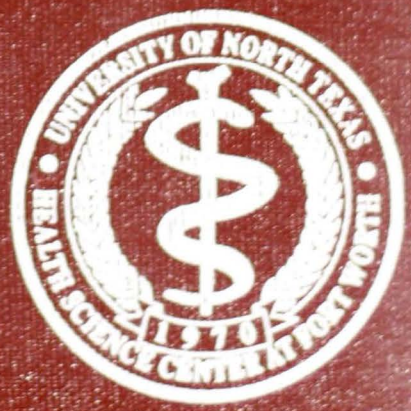
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Carotid baroreflex (CBR) function is reset upward and rightward to the prevailing blood pressure during dynamic and static exercise. Feedforward central neural inputs (central command) and negative feedback from skeletal muscle (exercise pressor reflex) both contribute to the resetting. The purpose of this investigation was to identify the individual roles of central command and the exercise pressor reflex in the resetting of the CBR during dynamic and static exercise. First, it was necessary to determine which receptor group that comprises the exercise pressor reflex , chemically-sensitive (chemoreceptors) or mechanically-sensitive (mechanoreceptors) receptors, was primarily involved in the regulation of the cardiovascular system. We observed the cardiovascular responses during exercise to individual activation of the chemoreceptors and the mechanoreceptors. We demonstrated an increased mean arterial pressure (MAP) response to mechanoreceptor activation that was not identified during chemoreceptor stimulation. This finding suggested that the mechanoreflex was the primary exercise pressor mediator of arterial blood pressure during exercise.

To identify the role of central command on CBR resetting, a second investigation increased central command by partial neuromuscular blockade during dynamic and static exercise. Resetting of CBR control of heart rate (carotid-cardiac; CSP-HR) and MAP (carotid-vasomotor; CSP-MAP) during control exercise was further reset upward and rightward by increased central command without alterations in sensitivity. In conclusion, central command, a feedforward mechanism, was actively involved in the resetting of the CBR during exercise.

To investigate the role of the exercise pressor reflex on CBR function, a third investigation activated the exercise pressor reflex with the application of medical anti-shock trousers (MAS) during dynamic and static exercise. From control exercise, carotid-vasomotor function was further reset upward and rightward by the application of MAS trousers while CSP-HR function was only reset rightward. Sensitivity of the CSP-MAP and CSP-HR function curves were unaltered. The negative feedback mechanism of exercise pressor reflex, primarily mediated by mechanoreceptors, appeared to act as a modulator of CBR resetting during exercise.

NEURAL CONTROL OF THE CAROTID BAROREFLEX

DURING EXERCISE

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LIST OF ABBREVIATIONS

ABP	arterial blood pressure
ANOVA	analysis of variance
CBR	carotid baroreflex
CP	centering point
CSP	carotid sinus transmural pressure
CSP_{sat}	Saturation carotid sinus pressure
CSP_{thr}	Threshold carotid sinus pressure
CVP	central venous pressure
DBP	diastolic blood pressure
ECG	electrocardiogram
EMG	electromyographic activity
G_{max}	maximal gain
HR	heart rate
IMP	intramuscular pressure
LBPP	lower body positive pressure
MAP	mean arterial pressure
MVC	maximal voluntary contraction
NP	neck pressure
NS	neck suction

LIST OF ABBREVIATIONS, continued

NTS	nucleus tractus solitaius
OP	operating point
Q_c	cardiac output
RPE	perceived exertion
RSNA	renal sympathetic nerve activity
SAT	saturation
SBP	systolic blood pressure
SE	standard error
SV	stroke volume
TPR	total peripheral resistance
Ve	Ventilation
VO_2	oxygen uptake
VO_{2max}	maximal oxygen uptake
VO_{2peak}	peak oxygen uptake
W	watts

CHAPTER I

INTRODUCTION

Potts et al. (30) demonstrated that carotid baroreflex control of blood pressure during dynamic exercise was reset to the prevailing blood pressure. In addition, they illustrated that the carotid baroreflex was reset in direct relation to the intensity of dynamic exercise with no attenuation of the maximum sensitivity or gain. It has also been reported, at rest and during muscle contraction, that the arterial baroreflex was modulated by changes in intramuscular pressure (29, 36). There are two neural mechanisms that have important roles in the regulation of the cardiovascular system during exercise, these being central command and the exercise pressor reflex (21). However, a lack of evidence on what are the specific roles of these neural mechanisms in the resetting of the carotid baroreflex during exercise exists. Furthermore, conflicting data exists regarding which of the skeletal muscle receptor groups (metaboreceptors and mechanoreceptors), collectively called the exercise pressor reflex, are primarily involved in the regulation of the cardiovascular system during exercise. Therefore, the proposed investigations were designed to individually alter the activity of one of these neural mechanisms while keeping the activity of the other mechanisms constant during both static and dynamic exercise to determine the effect of the stimulated neural mechanism on the carotid baroreflex. The

proposed experiments were intended to discern which exercise pressor reflex receptor (mechano- or metabo-) was primarily involved in the regulation of the cardiovascular system during exercise and what roles the two neural mechanisms (exercise pressor reflex and central command) have in the resetting of the carotid baroreflex during exercise.

REVIEW OF RELATED LITERATURE

Arterial Baroreceptor Reflex

Spray-type nerve endings, which respond to stretch, are located in the bifurcation of the carotid arteries and in the aortic arch. These mechanoreceptors, collectively called the arterial baroreflex, are involved in the moment-to-moment regulation of arterial blood pressure. Arterial blood pressure (ABP) is an outcome measure of three physiological variables, heart rate (HR), stroke volume (SV) and total peripheral resistance (TPR), and this relationship is expressed as follows: ABP = HR x SV x TPR. Arterial baroreflex control of ABP affects the three physiological variables, HR, SV and TPR in response to changes in ABP. The arterial baroreflex exerts its control by altering tonic inhibitory influence on sympathetic neural activity at the site of the nucleus tractus solitarius (NTS) (5). The influence of the baroreflex on sympathetic neural activity is altered by the amount of stretch detected in the arterial walls. Thus, when the arterial wall is stretched by elevations in blood pressure, the baroreflex responds by increasing its firing rate and, in turn, alters the autonomic neural outflow to produce a bradycardic and vasodilatory

response in order to return blood pressure back to the original set-point. In contrast, a tachycardia and vasoconstrictive response occurs in response to decreased arterial wall stretch in a hypotensive episode. Therefore, the arterial baroreflex acts as a classical negative feedback controller.

Autonomic Neural Pathways

The afferent input from the carotid and aortic sinuses travel to the cardiovascular control center via the glossopharyngeal nerve (cranial nerve nine) and the vagus nerve (cranial nerve ten) (4, 17). These afferents are thought to project to the NTS located in the medulla. From the NTS, autonomic parasympathetic outflow has been shown to be mediated primarily through cardiac vagal efferents traveling first via central parasympathetic neurons in the nucleus ambiguous to post-ganglionic neurons next to or in the walls of the heart chambers (16). Sympathetic efferent signals, regulated by baroreceptor afferent information projected to the NTS and relayed first to the caudal ventral-lateral medulla and then to the rostral ventral-lateral medulla, travel via the inner medial-lateral cell column within the spinal cord. These efferent signals travel via pre-ganglionic white ramus fibers which synapse with post-ganglionic neurons in the sympathetic ganglion (16). Thus, afferent input from the arterial baroreceptors interacts with both the sympathetic and parasympathetic neural systems.

In humans, direct stimulation or denervation of afferent and efferent neural pathways is not possible. As a result, less invasive techniques have been utilized to

perturb the baroreceptors in an attempt to evaluate their function. Historically, pharmacological methods have been used to perturb the aortic baroreceptors. On the other hand, carotid baroreceptors in humans have been studied using a variable-pressure neck chamber. Ernsting and Parry (10) developed a neck chamber consisting of a rigid-walled collar that encircled the neck from the shoulders to the lower part of the face. A vacuum cleaner produced negative pressures in the chamber, which increased transmural pressure across the carotid sinuses, thus increasing vascular diameter and physiologically stimulating the carotid baroreceptors. Eckberg et al. (8) simplified the neck chamber and modified it to sustain positive pressure, which in turn decreased transmural pressure across the carotid sinuses; decreased vascular diameter; and physiologically deactivated the carotid baroreceptors. The chamber consisted of a malleable lead collar that encompassed the anterior and lateral aspects of the neck. Recently, this modified collar has been demonstrated to transmit greater than 90% positive and negative pressures across the carotid sinuses in humans (31). Thus, this technique allowed for the creation of stimulus-response curves encompassing a range of baroreceptor activities above and below the tonic level of baroreceptor activity (28, 30, 36, 37) and was used to evaluate the carotid baroreflex function in our investigations.

Carotid Baroreflex Function During Exercise

At exercise onset or when increases in active muscle mass are superimposed on constant workload activity, both HR and ABP increase in a parallel fashion. Prior to the

1960's it was proposed that if the baroreflex system functioned as a negative feedback control mechanism, then simultaneous increases in HR and ABP would occur only if the baroreflex system had been deactivated by the onset of exercise. In 1966, Bevegard and Shephard (2) suggested that baroreflex activity of the human was unchanged by exercise. Melcher and Donald (1981) used isolated carotid sinus techniques in dogs and determined that during exercise carotid baroreceptors maintained their sensitivity (20). They demonstrated that the operating point of the baroreflex was shifted vertically at the beginning of exercise and that it was further shifted vertically with each incremental change in exercise intensity. Furthermore, the short time-course of this effect suggested that resetting of the baroreflex most likely was mediated by a feed-forward mechanism, which did not require an error signal, i.e. central command. Therefore, the shape (slope and gain) of the baroreflex function curve was not altered by exercise, the curve simply relocated vertically on the response arm of the function curve at the same operating pressure. The relocation of the baroreflex function curve was termed "resetting". Subsequently, DiCarlo and Bishop in 1992 used intravenous infusion of nitroglycerin to attenuate the exercise-related increase in ABP while recording efferent renal sympathetic nerve activity (RSNA) in rabbits exercising on a treadmill (6). When the rabbits exercised during nitroglycerin infusion the level of RSNA evoked by exercise was increased. The data of DiCarlo and Bishop (6) have been used as evidence that the arterial baroreceptor reflex was reset immediately at the start of exercise, which created a pressor error signal and resulted in the greater increase in RSNA.

Potts et al. using human subjects provided evidence that the baroreflex function curve actually was relocated upward on the response arm and rightward to a higher operating pressure (parallel resetting) and that the operating point was relocated away from the centering point closer to the threshold region (30). Thus, during exercise, baroreflex function was reset to operate around the prevailing blood pressure allowing for the baroreflex to respond to a wider range of carotid sinus hypertension (30). Papelier et al. confirmed that this resetting occured during moderate to high intensity exercise (25). It has also been determined that the parallel resetting occured during static exercise (7). The question remained as to which of the two neural mechanisms was responsible for the shift in baroreflex function during exercise.

To address this question, Rowell and O'Leary (33) presented a hypothetical scheme illustrating the role of central command and the muscle chemoreflex in the resetting of the arterial baroreflex, see figure 1. In Rowell and O'Leary's model, central command (A) resets the operating (OP_1) by a rightward shift to OP_2 by acting on a neuron pool receiving baroreceptor afferents. Activation of the muscle chemo-reflex (B) will cause a vertical shift in the OP because the stimulus interacts neurally only on the efferent sympathetically responsive arm of the reflex and not the central neuron pool controlling the reflex. A and B illustrates the predicted outcome of the integration of the combined effects of central command and the muscle chemoreflex.

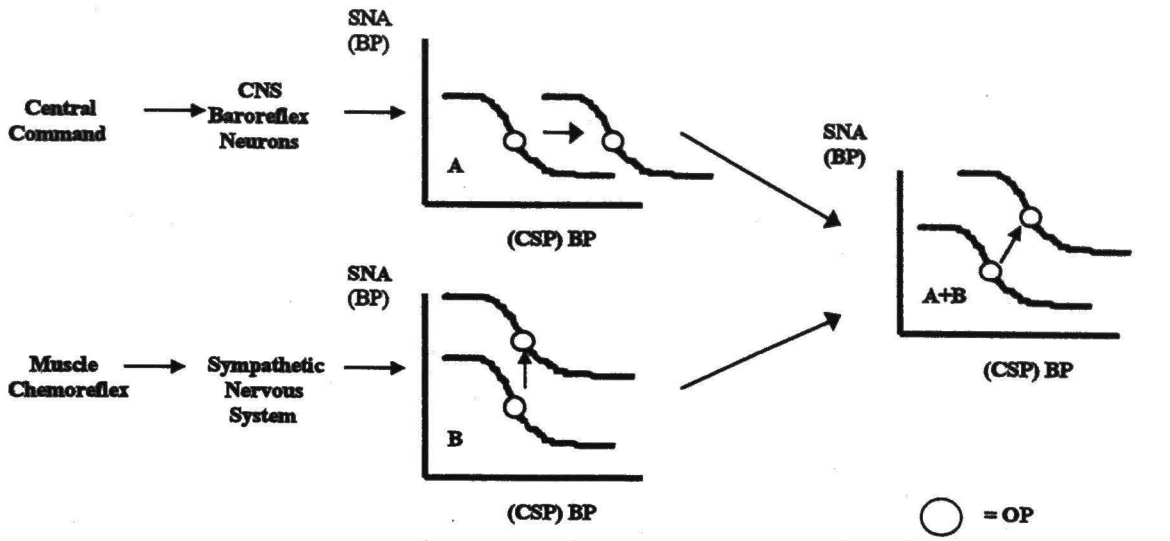

Figure 1- A model of arterial baroreflex resetting

Potts et al. confirmed the proposed model of the carotid arterial baroreflex in humans performing dynamic exercise (30). However, there were two major differences in regards to Rowell and O'Leary's model. First, Potts et al. defined the operating point (OP) as the pre-stimulus steady state HR or ABP and not the centering point as proposed by Rowell and O'Leary (33). Potts et al. demonstrated a distinction between baroreflex resetting of the centering point and the relocation of the OP (pre-stimulus HR or ABP) toward threshold enabling effective buffering of elevations in systemic blood pressure via reflex alterations in HR or MAP (30). Secondly, contrary to traditional thought, recent work (43, 44) has provided evidence that the muscle chemoreceptors are not tonically active and are not activated until metabolites build-up in the active muscle at the later stages of exercise. Thus it was not apparent whether it was the mechanoreflex, the

metaboreflex or both that provided the skeletal muscle modulation via central integration of the arterial baroreflex?

Central Command

Johansson (1895) originally proposed that motor outflow from the cerebral cortex might interact with the centers that elicit cardiovascular responses to exercise (13). This motor outflow later became known as central command. Central command is a "feed-forward" controller that at the beginning of exercise has a diffuse outflow of efferent communication from its proposed location in the subthalamic locomotor region that activates the motor cortex. In a parallel fashion, central command activates the cardiovascular control center found in the lateral reticular nucleus of the medulla (21). Central command elicits immediate changes in parasympathetic and sympathetic activity to the heart and blood vessels when activated (12, 18, 40). Many experiments have been conducted in animals in order to discern the role of central command in the regulation of the cadiovascular system during exercise (24, 42). Electrical or chemical stimulation of the proposed location of central command in the subthalamic locomotor region has demonstrated cardiovascular responses similar to those observed during exercise (41). However, this type of direct stimulation in humans is not possible. In addition, central command and the exercise pressor reflex are redundant mechanisms in regulating the cardiovascular system during exercise (21). Thus the challenge in studying central

command in humans is to use minimally invasive techniques that manipulate central command with limited perturbation to the exercise pressor reflex.

One model used to determine the role of central command utilizes partial neuromuscular blockade. Central command activates the cardiovascular center and in parallel is involved in motor unit recruitment. Hence, when muscle strength is reduced with partial neuromuscular blockade, increased motor unit recruitment occurs in order to produce the same absolute force in a weakened muscle. This increase in motor unit recruitment (central command) should result in a parallel increase in the activation of the cardiovascular center. Experiments with neuromuscular blockade have been performed during dynamic and static exercise (1,11). Recently, Pawelczyk et al. (26), using partial neuromuscular blockade with tubocurarine, demonstrated significant increases in HR, ABP and plasma noradrenaline during static hand grip in humans. Victor et al. (38) demonstrated increased muscle sympathetic nerve activity in partially curarized humans during static exercise.

In an earlier study by Goodwin et al. (12), several subjects performed constant isometric exercise between 20-50% of their maximal voluntary contraction (MVC). They demonstrated that a small vibration applied to a tendon of a muscle will stimulate a small contraction (10% of MVC) via activation of the muscle spindles. Therefore, if the vibration was applied to the tendon of the muscle performing the exercise, then the vibration would produce its own contraction making it easier to maintain the desired tension. In other words, less central command would be needed to maintain the same

absolute tension. The opposite occurred when the vibration was applied to the antagonist muscle tendon (disynaptic inhibition) resulting in the need for more central command to maintain a desired tension. Vibration of the agonist (less central command) tendon resulted in decreased responses of HR, ABP and ventilation (Ve). When the vibration was applied to the antagonist tendon (due to more central command) HR, ABP and Ve responses were exaggerated. Thus, ventilatory and cardiovascular responses were changed in accordance with the degree of central command. Furthermore, electromyographic activity (EMG), ratings of perceived exertion (RPE) and oxygen uptake (VO_2) have also been found to increase with increasing central command and thus have been used as indices of central command (23). Therefore, sufficient evidence exists that central command is involved in the regulation of the cardiovascular system (HR and MAP) during exercise. However, it remains to be determined what is the role of central command in the resetting of the carotid baroreflex during exercise?

Exercise Pressor Reflex

The exercise pressor reflex modulates autonomic nervous activity via neural afferent signals arising within the active skeletal muscle which reflexively activate the cardiovascular control centers located in the medulla. The muscle reflex consists of Group III and IV neural afferents arising from skeletal muscle and is considered an afferent input arm of a negative feedback controller. The Group III fibers were associated with collagen structures in the skeletal muscle (39), and they respond almost instantaneously to muscle

activation (14). Thus these receptors have been labeled mechanoreceptors (21). The Group IV fibers are associated with blood and lymphatic vessels (39) and have a delayed response to muscle contraction activation (14). The Group IV afferents predominately respond to the accumulation of metabolic products during muscular contraction, so they have been termed metaboreceptors (21). The proposed purpose of these reflexes was to detect a mismatch between blood supply and demand in active skeletal muscle and by efferent activation to correct the mismatch by increasing blood pressure and blood flow through the activated muscle.

Mitchell et al. provided evidence these reflexes were involved in the regulation of the cardiovascular system (22). The investigators electrically stimulated the peripheral ends of sectioned spinal ventral roots in cats to induce contraction of the hindlimb muscles. During these induced contractions, HR and ABP rose. However, when the dorsal roots of the spinal nerves supplying the hindlimb muscles were ligated, the induced contraction failed to increase HR and ABP. Thus it was clearly established that afferent impulses being conducted in the corresponding dorsal roots during static muscle contraction reflexively caused cardiovascular responses.

Conflicting reports exist on the role of the two receptors groups (mechanoreceptors or metaboreceptors) in the regulation of blood pressure during exercise. Previous experiments have used techniques such as terminal aortic occlusion (35), post-exercise ischemia (33) and lower body positive pressure (LBPP) (9, 32, 34) to create an ischemic environment or to trap metabolites in the exercising muscle. These

experiments have consistently reported increased blood pressure responses during exercise in response to trapped metabolites in the active muscle. Thus, they suggested that the metaboreceptors were the primary regulators of blood pressure during exercise. However, Williamson et al. (1994) demonstrated that LBPP of 15, 30 and 45 Torr applied to the exercising legs induced incremental increases in blood pressure at rest that were maintained throughout progressive exercise to maximal effort (43). Williamson et al. suggested that, since incremental increases in blood pressure at rest and low levels of exercise occurred when insufficient amounts of metabolites were produced that the mechanoreceptors were primarily the regulators of blood pressure during exercise (43). Thus, experiments using the same technique of LBPP during exercise contrasting interpretations of what increases the blood pressure were proposed, i.e. was the blood pressure increase due to the mechanoreceptor activation or to metaboreceptor activation?

Initial evidence does exist pertaining to the role of the exercise pressor reflex in the regulation of the carotid baroreflex. McWillaim et al. electrically stimulated the ventral roots of unanesthesized decerebate cats while determining carotid baroreflex function (19). During somatic activation the baroreflex response was attenuated. This implies that the sensitivity of the carotid baroreflex was reduced by somatic afferent activation. In addition, Shi et al. reported an attenuated carotid baroreceptor response to intramuscular stimulation by muscle compression with LBPP (36). Recently, Potts et al. found that the afferent input from arterial baroreceptors was a powerful modulator of sympathoexcitation evoked by mechanically and metabolically-sensitive skeletal muscle receptors (27). Thus,

there is a clear interaction between the two main afferent inputs to the cardiovascular center (exercise pressor reflex and arterial baroreceptors). However, the role of the exercise pressor reflex in the resetting of the carotid baroreflex during exercise, especially in humans, remains to be determined.

Summary

Central command and the exercise pressor reflex are two redundant neural control systems that regulate the cardiovascular responses that result in blood pressure achieved during exercise. The concept of whether central command is the prime mover in the resetting of the arterial baroreceptors to function at the exercising ABP or whether the resetting is an integration of the exercise pressor reflex information with that of central command is still unknown. In addition, it remains controversial as to which aspect of the exercise pressor reflex (mechanoreceptors or metaboreceptors) is primarily involved in the regulation of the cardiovascular system during exercise. However, it is evident that the arterial baroreflex is reset during exercise (3, 6, 25, 30).

By selectively activating the mechanoreceptors or metaboreceptors, we propose to identify their roles in the regulation of the cardiovascular system during exercise. We predict that by selectively altering central command or the exercise pressor reflex during exercise, we will to identify the role each neural mechanism has on the resetting of the arterial baroreflexes. These findings will assist in understanding the effects that peripheral

pathophysiologies, such as congestive heart failure, hypertension and intermittent claudication, have in the regulation of blood pressure during ambulatory activities.

SPECIFIC AIMS

Three primary objectives were developed for this dissertation. These are: a) to determine if the mechanoreceptors, metaboreceptors or both are primarily involved in the regulation of blood pressure during dynamic and static exercise; b) to examine and partition the role of the central command in the resetting of the carotid baroreflex control of HR and MAP during dynamic and static exercise; and c) to examine and partition the role of the exercise pressor reflex in the resetting of the carotid baroreflex control of HR and MAP during dynamic and static exercise. To accomplish these objectives, the following aims were established:

I. To test the hypothesis that the mechanoreceptors are the primary regulators of blood pressure during dynamic exercise.

II. To test the hypothesis that central command is the primary mechanism for the resetting of the carotid baroreflex during exercise. In addition, that increases in central command by produced partial neuromuscular blockade during constant workload dynamic or static exercise will reset the carotid baroreflex upward and rightward to a higher carotid sinus pressure.

III. To test the hypothesis that increases in intramuscular pressure during constant workload static or dynamic exercise will reset the carotid baroreflex rightward to regulate cardiovascular responses at the higher prevailing blood pressure.

EXPERIMENTAL DESIGN

Three individual experiments were designed to investigate specific aims I, II and III. These experiments are discussed in detail in chapters 2, 3 and 4. Below is a brief description of the experimental design utilized.

Increased Mechanoreceptor or Metaboreceptor Stimulation on Blood Pressure

To differentiate the roles of the mechanoreceptors and metaboreceptors during exercise, four dynamic cycling exercise protocols were completed to maximal effort. These consisted of control; exercise with thigh cuff occlusion of + 90 Torr to trap metabolites in the active skeletal muscle; exercise with LBPP to stimulate mechanoreceptors in the active muscle and a combination of the thigh cuff occlusion and LBPP. Cardiac output, ABP and HR were monitored to determine the cardiovascular responses to metaboreceptor and mechanoreceptor stimulation. EMG, RPE and VO_2 were measured to detect any alterations in central command. Blood lactate concentration was measured from the active skeletal muscle to determine if metabolites were trapped. The cardiovascular responses to these exercise conditions were compared to define the roles of these receptor groups in the regulation of ABP during exercise.

Increased Central Command on Carotid Baroreflex Resetting

To determine the contribution of central command on carotid baroreflex resetting during exercise, subjects performed three minutes of static (20% maximal contraction) and seven minutes of dynamic (cycling) leg exercise with: i) no intervention; and ii) with total body partial neuromuscular blockade using curare (Norcuron) to increase central command. At rest and during exercise, carotid baroreflex (CBR) stimulus-response curves were generated using a variable pressure rapid pulse protocol. This allowed for the determination of the effect of increased central command on the CBR at rest and during dynamic and static exercise.

Increased Exercise Pressor Reflex on Carotid Baroreflex Resetting

To determine the contribution of the exercise pressor reflex on carotid baroreflex resetting during exercise, subjects performed three minutes of static (20% maximal contraction) and seven minutes of dynamic (cycling) leg exercise with: i) no intervention and ii) with the application of medical anti-shock trousers to increase exercise pressor reflex stimulation. At rest and during exercise, carotid baroreflex (CBR) stimulus-response curves were generated using a variable pressure rapid pulse protocol. This determined the effect of exercise pressor reflex stimulation on the CBR at rest and during dynamic and static exercise.

METHODS

The methodology used in each study is discussed in the respective chapters, however, it is pertinent to discuss the major aspects of the neck pressure/neck suction (NP/NS) technique used to examine carotid baroreflex function. Due to the brevity of the exercise protocols in these investigations, a NP/NS protocol that utilized a rapid ramping of pressure stimuli was used. Computer controlled pulsatile pressures (seven) and suctions (five) were applied to the subjects' neck and transmitted to the carotid sinus. The pressure pulses started with four pressures which developed a chamber pressure (CP) in the collar of +40mmHg and then declined incrementally towards zero pressure. The suction pulses then increased by approximately -20 mmHg CP for each pulse (0, -20, -40, -60, -80 mmHg chamber pressure). Between each pressure pulse the chamber pressure was returned to atmospheric pressure. The computer software linked the pulses of pressure to occur 50 ms after initiation of the R-wave detected by the ECG and each pulse was 500 ms long. The 50 ms delay was to enable the artificial pressure/suction stimulus to coincide with the arterial pressure wave at the carotid sinus. Each NP/NS pulse train was conducted at end-expiratory breath-hold to eliminate the confounding effects of respiratory sinus arrhythmia. The HR and MAP response from the ramped rapid pulse protocols were plotted against the estimated carotid sinus pressure which was calculated by subtracting chamber pressure from the pre-stimulus MAP. The sigmoid shaped stimulus-response curves were then analyzed using the logistic function described by Kent et al. (15) (HR or MAP = $A1^* \{1 + e^{[A2(CSP-A3)]}\}^{-1} + A4$) where: CSP is the carotid

sinus pressure or MAP ± neck chamber pressure, A1 is the range of response of the dependent variable (max-min), A2 is the gain coefficient, A3 is the CSP required to elicit equal pressor and depressor responses (centering point), and A4 is the minimum HR or MAP response (Figure 2). Several characteristic parameters are derived from the resulting model including the estimated threshold, saturation pressures and the maximal gain of the carotid-cardiac and carotid-vasomotor reflexes. Baroreceptor threshold and saturation are described as the minimum and maximum carotid sinus pressures, respectively, that elicit a reflex change in HR and MAP.

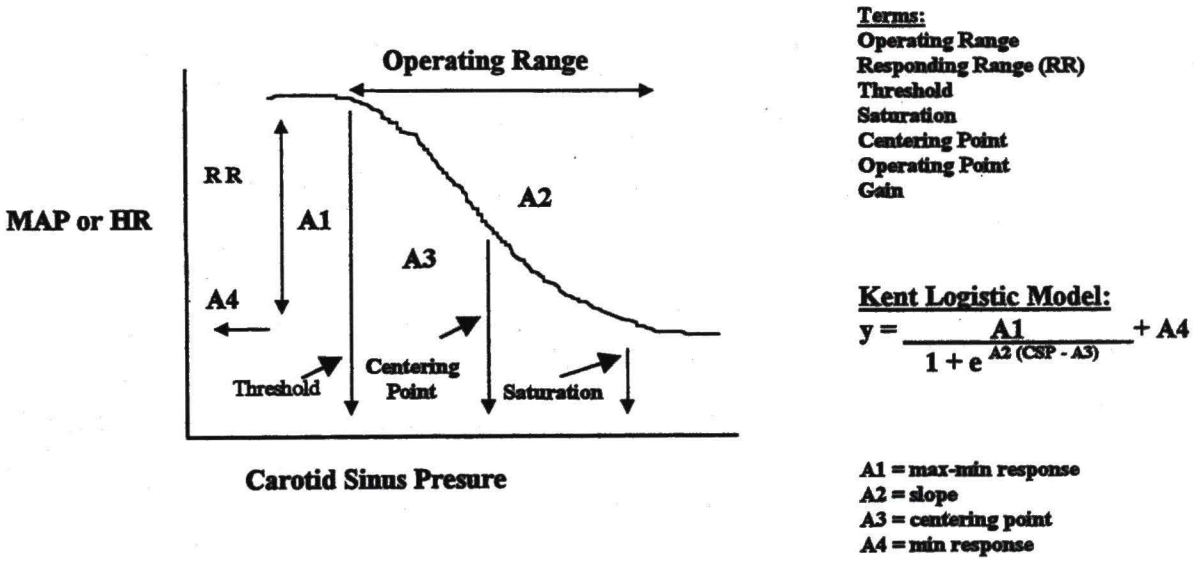

Figure 2: Schematic illustration of a carotid baroreflex stimulus-response curve and the Kent logistical equation.

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CHAPTER II

INCREASES IN INTRAMUSCULAR PRESSURE RAISE ARTERIAL BLOOD PRESSURE DURING DYNAMIC EXERCISE

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ABSTRACT

This investigation was designed to determine the role of intramuscular pressure-sensitive mechanoreceptors and chemical-sensitive metaboreceptors in affecting the blood pressure response to dynamic exercise in humans. Ten subjects performed incremental cycle exercise (20 $W \bullet min^{-1}$) to fatigue under four conditions: control; exercise with thigh cuff occlusion of +90 Torr (Cuff occlusion); exercise with lower body positive pressure (LBPP) of 45 Torr; and a combination of thigh cuff occlusion and LBPP (Combination). Indices of central command (heart rate, oxygen uptake, ratings of perceived exertion and electromyographic activity), cardiac output, stroke volume and total peripheral resistance were not significantly altered by the application of the three conditions. Mechanical stimulation by LBPP and Combination resulted in significant elevations in intramuscular pressure and mean arterial pressure (MAP) from control at rest and throughout the incremental exercise protocol ($P < 0.05$). Conversely, no changes in MAP occurred when the metaboreflex was stimulated with Cuff occlusion. These findings suggest that under normal conditions the mechanoreflex is tonically active and is the primary *exercise pressor* mediator of arterial blood pressure during dynamic exercise.

INTRODUCTION

Afferent neural signals from exercising skeletal muscle (exercise pressor reflex) in conjunction with contributions from higher brain centers (i.e., central command) are capable of increasing sympathetic nerve activity (30) and blood pressure (1, 8, 12, 13). These afferent nerve signals arise from mechanically (mechanoreceptors) and chemically sensitive (metaboreceptors) nerve endings located strategically within the muscle (11). Previously, Williamson et al. (31) reported that the application of +45 Torr lower body positive pressure (LBPP) to the lower limbs of the resting human significantly increased mean arterial pressure (MAP). Subsequently, the use of epidural anesthesia to inhibit afferent feedback from resting skeletal muscle was reported to eliminate the reflex increase in MAP elicited by lower limb compression (32). The authors suggested that a pressure sensitive, or mechanoreceptor, activated reflex within skeletal muscle was the mechanism by which MAP was increased. Other investigations have confirmed in animals the presence of mechanically sensitive receptors that reflexively increased MAP (10, 17, 27).

Williamson et al. (31) further demonstrated that 15, 30 and 45 Torr LBPP induced incremental increases in MAP at rest that were maintained throughout a progressive exercise test to maximal effort. With LBPP of 45 Torr at exercise work rates greater than 200 W MAP was further augmented in addition to the previously induced incremental increase in MAP. The investigators (31) suggested that the mechanoreceptor reflex was

tonically active and may be the primary exercise pressor reflex modulator of blood pressure during dynamic exercise. They speculated that a critical reduction in muscle blood flow was required before a muscle metaboreflex could be activated.

Utilizing terminal aortic occlusion to progressively reduce blood flow to the back legs of exercising dogs, Sheriff et al. (24) demonstrated that a threshold reduction in blood flow induced a powerful muscle metaboreflex at moderate workloads. Rowell et al. (22) illustrated that progressive increases in LBPP (25, 35, 45 and 50-60 Torr) reduced leg blood flow by 5.3% to 19.9% in exercising humans. This investigation reported a stepwise increase in blood pressure to increases in LBPP at rest that was maintained throughout exercise without eliciting any threshold increase in MAP. This data confirmed reports by Eiken and Bjurstedt (4) using LBPP of 50 Torr. The findings suggested that a reduction in leg blood flow by LBPP resulted in a mismatch between skeletal muscle blood flow and metabolism activating the metaboreceptor sensitive reflex. The authors argued that the muscle metaboreflex was the mechanism by which MAP was increased with no apparent threshold. Thus, separate experiments (4, 22, 31) using the same LBPP technique have demonstrated that afferent neural signals arising from active skeletal muscle contribute to the increase in blood pressure during exercise. However, the conclusions drawn disagree as to whether the LBPP induced increases in MAP were primarily due to metaboreceptor or mechanoreceptor activation. Recent findings by Smith et al. (26) suggest that the metaboreceptors were not tonically active but were activated

by a critical reduction in blood flow by which they served primarily as a ventilatory stimulus.

In the present investigation, we attempted to isolate the metaboreceptor response via reductions in venous outflow utilizing two-legged cuff inflation to 90 Torr and comparing the response to control, 45 Torr LBPP and a combination of LBPP and cuff inflation during progressive workload dynamic cycle exercise to maximum. The investigation was designed to determine the role of intramuscular pressure sensitive mechanoreceptors and chemically sensitive metaboreceptors in affecting the blood pressure response to dynamic exercise.

METHODS

Subjects: Six men and four women, mean (± SE) age of 26.5 ± 1 years, volunteered to participate in this investigation (Study 1). In a subgroup of six additional subjects (four men: two women; mean age = 27.3 ± 2 years), a second set of experiments (Study 2) was performed. Prior to testing, subjects were informed of all aspects of the study and each signed an informed consent approved by the Institutional Review Board for the use of Human Subjects at the University of North Texas Health Science Center at Fort Worth. All subjects were non-smokers, were not taking medication, and were asymptomatic for cardiovascular and respiratory disease. The subjects were familiarized with all testing procedures and were asked to abstain from alcoholic beverages and

exercise for 24 hours and caffeinated beverages for 12 hours prior to any scheduled testing session. Subject data are summarized in Table 1.

Exercise Testing: Each subject performed a preliminary incremental work rate (100 kg-m/min) exercise test on a cycle ergometer (Quinton 845) to volitional fatigue for the determination of peak oxygen uptake (VO_{2peak}). Since none of the subjects achieved a plateau of VO_2 with increasing workrates, the maximum oxygen uptake (VO_{2max}) achieved was presented as VO_{2peak}. On separate days following the initial exercise test, the subjects performed four additional incremental exercise tests administered in random order. The four exercise tests were performed in a 70° back-supported semi-recumbent position with increments of 20 watts·min^{-1} (W). All four tests were performed under distinctly different conditions; these being (i) exercise with no intervention (control); (ii) bilateral thigh cuff occlusion of +90 Torr (Cuff occlusion); (iii) lower body positive pressure of 45 Torr (LBPP); and (iv) a combination of thigh cuff occlusion of +90 Torr and 45 Torr LBPP (Combination). The administration of thigh cuff occlusion, LBPP or the combination of both was applied to the subject at rest and exercise was initiated after a collection period of baseline measurements for five minutes.

Two exercise tests were performed on a single day separated by a minimum of three hours with each testing day separated by a minimum of four weeks. Since the data obtained from the initial upright incremental exercise test and the randomized exercise test without intervention in the semi-recumbent position were similar, the latter test was referred to as the control test. A custom-designed LBPP chamber (Figure 1) equipped

with a computerized, electromagnetically braked cycle ergometer (Intellifit, Inc., Houston, TX) allowed subjects to exercise in a semi-recumbent position (back angle at 70°). This back angle was chosen in order to simulate upright exercise as much as possible to allow for maximal effort and subject comfort. The subjects' lower body was sealed with a polypropylene skirt fitted snugly around the iliac crest. Chamber pressure was continuously monitored from a digital transducer (Universal Pressure Meter, Bio-Tek). Positive pressure was applied to the subjects inside the chamber driven by vacuum motor pumps. Shoulder straps attached to the seat back were utilized to maintain the subject's position when LBPP was applied. During cuff occlusion and Combination conditions, venous occlusion pressures were applied with large adult blood pressure cuffs secured around the subjects upper thigh. The cycle ergometer was adjusted for each subject so that a knee angle at maximal leg extension was consistent for all tests. Subjects were instructed to keep their non-instrumented arm relaxed at their side and the instrumented arm relaxed on an arm tray set at heart level.

The cycle ergometer was interfaced with a personal computer that was pre-programmed to begin load at 13 W for an initial three minute warm-up stage, increase to 20 W for stage two and increase by 20 W each minute until the subject achieved volitional fatigue. Subjects were requested to maintain a pedal cadence of 60 rpm for the duration of the test verifyable by visual feedback from a computer monitor.

Measurements: Study 1 During each exercise test, heart rate (HR) was monitored by a standard lead II electrocardiogram. Arterial blood pressure (ABP) was monitored in

six subjects by a Teflon catheter (Angiocath 20GA) inserted in the right radial artery. In four subjects, ABP was measured by a finger cuff using an optico-mechanical photoplethysmographic method (Finapres, Ohmeda). Previously, we have (20, 25) demonstrated validity correlations (0.93 to 0.99) with no significant difference in the intercept value from zero, between systolic, mean, and diastolic blood pressure between radial arterial lines and the indirect Finapres during progressive exercise to fatigue. Central venous pressure (CVP) was monitored by a double lumen catheter (Cook Critical Care) positioned via each subject's median antecubital vein into the superior vena cava at the level between the 3rd-4th intercostal space. Placement was confirmed under fluoroscopic observation (BV22, Philips, Eindhoven, The Netherlands). Both CVP and ABP catheters were connected to a sterile disposable pressure transducer (Cobe, Lake Wood, CO) interfaced with a pressure monitor (model Hewlett-Packard 78205D/7803B, or Tektronix 414). The zero reference pressure was set at heart level for both CVP and ABP (direct and indirect) measures.

Changes in intramuscular pressure (ΔIMP) were monitored by insertion of an intramuscular catheter into the *rectus femoris muscle* between the iliac crest and the medial condyle of the tibia approximately 2/3 distal to the iliac crest. Change in intramuscular pressure was monitored with a micro-tip pressure transducer (model PC-330A, Millar, Houston, TX.). During each experiment the HR, CVP, ΔIMP and ABP, (i.e., mean (MAP), systolic (SBP) and diastolic (DBP) blood pressures), were acquired using a beat-to-beat customized software data acquisition system interfaced with a

personnel computer (Gateway 2000). In addition, ratings of perceived exertion (RPE) were obtained for both whole body (RPE_{Body}) and exercising legs (RPE_{Legs}) during warmup, at 20W and at each additional 40W using a Borg scale (3). Electrodes were placed on the *vastus medialis muscle* and the *vastus lateralis muscle* for the indirect monitoring of electromyographic activity (EMG). Thirty second averages of the integrated signal during each workrate, including rest, were transmitted to a monitoring system (Mespec 4001 EMG system, Kuopio, Finland).

The subjects respired through a mouthpiece attached to a low-resistance turbine volume transducer (Sensor Medics, VMM Series) for measurement of breath volumes while respiratory gases were continuously sampled from the mouthpiece for analysis of fractional concentrations of O_2, CO_2, and N_2 by mass spectrometry to determine oxygen uptake (Perkin-Elmer MGA1100B). The mass spectrometer was calibrated before each test using known high-precision standard gases. Device input signals underwent analog-to-digital conversion and computer analysis (Dell Optiplex GXi) for on-line, breath-by-breath determinations. A customized software package was employed to correct for equipment delay and response times. Standardized calculations of metabolic data were corrected for ambient conditions and measurements were averaged for each workload. In addition, cardiac output (Q_c) was determined by using the acetylene rebreathe technique (29). Cardiac outputs were determined at rest, warmup, 40 W and each additional 60W throughout the protocol until maximum. Stroke volume (SV) was calculated as Q_c/HR and total peripheral resistance was calculated as MAP/Q_c.

Study 2 This study consisted of repeating the protocol used in study 1 with six different subjects using the previously described measurements of HR, ABP (direct arterial catheter in 4 subjects and indirect in 2 subjects) and VO_2. In this protocol venous blood samples were obtained via a 20 gauge angiocatheter inserted in the median antecubital vein of the right arm using sampling techniques described previously (31). In addition, an eight inch femoral venous catheter (Arrow 16 gauge) was inserted into the femoral vein and passed slowly retrograde from the area below the inguinal canal to a measured distance that insured the tip of the catheter was below the venous occlusion cuff. This allowed for blood sampling below the occlusion cuff in the active skeletal muscle. Triplicate samples obtained every 40 watts of exercise from both venous catheters were analyzed for blood lactate concentrations (average values reported) using an enzymatic technique (Radiometer, Copenhagen, Denmark). Study 2 did not contain measurements of CVP, ΔIMP, Q_c and EMG.

Statistical analysis: A two-way analysis of variance (ANOVA) with repeated measures across the main effects of the four different conditions and work rate was employed to determine significant differences during incremental work rate exercise. The absolute work rates were used for the calculation of group means for each condition. Student-Newman-Keuls *post-hoc* pairwise comparisons were used to establish significant group mean differences. Data are presented as mean values with standard errors (mean ± SE). The alpha level was set at $P < 0.05$. All analyses were conducted using Statistical Analysis Systems (SAS Institute Inc., Cary, NC.) and Sigma Stat (Jandell Corp.).

RESULTS

During incremental exercise, VO_{2peak} and peak work rate were significantly decreased from control exercise during each experimental exercise condition: Cuff occlusion, LBPP and Combination, see Table 2. Tests were typically terminated when the subject could no longer maintain pedal cadence or requested that the session end. Most of the subjects reported that leg fatigue was the primary reason for the cessation of exercise rather than cardiorespiratory limitations. This was reflected by significant elevations at all work rates in the ratings of perceived exertion of the legs (RPE_{Legs}) in each condition from control until 160 watts (RPE_{Legs} data not shown).

There were no significant alterations in HR, EMG, VO_2 and RPE_{Body} across the four exercise conditions at all work rates including rest (Figure 2). The application of Cuff occlusion, LBPP and Combination conditions did not significantly alter Qc, SV and TPR from control at rest nor during any work rates (Figure 3) except for TPR at 13 watts during Combination. In addition, the data presented in Figure 3 illustrate that CVP was significantly elevated from control and Cuff occlusion with the application of LBPP and during Combination conditions with exercise. Central venous pressure during the LBPP condition became significantly increased from the Combination condition after 60 W. This occurred because CVP during the Combination condition began to decrease after 20 W and approached the CVP measured during Cuff occlusion and control conditions.

Mean arterial pressure and DBP were significantly elevated from control with the application of both LBPP and the Combination conditions (Figure 4). These elevations were initiated at rest and were preserved throughout the incremental exercise protocol. Systolic blood pressure was significantly elevated from control at 40, 60, 80 and 100 W during both LBPP and Combination (Figure 4). Cuff occlusion did not produce significant elevations in MAP, SBP and DBP from control. Figure 5 contains one individuals representative MAP responses to the four exercise conditions from the initiation of exercise to maximum. The slope of representative beat-by-beat measurements of MAP exhibited linear increases with no alterations until maximal exercise for all exercise conditions. Changes in intramuscular pressures (ΔIMP) were significantly elevated from control and Cuff occlusion at rest and throughout exercise during both LBPP and the Combination condition suggesting a mechanical stimulus was activated (Figure 4). There was no difference in ΔIMP between control and the Cuff occlusion conditions.

In study 2, HR, SBP, DBP, MAP and VO_2 demonstrated similar responses as in study 1(data not presented). Lactate concentration measured from the venous blood draining active skeletal muscle was significantly elevated from control at 120, 160 and 200 W during Cuff occlusion, LBPP and the Combination condition (Figure 6). However, lactate conentration was not significantly different between Cuff occlusion, LBPP and the combination condition. Peripherally measured lactate concentration (estimating total body lactate concentration) was not significantly altered from control by any of the conditions (Figure 6).

DISCUSSION

Previous work has demonstrated an augmented blood pressure response with the application of LBPP of 45 Torr (4, 22, 31). However, these investigations disagreed about whether this augmented blood pressure response was primarily due to the mechanical affects of externally applied pressure (mechanoreflex) or to the inhibition of venous outflow from the legs trapping metabolites (metaboreflex). We confirmed the augmented blood pressure response with the application of LBPP of 45 Torr. The major new finding from this investigation was that the augmented blood pressure response did not occur when metabolites were trapped in active muscle with the application of thigh cuff occlusion alone. The responses suggest that activation of pressure sensitive mechanoreceptors were the dominant exercise pressor reflex mediators of blood pressure during exercise.

The cardiovascular responses to exercise have been demonstrated to be mediated in part by signals from central command (5-7, 9, 23). Consistent with previous studies (4, 31), we demonstrated reductions in peak work rate and VO_{2peak} from control with the application of three conditions of Cuff occlusion, LBPP and Combination (Table 2). This decrease in work performance could be attributed to fatigue which would increase demand leading to recruitment of additional muscle fibers through the activation of central command. Historically, certain variables (RPE_{Body}, HR, EMG, VO_2) have been used as indices of central command (6, 8, 12, 14, 23). We did not demonstrate any significant

differences in HR, EMG, VO_2, RPE_{Body}, Qc, SV or TPR at the same absolute work rates (Figures 2 and 3) between control and the application of Cuff occlusion, LBPP or the Combination conditions. This would suggest that central command was not altered during each exercise condition at the same absolute work rates. In addition, subjects did not report any pain during the exercise bouts suggesting that there was no enhancement of nocioreceptor activation. Therefore, reflex input emanating from active skeletal muscle was isolated by working subjects at the same absolute workload at the same HR, EMG, VO_2 and RPE_{Body}. We reasoned the increase in blood pressure would be primarily due to the reflex stimulus from the active skeletal muscle with minimal influence from central command resulting in sympathetically mediated increase in vascular resistance (30).

Alam and Smirk (1) and Rowell et al. (21) have reported that the use of total circulatory occlusion, immediately prior to the termination of maximal exercise, trapped metabolites in active muscle, resulting in a sustained increases in MAP. They attributed this increase in MAP to the activation of muscle metaboreceptors. Sheriff et al. (24) and Wyss et al. (33) induced large decreases in hindlimb blood flow in dogs by terminal aortic occlusion. They demonstrated significant increases in aortic and femoral pressures that were due to decreased perfusion and presumably activation of the muscle metaboreflex. However, Wyss et al. (33) suggested signals other than feedback from muscle must be involved in the regulation of the cardiovascular system during exercise since they could only induce responses at moderate-to-high work rates with restricted muscle perfusion. Sheriff et al. (24) have suggested that these signals arise from either central command or

the skeletal muscle mechanoreflex. It appears that the use of terminal aortic ligation and total circulatory occlusion are more representative of a pathological state than a physiological one since the blood pressure responses only occurred when oxygen delivery was reduced below some critical point (ischemia).

Since total circulatory occlusion with thigh cuffs would hinder a subject's ability to exercise, in the present investigation we used thigh cuff occlusion of only 90 Torr in order to impede venous outflow from the legs during exercise trapping metabolites. This Cuff occlusion technique allowed us to trap metabolites in the working skeletal muscle without the confounding mechanical affects of external pressure with LBPP. Previously, Stegall (28) has determined that during forceful rhythmic contractions, calf muscles were capable of translocating blood toward the central circulation with a driving force of 90 Torr. Furthermore, Oelberg et al. (16) reported that Cuff occlusion of 45 Torr was capable of trapping a sufficient amount of metabolites to significantly reduce pH by approximately 0.2 in the legs at moderate workloads. Blood samples drawn from a venous catheter threaded retrograde into the femoral vein below the thigh cuff, found that lactate concentration measured from active skeletal muscle was significantly elevated from control at 120, 160 and 200 watts during Cuff occlusion, LBPP and Combination conditions (Figure 6). However, lactate concentration was not significantly different between Cuff occlusion, LBPP and the combination condition. Peripherally measured lactate concentration (estimating total body lactate) was not significantly altered from control by any of the conditions (Figure 6). Thus, Cuff occlusion, LBPP and the

Combination condition appeared to trap metabolites equivalently. This finding should not suggest that lactate was the primary stimulus for metaboreceptors or that a mismatch in blood supply and demand was necessary to stimulate metaboreceptors. However, this provides evidence that thigh cuff occlusion of + 90 Torr significantly hinders venous outflow.

Lower body positive pressure was also known to trap metabolites at moderate workloads. Rowell et al. (22) demonstrated that LBPP of 45 Torr was capable of trapping a sufficient amount of metabolites to reduce pH by approximately 0.1 in the legs at moderate workloads. Thus, both Rowell et al. (22) and Eiken and Bjurstedt (4) attributed LBPP-induced increases in blood pressure to metaboreflex activation. This decrease in pH with LBPP was similar to the decrease in pH of 0.2 previously reported by Oelberg using cuff occlusion of + 45 Torr (16). However, LBPP also increased intramuscular pressure (Figure 4) and acts as a mechanical stimulus. Given that LBPP and Cuff occlusion used in this investigation decrease pH to a similar degree but only LBPP increases intramuscular pressure, we reasoned that any differences in pressure responses were due to the mechanical stimulus induced by LBPP.

In addition, Nobrega et al. (15) have demonstrated that thigh cuff occlusion of + 100 Torr was sufficient to significantly decrease left-ventricular volumes (end-diastolic dimensions) at the beginning of exercise. The data presented in Figure 3 indicated that CVP during Cuff occlusion exhibited a trend to decrease from control at the later stages of exercise. In addition, both LBPP and the Combination condition induced significant

increases in CVP at the initiation of exercise. However, CVP during LBPP remained elevated while CVP during the Combination condition slowly returned towards control values. These trends for decreases in CVP during Cuff occlusion alone and the Combination condition were probably a result of thigh cuff occlusion restricting venous outflow from the legs thereby decreasing venous return to the heart. This further substantiated that Cuff occlusion of + 90 Torr was capable of trapping metabolites stimulating metaboreceptors without presenting an additional mechanical stimulus.

Using this Cuff occlusion technique, we were unable to induce any significant increases in blood pressure with metabolite trapping from rest to maximum workloads. This supports the contention of Williamson et al. (31) that the metaboreflex is not tonically active in the regulation of blood pressure. In addition, Williamson et al. (31) reported that during dynamic exercise with the application of LBPP additional increases in blood pressure occur, above LBPP-induced elevations at the later stages of exercise. They concluded that the additional break in blood pressure occurred when a sufficient amount of metabolites were produced and trapped in the muscle to activate the muscle metaboreflex. Therefore, we attempted to analyze beat-to-beat blood pressure responses to maximum in each individual in order to determine if any additional increases in blood pressure resulting from metaboreflex activation were present. However, we were unable to demonstrate any non-linear changes in the blood pressure response in any condition up to maximal exercise (Figure 5). Thus, we question if the metaboreflex was active during exercise in the regulation of blood pressure. However, it was possible that due to the

redundant or the polymorphic nature of the metabo- and mechano-receptors that sufficient activation of mechanoreceptors throughout exercise may have masked or attenuated metaboreceptor activation. In addition, we have recently demonstrated that intramuscular metaboreceptors are a major regulator of ventilation during dynamic exercise to maximum (26). Therefore, it appeared that the metaboreflex was active during exercise but may only be involved in the regulation of cardiovascular responses when: i) the mechanoreflex was abolished (post-exercise occlusion) and the metaboreflex was activated through a redundant mechanism (14); or ii) there exists some crucial decrease in flow (25) such as in ischemia induced by claudication.

Therefore, we concluded that the increases in blood pressure observed at rest and during exercise were due to the activation of a muscle pressure sensitive mechanoreflex. The data presented in Figure 4 demonstrates that LBPP of 45 Torr resulted in an immediate increase in intramuscular pressure to the same degree at rest as throughout exercise. These data suggest that LBPP resulted in an immediate activation of the muscle mechanoreflex. Therefore the immediate increase in blood pressure that occurred with the application of LBPP at rest that remained throughout the duration of exercise suggested that the mechanoreflex was tonically active. In addition, LBPP induced changes in blood pressure at rest and the lower workloads of exercise were due to the mechanoreflex, since insufficient metabolites were being produced to activate a metabolically sensitive reflex. Therefore we propose that during progressive workload exercise without the addition of

LBPP, the progressive rise in MAP was due to mechanoreceptor activation with contributions from central command and arterial baroreceptor resetting (18, 19).

A limitation in this study was that the increase in MAP demonstrated during the LBPP and Combination conditions was not supported by significant differences in either Qc or TPR. Thus, we used previously described techniques (22, 31) to determine the relative contributions of these variables to the increase in MAP. These calculations demonstrated that the increase in MAP during the LBPP and Combination conditions was mainly derived from changes in TPR with minimal influence from Qc (Table 3). We suggest that the discrepancy may be due to the mathematical calculation of TPR resulting in large variations which make it difficult to demonstrate significant differences. In contrast, Qc was a directly measured value and had less variation. Therefore, the increases in MAP demonstrated during LBPP and Combination conditions were a result of mechanoreflex stimulation in the active skeletal muscle and the resultant sympathetically mediated increase in TPR.

In contrast to our data, Eiken and Bjurstedt (4) demonstrated increases in VO_2,Qc and HR with the application of LBPP of 50 Torr and Rowell et al. (22, 31) reported increases in HR and Qc indicative of central command involvement. However, these data were collected on subjects in the supine position rather than the semi-recumbent position. This may have allowed the activation of different muscle groups (utilizing additional oxygen) and maximized the fluid translocation that occurs with LBPP (possibly inducing a Bainbridge-type reflex). Such methodological differences could account for the disparity

in results reported. Body position has previously been determined to be an important influence in the cardiovascular responses at rest and during exercise (2).

In summary, blood pressure was not significantly increased when metabolites were trapped in the active skeletal muscle by Cuff occlusion. However, significant increases in blood pressure at rest and throughout exercise occurred with the application of LBPP and the Combination condition. Cuff occlusion and LBPP appeared to trap metabolites similarly suggesting that any differences in the blood pressure response between the two conditions was primarily due to the mechanical effects of LBPP. Furthermore, these changes in blood pressure do not appear to be influenced by central command since there was no alteration in HR, EMG, VO2 and RPE_{Body} with all exercise conditions employed at the same absolute work rates. In conclusion, the metaboreflexes do not appear to be involved in the regulation of blood pressure during dynamic exercise at low-to-moderate workloads and have recently been demonstrated to be primarily an intramuscular ventilatory stimulus (26). Therefore, we suggest that physiologically the mechanoreflex is the primary *exercise pressor* mediator of arterial blood pressure during dynamic exercise.

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TABLE 1. Subject information

	Age (yr)	Height (cm)	Weight (kg)	VO_{2peak} ($ml \cdot min^{-1} \cdot kg^{-1}$)
Study 1 (n=10)	26.5 ± 1.2	173.7 ± 3.1	73.5 ± 4.0	40.3 ± 1.7
Study 2 (n=6)	27.3 ± 2.4	173.7 ± 3.6	73.5 ± 4.8	36.0 ± 1.9

Mean ± standard error; VO_{2peak} = maximal oxygen uptake; n = subject number

TABLE 2. Peak oxygen uptake and peak work rates achieved during each exercise condition.

	Control	Cuff occlusion (+90 Torr)	LBPP (+45 Torr)	Combination
VO_{2peak} ($L \cdot min^{-1}$)	2.99 ± 0.32	2.47 ± 0.67*	2.38 ± 0.63*	2.24 ± 0.79*
$Workload_{peak}$ ($Watts \cdot min^{-1}$)	266 ± 24	212 ± 24*	208 ± 16*	187 ± 22*

Mean ± SEM; * Indicates significance from control

TABLE 3. Contributions of changes in cardiac output and total peripheral resistance to increases in mean arterial pressure due to Cuff occlusion, LBPP and the Combination condition.

	Cuff Occlusion (+90 Torr)		LBPP (+45 Torr)		Combination	
Watt·min^{-1}	% Q_c	% TPR	% Q_c	% TPR	% Q_c	% TPR
0	21.9 ± 12.0	68.1 ± 14.0	47.3 ± 14.5	52.8 ± 14.5	46.5 ± 14.9	53.5 ± 14.9
13	31.1 ± 14.9	68.9 ± 14.9	55.4 ± 17.5	50.1 ± 16.7	16.2 ± 11.3	83.8 ± 11.3
40	35.8 ± 14.3	64.2 ± 14.3	29.8 ± 14.8	69.1 ± 14.6	33.8 ± 14.0	66.2 ± 14.0
100	48.6 ± 15.9	51.4 ± 15.9	26.4 ± 16.3	73.3 ± 16.3	23.8 ± 13.0	76.2 ± 13.0
160	33.3 ± 20.7	66.7 ± 20.7	38.6 ± 19.6	61.4 ± 19.6	22.2 ± 13.8	72.5 ± 19.0
Average	34.1	63.9	39.5	60.5	28.5	71.5

Mean ± SEM; 0 watts·min^{-1} = Rest with conditions applied; % Q_c = percent increase in MAP due to change in cardiac output; % TPR = percent increase in MAP due to change in total peripheral resistance.

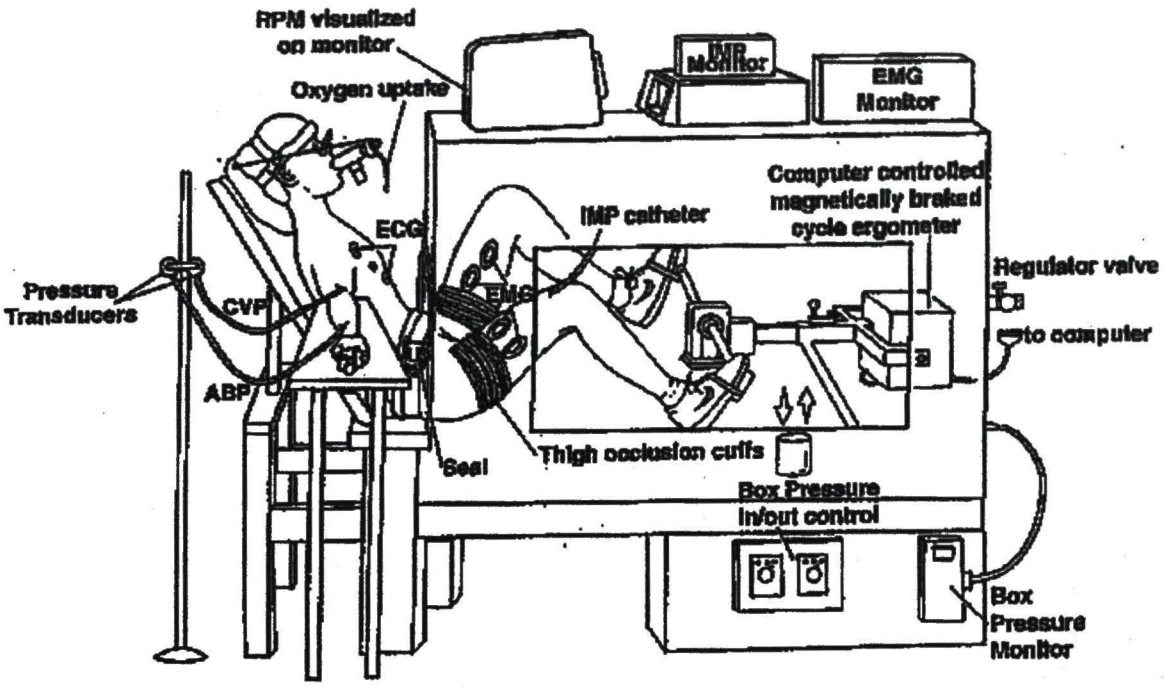

Figure 1 - The experimental set-up included a computer-controlled cycle ergometer housed inside a lower-body positive pressure (LBPP) chamber. LBPP was manually controlled with variable autotransformers and the pressure inside the chamber was measured by a digital pressure monitor. Catheters placed in the radial artery, antecubital vein and *rectus femoris* were connected to pressure transducers to measure arterial (ABP), central venous (CVP) and intramuscular (IMP) pressures, respectively. Breath-by-breath O_2 uptake was measured with a turbine flowmeter and mass spectrometer. Electromyographic (EMG) measurements of quadriceps activity were obtained from surface EMG electrodes. Not pictured is the Finapres that was used in four subjects, the cardiac output rebreathe bag or the shoulder harness used to maintain subject placement when LBPP was applied.

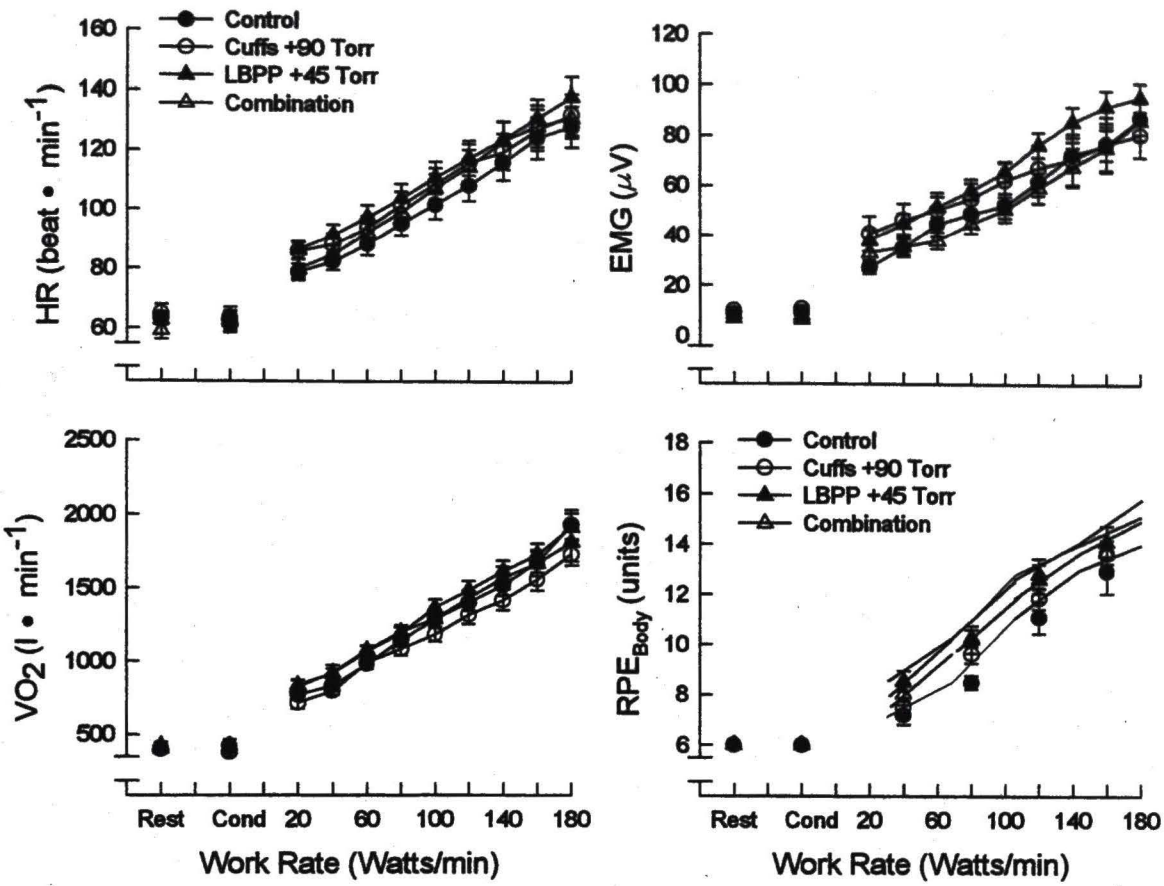

Figure 2 - Heart rate (HR), oxygen uptake (VO_2), electromyographic activity (EMG) and perceived exertion of the body (RPE_{body}) responses to incremental work rate exercise during control and with the application of thigh cuff occlusion (+ 90 Torr), LBPP (45 Torr) and a combination of cuff occlusion/LBPP. Mean (± SEM) are presented at rest and during exercise. There were no significant effects of the four conditions on any of these variables. Cond. = rest with conditions applied.

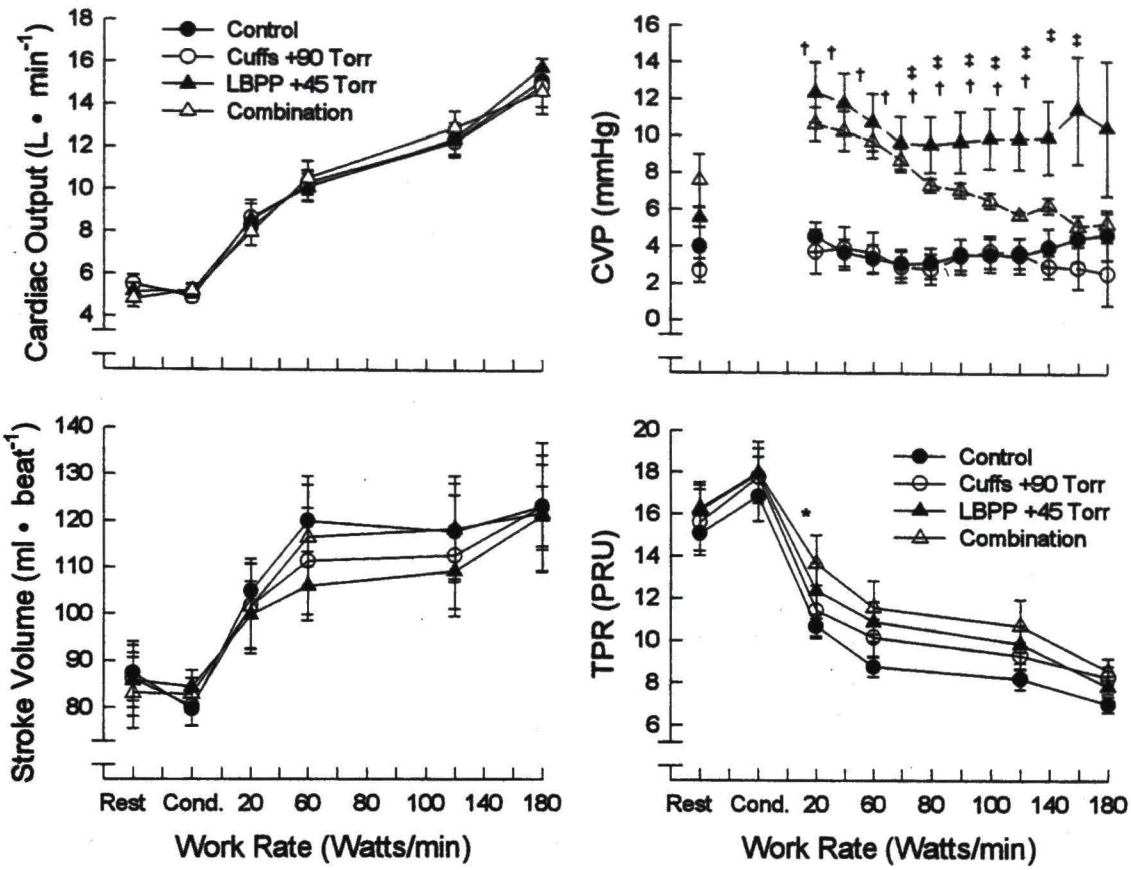

Figure 3 - Cardiac output (Q_c), stroke volume (SV), central venous pressure (CVP) and total peripheral resistance (TPR) to incremental exercise during control, Cuff occlusion, LBPP and Combination (Mean ± SEM). There were no significant effects by these conditions on Q_c, SV and TPR. Both LBPP and Combination conditions elicited significant increases from control and Cuff occlusion during exercise. * Significantly different from control, † Indicates LBPP and Combination condition significantly different then Control and Cuff occlusion, ‡ significantly different from Combination, Cuff occlusion and control, $P < 0.05$. Cond. = rest with conditions applied.

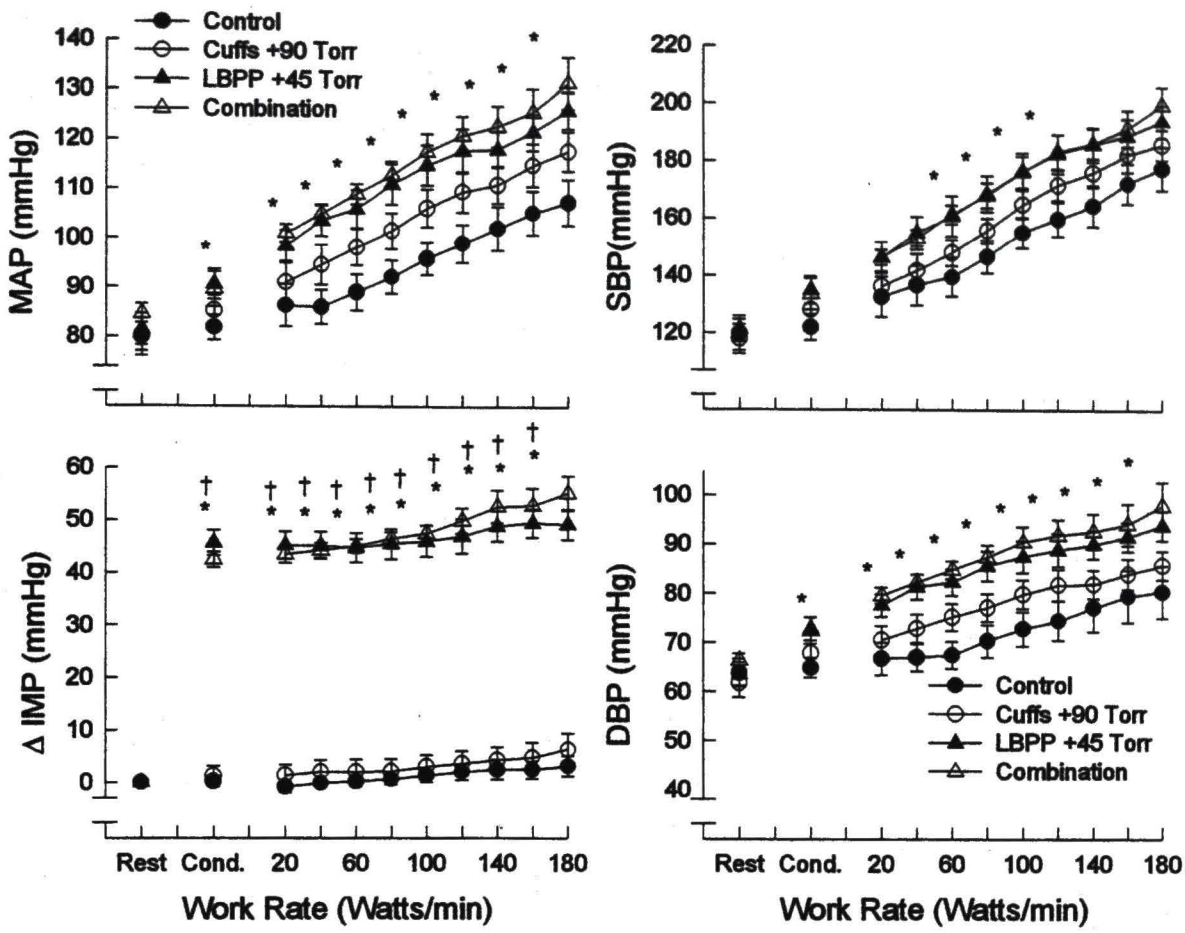

Figure 4 - Mean arterial (MAP), systolic (SBP), diastolic (DBP) blood pressure and change in intramuscular pressure (ΔIMP) to incremental exercise during control, Cuff occlusion, LBPP and the Combination condition (Mean ± SEM). Both LBPP and the Combination condition elicited significant increases from control for all these variables. In addition, ΔIMP during both LBPP and the Combination condition were also significantly elevated from the Cuff occlusion condition. * Indicates both LBPP and Combination condition significantly different then Control, † Indicates LBPP and Combination

condition significantly different then Control and Cuff occlusion, $P < 0.05$. Cond. = rest with conditions applied.

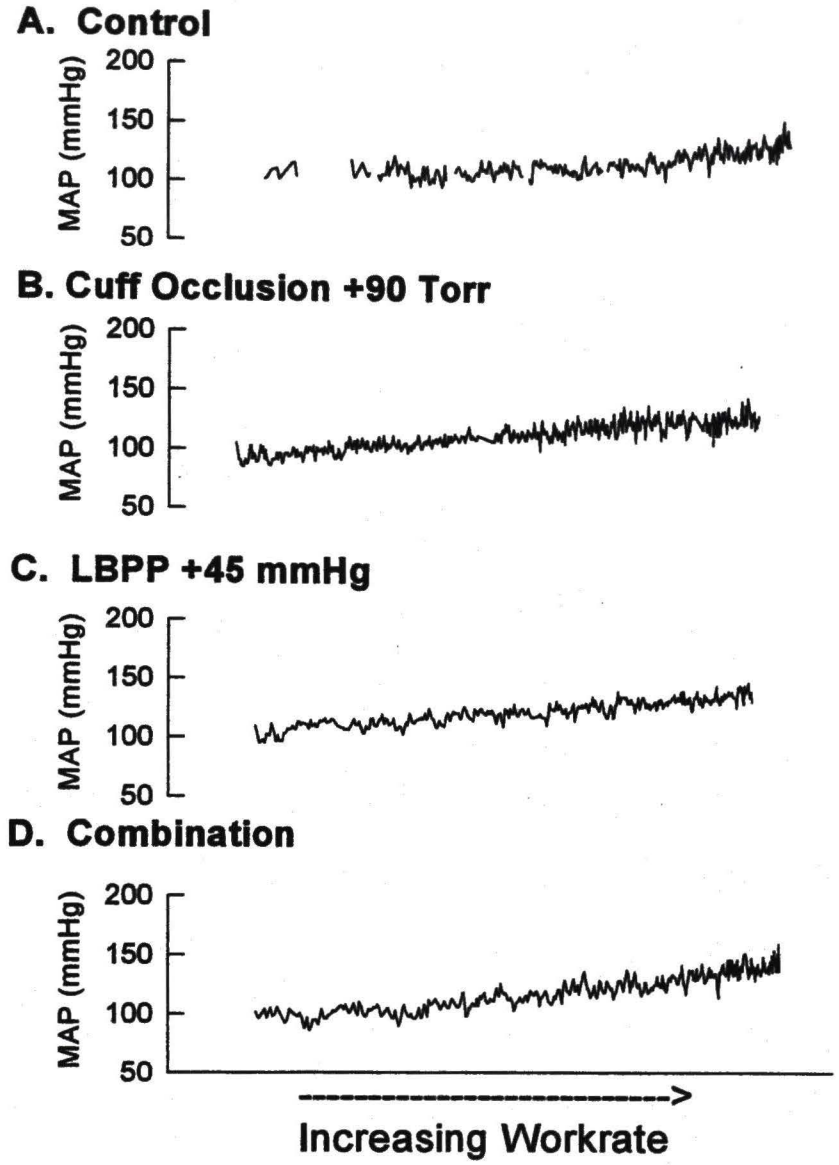

Figure 5 - One individual's representative mean arterial pressure (MAP) responses from the initiation of exercise to maximum with the application of Cuff Occlusion, LBPP and Combination conditions. The slope of beat-by-beat measurements of MAP exhibited linear increases with no alterations until maximal exercise for all exercise conditions.

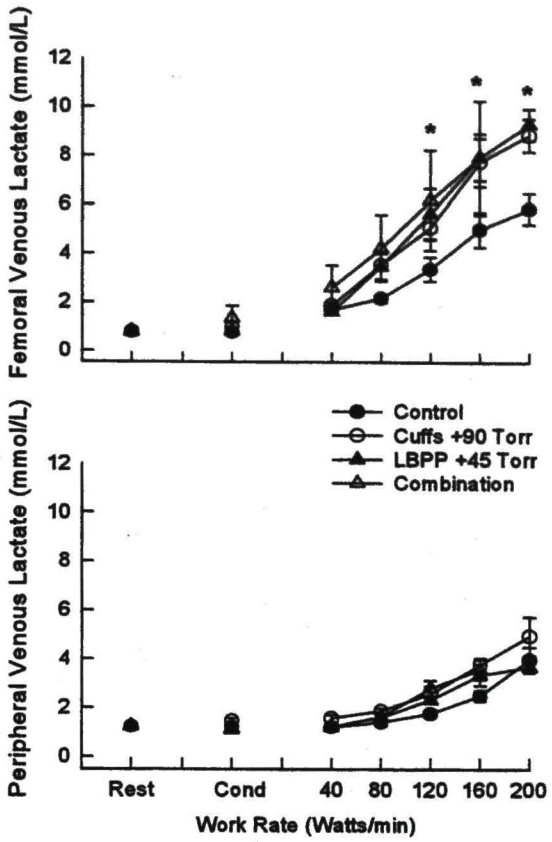

Figure 6 - Active skeletal muscle and peripheral lactate concentration responses to incremental work rate exercise during control and with the application of thigh cuff occlusion (+ 90 Torr), LBPP (45 Torr) and a combination of cuff occlusion/LBPP. Mean (± SEM) are presented at rest and during exercise. Lactate concentration measured from the active skeletal muscle was significantly elevated from control at 120, 160 and 200 W during Cuff occlusion, LBPP and the Combination condition. However, lactate concentration was not significantly different between Cuff occlusion, LBPP and the combination condition. Peripherally measured lactate concentration (estimating total body lactate concentration) was not significantly altered from control by any of the conditions. Cond. = rest with conditions applied. * Cuff occlusion, LBPP and Combination significantly different from control, $P < 0.05$.

PREFACE TO CHAPTER III

In 1990, Rowell and O'Leary presented a hypothetical scheme suggesting that both central command and the muscle chemoreflex in the resetting of the arterial baroreflex. The results of the previous investigation illustrate that under normal conditions the mechanoreflex is tonically active and is the primary exercise pressor mediator of arterial blood pressure during exercise. This information might predict that the muscle mechanoreflex is more involved in the resetting of the arterial baroreflex than the muscle chemoreflex. Therefore, Rowell and O'Leary's model can be adapted to suggest that both central command and the muscle mechanoreflex aspect of the exercise pressor reflex are involved in the resetting of the arterial baroreflex under normal conditions (Figure 1). However, it remains to be determined the exact roles of the muscle mechanoreflex and central command in arterial baroreflex resetting. Therefore, the second investigation was designed to demonstrate the effect of increased central command using partial neuromuscular blockade in the resetting of the carotid baroreflex during dynamic and static exercise.

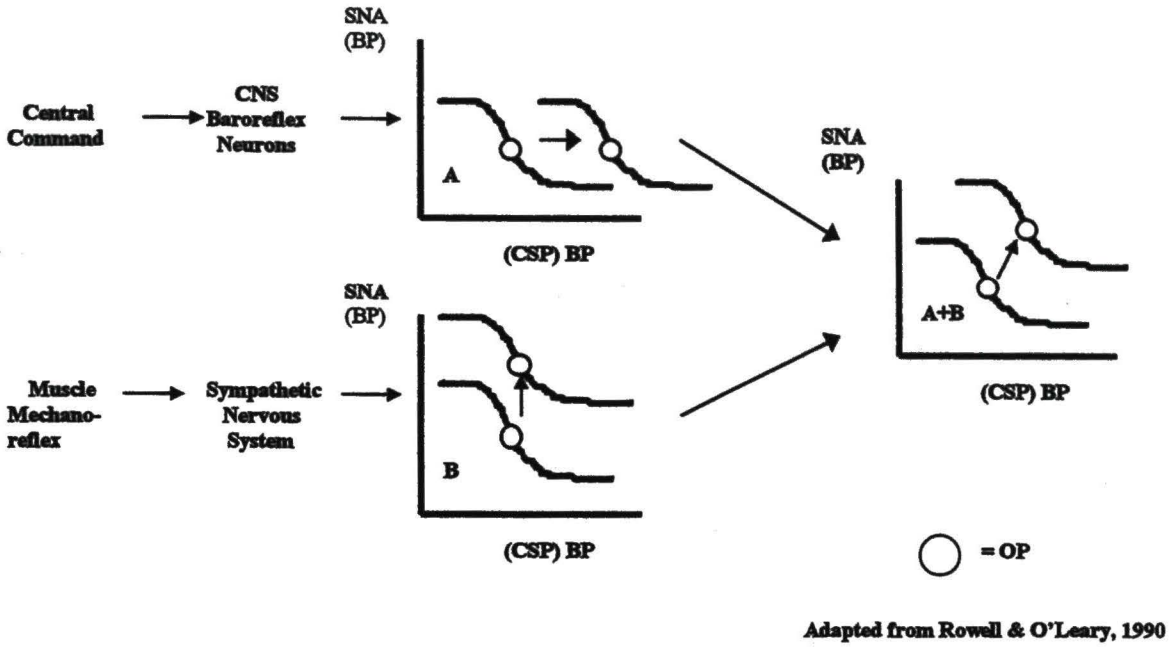

Figure 1- Updated model of arterial baroreflex resetting

CHAPTER III

EFFECTS OF PARTIAL NEUROMUSCULAR BLOCKADE ON CAROTID BAROREFLEX FUNCTION DURING EXERCISE IN HUMANS

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ABSTRACT

This investigation was designed to determine the contribution of central command to the resetting of the carotid baroreflex during static and dynamic exercise in humans. Thirteen subjects performed three and a half minutes of static one-legged exercise (20% maximal voluntary contraction) and seven minutes dynamic cycling (20% maximal oxygen uptake) under two conditions: control (no intervention) and partial neuromuscular blockade (to increase central command influence) using Norcuron (curare). Carotid baroreflex function (CBR) was determined at rest and during steady-state exercise using a rapid neck pressure/neck suction technique. Whole body Norcuron was repeatedly administered to effectively reduce hand-grip strength by approximately 50% of control. Partial neuromuscular blockade increased heart rate, mean arterial pressure, perceived exertion, lactate concentration and norepinephrine concentration during both static and dynamic exercise when compared to control ($P < 0.05$). No effect was seen at rest. Carotid baroreflex resetting was significantly augmented from control static and dynamic exercise by partial neuromuscular blockade without alterations in gain. In addition, the operating point of the reflex was significantly relocated upwards away from the centering point (i.e. closer to threshold) during exercise by partial neuromuscular blockade. These findings suggest that central command actively resets the CBR during dynamic and static exercise.

INTRODUCTION

Concomitant increases in HR and MAP in response to physical activity have lead investigators to conclude that the arterial baroreflex is either attenuated or not necessary during exercise (3, 21, 23). However, Melcher and Donald determined that during exercise the carotid baroreflex maintained its sensitivity (24). In addition, they suggested that the operating point of the baroreflex was relocated upward on the response arm of the baroreflex function curve in direct relation to the intensity of exercise. The relocation of the arterial baroreflex would enable a coincident increase in both HR and MAP. Subsequently, DiCarlo and Bishop demonstrated that the arterial baroreflex immediately resets at the start of exercise (5). Recently, Potts et al. (34) have provided evidence that baroreflex function was maintained during exercise and was relocated upward on the response arm and rightward to higher operating pressures (classical resetting). Furthermore, this study described a relocation of the operating point away from the centering point and closer to the threshold pressure region of the baroreflex function curve. These data suggested that baroreflex function was reset to operate around the prevailing exercise-induced blood pressure. In addition, the relocation of the operating point allowed the baroreflex to respond to a wider range of carotid sinus hypertension. It has been confirmed that the resetting of the carotid baroreflex occurs in direct relation to the intensity of exercise (rest to maximum exercise) (26, 29). Furthermore that the resetting of the CBR occurs during static exercise (7).

In 1990, Rowell and O'Leary (37) presented a hypothetical scheme suggesting that two neural mechanisms were primarily involved in the resetting of the carotid baroreflex during exercise. They proposed that a feed-forward neural mechanism (central command), which activates cardiovascular and motor responses in parallel, was responsible for relocating the operating point of the carotid baroreflex to higher arterial blood pressure (rightward) during exercise. This would allow for the reflex to remain operational despite the increased blood pressure that occurs with exercise. In addition, they proposed that a negative feedback mechanism originating in the exercising muscle (exercise pressor reflex) was also involved in the resetting of the baroreflex. It was suggested that the exercise pressor reflex would activate sympathetic neural activity resulting in a vertical relocation of the operating point of the arterial baroreflex. Together, these two neural mechanisms would result in the rightward and upward resetting of the baroreflex during exercise.

Previously, Goodwin et al. (11) have provided evidence that cardiorespiratory control was altered in direct relation to changes in central command during exercise. Furthermore, the use of partial neuromuscular blockade to activate central command has demonstrated increases in HR, arterial blood pressure (31) and muscle sympathetic nerve activity (46). Norton et al. (27) demonstrated that during prolonged steady-state exercise, carotid baroreflex resetting was directly related to development of muscle fatigue. They hypothesized that since central command was known to influence somatomotor responses, their findings provided evidence of its possible involvement in the resetting of the carotid

baroreflex during exercise. However, the influence of central command on the resetting of the carotid baroreflex has yet to be directly investigated.

In the present study, we attempted to increase central command influence during steady-state dynamic and static exercise with partial neuromuscular blockade without altering the magnitude of exercise pressor reflex input. The investigation was designed to determine the role of central command in the resetting of the carotid baroreflex during static and dynamic exercise in humans.

METHODS

Subjects: Eleven men and two women with a mean age of 27.1± 1.1 (± SE), height of 180.9 ± 1.9 cm, weight of 74.4 ± 1.7 kg and maximum oxygen uptake of 46.9 ± 1.7 ml $O_2 \bullet kg^{-1} \bullet min^{-1}$, volunteered to participate in this investigation. Prior to testing, each subject was informed of all risks and aspects of the study and signed an informed consent approved by the Fredricksberg Municipal Ethical Committee of Copenhagen, Denmark. All subjects were non-smokers, were not taking medication and were asymptomatic for cardiovascular and respiratory disease. The subjects were asked to abstain from alcoholic beverages and exercise for 24 hours and caffeinated beverages for 12 hours prior to any scheduled testing session.

Exercise testing: Each subject performed a preliminary incremental work rate (0.5 kg/min) exercise test on a cycle ergometer (modified Krogh) to volitional fatigue for the determination of peak oxygen uptake (VO_{2peak}). Since none of the subjects achieved a

plateau of VO_2 with increasing work rate, the maximum oxygen uptake (VO_{2max}) achieved was presented as VO_{2peak}. After the maximal exercise test, the subject was familiarized with the protocols for baroreflex testing and static exercise.

On a separate day following the initial exercise test, the subjects performed static and dynamic exercise with and without the administration of whole body curare (Norcuron). For both protocols the subjects were seated in a semi-recumbent position on a hospital bed which supported the subjects entire upper body. The hospital bed was modified to allow the subjects to perform one-legged static knee extension from a 70 ° knee angle and two-legged dynamic cycling. Preceding any exercise, the subjects attempted three static knee extensions to determine maximal voluntary contraction (MVC). Two bouts of control static knee extension at 20% of MVC were performed for 3 1/2 minutes. The static exercise bouts were followed by a 7 minute dynamic exercise protocol at 20% VO_{2peak}. All exercise bouts were separated by a minimum of 30 minutes. After a minimum of 1 hour the static and dynamic exercise bouts were repeated at the same absolute (20% of control MVC and VO_{2peak}) workloads after the administration of whole-body curare. Each exercise bout was preceded by a five minute collection period for resting baseline measurements.

Static knee extension was accomplished by placing a padded strap around the ankle of the subjects dominant leg. Force was recorded by a strain gauge dynamometer (model 540 DNH, Holland). Visual feedback of force was provided to the subject by a monitor in order for the subject to maintain the desired force. However, due to curare's effect on vision, verbal feedback was used to maintain force during the curare condition.

For dynamic exercise, the cycle ergometer was adjusted for each subject so that a knee angle at maximal leg extension was consistent for both tests. Subjects were requested to maintain a pedal cadence of 60 rpm per metronome for the duration of the test. Subjects were instructed to keep their entire upper body relaxed during all testing.

Whole-body curare (Norcuron, 10mg/10 cc) was administered through venous access in the back of the hand. Prior to curare administration, static handgrip MVC was determined in arbitrary units. A bolus dose of curare was injected followed by 10mL of saline. Supplemental doses were administered until handgrip strength (arbitrary units) was reduced to approximately 50% of control. After the desired reduction in strength was achieved, the five minute rest collection period was initiated followed by the exercise bout. The injections were repeated as required in order to maintain the targeted reduction in muscle strength. At all times an Ambu-E resuscitator apparatus, neostigmine and atropine were available.

Measurements: During each test, heart rate (HR) was monitored by a standard lead II electrocardiogram. Arterial blood pressure (ABP) was monitored by a Teflon catheter (20 gauge) placed in the brachial artery of the non-dominant arm. The ABP catheter was connected to a sterile disposable pressure transducer (Baxter, Uden, Holland) interfaced with a pressure monitor (Danico Electronic - Dialogue 2000, Denmark). The zero reference pressure was set at heart level. During each experiment the HR and ABP [i.e. mean (MAP), systolic (SBP) and diastolic (DBP) blood pressures] were acquired using a beat-to-beat customized software data acquisition system interfaced with a personnel computer. In addition, ratings of perceived exertion (RPE) were obtained

during the last 30 seconds of static exercise and at the 4th and 7th minute of dynamic exercise using the 6 to 20 Borg scale (2).

The subjects respired through a mouthpiece attached to a low-resistance turbine volume transducer (Pneumotach, MedGraphics) for measurements of breath volumes while gases were continuously sampled from the mouthpiece for analysis of fractional concentrations of O_2, CO_2 and N_2 to determine oxygen uptake (2001; Medical Graphics Corporation, St. Paul, MN.). The Med-Graphics system was calibrated before each test using known high-precision standard gases. Device input signals underwent analog-to-digital conversion for on-line breath-by-breath determination. Standardized calculations of metabolic data were corrected for ambient conditions.

Samples of arterial blood were obtained at rest and during the last thirty seconds of exercise for determination of plasma catecholamines ($nmol \bullet L^{-1}$) and lactate concentration ($mmol \bullet L^{-1}$). Blood was placed in tubes kept on ice containing reduced glutathione and ethylene glycol-bis (β-aminoethyl ether)-N,N,N',N'-tetraacetic acid and centrifuged at 3000 g for 5 minutes at 3°C. The plasma fraction was stored at -20°C for blinded analysis of norepinephrine (NE) and epinephrine (E). Samples were assayed by a single isotope radioenzymatic method (Knigge, 1990). Remaining syringe blood samples were immediately used for lactate determination (Lac TSI 2300; Yellow Springs Instrument Co., Inc., Ohio).

Carotid baroreflex (CBR) control of HR and MAP was assessed utilizing a neck pressure/neck suction (NP/NS) technique. Pressure stimuli were applied through a

cushioned malleable collar placed around the anterior 2/3 of the neck. The neck collar was modified from a design previously described by Sprenkle et al. (45). Due to the brevity of the exercise protocols, a NP/NS technique that utilized a rapid ramping of pressure was used. Computer controlled pulsatile pressures ranging from +40 to -80 mmHg were generated by a variable pressure source and delivered to the neck collar through large bore two-way solenoid valves (model 8215B, Asco, Florham Park, NJ). Between each pressure pulse the neck chamber pressure was vented to atmospheric pressure. The generated neck collar pressure was measured by a pressure transducer (model DP45, Validyne Engineering, Northridge, CA). The computer software gated the pulses of pressure to occur 50 ms after initiation of the R-wave detected by ECG. The 50 ms delay allowed the artificial pressure/suction to coincide with the arterial pressure wave at the carotid sinus. Each pulse was 500 ms in duration. The NP/NS pulse train was conducted at end-expiratory breath hold to eliminate the confounding effects of respiratory sinus arrhythmia. The total duration of breath hold varied between 10 -12 seconds. Six subjects were unable to maintain the end-expiratory breath hold throughout the entire NP/NS pulse train during dynamic exercise. Therefore only seven subjects were included in the dynamic exercise data. During static exercise, two CBR trains were obtained after the second minute of exercise. Three to four curves were obtained during dynamic exercise after the fourth minute of exercise. A minimum of 45 seconds of recovery time were allotted between rapid pulse trains of NP/NS. Pulse trains of NP/NS were also performed at rest before all exercise bouts.

Data and Statistical Analysis: The dependent variables HR and MAP were used to create either the carotid-cardiac (CSP-HR) or carotid-vasomotor (CSP-MAP) stimulus-response function curves when plotted against the independent variable of estimated carotid sinus pressure (CSP). These curves were individually fit for each subject to a four parameter logistic function described by Kent et al. (15). This function incorporates the following equation:

$$\text{HR or MAP} = A_1 \bullet \{1 + e^{[A_2(\text{CSP}-A_3)]}\}^{-1} + A_4$$

Carotid sinus pressure was calculated by subtracting the chamber pressure from the pre-stimulus MAP. Parameter A_1 was the range of response of the dependent variable (maximum - minimum), A_2 was the gain coefficient, A_3 was the CSP required to elicit equal pressor and depressor responses (centering point) and A_4 was the minimum response of HR or MAP. Individual data were applied to this model by a non-linear least-squares regression that predicts a curve of "best fit" for the data and minimizes the sum of squares error.

Several characteristic parameters are derived from the resulting model including the estimated threshold (CSP_{thr}), saturation (CSP_{sat}) and maximal gain (G_{max}) of the CSP-HR and CSP-MAP reflexes. Baroreceptor CSP_{thr} and CSP_{sat} were described as the minimum and maximum CSPs, respectively, that elicit a reflex change in HR or MAP. The calculation of CSP_{thr} and CSP_{sat} utilized equations described by Chen and Chang (4): $CSP_{thr} = -2.0/ A_2 + A_3$ and $CSP_{sat} = -2.0/ A_2 + A_3$. They determined that these calculations of CSP_{thr} and CSP_{sat} represent the CSP at which MAP or HR was within 5% of their maximal or minimal response. The gains of the CSP-HR and CSP-MAP reflexes

were derived from the first derivative of the Kent logistic function with the maximal gain being defined as the gain value located at the centering point (CP) of the reflex. In addition, the operating point (OP) was defined as the intersection of the pre-stimulus HR or MAP and CSP (i.e resting MAP). Parameters for all subjects within an experimental condition were averaged to provide group mean responses.

A two-way analysis of variance (ANOVA) with repeated measures was employed to determine significant differences at rest and exercise between either static or dynamic exercise with or without curare . Student-Newman-Keuls *post-hoc* pairwise comparisons were used to establish significant group mean differences. In addition, a paired t-test was used for individual comparisons. Data are presented as mean values with standard errors (mean ± SE). The alpha level was set at $P < 0.05$. All analyses were conducted using Sigma Stat (Jandell Corp.)

RESULTS

Selected physiologic responses: Partial neuromuscular blockade with curare (Norcuron) significantly reduced static handgrip strength approximately 50-60% during rest, static and dynamic exercise (Table 1). The subjects reported that after partial neuromuscular blockade increased effort was required to maintain the same absolute workload as control. This was reflected by significantly increased ratings of perceived exertion (RPE) during static and dynamic curare exercise as compared to the control exercise condition (Table 1). In addition, HR and MAP were significantly elevated by curare during static and dynamic exercise (Figures 1 and 2). Heart rate and mean arterial

pressure reached steady-state without additional elevations at the second minute of static exercise and at the fourth minute of dynamic exercise during control and neuromuscular blockade.

Plasma venous norepinephrine and lactate concentrations were significantly increased during static and dynamic exercise with curare from control (Table 1). Heart rate, MAP and norepinephrine were unaffected by curare at rest. However, lactate concentration was significantly elevated from control rest after curare administration prior to static exercise but not prior to dynamic exercise. At the same absolute work rate oxygen uptake and plasma epinephrine concentration were unaltered by curare at rest and throughout exercise (Table 1).

Logistic parameters of carotid baroreflex: The stimulus-response relationships for baroreflex control of HR (CSP-HR) and MAP (CSP-MAP) at rest and during static and dynamic exercise are shown in Figures 3 and 4. The four logistic parameters describing carotid baroreflex control of HR and MAP during static and dynamic exercise are presented in Table 2. The centering point of the reflex (A_3) was progressively relocated from rest during control exercise and was significantly increased from rest and control exercise during partial neuromuscular blockade. The minimal HR and MAP response (A_4) was significantly increased during control exercise and was further augmented by the administration of curare. The range of HR and MAP responses (A_1) and the gain coefficient (A_2) were unaltered by control and curare exercise.

Carotid baroreflex variables during static exercise. The calculated variables describing the CSP-HR and CSP-MAP stimulus-response curves during static exercise are

shown in Tables 3 and 4. The maximal gains of the HR and MAP responses were found to be unaltered from that of rest by control and curare static exercise. Threshold carotid sinus pressure (CSP_{thr}) and CSP_{sat} for CSP-HR and CSP-MAP responses were relocated to higher levels of CSP from rest during control static exercise and were significantly increased from control exercise by partial neuromuscular blockade. It should be noted that the difference between the control exercise and curare exercise condition of CSP_{thr} and CSP_{sat} was only significant using an 'a priori' paired t-test. Operating point (OP) and CP for CSP-HR and CSP-MAP responses were significantly increased from rest by control static exercise and were further significantly augmented by partial neuromuscular blockade. The relationship between OP and CP was not altered by control static exercise, however curare exercise significantly increased the CSP-HR operating point distance from the CSP-HR centering point moving closer to threshold of the reflex (Table 5). The relationship between CSP-MAP operating point and centering point was unaltered by control and curare exercise. Collectively, the relocation upward on the response arm and rightward to higher operating pressures of the CSP-HR and CSP-MAP stimulus-response curves suggested resetting of the CBR during control exercise which was further augmented by partial neuromuscular blockade or an increased central command influence (Figure 3).

Carotid baroreflex variables during dynamic exercise. The calculated variables describing the stimulus-response curve for CSP-HR and CSP-MAP stimulus-response curves during dynamic exercise are shown in Tables 3 and 4. The maximal gains of the HR and MAP responses were unaltered by control and curare dynamic exercise.

Threshold carotid sinus pressure (CSP_{thr}) and CSP_{sat} for CSP-HR and CSP-MAP responses were relocated to higher levels of carotid sinus pressure from rest during control dynamic exercise and were significantly increased from control exercise by partial neuromuscular blockade. Operating point and CP for CSP-HR responses were significantly increased from rest by control dynamic exercise. The CP for HR responses was significantly increased further by partial neuromuscular blockade. In addition, the operating point of CSP-HR was significantly relocated away from the centering point of the reflex and closer to threshold during control exercise, however partial neuromuscular blockade had no additional effect (Table 5). Operating point and centering point for CSP-MAP responses were not altered by control exercise, but were significantly elevated from control exercise by partial neuromuscular blockade. In addition, the relationship between operating point and entering point for MAP was not altered by control dynamic exercise, however curare exercise significantly relocated the operating point away from the centering point closer to the threshold of the reflex when compared to control (Table 5). Collectively, the relocation upward on the response arm and rightward to higher operating pressures of the stimulus-response curves for CSP-HR and CSP-MAP suggest resetting of the CBR during control exercise which was augmented by partial neuromuscular blockade or when central command was increased (Figure 4).

DISCUSSION

Previous work has demonstrated that the carotid baroreflex resets during dynamic and static exercise without alterations in sensitivity or maximal gain (5, 7, 24, 34). In

addition, the carotid baroreflex has been reported to continuously reset in direct relationship to the intensity of exercise (26, 29). Rowell and O'Leary hypothesized that afferent neural signals from the exercise pressor reflex and efferent signals from central command combine to produce carotid baroreflex resetting during exercise (37). The present investigation was designed to selectively increase central command in order to determine its' role in the resetting of the carotid baroreflex during dynamic and static exercise. We confirmed that the carotid baroreflex was classically reset during both static and dynamic exercise. The major new finding from this study was that the carotid baroreflex was further reset upward on the response arm and rightward to higher operating pressures from control exercise when central command was enhanced without alterations in gain. This response suggests that central command actively contributes to the resetting the carotid baroreflex during static and dynamic exercise.

The cardiovascular responses to exercise are mediated in part by central command input (11, 13). Central command is a "feed-forward" controller that when activated has a diffuse outflow of efferent communication from its putative location in the hypothalamic locomotor region. Central command activates the motor cortex and, in parallel fashion, activates the cardiovascular control center within in the lateral reticular nucleus of the medulla. Central command activation elicits motor unit recruitment and adjusts cardiovascular activity in a manner appropriate for the work (exercise) being performed (48). One model that has been used to independently study central command has utilized partial neuromuscular blockade (9, 17, 31, 46, 47). Subjects exercising during partial neuromuscular blockade require increased motor unit recruitment to maintain the same

absolute work rates as control exercise. Therefore, since central command contributes to motor unit recruitment, partial neuromuscular blockade was hypothesized to augment central command (25).

We used whole-body curare (Norcuron) to partially block the neuromuscular junction during exercise in order to increase central command input. Each subjects' handgrip strength was reduced to approximately 40-50% of their control MVC during partial neuromuscular blockade (Table 1). Therefore, subjects required an increase in effort, i.e. central command, in order to maintain the same absolute work rates as during control exercise. This augmentation of central command was reflected by increased ratings of perceived exertion (RPE) from control exercise during partial neuromuscular blockade (Table 1). In addition, complementing previous work (17, 31), HR and MAP responses were augmented when exercise was made difficult during partial neuromuscular blockade (Figures 1 and 2). Interestingly, oxygen uptake appeared to be unaffected by partial neuromuscular blockade. Despite the increased central effort needed to execute the work, the subjects were still performing the same absolute amount of work. In other words, increased central command activated additional motor units, however due to the neuromuscular blockade, the same amount of muscle fibers were required to achieve the same absolute work. Therefore, due to its effects on HR and RPE, it is apparent partial neuromuscular blockade effectively augmented central command without increasing the work of the active muscle, thereby maintaining exercise pressor reflex input constant between conditions.

Victor et al. (46, 47) have provided evidence that central command is involved in the regulation of muscle sympathetic nerve activity (MSNA). They demonstrated only a modest increase in MSNA when subjects attempted a static contraction at 30% MVC. However, intermittent static contractions during neuromuscular blockade resulted in synchronization of MSNA and contractions with workloads less than 25% MVC. Furthermore, during fatiguing exercise, MSNA was directly related to muscle fatigue as indicated by electromyographic activity (41) and to the rating of subjective fatigue sensation (39). Partial neuromuscular blockade during both static and dynamic exercise resulted in significant elevations in plasma norepinephrine concentrations when compared to control exercise. However, plasma epinephrine concentration was unaffected by partial neuromuscular blockade (Table 1). In contrast, previous experiments have demonstrated significant elevations in both norepinephrine and epinephrine concentrations (9, 16, 17, 31). The selective increase in plasma norepinephrine concentration during the experiment may reflect (spillover) release from activated peripheral nerve endings from activation of the sympathetic nervous system. It is tempting, given the findings of Victor et al. (46,47), to speculate this increase in norepinephrine spillover is due to increased sympathetic nervous activity. As such, these data provide evidence that central command's influence on cardiovascular variables may be regulated, in addition to the parasympathetic nervous system, via the sympathetic nervous system.

A unique finding of the present investigation was that partial neuromuscular blockade significantly increased lactate concentration above control exercise during both dynamic and static paradigms (Table 1). It has been suggested that curare selectively

inhibits slow-twitch muscle fibers resulting in a predominance of fast-twitch fibers performing work (9). Activation of primarily fast-twitch muscle fibers would result in an augmentation of glycolytic production of lactate. It was also possible that activation of the sympathetic nervous system by central command may have directly stimulated the glycolytic pathway. Increased lactate production could also reflect the use of auxiliary muscles when work became difficult during neuromuscular blockade. This is unlikely, however, because the oxygen uptake during exercise was unaffected by neuromuscular blockade.

Elevated lactate values does raise the possibility of activation of the exercise pressor reflex via stimulation of chemically-sensitive (metaboreceptor). However, our laboratory has recently provided evidence that the metaboreflex was not activated during exercise until a critical reduction in oxygen delivery occurred (10,49). In the current investigation, it was assumed that partial neuromuscular blockade had no effect on oxygen delivery to active muscle groups. In addition, Gallagher et al. (10) have demonstrated that no significant increases in MAP and HR are elicited by the trapping of lactate (> 7 mmol/L) in active skeletal muscle (10). Therefore, it appeared unlikely that metaboreflex activation during exercise in this study would be altered by partial neuromuscular blockade. It also was unlikely that mechanoreflex activity would be altered by neuromuscular blockade since the same absolute work was performed and oxygen uptake was not affected. Thus, we reasoned that any change in the hemodynamics and carotid baroreflex control of blood pressure during neuromuscular blockade was primarily due to central command activation.

Activation of proposed locations of central command origin in the motor cortex, insular cortex and the posterior hypothalamus (1, 6, 40, 48) have demonstrated alterations in baroreflex control of HR. In addition, medullary neurons that form the central baroreceptor pathway have been determined to receive synaptic input from central command (22, 32, 48). Thus, central command input may actively reset the carotid baroreflex by modulating medullary neuron pools that form the central baroreceptor pathway. During dynamic and static exercise in the present investigation, threshold and saturation carotid sinus pressures and the minimal response for the carotid-cardiac and carotid-vasomotor baroreflex curves were increased from rest during control exercise and were significantly elevated from control exercise by partial neuromuscular blockade. In addition, the centering point of the responses (A_3) were significantly raised by control exercise and further significantly increased during neuromuscular blockade. The maximal gains of the HR and MAP responses were found to be unaltered by either control or neuromuscular blockade exercise. These responses coincide with Heesch and Carey's (12) description of resetting of the carotid baroreflex as parallel increases in saturation and threshold without alterations in gain. Therefore, the stimulus-response carotid-cardiac and carotid-vasomotor curves were reset by control dynamic and static exercise and with resetting being further augmented upward on the response arm and rightward to higher operating pressures by neuromuscular blockade. The data of the present investigation suggests that central command was actively involved in the classic upward and rightward resetting of the carotid baroreflex during both dynamic and static exercise.

Potts et al. (34) and Norton et al. (26) reported that steady-state HR and MAP (or operating point) are relocated away from the centering point and progressively closer to the threshold region of the stimulus-response curve with each increment in dynamic exercise intensity. These findings suggested that a relocation of the operating point permits the carotid baroreflex to respond to a wider range of carotid sinus hypertension. We did not demonstrate any shifts in the location of the operating point on the baroreflex stimulus response curves during static and dynamic exercise, except for the HR response to dynamic exercise. This was possibly due to the low dynamic and static work rates used in the present experiment. However, relocation of the pre-stimulus HR and MAP away from the centering point and closer to the threshold did occur during neuromuscular blockade static and dynamic exercise (Table 5). Therefore, central command appears to contribute to the relocation of the operating point during exercise previously reported (26,34). This relocation may enable the carotid baroreflex to respond to systemic hypertension during exercise with a greater range of response, a concept demonstrated by Sheriff et al. (42) to provide a functional brake on the exercise pressor reflex.

The findings of the present investigation by no means exclude the involvement of the exercise pressor reflex in the resetting of the carotid baroreflex during exercise. The redundant nature of central command input and the exercise pressor reflex in the regulation of the cardiovascular system is generally accepted (25). In addition, several studies have provided evidence of vertical resetting of the carotid baroreflex during exercise pressor reflex stimulation (8, 30, 43, 44). Recently, Potts and Mitchell have demonstrated rightward relocation of threshold CSP with activation of skeletal muscle

afferents (33). Furthermore, it has been determined that medullary neurons that form the central baroreceptor pathway receive synaptic input from skeletal muscle receptors (14, 28, 48). Thus, it appears that the exercise pressor reflex is involved in the resetting of the carotid baroreflex. Given the findings of the present study, we suggest that central command (a feed-forward mechanism) was the primary mediator of carotid baroreflex resetting during exercise. Further, the magnitude of resetting may be modulated by exercise pressor reflex input (a feedback mechanism) in response to mechanical and/or metabolic demands placed on active muscle.

Due to the nature of the present study, a discussion of the assumptions and limitations of the investigation is warranted. First, there existed a lack of significant increases in saturation and threshold during control static and dynamic exercise at the respective work rates of 20% MVC and 20% VO_{2peak} is a cause for concern. Potts et al. found similar non-significant increases in saturation, threshold and centering point from rest during exercise at 25% VO_{2peak}. However they found significant elevations at exercise of 50% VO_{2peak} (34). More importantly, DiCarlo and Bishop have provided evidence that the carotid baroreflex was reset immediately at the initiation of exercise (5). In addition, it has been demonstrated that the carotid baroreflex resets in direct relation to the intensity of exercise (26, 29). We found significant increases in the centering point of the carotid-cardiac and carotid-vasomotor stimulus-response curves during control static and dynamic exercise. Thus, we concluded that the carotid baroreflex was indeed reset during control static and dynamic exercise at the low work rates of 20% MVC and 20% VO_{2peak}.

A second potential limitation was that threshold and saturation carotid sinus pressure of MAP responses were determined to be significantly elevated from control dynamic exercise by neuromuscular blockade using an 'a priori' paired t-test. The lack of significance using a two-way repeated measures ANOVA was most likely due to the high variance of the resultant variables. However, since centering point was significantly elevated using the two-way ANOVA, we feel the data still represents significant resetting of the carotid baroreflex using neuromuscular blockade.

A third potential limitation was that the precise pressure transmission to the carotid sinus during neck pressure (NP) and neck suction (NS) remains unknown. Ludbrook et al. demonstrated asymmetric reductions in transmission characteristics of NP and NS directly measured with a fluid-filled catheter (19). More recently, Querry et al. have reported greater than 90% transmission of NP and NS directly measured with a pressure-tipped (Milar) catheter at rest and during exercise (35). They suggested that NS would influence the fluid volume in the fluid-filled catheter confounding measurements and that the use of a pressure-tipped catheter to determine transmission characteristics was more appropriate. Therefore, we considered NP and NS to be fully transmitted to the carotid sinus at rest and during exercise.

A final potential limitation to this study is the brief nature of the stimulus in the NP/NS technique. The brief pulses (500ms) were used in order to fully assess the carotid baroreflex in a limited amount of time, such as during the static contractions. In addition, such brief stimulations were thought to stimulate the carotid baroreceptors with minimal or no effect on the extra-carotid baroreceptors (cardiopulmonary and aortic) (34).

However, the brief stimuli limit the ability to fully assess the carotid-vasomotor response as a 20 to 40 second stimulus is required to establish the complete sympathetic neural response (38). Yet estimations of the carotid-vasomotor reflex can be derived from the mean arterial pressure responses to the NP/NS protocol. Rea and Eckberg have demonstrated almost immediate alterations in MSNA to brief periods of NP and NS (36). Furthermore, it has been determined that brief periods of NP and NS fail to elicit significant changes in stroke volume (18) and additionally the steady-state changes in cardiac output after two minute change in CSP could only account for 50% of the observed change in blood pressure (20). Thus, brief NP/NS induced changes in blood pressure were caused in-part by reflex-induced changes in peripheral vascular resistance and were used to estimate the carotid-vasomotor reflex.

In summary, we confirmed that the stimulus-response relationship of the carotid baroreflex was reset during dynamic and static exercise to the prevailing systemic pressure. We also demonstrated that increased central command further resets the carotid baroreflex upward on the response arm and rightward to higher operating pressures (classical resetting) in the same manner during dynamic and static exercise without altering the gain of the reflex. In addition, we found that increased central command relocated the pre-stimulus HR and MAP, i.e. operating point, away from the centering point and closer to the threshold of the significance during exercise. We concluded that central command was actively involved in the "classical resetting" of the carotid baroreflex that occurred from rest to the onset of exercise. Furthermore, the degree of resetting of the baroreflex

would be directly related to the intensity of the exercise commensurate with the magnitude of central command activation.

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Table 1. Selected physiological responses

	RPE	VO_2 $Ml \bullet min^{-1}$	Strength %	Lactate $mmol \bullet L^{-1}$	NE $nmol \bullet L^{-1}$	E $nmol \bullet L^{-1}$
CONTROL						
Rest	----------	0.332 ± 0.03	100	0.71 ± 0.09	1.25 ± 0.17	0.51 ± 0.15
Static	12.9 ± 0.5	0.460 ± 0.04	----------	0.78 ± 0.08	1.70 ± 0.22	0.89 ± 0.16
Rest	----------	0.338 ± 0.04	----------	0.63 ± 0.08	1.20 ± 0.12	0.59 ± 0.21
Dynamic-1	10.2 ± 0.4	0.897 ± 0.04	----------	----------	----------	----------
Dynamic-2	10.7 ± 0.4	0.921 ± 0.04	----------	0.68 ± 0.10	1.92 ± 0.25	0.67 ± 0.12
CURARE						
Rest	----------	0.332 ± 0.02	45.9 ± 7.0†	1.06 ± 0.10*	1.65 ± 0.18	0.51 ± 0.12
Static	15.7 ± 0.6*	0.487 ± 0.03	46.8 ± 5.4†	1.14 ± 0.12*	2.36 ± 0.32*	0.88 ± 0.22
Rest	----------	0.443 ± 0.07	41.6 ± 7.1†	0.79 ± 0.08	1.46 ± 0.16	0.81 ± 0.15
Dynamic-1	16.4 ± 0.9*	1.013 ± 0.07	----------	----------	----------	----------
Dynamic-2	15.5 ± 0.7*	0.915 ± 0.06	46.1 ± 4.9†	1.04 ± 0.1*	2.82 ± 0.30*	0.99 ± 0.24

Values are mean ± SE; RPE, Ratings of perceived exertion; VO_2, oxygen uptake; Strength, grip strength remaining after curare administration compared to control; NE, Norepinephrine; E, epinephrine; Static (n=13), static contraction at 3rd minute; Dynamic-1 (n=7), dynamic cycling at 4th minute; Dynamic-2, dynamic cycling at 7th minute.

* Significantly different from control exercise, † Significantly different from resting condition; $P < 0.05$.

Table 2. Logistic model parameters describing carotid sinus baroreceptor reflex control of HR and MAP

	A_1	A_2	A_3	A_4
Carotid-cardiac baroreflex	(beats•min^{-1})		(mmHg)	(mmHg)
Rest Control	22.4 ± 2.0	0.19 ± 0.06	94.3 ± 3.1	51.5 ± 3.0
Static Control	23.6 ± 2.2	0.14 ± 0.01	103.2 ± 3.7	63.6 ± 4.4†
Dynamic Control	25.0 ± 1.8	0.18 ± 0.06	105.0 ± 3.1	65.9 ± 4.8†
Rest Curare	22.2 ± 2.1	0.17 ± 0.04	96.4 ± 3.2	54.8 ± 3.0
Static Curare	23.8 ± 2.5	0.11 ± 0.02	121.8 ± 4.6*†	68.3 ± 5.0*†
Dynamic Curare	22.3 ± 2.4	0.13 ± 0.02	127.3 ± 8.5*†	80.6 ± 11.0*†
Carotid-vasomotor baroreflex	(mmHg)		(mmHg)	(mmHg)
Rest Control	20.4 ± 2.3	0.10 ± 0.01	86.6 ± 4.5	76.6 ± 2.6
Static Control	19.4 ± 1.9	0.09 ± 0.01	102.5 ± 3.3	91.5 ± 2.0†
Dynamic Control	18.5 ± 0.5	0.09 ± 0.01	91.9 ± 5.3	81.0 ± 4.4†
Rest Curare	20.7 ± 1.7	0.08 ± 0.01	89.8 ± 4.2	84.1 ± 3.1*
Static Curare	21.1 ± 1.8	0.11 ± 0.03	111.5 ± 4.2*†	97.8 ± 3.6*†
Dynamic Curare	26.3 ± 3.5	0.11 ± 0.02	111.4 ± 9.3*†	89.6 ± 5.3*†

Values are mean ± SE. A_1, range (maximum-minimum); A_2, gain coefficient; A_3, carotid sinus pressure (CSP) at midpoint (centering point); A_4, minimal response.

* Significantly different from control exercise, † Significantly different from resting condition, $P < 0.05$.

Table 3. Derived variables describing the stimulus-response relationship for carotid baroreflex control of heart rate

	Control			Curare		
	Rest	Static	Dynamic	Rest	Static	Dynamic
CSP_{thr} mmHg	73.3 ± 4.0	84.7 ± 4.0	84.4 ± 4.7	77.7 ± 2.9	98.4 ± 5.9*†	107.5 ± 8.2*†
CSP_{sat} mmHg	113.0 ± 4.9	121.6 ± 4.1	125.8 ± 5.8	114.5 ± 4.4	143.3 ± 5.4*†	147.4 ± 9.6*†
HR_{op} beats•min^{-1}	63.6 ± 4.1	77.1 ± 3.5†	89.3 ± 4.3†	67.6 ± 5.2	87.1 ± 7.7*†	103.0 ± 7.6*
HR_{cp} beats•min^{-1}	62.6 ± 3.2	75.3 ± 4.5†	78.5 ± 4.6†	65.9 ± 3.6	80.2 ± 5.1*†	91.7 ± 10.2*†
Max gain beats•min^{-1} •mmHg^{-1}	-1.15 ± 0.47	-0.82 ± 0.12	-1.0 ± 0.26	-0.74 ± 0.10	-0.72 ± 0.13	-0.72 ± 0.14

Values are means ± SE, CSP_{thr}, carotid sinus threshold pressure; CSP_{sat}, carotid sinus saturation pressure; HR_{op}, HR at operating point; HR_{cp}, HR at centering point of reflex; max gain, point of greatest slope (i.e. gain coefficient) on 1st derivative curve of logistic function. * Significantly different from control exercise, † Significantly different from resting condition, $P < 0.05$.

Table 4. Derived variables describing the stimulus-response relationship for carotid baroreflex control of mean arterial pressure

	Control			Curare		
	Rest	Static	Dynamic	Rest	Static	Dynamic
CSP_{thr} mmHg	65.9 ± 4.6	73.6 ± 6.3	68.3 ± 5.4	62.8 ± 4.4	83.7 ± 6.4*†	87.6 ± 12.5*†
CSP_{sat} mmHg	107.3 ± 5.1	131.4 ± 4.2†	115.5 ± 5.5	116.8 ± 5.6	139.3 ± 4.4*†	135.1 ± 7.5*†
MAP_{op} MmHg	89.5 ± 2.1	99.7 ± 1.8†	91.7 ± 2.2	94.6 ± 2.5	111.5 ± 3.6*†	114.6 ± 6.5*†
MAP_{cp} MmHg	86.8 ± 2.1	101.2 ± 2.0†	90.2 ± 4.4	94.5 ± 2.8*	108.4 ± 3.1*†	102.7 ± 6.3*†
Max gain $mmHg \bullet min^{-1} \bullet mmHg^{-1}$	-0.51 ±0.06	-0.38 ± 0.05	-0.41 ± 0.03	-0.41 ± 0.06	-0.49 ± 0.1	-0.63 ± 0.06

Values are means ± SE, CSP_{thr}, carotid sinus threshold pressure; CSP_{sat}, carotid sinus saturation pressure; MAP_{op}, MAP at operating point; MAP_{cp}, MAP at centering point of reflex; max gain, point of greatest slope (i.e. gain coefficient) on 1st derivative curve of logistic function. * Significantly different from control exercise, † Significantly different from resting condition, $P < 0.05$

Table 5. Calculated differences between operating point and centering point

	Control			Curare		
	Rest	Static	Dynamic	Rest	Static	Dynamic
dHr beats•min^{-1}	1.0 ± 1.8	1.8 ± 2.0	10.8 ± 2.0†	1.7 ± 1.9	6.9 ± 2.7*†	11.3 ± 3.6†
DMAP MmHg	2.7 ± 2.1	-1.5 ± 3.0	1.5 ± 2.8	0.1 ± 1.5	3.1 ± 2.5	11.7 ± 7.4*†

Values are means ± SE, dHr, HR operating point (pre-stimulus HR) minus HR centering point; dMAP, MAP operating point (pre-stimulus MAP) minus MAP centering point. * Significantly different from control exercise, † Significantly different from resting condition, $P < 0.05$.

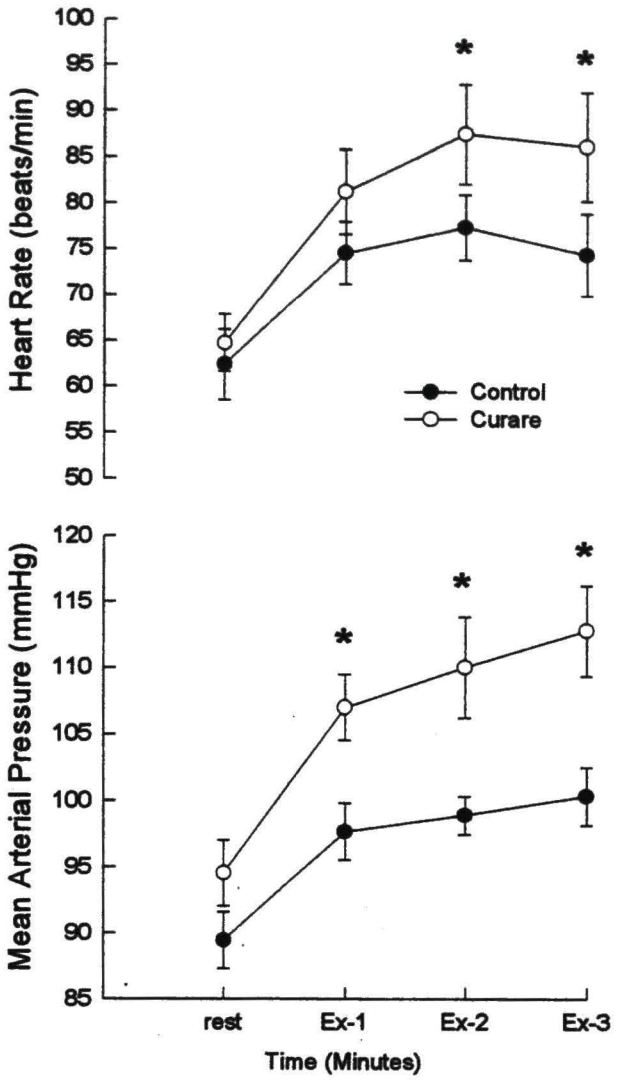

Figure 1 - Heart Rate and mean arterial pressure responses at rest and during three minute one-leg static exercise (20% maximal voluntary contraction) without (o) and with (●) administration of curare (partial neuromuscular blockade). Values are means ± SE.

*** Significant difference between control and partial neuromuscular blockade exercise ($P < 0.05$).**

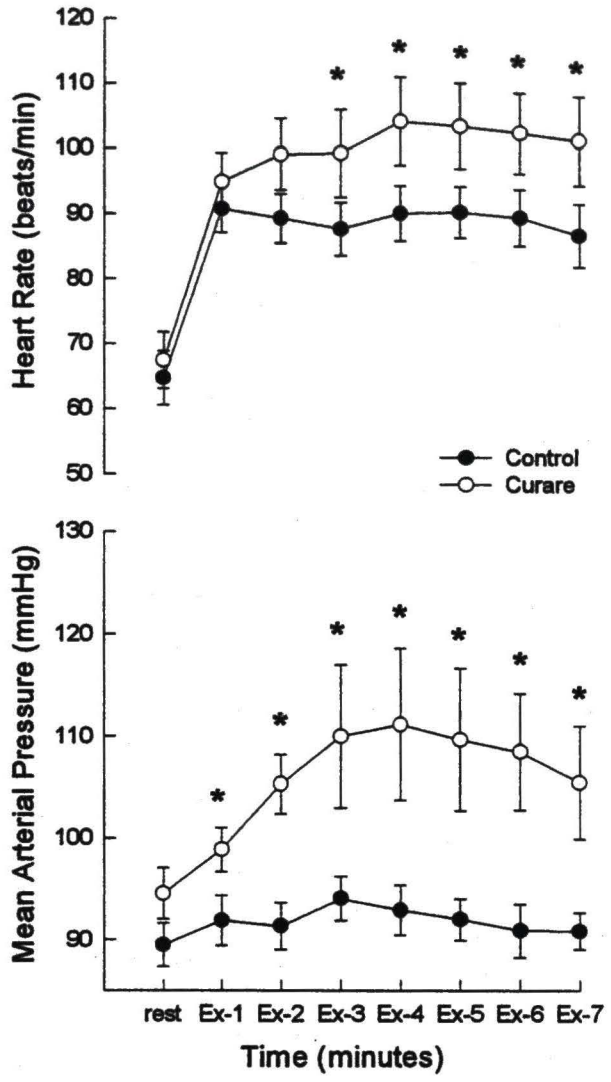

Figure 2 - Heart Rate and mean arterial pressure responses at rest and during seven minutes dynamic cycling exercise (20% maximum oxygen uptake) without (o) and with (●) administration of curare (partial neuromuscular blockade). Values are means ± SE. * Significant difference between control and partial neuromuscular blockade exercise ($P < 0.05$).

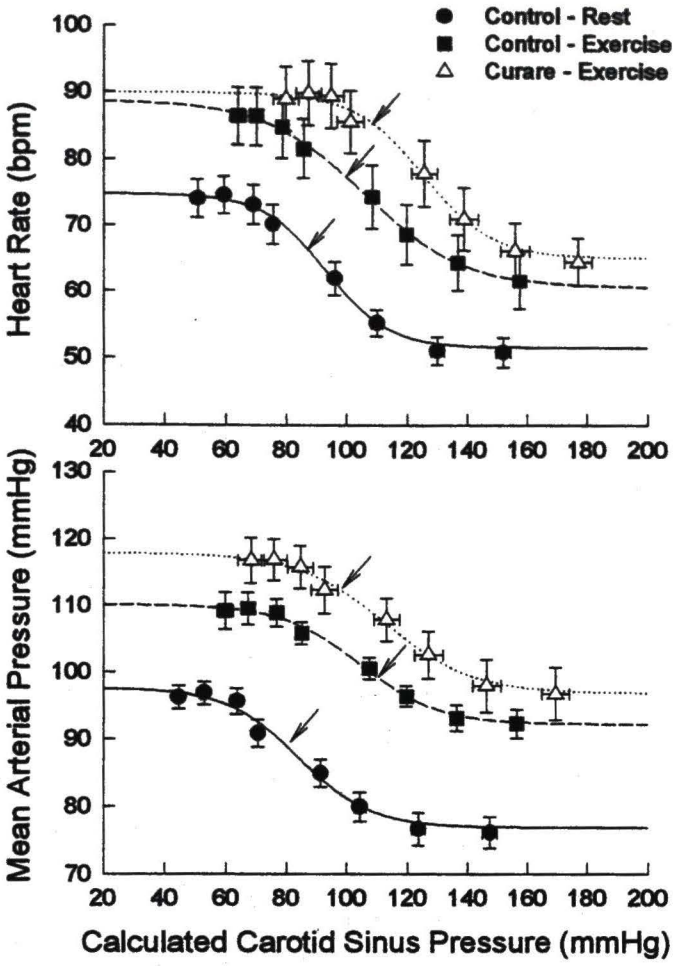

Figure 3 - Reflex responses in HR (carotid-cardiac) and MAP (carotid-vasomotor) after perturbations to carotid sinus baroreceptors at rest (●), during control static (20% MVC) one-legged exercise (■) and during static exercise after administration of curare (Norcuron) for partial neuromuscular blockade (Δ). Data points represent means ± SE. Lines represent mean fit of individual subjects' data. ← indicates operating point. Curare-Rest curves were not significantly different from control-rest curves and have been omitted for clarity.

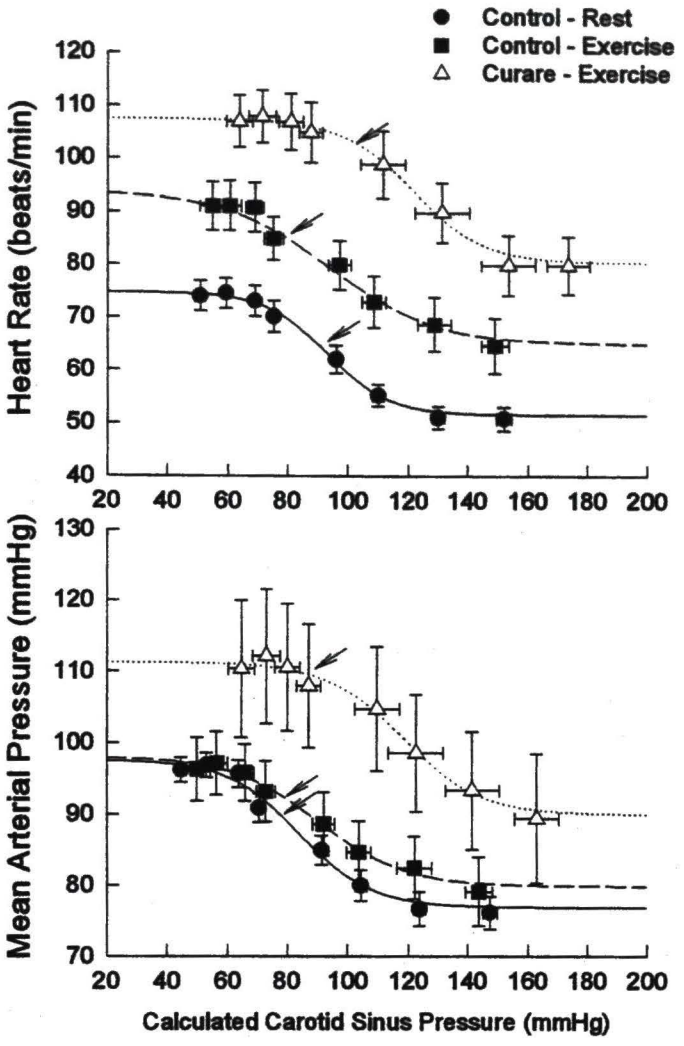

Figure 4 - Reflex responses in HR (carotid-cardiac) and MAP (carotid-vasomotor) after perturbations to carotid sinus baroreceptors at rest (●), during control dynamic (20% MVC) cycling exercise (■) and during dynamic exercise after administration of curare (Norcuron) for partial neuromuscular blockade (Δ). Data points represent means ± SE. Lines represent mean fit of individual subjects' data. ← indicates operating point. Curare-Rest curves were not significantly different from control-rest curves and have been omitted for clarity.

PREFACE TO CHAPTER IV

In 1990, Rowell and O'Leary presented a hypothetical scheme suggesting that both central command and the muscle chemoreflex are involved in the resetting of the arterial baroreflex. Chapter II predicted that the muscle mechanoreflex is more involved in the resetting of the arterial baroreflex than the muscle chemoreflex. The previous investigation provided evidence that increased central command actively resets the carotid baroreflex upward on the response arm and rightward to a higher operating pressure (classical resetting). This suggests that central command actively resets the carotid baroreflex during static and dynamic exercise. Therefore, Rowell and O'Leary's model can be adapted to suggest that central command is involved in the resetting of the arterial baroreflex under normal conditions (Figure 1). However, it remains to be determined the exact role of the muscle mechanoreflex/exercise pressor reflex in arterial baroreflex resetting. Therefore, the third investigation was designed to demonstrate the effect of increased exercise pressor reflex stimulation using medical anti-shock trousers on the resetting of the carotid baroreflex during dynamic and static exercise.

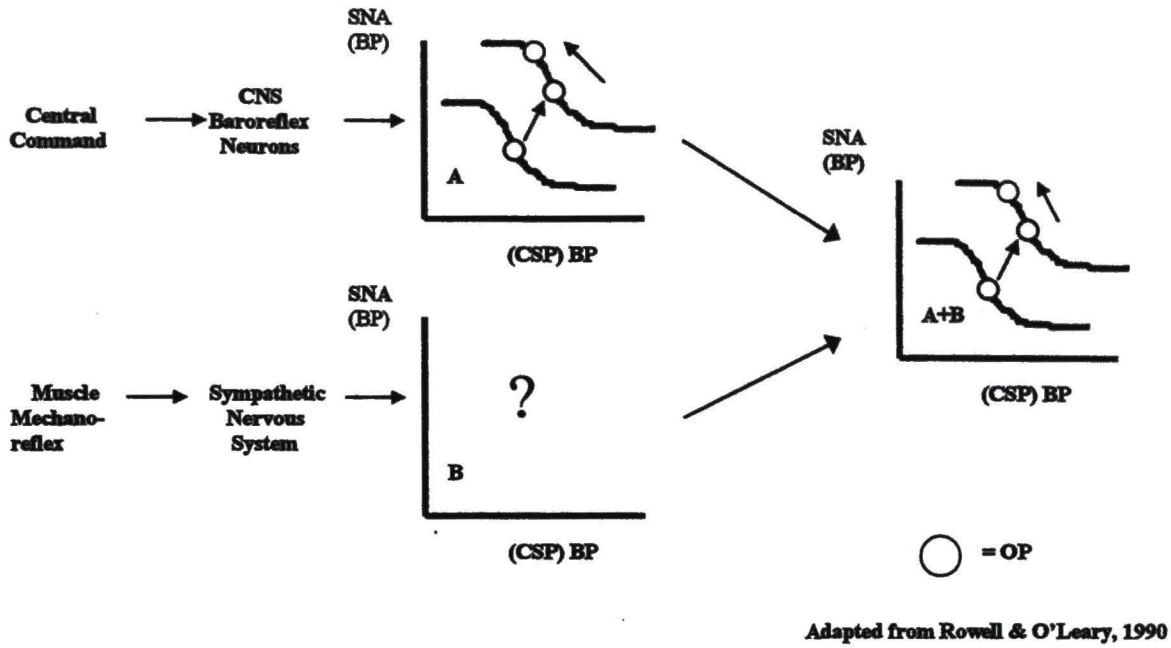

Figure 1- A updated model of arterial baroreflex resetting

CHAPTER IV

EFFECTS OF EXERCISE PRESSOR REFLEX ACTIVATION ON CAROTID BAROREFLEX FUNCTION DURING EXERCISE IN HUMANS

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ABSTRACT

The purpose of the investigation was to determine the contribution of the exercise pressor reflex to the resetting of the carotid baroreflex during exercise. Ten subjects performed 3 ½ minutes of static one-leg exercise (20% maximal voluntary contraction) and 7 minutes dynamic cycling (20% maximal oxygen uptake) under two conditions: control (no intervention) and with the application of medical anti-shock trousers (MAS) inflated to 100 mmHg (to activate the exercise pressor reflex). Carotid baroreflex function (CBR) was determined at rest and during steady-state exercise using a rapid neck pressure/neck suction technique. During exercise, the MAS trouser condition increased mean arterial pressure (MAP), plasma norepinephrine concentration (dynamic exercise only) and perceived exertion (dynamic exercise only) when compared to control ($P<0.05$). No effect of MAS trousers was seen at rest. The MAS trousers condition had no effect on heart rate (HR), plasma lactate or epinephrine concentration and oxygen uptake at rest and during exercise. The CBR was reset upward on the response arm and rightward to a higher operating pressure by control exercise without alterations in gain. Activation of the exercise pressor reflex by MAS trousers further reset CBR control of MAP upward and rightward. However, CBR control of HR was only shifted rightward to higher operating pressures by MAST trousers. Sensitivity of the CBR was unaltered by exercise pressor reflex activation. These findings suggested that during dynamic and static exercise the

exercise pressor reflex was capable of actively resetting CBR control of MAP, however it would appear only to modulate CBR control of HR.

INTRODUCTION

During exercise, heart rate (HR) and mean arterial pressure (MAP) simultaneously increase in relation to the intensity of exercise. A finding that has resulted in many investigators concluding that the baroreflex was attenuated or was not operable during static and dynamic exercise (15, 18). However, both animal and human subject investigations have identified that the arterial baroreflex maintains it sensitivity during exercise (19) and is actually reset upward on the response arm and rightward on the operating arm to the prevailing blood pressure during dynamic (3, 28) and static (4) exercise. This resetting allowed for the simultaneous increase in HR and MAP (28). Rowell and O'Leary have suggested that two neural mechanisms were primarily involved in the resetting of the carotid baroreflexes regulation of sympathetic nerve activity during exercise (32). First, a feedforward mechanism, referred to as central command, acts through central processes to regulate the cardiovascular and somatomotor systems (7, 36). Secondly, mechanically and chemically sensitive afferent signals arising from skeletal muscle regulate cardiovascular responses through negative feedback to the brainstem (10, 16, 21). Collectively, the afferent signals arising from skeletal muscle have been termed the *exercise pressor reflex* (21).

Recently, Iellamo et al. (8) have confirmed that in human subjects central command and the exercise pressor reflex together are involved in the resetting of the

baroreflex during exercise. In addition, we have demonstrated in humans that an increased central command actively resets the carotid baroreflex upward and rightward during dynamic and static exercise without alterations in sensitivity (6). However, the exact role of the exercise pressor reflex remains controversial. Papelier et al. (25) reported in human subjects that activation of chemically sensitive receptors using post-exercise occlusion altered the sensitivity and the reflex characteristics of the carotid baroreflex MAP stimulus-response curve (carotid-vasomotor). However, the sensitivity of the HR stimulus-response curve (carotid-cardiac) was unaffected. Chemoreflex activation apparently enhanced the carotid-vasomotor response to hypotension but diminished its response to hypertension. Alternatively, Eiken et al. (5) found that exercise pressor reflex activation with lower-body positive pressure reset the carotid-cardiac stimulus-response curve and increased its sensitivity when created using a neck pressure/neck suction stimulus-response of changes in R-R interval. Lower-body positive pressure has also been reported to decrease the sensitivity of the carotid baroreflex (34). Finally, Potts et al. (27) have demonstrated that activation of afferents from skeletal muscle receptors resets the threshold of the carotid baroreflex to a higher operating range.

Therefore, the previous work suggests that the exercise pressor is capable of resetting the carotid baroreflex threshold to a higher operating range (i.e. a rightward shift). However, its remains to be determined what role the exercise pressor reflex has in the resetting of the entire carotid baroreflex function curve during exercise (28). In addition, the effect of activation of the exercise pressor reflex on the sensitivity of the carotid baroreflex remains controversial. In the present investigation, we attempted to

activate the exercise pressor reflex in active skeletal muscle during steady-state dynamic and static exercise with the application of medical anti-shock trousers (MAS). The investigation was designed to determine the role of the exercise pressor reflex in the resetting of the carotid baroreflex during static and dynamic exercise in humans.

METHODS

Subjects: Eight men and two women with a mean age of 27.7 ± 1.1 (± SE) years, height of 179.6 ± 2.0 cm, weight of 74.0 ± 1.5 kg and maximum oxygen uptake of 47.6 ± 2.1 ml $O_2 \bullet kg^{-1} \bullet min^{-1}$, volunteered to participate in this investigation. Prior to testing, each subject was informed of all risks and aspects of the study and signed an informed consent approved by the Fredricksburg Municipal Ethical Committee of Copenhagen, Denmark. All subjects were non-smokers, were not using prescribed or over the counter medications. The subjects were asymptomatic for cardiovascular and respiratory disease. The subjects were asked to abstain from alcoholic beverages and exercise for 24 hours and caffeinated beverages for 12 hours prior to any scheduled testing session.

Exercise testing: Each subject performed a preliminary incremental work rate (0.5 kg/min) exercise test on a cycle ergometer (modified Krogh) to volitional fatigue for the determination of peak oxygen uptake (VO_{2peak}). Since none of the subjects achieved a plateau of VO_2 with increasing work rate, the maximum oxygen uptake (VO_{2max}) achieved was presented as VO_{2peak}. After the maximal exercise test, the subject was familiarized with the protocols for baroreflex testing and static exercise.

On a separate day following the initial exercise test, the subjects performed static and dynamic exercise with and without the application of medical anti-shock trousers (MAS) inflated to a pressure of 100 mmHg in order to activate the exercise pressor reflex via stimulation of the mechanoreflex (37). For both protocols the subjects were seated in a semi-recumbent position on a hospital bed which supported the subjects entire upper body. The hospital bed was modified to allow the subjects to perform one-legged static knee extension from a 70 ° knee angle and two-legged dynamic cycling. Preceding any exercise, the subjects attempted three static knee extensions to determine maximal voluntary contraction (MVC). Two bouts of control static knee extension at 20% of MVC were performed for 3 1/2 minutes. In addition, the subjects performed a 7 minute dynamic exercise protocol at 20% VO_{2peak}. The static and dynamic exercise bouts were repeated with the application of MAS trousers inflated to a pressure of 100 mmHg. All exercise bouts were randomized and separated by a minimum of 30 minutes. Each exercise bout was preceded by a five minute collection period for resting baseline measurements.

Static knee extension was accomplished by placing a padded strap around the ankle of the subjects dominant leg. Force was recorded by a strain gauge dynamometer (model 540 DNH, Holland). Visual feedback of force was provided to the subject by a monitor in order for the subject to maintain the desired force. For dynamic exercise, the cycle ergometer was adjusted for each subject so that a knee angle at maximal leg extension was consistent for both tests. Subjects were requested to maintain a pedal cadence of 60 rpm per metronome for the duration of the test. Subjects were instructed to keep their entire upper body relaxed during all testing.

Medical anti-shock trousers were applied to both lower extremities of the subject and inflated to 100 mmHg. The MAS trousers were designed without inflation bladders around the knees and ankles which allowed the subjects to exercise. The abdomen section of the MAS trousers were not applied to the subjects to eliminate abdominal and bladder reflexes. The subjects reported no discomfort with the MAS trousers.

Measurements: During each test, heart rate (HR) was monitored by a standard lead II electrocardiogram. Arterial blood pressure (ABP) was monitored by a Teflon catheter (20 gauge) placed in the brachial artery of the non-dominant arm. The ABP catheter was connected to a sterile disposable pressure transducer (Baxter, Uden, Holland) interfaced with a pressure monitor (Danico Electronic - Dialogue 2000, Denmark). The zero reference pressure was set at heart level. During each experiment HR and ABP [i.e. mean (MAP), systolic (SBP) and diastolic (DBP) blood pressures] were acquired using a beat-to-beat customized software data acquisition system interfaced with a personnel computer. In addition, ratings of perceived exertion (RPE) were obtained during the last 30 seconds of static exercise and at the 4th and 7th minute of dynamic exercise using the 6 to 20 Borg scale (range 6 to 20) (1).

The subjects respired through a mouthpiece attached to a low-resistance turbine volume transducer (Pneumotach, MedGraphics) for measurements of breath volumes while gases were continuously sampled from the mouthpiece for analysis of fractional concentrations of O_2, CO_2 and N_2 to determine oxygen uptake (2001; Medical Graphics Corporation, St. Paul, MN.). The Med-Graphics system was calibrated before each test using known high-precision standard gases. Device input signals underwent analog-to-

digital conversion for on-line breath-by-breath determination. Standardized calculations of metabolic data were corrected for ambient conditions.

Samples of arterial blood were obtained at rest and during the last thirty seconds of exercise for determination of plasma catecholamine concentration ($nmol \bullet L^{-1}$) and lactate concentration ($mmol \bullet L^{-1}$). Blood was placed in tubes kept on ice containing reduced glutathione and ethylene glycol-bis (β-aminoethyl ether)-N,N,N',N'-tetraacetic acid and centrifuged at 3000 g for 5 minutes at 3°C. The plasma fraction was stored at -20°C for blinded analysis of norepinephrine (NE) and epinephrine (E). Samples were assayed by a single isotope radioenzymatic method. Remaining syringe blood samples were immediately used for lactate determination (Lac TSI 2300; Yellow Springs Instrument Co., Inc., Ohio).

Carotid baroreflex (CBR) control of HR and MAP was assessed utilizing a neck pressure/neck suction (NP/NS) technique. Pressure stimuli were applied through a cushioned malleable collar placed around the anterior 2/3 of the neck. The neck collar was modified from a design previously described by Sprenkle et al. (35). Due to the brevity of the exercise protocols, a NP/NS technique that utilized a rapid ramping of pressure was used. Computer controlled pulsatile pressures ranging from +40 to -80 mmHg were generated by a variable pressure source and delivered to the neck collar through large bore two-way solenoid valves (model 8215B, Asco, Florham Park, NJ). Between each pressure pulse the neck chamber pressure was vented to atmospheric pressure. The generated level of neck collar pressure was measured by a pressure

transducer (model DP45, Validyne Engineering, Northridge, CA). The computer software gated the pulses of pressure to occur 50 ms after initiation of the R-wave detected by ECG. The 50 ms delay allowed the artificial pressure or suction to coincide with the arterial pressure wave at the carotid sinus. Each pulse of pressure or suction was 500 ms in duration. The NP/NS pulse train was conducted at end-expiratory breath hold to eliminate the confounding effects of respiratory sinus arrhythmia. The total duration of breath hold varied between 10 -12 seconds. Four subjects were unable to maintain the end-expiratory breath hold throughout the entire NP/NS pulse train during dynamic exercise. Therefore only six subjects were included in the dynamic exercise data. During static exercise, two CBR NP/NS pressure-response curves were obtained after the second minute of exercise. Three to four NP/NS pressure-response curves were obtained during dynamic exercise after the fourth minute of exercise. A minimum of 45 seconds of recovery time were allotted between rapid pulse trains of NP/NS. Rapid pulse trains of NP/NS were also obtained at rest before all exercise bouts.

Data and Statistical Analysis: The dependent variables HR and MAP were used to create either the carotid-cardiac (HR) or carotid-vasomotor (MAP) stimulus-response function curves when plotted against the independent variable of estimated carotid sinus pressure (CSP). These curves were individually fit for each subject to a four parameter logistic function described by Kent et al. (11). This function incorporates the following equation:

$$\text{HR or MAP} = A_1 \bullet \{1 + e^{[A_2(\text{CSP}-A_3)]}\}^{-1} + A_4$$

Carotid sinus pressure was calculated by subtracting the chamber pressure from the pre-stimulus MAP. Parameter A_1 was the range of response of the dependent variable (maximum - minimum), A_2 was the gain coefficient, A_3 was the CSP required to elicit equal pressor and depressor responses (centering point) and A_4 was the minimum response of HR or MAP. Individual data were applied to this model by a non-linear least-squares regression that predicted a curve of "best fit" for the data and minimized the sum of squares error.

Several characteristic parameters were derived from the resulting model including the estimated threshold (CSP_{thr}), saturation (CSP_{sat}) and maximal gain (G_{max}) of the carotid-cardiac and carotid-vasomotor reflexes. Baroreceptor CSP_{thr} and CSP_{sat} were described as the minimum and maximum CSP's, respectively, that elicited a reflex change in HR or MAP. The calculation of CSP_{thr} and CSP_{sat} utilized equations described by Chen and Chang (2): $CSP_{thr} = -2.0/ A_2 + A_3$ and $CSP_{sat} = -2.0/ A_2 + A_3$. These calculations of CSP_{thr} and CSP_{sat} have been found to be the CSP at which MAP or HR are within 5% of their maximal or minimal response. The gains of the carotid-cardiac and the carotid-vasomotor reflexes were derived from the first derivative of the Kent logistic function with the maximal gain defined as the gain value located at the centering point (CP) of the reflex. In addition, the operating point (OP) was defined as the intersection of the pre-stimulus HR or MAP and CSP at rest. Parameters for all subjects within an experimental condition were averaged to provide group mean responses.

A two-way analysis of variance (ANOVA) with repeated measures was employed to determine significant differences at rest and exercise between either static or dynamic

exercise with or without MAS trousers. Student-Newman-Keuls *post-hoc* pairwise comparisons were used to establish significant group mean differences. In addition, a paired t-test was used for individual comparisons. Data are presented as mean values with standard errors (mean ± SE). The alpha level was set at $P < 0.05$. All analyses were conducted using Sigma Stat (Jandell Corp.)

RESULTS

Selected physiologic responses: Ratings of perceived exertion (RPE) during static exercise was not affected by the MAS trouser condition. However, RPE was significantly elevated from control during dynamic exercise with MAS trousers (Table 1). The subjects did not report any discomfort or increased difficulty performing the dynamic exercise with the MAS trousers. Heart rate (HR) was unaffected by the MAS trousers condition at rest and during exercise when compared to control, however MAP was significantly increased above the control condition by the MAS trouser condition during steady-state dynamic and static exercise (Figures 1 and 2). Heart rate and MAP reached steady-state without additional elevations at the second minute of static exercise and at the fourth minute of dynamic exercise during the control and MAS trouser conditions. Oxygen uptake was significantly increased from rest by control and MAS trouser dynamic and static exercise. However, oxygen uptake at the same absolute work rates was unaltered by the MAS trouser condition when compared to control (Table 1).

Plasma norepinephrine concentration (NE) demonstrated significant increases from rest during control and MAS trouser dynamic and static exercise (Table 1). Furthermore,

the MAS trouser condition significantly elevated NE above the control condition during dynamic exercise. This increase was not seen during static exercise. Plasma epinephrine and lactate concentrations were unaffected by the MAS trouser condition when compared to control (Table 1).

Logistic parameters of carotid baroreflex: The four logistic parameters describing CBR control of HR (carotid-cardiac) and MAP (carotid-vasomotor) during static and dynamic exercise are presented in Table 2. The range of HR and MAP responses (A_1) and gain coefficient (A_2) were unaltered by control and MAS trouser exercise. The centering point of the reflex (A_3) demonstrated a progression from rest during control exercise and was significantly increased from control exercise by the MAS trouser condition. Responses between A_1, A_2 and A_3 were the same between static and dynamic exercise. The minimal HR response (A_4) was significantly increased during control static and dynamic exercise and was unaffected by the MAS trouser condition. The minimal MAP response (A_4) was increased by control static exercise. In addition, the MAS trouser condition significantly increased the minimal MAP response (A_4) from control during static and dynamic exercise.

Carotid-cardiac (CSP-HR) stimulus-response curves during static exercise: The stimulus response relationships for carotid-cardiac (CSP-HR) and carotid-vasomotor (CSP-MAP) at rest and during static exercise with or without the application of MAS trousers are shown in Figures 3. The calculated variables describing the CSP-HR and CSP-MAP stimulus-response curves are shown in Tables 3 and 4. The maximal gain of the CSP-HR stimulus-response curve was found to be unaltered by control and MAS

static exercise. Threshold carotid sinus pressure (CSP_{thr}) and saturation carotid sinus pressure (CSP_{sat}) for the CSP-HR response curve demonstrated an increase from rest during control exercise and CSP_{sat} was significantly elevated from control exercise during static MAS trouser exercise. The operating point (OP) and centering point (CP) of the CSP-HR responses were significantly increased by static exercise but were unaltered from control exercise by the MAS trouser condition. However, the relationship between OP and CP for the CSP-HR reponse curve was unaffected by static exercise with or without MAS trousers (Table 5). The resetting of the of the CSP-HR stimulus-response curve during control exercise was only relocated rightward to a higher operating pressure by activation of the exercise pressor reflex during the MAS trouser condition (Figure 3).

Carotid-vasomotor (CSP-MAP) stimulus-response curves during static exercise: The maximal gain of the CSP-MAP stimulus-response curve was found to be unaltered by control and MAS static exercise. Threshold carotid sinus pressure (CSP_{thr}) and CSP_{sat} for the CSP-MAP response curve demonstrated an increase from rest during control exercise and was significantly elevated from control rest during static MAS trouser exercise. The operating point (OP) and CP of the CSP-MAP response was significantly increased by static exercise and increased further from control exercise by the MAS trouser condition. However, the relationship between OP and CP for the CSP-MAP response curve was unaffected by static exercise with or without MAS trousers (Table 5). Differences between control and MAS trouser condition OP and CP was obtained using a paired 'a priori' t-test. The CSP-MAP response curve was reset upward on the response arm and rightward to a higher operating pressure which was further augmented upward and

rightward by the MAS trouser condition (activation of the exercise pressor reflex) (Figure 3).

Carotid-cardiac (CSP-HR) stimulus-response curves during dynamic exercise: The stimulus response relationships for CSP-HR and CSP-MAP stimulus response curves at rest and during dynamic exercise with or without the application of MAS trousers are shown in Figures 4. The calculated variables describing stimulus-response curves are shown in Tables 3 and 4. The maximal gain of the CSP-HR stimulus-response curve was found to be unaltered by control and MAS dynamic exercise. Threshold carotid sinus pressure (CSP_{thr}) and CSP_{sat} for the CSP-HR response curve demonstrated an increase from rest during exercise. In addition, CSP_{thr} and CSP_{sat} for the CSP-HR response curve was significantly increased from control exercise by MAS trousers. The OP and CP of the CSP-HR responses were significantly increased by dynamic exercise but were unaltered from control by the MAS trouser condition. The OP was relocated away from CP for the CSP-HR response curve during dynamic exercise but was unaffected by exercise with MAS trousers (Table 5). The upward and rightward resetting of the of the CSP-HR response curve during control exercise was only relocated rightward to higher operating pressures by activation of the exercise pressor reflex during the MAS trouser condition (Figure 4).

Carotid- vasomotor (CSP-MAP) stimulus-response curves during dynamic exercise: The maximal gain of the CSP-MAP stimulus-response curve was found to be unaltered by control and MAS dynamic exercise. Threshold carotid sinus pressure and CSP_{sat} for CSP-MAP response curve were significantly increased from control exercise by

MAS trousers. Operating point and CP for CSP-MAP responses were not altered from rest by control dynamic exercise, however OP and CP were significantly increased from rest and control exercise by MAS trousers. The relationship between OP and CP for the CSP-MAP response curve was unaffected by exercise with or without MAS trousers (Table 5). Collectively, this relocation upward on the response arm and rightward to a higher operating pressures of the CSP-MAP stimulus-response curve suggesting resetting of the CBR during control dynamic exercise was further augmented by the MAS trouser condition (activation of the exercise pressor reflex) (Figure 4).

DISCUSSION

The major new finding from this study was that activation of skeletal muscle receptors (exercise pressor reflex) by medical anti-shock trousers during exercise reset the carotid-vasomotor response curve upward on the response arm and rightward to a higher operating pressure and the carotid-cardiac response curve rightward only. Sensitivity of the carotid-vasomotor and carotid-cardiac response curves was unaltered by exercise pressor reflex activation. In addition, activation of skeletal muscle receptors with MAST trousers during exercise failed to relocate the OP of the carotid-vasomotor and carotid-cardiac response curves away from the CP. The original hypothesis by Rowell and O'Leary suggested that the exercise pressor reflex relocates the CBR upward on the response arm (32). However, these data suggest that the exercise pressor reflex is capable of actively resetting the carotid-vasomotor stimulus response curve during dynamic and

static exercise, however it appears only to modulate the carotid-cardiac stimulus response curve.

In 1981, Melcher and Donald (19) determined that the carotid baroreflex maintained its ability to regulate arterial pressure during exercise. Subsequently, DiCarlo and Bishop (3) demonstrated in rabbits that the arterial baroreflex was shifted to higher pressures at the initiation of exercise. Augmented renal sympathetic and HR responses occurred during exercise when the normal pressure response was reduced by nitroglycerin. In 1993, Potts et al. (28) artificially stimulated the carotid baroreceptors using NP/NS during rest and exercise in humans. They reported that the carotid baroreflex was reset upward on the response arm and rightward to higher operating pressures (classical resetting) in relation to the intensity of exercise without alterations in gain. In addition, they determined that the pre-stimulus HR or MAP (or operating point) of the response curve was relocated away from the centering point and closer to threshold. They suggested that relocation of the operating point permits the carotid baroreflex to respond to a wider range of carotid sinus hypertension (28). This resetting of the carotid baroreflex has been confirmed to occur during static exercise (4) and in direct relation to the intensity of exercise including maximum (22, 24).

Rowell and O'Leary have hypothesized that two neural inputs, central command and the exercise pressor reflex, are involved in the resetting of the carotid baroreflex during exercise(32). Central command is a "feed-forward" controller involved in the regulation of somatomotor and cardiovascular responses (36). From its putative location in the hypothalamic locomotor region, it has been demonstrated to provide regulatory

synaptic input to medullary neurons that comprise the central baroreceptor pathways (36). Recently, we increased central command during dynamic and static exercise using partial neuromuscular blockade (6). We found that increased central command further reset the carotid-vasomotor and the carotid-cardiac response curves upward and rightward from control exercise without alterations in gain. In addition, neuromuscular blockade augmented the relocation of the operating point away from the centering point and closer to threshold. We concluded therefore that the feed-forward central command actively regulates the resetting of the carotid baroreflex during exercise.

Thus, central command was involved in the resetting of the carotid baroreflex during exercise, however the exact role of the exercise pressor reflex in baroreflex resetting has yet to be elucidated. The exercise pressor reflex entails negative feedback from chemically-sensitive (chemoreceptors) and mechanically-sensitive (mechanoreceptors) receptors located in skeletal muscle. Cardiovascular responses to exercise have been demonstrated to be mediated in part by these receptor groups (10, 20). In 1997, Papelier et al. (25) used post-exercise ischemia to determine the effect of chemoreceptor activation on the carotid baroreflex. They determined that chemoreflex activation overall diminished the sensitivity of the carotid -vasomotor response curve without altering the carotid-cardiac response curve. Additionally, they found that the carotid-vasomotor response curve had an increased sensitivity to hypotensive stimuli and a decreased sensitivity to hypertensive stimuli. However, they did not determine the effect of chemoreceptor activation during exercise. Shi et al. (34) has similarly found that exercise pressor reflex activation at rest diminished the sensitivity of the carotid-

vasomotor and carotid-cardiac response curves to both hypotensive and hypertensive stimuli. Potts et al. (28) have recently reported that electrically stimulated contractions of skeletal muscle resulted in a rapid resetting of the carotid baroreflex threshold pressure to higher operational pressure. Potts et al.'s data confirmed the exercise pressor reflex involvement in the resetting of the carotid baroreflex. However, they did not examine the entire stimulus-response curve.

In the present investigation, we applied MAS trousers inflated to 100 mmHg to the lower limbs to activate muscle mechanoreceptors and chemoreceptors during static and dynamic exercise. Williamson et al. (37) demonstrated augmented blood pressure responses with the application of MAS trousers. They eliminated this response by blocking the afferent feedback from the compressed muscle by epidural blockade. Similar to Williamson et al. (37), we found an augmented MAP response during exercise with the application of MAS trousers, with no effect on HR (Figures 1 and 2). In addition, the MAS trouser condition had no effect on VO_2 or plasma lactate and epinephrine concentrations (Table 1). We did demonstrate an increased plasma norepinephrine concentration and RPE response during dynamic exercise with inflated MAS trousers (Table 1). The subjects did not report any discomfort with the MAS trousers. However, due to inflated bladders of the trousers located at the inner thigh, the subjects were required to displace their legs laterally in order to perform dynamic cycling. This could explain why RPE was only elevated during dynamic exercise with MAS trousers. The increased RPE does imply central command activation during dynamic MAS trouser cycling which might confound the data. However, since HR was not affected by MAS

trousers and the overall results were similar between static and dynamic exercise, we suggest that any increase in central command during dynamic exercise was minimal.

During dynamic and static exercise, CSP centering point (A_3), threshold CSP and saturation CSP were elevated from rest by control exercise and was significantly increased from control by the MAS trouser condition (Tables 2, 3, 4). Sensitivity of the carotid-vasomotor and carotid-cardiac response curves were not altered by either control or MAS trouser static and dynamic exercise (Tables 3 and 4). The threshold and saturation pressure responses along with the CSP centering point responses indicate that activation of the exercise pressor reflex reset the carotid-vasomotor and carotid-cardiac response curves rightward to higher operating pressures without alterations in gain (Figures 3 and 4).

The MAP operating point and centering point demonstrated progressive increases from rest during static control exercise and static MAS trouser exercise and was significantly elevated above control dynamic exercise by the MAS trouser condition (Table 4). The minimal response of MAP (A_4) was significantly increased from control static and dynamic exercise by the MAS trouser condition (Table 2). The HR operating point, centering point and minimal response were increased by control static and dynamic exercise but were unaltered by the MAS trouser condition (Table 3). The operating point and centering point along with minimal response of HR and MAP suggest that exercise pressor activation reset the carotid-vasomotor function curve upward, however this upward resetting was not shown by the carotid-cardiac function curve (Figures 3 and 4).

The data of the present investigation indicate that the carotid-vasomotor stimulus response curve was reset by control exercise and was additionally reset upward on the response arm and rightward to higher operating pressures by the MAS trouser condition during static and dynamic exercise. However, the MAS trouser condition only reset the carotid-cardiac stimulus-response curve rightward to higher operating pressures (Figures 3 and 4). This data coincides with recent data from Raymond et al. (30). They artificially induced dynamic leg cycling (eliminating central command) in able-bodied subjects and in paraplegics (no afferent feedback from the skeletal muscle receptors). In able-bodied subjects when central command was eliminated during non-voluntary exercise, they found an upward and rightward resetting of the carotid-vasomotor and carotid-cardiac stimulus-response curves. While in paraplegics during electrically stimulated cycling (no central command or exercise pressor feedback) the carotid-vasomotor stimulus response curve was not reset and the carotid-cardiac curve was only reset upward. Interestingly, the upward resetting of the carotid-cardiac stimulus-response curve in the paraplegics must have been a result of a mechanism other than central command or the exercise pressor reflex. The results of Raymond et al. confirm the findings of the present investigation in that exercise pressor reflex activation resets the carotid-vasomotor curve upward on the response arm and rightward to higher operating pressures and the carotid-cardiac curve rightward to higher operating pressures only.

Evidence exists demonstrating that afferent fibers from baroreceptors and skeletal muscle receptors synapse in the nucleus tractus solitarius (NTS) (9, 17, 23, 26, 36). In addition, the central baroreceptor pathway consists of excitatory projections from the NTS

to the caudal ventrolateral medulla (cVLM) (36). McMahon et al. (17) reported that somatosensory input from peroneal nerve stimulation resulted in inhibition of barosensitive neurons in the NTS. Potts et al. (27) suggested that activation of skeletal muscle afferents would inhibit the barosensitive neurons in the NTS and would require a greater input stimulus to activate the baroreflex. This would result in a reflex that operates at a higher pressure range without a change in sensitivity. Additionally, central cortical (central command) neural inputs also synapse with the above described baroreceptor neural pathways (36). Thus, it seems reasonable that both central command and the exercise pressure reflex are involved in the regulation of the carotid baroreflex during exercise. However, since central command is a feedforward mechanism and has been previously shown to actively reset the carotid baroreflex (6), it seems apparent that central command would act more as the primary regulator of carotid baroreflex resetting. Furthermore, the results in the present investigation lend more to the exercise pressor reflex being a negative feedback modulator of carotid baroreflex resetting using sympathetic neural activation as previously described by Rowell and O'Leary (32).

Due to the nature of the present study, a discussion of the assumptions and limitations of the investigation is warranted. First, there existed a lack of significant increases in saturation and threshold during control static and dynamic exercise at the respective workrates of 20% MVC and 20% VO_{2peak} is a cause for concern. Potts et al. found similar non-significant increases in saturation, threshold and centering point from rest during exercise at 25% VO_{2peak}. However they found significant elevations at exercise of 50% VO_{2peak} (28). More importantly, DiCarlo and Bishop have provided evidence that

the carotid baroreflex was reset immediately at the initiation of exercise (3). In addition, it has been demonstrated that the carotid baroreflex resets in direct relation to the intensity of exercise (22, 24). We found significant increases in the centering point of the carotid-cardiac and carotid-vasomotor stimulus-response curves during control static and dynamic exercise. Thus, we concluded that the carotid baroreflex was indeed reset during control static and dynamic exercise at the low work rates of 20% MVC and 20% VO_{2peak}.

A second potential limitation was that the precise pressure transmission to the carotid sinus during neck pressure (NP) and neck suction (NS) remains unknown. Ludbrook et al. (13) demonstrated asymmetric reductions in transmission characteristics of NP and NS directly measured with a fluid-filled catheter. More recently, Querry et al. (29) have reported greater than 90% transmission of NP and NS directly measured with a pressure-tipped (Milar) catheter at rest and during exercise. They suggested that NS would influence the fluid volume in the fluid-filled catheter confounding measurements and that the use of a pressure-tipped catheter to determine transmission characteristics was more appropriate. Therefore, we considered NP and NS to be faithfully transmitted to the carotid sinus at rest and during exercise.

A final potential limitation to this study is the brief nature of the stimulus in the NP/NS technique. The brief pulses (500ms) were used in order to fully assess the carotid baroreflex in a limited amount of time, such as during the static contractions. In addition, such brief stimulations were thought to stimulate the carotid baroreceptors with minimal or no effect on the extra-carotid baroreceptors (cardiopulmonary and aortic) (28). However, the brief stimuli limit the ability to fully assess the carotid-vasomotor response

as a 20 to 40 second stimulus is required to establish the complete sympathetic neural response (33). Yet estimations of the carotid-vasomotor reflex can be derived from the mean arterial pressure responses to the NP/NS protocol. Rea and Eckberg have demonstrated almost immediate alterations in MSNA to brief periods of NP and NS (31). Furthermore, it has been determined that brief periods of NP and NS fail to elicit significant changes in stroke volume (12). Additionally the steady-state changes in cardiac output after two minute change in CSP could only account for 50% of the observed change in blood pressure (14). Thus, brief NP/NS induced changes in blood pressure were caused in-part by reflex-induced changes in peripheral vascular resistance and were used to estimate the carotid-vasomotor reflex.

In summary, we confirmed that the stimulus-response relationship of the carotid baroreflex was reset during dynamic and static exercise to the prevailing systemic pressure. We also demonstrated that activation of the exercise pressor reflex further resets the carotid-vasomotor baroreflex upward on the response arm and rightward to higher operating pressures (classical resetting) in the same manner during dynamic and static exercise without alterations in gain. Whereas, the exercise pressor reflex only resets the carotid-cardiac baroreflex rightward to higher operating pressures. In addition, the exercise pressor reflex does not appear to have an active role in relocating the pre-stimulus HR and MAP, i.e. operating point, away from the centering point and closer to the threshold during exercise. We conclude that the exercise pressor reflex is capable of resetting the carotid-vasomotor response and modulating the carotid-cardiac response during exercise. However, due to the negative feedback nature of the exercise pressor

reflex, it seems reasonable to conclude that the exercise pressor acts more as a modulator of carotid baroreflex resetting in response to the demands of the skeletal muscle.

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Table 1. Selected physiological responses

	RPE	VO_2 $ml \bullet min^{-1}$	Lactate $mmol \bullet L^{-1}$	NE $nmol \bullet L^{-1}$	E $nmol \bullet L^{-1}$
CONTROL					
Rest	--	0.337 ± 0.03	0.78 ± 0.09	1.25 ± 0.17	0.51 ± 0.15
Static	12.6 ± 0.5	0.482 ± 0.04†	0.82 ± 0.10	1.71 ± 0.22	0.89 ± 0.16
Rest	--	0.336 ± 0.03	0.63 ± 0.09	1.15 ± 0.12	0.59 ± 0.21
Dynamic-1	9.9 ± 0.4	0.903 ± 0.03†	--	--	--
Dynamic-2	10.6 ± 0.4	0.925 ± 0.04†	0.69 ± 0.12	1.92 ± 0.22†	0.67 ± 0.13
MAS					
Rest	--	0.346 ± 0.02	0.52 ± 0.05	1.20 ± 0.11	0.55 ± 0.18
Static	13.2 ± 0.5	0.452 ± 0.03†	0.63 ± 0.09	2.05 ± 0.29†	0.76 ± 0.20
Rest	--	0.382 ± 0.05	0.53 ± 0.06	1.26 ± 0.16	0.55 ± 0.15
Dynamic-1	12.3 ± 0.5*	0.915 ± 0.04†	--	--	--
Dynamic-2	13.5 ± 0.5*	0.923 ± 0.04†	0.76 ± 0.12	2.34 ± 0.22†*	0.89 ± 0.30

Values are mean ± SE; RPE, Ratings of perceived exertion; VO_2, oxygen uptake; NE, Norepinephrine; E, epinephrine; Static (n=10), static contraction at 3rd minute; Dynamic-1 (n=6), dynamic cycling at 4th minute; Dynamic-2, dynamic cycling at 7th minute. * Significantly difference from control exercise, † Significantly different from resting condition; $P < 0.05$.

Table 2. Logistic model parameters describing carotid sinus baroreceptor reflex control of HR and MAP

	A_1	A_2	A_3	A_4
Carotid-cardiac Baroreflex	(beats•min^{-1})		(mmHg)	(mmHg)
Rest Control	24.6 ± 2.2	0.14 ± 0.02	92.8 ± 4.1	49.1 ± 3.3
Static Control	24.3 ± 1.2	0.13 ± 0.02	99.4 ± 3.6	66.0 ± 4.4†
Dynamic Control	29.7 ± 3.0	0.13 ± 0.02	102.0 ± 3.5	62.7 ± 4.1†
Rest MAS	23.2 ± 1.3	0.14 ± 0.03	98.3 ± 4.6	49.7 ± 3.5
Static MAS	28.9 ± 1.8	0.08 ± 0.01	107.7 ± 2.8†*	58.8 ± 5.3†
Dynamic MAS	30.9 ± 1.9†	0.12 ± 0.02	116.7 ± 5.6†*	65.0 ± 5.3†
Carotid-vasomotor Baroreflex	(mmHg)		(mmHg)	(mmHg)
Rest Control	21.2 ± 2.9	0.10 ± 0.01	90.6 ± 4.8	75.5 ± 3.3
Static Control	22.1 ± 2.9	0.07 ± 0.02	103.6 ± 3.3†	90.5 ± 3.1†
Dynamic Control	21.4 ± 2.0	0.09 ± 0.01	91.0 ± 2.9	76.3 ± 3.5
Rest MAS	21.4 ± 2.5	0.07 ± 0.01	101.2 ± 5.8	77.8 ± 2.2
Static MAS	23.9 ± 2.1	0.06 ± 0.01	111.8 ± 3.4†*	97.7 ± 2.4†*
Dynamic MAS	22.9 ± 2.6	0.08 ± 0.01	104.5 ± 3.6*	90.4 ± 3.1†*

Values are mean ± SE. A_1, range (maximum-minimum); A_2, gain coefficient; A_3, carotid sinus pressure (CSP) at midpoint (centering point); A_4, minimal response.

* Significantly difference from control exercise, † Significantly different from resting condition, $P < 0.05$.

Table 3. Derived variables describing the stimulus-response relationship for carotid baroreflex control of heart rate

	Control			MAS		
	Rest	Static	Dynamic	Rest	Static	Dynamic
CSP_{thr} mmHg	74.9 ± 3.7	78.8 ± 5.1	84.0 ± 3.8	79.1 ± 4.2	78.0 ± 4.9	95.7 ± 4.9†*
CSP_{sat} mmHg	110.7 ± 6.4	120.0 ± 5.1	120.1 ± 4.7	117.9 ± 6.1	137.5 ± 2.5†*	133.3 ± 7.4†*
HR_{op} beats•min^{-1}	64.7 ± 4.3	74.1 ± 5.1†	85.0 ± 4.4†	64.7 ± 4.2	75.5 ± 5.2†	89.9 ± 5.1†
HR_{cp} beats•min^{-1}	61.8 ± 3.7	72.1 ± 4.4†	77.5 ± 4.2†	61.2 ± 3.6	73.2 ± 4.9†	80.4 ± 5.1†
Max gain beats•min^{-1} •mmHg^{-1}	-0.61 ± 0.20	-0.66 ± 0.20	-0.96 ± 0.12	-0.74 ± 0.12	-0.58 ± 0.09	-0.89 ± 0.15

Values are means ± SE, CSP_{thr}, carotid sinus threshold pressure; CSP_{sat}, carotid sinus saturation pressure; HR_{op}, HR at operating point; HR_{cp}, HR at centering point of reflex; max gain, point of greatest slope (i.e. gain coefficient) on 1st derivative curve of logistic function. * Significantly difference from control exercise, † Significantly different from resting condition, $P < 0.05$.

Table 4. Derived variables describing the stimulus-response relationship for carotid baroreflex control of mean arterial pressure

	Control			MAS		
	Rest	Static	Dynamic	Rest	Static	Dynamic
CSP_{thr} mmHg	69.6 ± 5.2	71.9 ± 7.8	66.0 ± 3.5	66.2 ± 3.0	79.4 ± 5.4†	77.1 ± 5.4†*
CSP_{sat} mmHg	111.6 ± 5.7	137.3 ± 5.1†	116.0 ± 4.4	127.6 ± 3.6†	144.3 ± 2.6†	131.8 ± 2.4*
MAP_{op} mmHg	84.6 ± 1.8	100.1± 2.9†	87.9 ± 3.6	90.4 ± 2.2	108.8± 3.7†	100.9 ± 2.9†*
MAP_{cp} mmHg	86.1 ± 2.6	101.5 ± 2.6†	87.0 ± 3.6	88.5 ± 2.2	109.6 ± 2.3†	101.8 ± 3.0†*
Max gain mmHg•min^{-1} •mmHg^{-1}	-0.53 ± 0.08	-0.35 ± 0.04	-0.44 ± 0.02	-0.38 ± 0.04	-0.38 ± 0.04	-0.42 ± 0.03

Values are means ± SE, CSP_{thr}, carotid sinus threshold pressure; CSP_{sat}, carotid sinus saturation pressure; MAP_{op}, MAP at operating point; MAP_{cp}, MAP at centering point of reflex; max gain, point of greatest slope (i.e. gain coefficient) on 1st derivative curve of logistic function. * Significantly difference from control exercise, † Significantly different from resting condition, $P < 0.05$.

Table 5. Calculated differences between operating point and centering point

	Control			MAS		
	Rest	Static	Dynamic	Rest	Static	Dynamic
dHR (beats•min^{-1})	3.3 ± 1.1	2.0 ± 1.3	7.5 ± 1.2†	3.4 ± 1.0	2.3 ± 1.2	9.5 ± 1.2†
dMAP (mmHg)	-0.3 ± 1.5	-1.4 ± 1.6	0.9 ± 0.8	1.9 ± 1.0	-0.9 ± 1.5	-1.0 ± 1.5

Values are means ± SE, dHr, HR operating point (pre-stimulus HR) minus HR centering point; dMAP, MAP operating point (pre-stimulus MAP) minus MAP centering point. * Significantly difference from control exercise, † Significantly different from resting condition, $P < 0.05$.

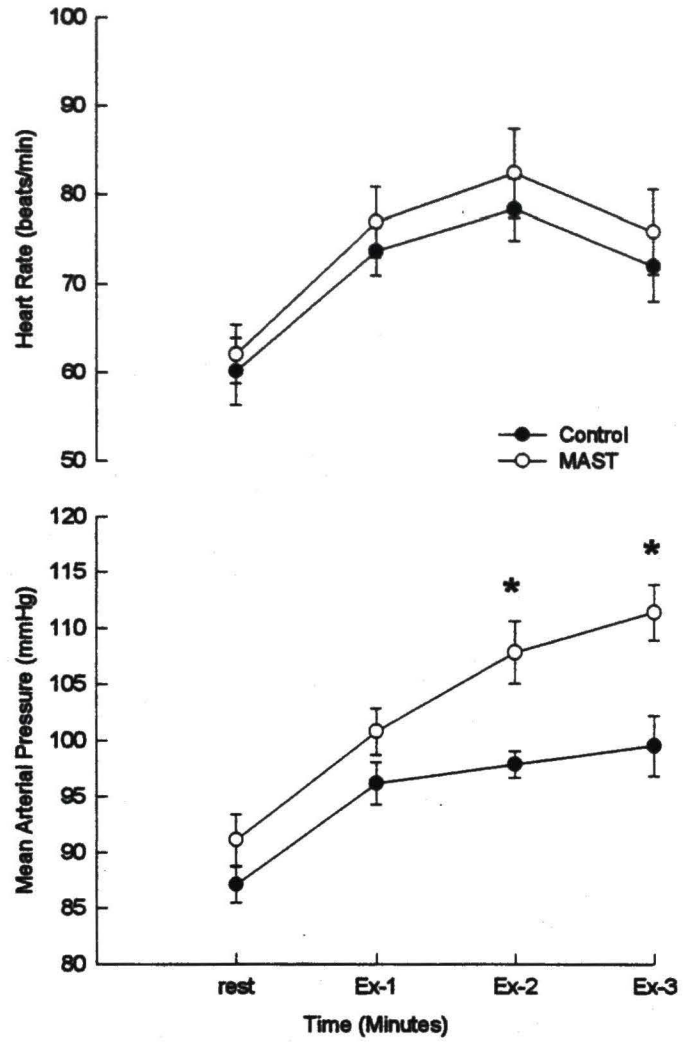

Figure 1 - Heart Rate and mean arterial pressure responses at rest and during three minute one-legged static exercise (20% maximal voluntary contraction) without (o) and with (●) application of medical anti-shock trousers (MAST). Values are means ± SE. * Significant difference between control and MAST ($P < 0.05$).

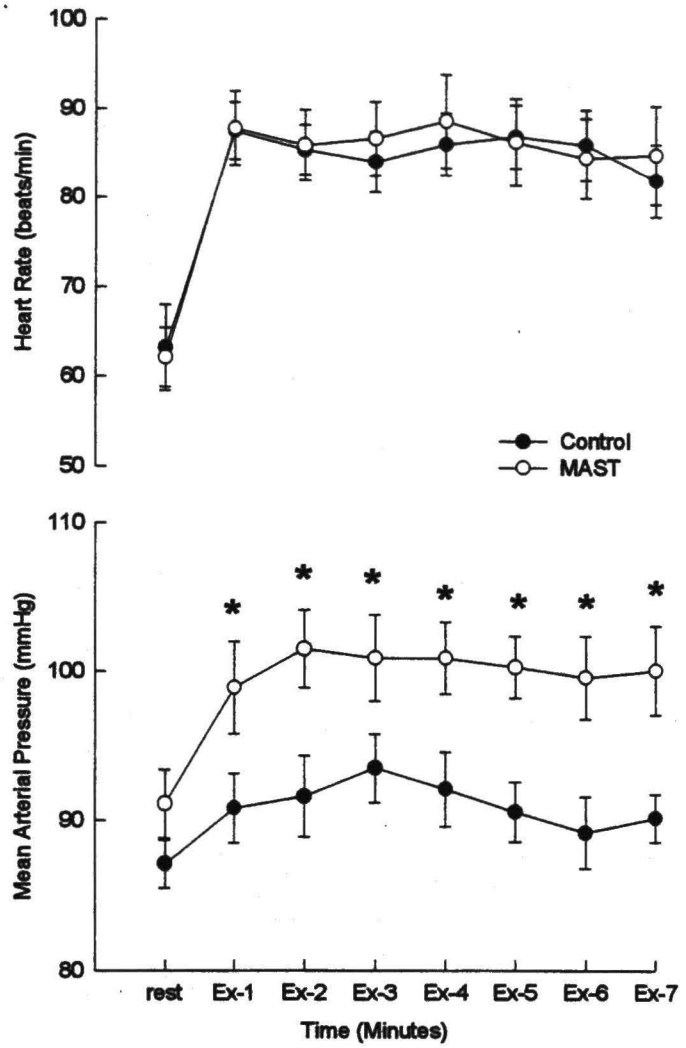

Figure 2 - Heart Rate and mean arterial pressure responses at rest and during seven minutes dynamic cycling exercise (20% maximum oxygen uptake) without (o) and with (●) application of medical anti-shock trousers (MAST). Values are means ± SE.

*** Significant difference between control and MAST ($P < 0.05$).**

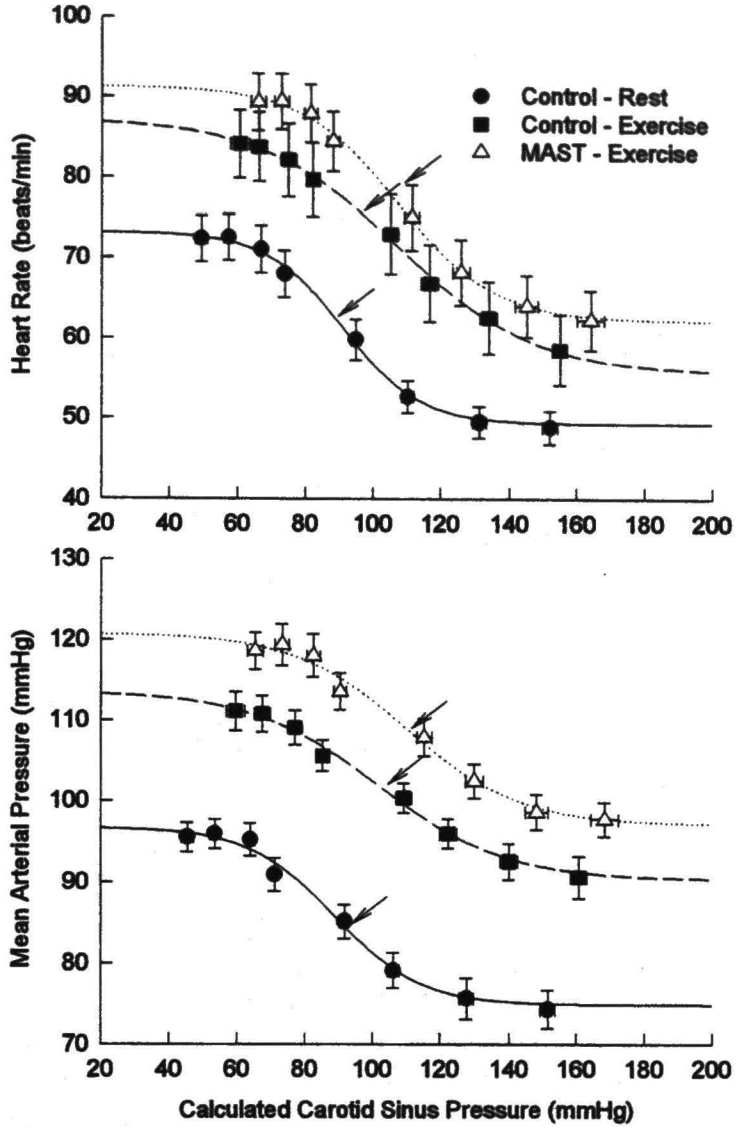

Figure 3 - Reflex responses in HR (carotid-cardiac) and MAP (carotid-vasomotor) after perturbations to carotid sinus baroreceptors at rest (●), during control static (20% MVC) one-legged exercise (■) and during static exercise after application of medical anti-shock trousers (MAST) (Δ). Data points represent means ± SE. ← indicates operating point. Lines represent mean fit of individual subjects' data. MAS trouser rest curves were not significantly different from control rest curves and have been omitted for clarity.

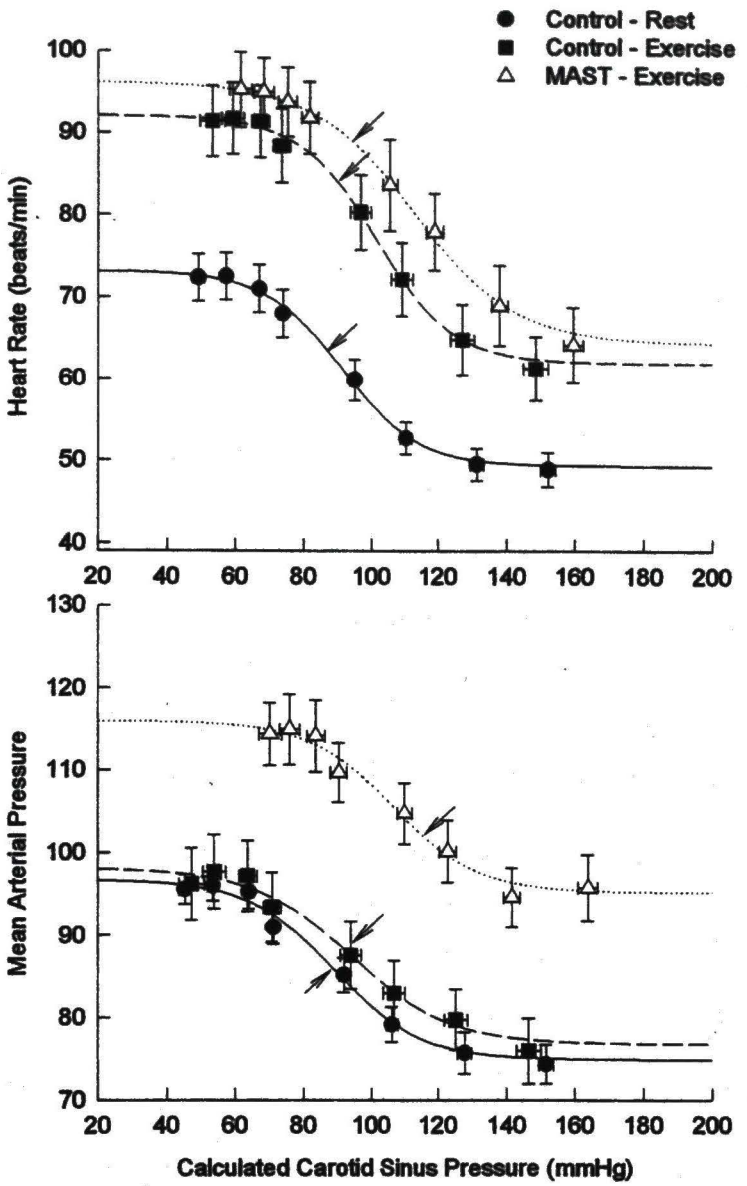

Figure 4 - Reflex responses in HR (carotid-cardiac) and MAP (carotid-vasomotor) after perturbations to carotid sinus baroreceptors at rest (●), during control dynamic (20% MVC) cycling exercise (■) and during dynamic exercise after application of medical anti-shock trousers (MAST) (Δ). Data points represent means ± SE. ← indicates operating point. Lines represent mean fit of individual subjects' data. MAS trouser rest curves were not significantly different from control rest curves and have been omitted for clarity.

CHAPTER V

CONCLUSIONS

Rowell and O'Leary originally hypothesized that upward resetting on the response arm of the reflex due to exercise pressor reflex activation and a rightward relocation to a higher operating pressure due to central command activation combine to create the typical resetting of the carotid baroreflex that occurs during exercise. The results of the three investigations described herein provide new evidence suggesting that carotid baroreflex resetting during exercise is predominately mediated by the "feedforward" central command with modulation feedback from the exercise pressor reflex (mechanoreceptors).

The first investigation demonstrated that activation of mechanically-sensitive receptors (mechanoreceptors) during exercise resulted in an augmented blood pressure response. In addition, stimulation of chemically-sensitive receptors (chemoreceptors) in the exercise pressor reflex by trapping metabolites in active skeletal muscle failed to produce any increases in arterial blood pressure. This resulted in the conclusion that under normal conditions the mechanoreflex was tonically active and was the primary mediator of arterial blood pressure during exercise (Figure 1).

The second investigation demonstrated that central command was capable of actively resetting the carotid baroreflex upward on the response arm and rightward to a

higher operating pressure without alterations in the gain of the reflex during exercise. Additionally, it was demonstrated that central command activation further relocated the operating point of the baroreflex away from the centering point and closer to the threshold region. This relocation of the operating point would allow the carotid baroreflex to respond to greater ranges of hypertension during exercise. Due to the feedforward nature of central command and its known interaction with central baroreceptor pathways, we contend that central command was primarily responsible for carotid baroreflex resetting during dynamic and static exercise (Figure 1).

The third investigation demonstrated that the exercise pressor reflex was capable of resetting the carotid-vasomotor reflex upward on the response arm and rightward to higher operating pressures during exercise without alterations in gain. However, the exercise pressor reflex only resets the carotid-cardiac response curve rightward to higher operating pressures during exercise. In addition, the exercise pressor reflex does not appear to be involved in the relocation of the operating point away from the centering point which was normally seen in carotid baroreflex resetting. Therefore, due to the negative feedback nature of the exercise pressor reflex and its incomplete involvement in carotid baroreflex resetting, we suggest that the exercise pressor reflex acts more as a modulator of baroreflex resetting in response to demands placed on the skeletal muscle receptors (Figure 1).

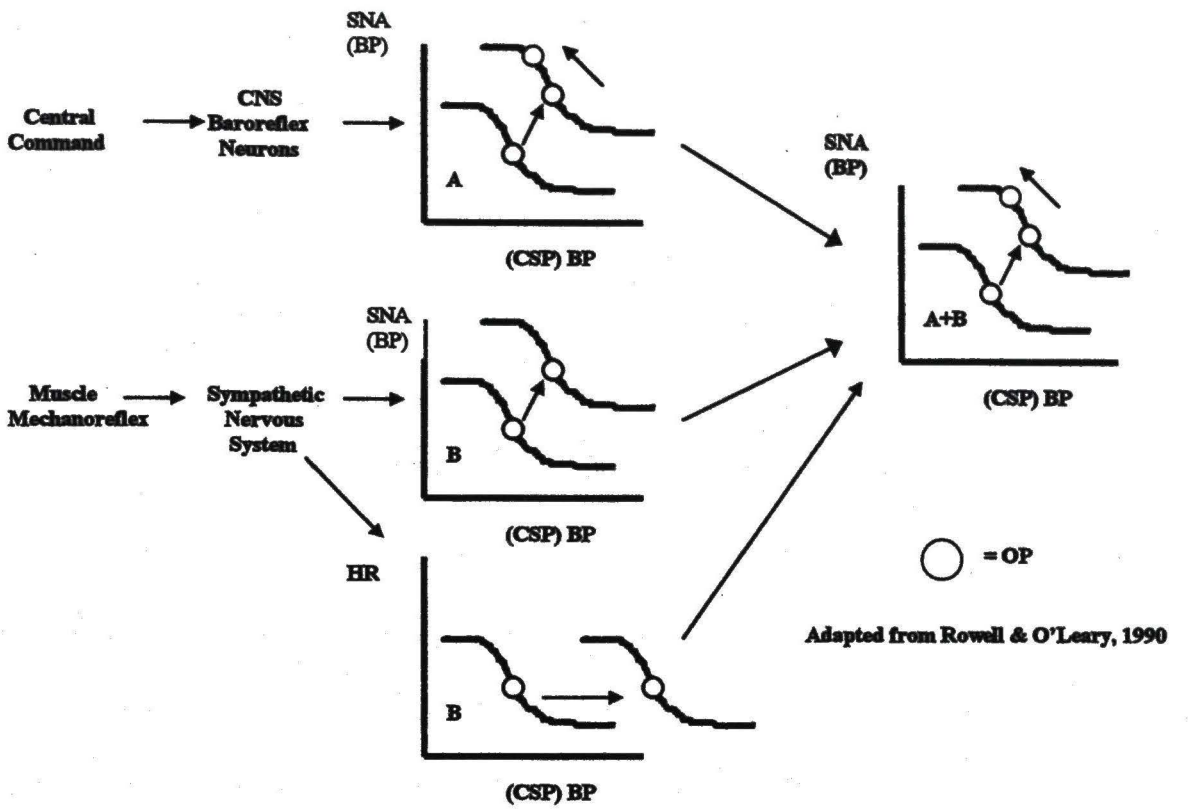

Figure 1- A updated model of arterial baroreflex resetting

CHAPTER IV

Although the research presented produced several new findings in reference to the resetting of the carotid baroreflex during exercise, many questions have yet to be addressed. For example, we only studied the effects of the enhancement of central command and exercise pressor reflex of carotid baroreflex resetting. To determine if the findings during enhanced central command and exercise pressor reflex are opposite when these neural processes are decreased or eliminated would be of great value. Additionally, to observe the effect of simultaneous increases in central command and the exercise pressor reflex would be beneficial. Below is a list of several potential investigations designed to further examine the roles of central command and the exercise pressor reflex in the control of carotid baroreflex resetting during exercise.

I. To test the hypothesis that diminished central command results in a negative resetting (downward and leftward) of the carotid baroreflex during exercise. In an earlier study by Goodwin et al. (1972), subjects performed isometric contractions with the aid or the inhibitory effects of vibration. They demonstrated that if a small vibrator was applied to a tendon of a muscle that it can stimulate a small contraction (10% of MVC) via activation of the muscle spindles. Therefore, if the vibrator was applied to the tendon of the muscle performing the exercise, then it would produce its own contraction making it

easier to maintain the desired tension. In other words, less central command would be needed to maintain the same absolute tension. The opposite occurs when the vibration was applied to the antagonist muscle (disynaptic inhibition) resulting in the need for more central command to maintain a desired tension. An experiment could be designed to determine carotid baroreflex function during static and dynamic leg extension with the aid or with the antagonism of the vibratory stimulus. This would determine the effect of increased and decreased central command on carotid baroreflex resetting during exercise. We would anticipate that increased central command would produce similar results as Chapter III. In addition, we would predict that decreased central command would result in a reversal of carotid baroreflex resetting. However, since the exercise pressor reflex and central command are considered redundant mechanisms, it is possible that the exercise pressor reflex would compensate for the decreased central command. This investigation would provide evidence of the interaction between the two neural mechanisms. Additional methods of decreasing/eliminating central command would be through the use of hypnosis or exercise produced by electrically stimulated contractions of the muscles.

II. To further test the hypothesis that the exercise pressor reflex plays a significant role in the resetting of the carotid baroreflex. Epidural blockade has been used in previous investigations to effectively eliminate afferent feedback from active muscle. A similar experiment as used in Chapter IV could be designed with the addition of epidural blockade. Thus, the effect of eliminating the exercise pressor reflex (leaving only central command) on carotid baroreflex resetting could be determined. From the findings that

central command actively resets the carotid baroreflex (Chapter III), we would predict that the carotid baroreflex would still actively reset in an epidural blocked condition. This information would provide further evidence of the importance of central command in the resetting of the carotid baroreflex during exercise. It would also provide additional support concerning the redundant nature of these two neural processes.

III. To further test the hypothesis that central command and the exercise pressor reflex play significant roles in the resetting of the carotid baroreflex. Dynamic and static exercise could be performed with and without the combined enhancement of central command (neuromuscular blockade) and the exercise pressor reflex (medical anti-shock trousers). We would predict that the combined enhancement would result in an additional upward and rightward resetting of the carotid-vasomotor stimulus-response curve when compared to the curare experiments (Chapter III). In addition, the carotid-cardiac stimulus-response curve would additionally reset only rightward when compared to the curare data. This would provide information that central command plays a vital role in the resetting of the carotid-cardiac and carotid-vasomotor stimulus-response curves. Further, that the exercise pressor reflex acts as a modulator of carotid baroreflex resetting during exercise.

Combined these experiments would determine if central command is the primary mechanism involved in the resetting of the carotid baroreflex during exercise and that the exercise pressor reflex acts more as a modulator of the resetting. However, it is possible that these experiments would provide information that identifies that both the two neural

mechanisms are redundant mechanisms involved in the resetting of the carotid baroreflex during exercise.