral sympathoexcitation. Presumably, following passive exercise, an increase in peripheral sympathetic activity was not opposed by the action of exercise-borne vasodilating substances, resulting in increased TPR and BP. This highlights the importance of exercise-borne vasodilationg substances to the BP reductions often observed following active exercise. Also the present data demonstrated that during passive exercise the muscle tissue O_2 content increases despite the augmentation in oxygen uptake. This may suggest that during passive exercise, a very light exercise modality, the increase in blood flow may exceed tissue O_2 utilization, resulting in increased tissue oxygenation.

Extensive future research is however required to elucidate the interaction of muscle mechanoreflex with central command and muscle metaboreflex on baroreflex cardiovascular control, during and following exercise.

Hypotheses

Hypothesis 1. H_1: Passive exercise will decrease the cardiac baroreflex sensitivity - **ACCEPT.**

Hypothesis 2. H_1: Passive exercise will result in cardiac vagal withdrawal causing a shift of the sympathovagal balance - **ACCEPT.**

Hypothesis 3. H_1: The affects of passive exercise on spontaneous baroreflex sensitivity and cardiac chronotropic state will override those caused by postural changes -**ACCEPT.**

Hypothesis 4. H_1: Passive exercise will provoke a reduction in post-exercise BP values -**REJECT.**

Hypothesis 5. H_1: Spontaneous baroreflex sensitivity will be increased following passive exercise - **REJECT.**

Hypothesis 6. H_1: After passive exercise the cardiac vagal modulation will be enhanced -**ACCEPT.**

8.3. Future research directions

Findings from the present thesis have contributed to the understanding of the baroreflex control and the cardiac sympathovagal balance; however, some aspects remain to be elucidated. The outcomes of this thesis have identified particular avenues that future researchers in this area may wish to address to further the understanding of cardiovascular control.

In the present thesis the baroreflex control was investigated using the spontaneous method. The spontaneous BRS method has the advantage that assesses this feedback mechanism under normal physiological conditions, as it do not require the infusion of drugs nor the use of forces to forces to load/unload the baroreceptos that interfere with the closed-loop nature of the reflex. However, it evaluates the baroreflex control of BP at the baroreflex's operating point. It is pertinent that future researchers further

evaluate the whole full baroreflex function-curve during passive exercise using the variable of neck chamber.

The fine-tuned cardiovascular control during exercise is controlled by complex mechanisms, as various reflexogenic areas are activated, namely central command, the muscle mechanoreflex and metaboreflex, and the consequent upward resetting of the baroreflex allows this feedback mechanism to remain the main BP controller. In addition, a manoeuvre that alters CBV, such as postural shift, loads the carotid and cardiopulmonary baroreceptors affecting the autonomic outflow, via afferent activity to the brainstem. A large body of literature has focused on the independent contribution of each of these reflexogenic areas to baroreflex function and cardiovascular activity, in response to homeostatic disturbances such as exercise or postural changes. Along with these lines, the studies contained in the present thesis focused on elucidating the role of the muscle mechanoreflex, as well as its interaction with the cardiopulmonary baroreceptors on cardiac baroreflex control and autonomic traffic, while limiting the contribution other reflexogenic areas implicated in circulatory control. Future studies are required to further elucidate the interaction between the different reflexogenis areas implicated in circulatory control, such as the interaction between cardiopulmonary baroreflex and metaboreflex stimulation on autonomic outflow; or the interaction between peripheral sympathetic activity and exercise-borne vasodilating substances on vascular conductance and PEH.

The use of microneurography following exercise would provide insight of the sympathetic activity on the vasculature, while the use microdialysis could provide information of interstitial concentration of metabolites. This could further the

understanding of the interaction of sympathetic activity and exercise-borne vasodilating substances on the control of the vasculature and thus TPR and PEH.

The studies contained in the present thesis investigated the acute effect of passive exercise on BRS, autonomic outflow, and the cardiovascular control; while longitudinal study investigating the effect of repeated bouts of passive exercise on these cardiovascular parameters has not yet been attempted. There is sufficient scientific evidence to suggest that the circulatory control and the cardiovascular responses to active exercise may differ between elite athletes and healthy sedentary. Whether these differences are also present during passive exercise remain to be established. Cross-sectional examination of highly trained athletes, in comparison with healthy sedentary subjects would provide further insight whether the difference in physical activity levels also influence the cardiovascular control during passive exercise.

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