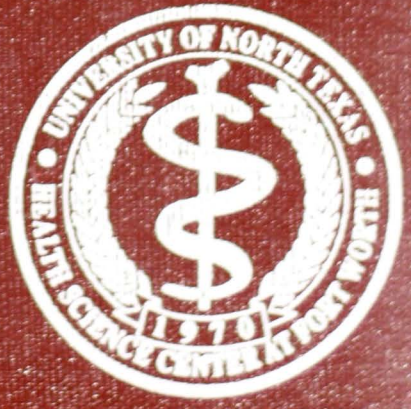
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Bryant, Kristin, Resetting of the Carotid Arterial Baroreflex during Dynamic Exercise Doctor of Philosophy (Biomedical Sciences), August, 1997; 121 pp; 8 tables; 20 figures, bibliography, 82 titles.

Following the initial response to the onset of dynamic exercise, prolonged exercise at a constant workload is characterized by a progressive decrease in stroke volume (SV) and mean arterial pressure (MAP) and a concomitant rise in heart rate (HR). These data raise the question as to whether there is a loss of baroreflex regulation of arterial blood pressure during prolonged dynamic exercise. However, we propose that the carotid baroreflex (CBR) is continually reset during prolonged exercise, with the operating point being shifted toward the reflex threshold, in relation to a progressive increase in central command activity as motor fibers are recruited in response to muscle fatigue. Therefore, the baroreflex is unresponsive to the fall in MAP. In order to investigate this hypothesis, volunteer subjects performed one hour of dynamic leg cycling exercise at 65% of maximal oxygen uptake ($\dot{V}O_{2max}$) with: I) no intervention; and ii) maintenance of cardiac filling volume via continuous infusion of a 6% dextran in saline solution to counteract the fall in SV. At 10 and 50 minutes of exercise, CBR stimulus-response curves were generated using the neck pressure / neck suction technique. The maintenance of cardiac filling volume and thus SV resulted in a diminished drift in MAP. However, indices of central command such as HR, VO_2 and ratings of perceived exertion (RPE) increased to the same extent regardless of exercise condition.

Furthermore, there was augmented resetting of the CBR at 50 minutes of exercise as compared to 10 minutes under both exercise conditions.

In order to further investigate the effects of central command on baroreflex control of blood pressure, a second investigation was designed to demonstrate the effects of exercise type and intensity on CBR function. Stimulus-response relationships were compared during dynamic exercise at a wide range of exercise intensities performed with either leg exercise alone or leg exercise combined with arm exercise. Increases in exercise intensity to maximal exercise resulted in increases in indices of central command such as HR and $\dot{V}O_2$ as well as an augmentation of the magnitude of the lateral shift in the CBR stimulus-response curve (with the operating point being shifted further toward the threshold of the reflex) relative to the activation of central command. In addition, the performance of combined arm and leg exercise elicited an augmented shift in the carotid-vasomotor stimulus-response relationship as compared to leg exercise alone at the same exercise intensity. As arm exercise compared to leg exercise performed at the same absolute $\dot{V}O_2$ results in an increased lactate accumulation in the venous system, the augmented resetting of the CBR is likely due to a disproportionate activation of the muscle metaboreflex component of the muscle pressor reflex. Therefore we propose that central command is the primary mechanism by which the CBR is reset at the onset of dynamic exercise through feed-forward control. However, additional, feed-back modulation can be exerted by the muscle pressor reflex upon the development of mechanical or chemical error signals in the exercising muscle.

RESETTING OF THE CAROTID ARTERIAL BAROREFLEX

DURING DYNAMIC EXERCISE

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RESETTING OF THE CAROTID ARTERIAL BAROREFLEX DURING DYNAMIC EXERCISE

DISSERTATION

Presented to the Graduate Council of the

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University of North Texas Health Science Center at Fort Worth

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For the Degree of

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By

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Original Articles

Manor D., S. Williams, R. Ator, K. Bryant, and K.W. Scheel. Reduced collateral perfusion is a direct consequence of elevated right atrial pressure. *Am. J. Physiol. 267 (Heart Circ. Physiol. 36):* H1151-H1156, 1994.

Manor D., S. Williams, R. Ator, K. Bryant, and K.W. Scheel. Left ventricular mechanics in the arrested dog heart: effects of ventricular interaction and vascular volumes. *Am. J. Physiol. 268 (Heart Circ. Physiol. 37):* H2125-H2132, 1995.

Manor D., S. Williams, R. Ator, K.D. Chen, J.K. Schofield, K. Bryant, and K.W. Scheel. Evidence for a venous gregg and gardenhose effect with venous hypertension. submitted, *Am. J. Physiol. (Heart Circ. Physiol.)*.

Manor D., S. Williams, R. Ator, K. Bryant, and K.W. Scheel. Modulation of coronary flow by left ventricular volume in the presence and absence of vasomotor tone. *Am. J. Physiol. 269 (Heart Circ. Physiol. 38),* H2010-H2016, 1995.

Shi, X., K.M. Gallagher, R.G. Querry, K.H. Bryant, and P.B. Raven. Diminished forearm vasomotor response to central hypervolemic loading in aerobically fit individuals. *Med. Sci. Sport Ex.*, 12(28): 1388-1401, 1996.

Bryant, K.H., R. Boushel, S. Strange, B. Saltin, and P.B. Raven. Resetting of the carotid arterial baroreflex during dynamic exercise in humans. *J. Appl. Physiol.*, submitted, 1997.

Bryant, K.H., K.M. Gallagher, S.A. Smith, R.Q. Querry, R.M. Welch-O'Connor and P.B. Raven. Carotid Arterial Baroreflex Function during Prolonged Exercise. *J. Appl. Physiol.*, submitted, 1997.

Book Chapters

Scheel, K.W., D. Manor, K. Bryant. Influences of Coronary Venous Pressure on Left Ventricular Interactions. In Cardiac-Vascular Remodeling and Functional Interactions. Y. Maruyama, M. Hori, and J.S. Janicki (EDS.) Springer Verlag, Tokyo. In press.

Abstracts

Manor D., S. Williams, R. Ator, K. Bryant, and K. W. Scheel: Elevated right atrial pressure, a possible consequence of heart failure, reduces coronary collateral flow. *The FASEB Journal,* Vol. I, p. A293, 1994.

Scheel K. W., D. Manor, S. Williams, R. Ator, and K. Bryant: Coronary vascular compression increases with elevated venous pressures. *The FASEB Journal,* Vol. II, p. A851, 1994.

Bryant, K., J. Parker, S. Williams, and K. Scheel. Contribution of coronary arteries to coronary arteries to coronary sinus drainage. *UNT Health Science Center Research Appreciation Day*, 1994.

Bryant, K., A. Robberts, X. Shi, and P.B. Raven. Heart rate variability during central hypovolemia in aging. *SEBM - Southwest Section, Abstracts,* 1994 * second place award in poster competition.

Scheel, K.W., D. Manor, S. Williams, R. Ator, and K. Bryant : Passive diastolic left ventricular compliance is decreased by elevated right heart pressure. *The FASEB Journal,* 1995.

Manor, D., S. Williams, R.Ator, K. Bryant, and K.W. Scheel : Coronary flow response to changes in left ventricular volume with and without vasodilation. *The FASEB Journal,* 1995.

Bryant, K.H., J.A. Pawelczyk, X. Shi , and P.B. Raven Assessment of heart rate changes during progressive exercise using power spectral analysis. *The FASEB Journal,* 1995, *The Texas Regional Chapter of the American College of Sports Medicine* 1995, *UNT Health Science Center Research Appreciation Day,* 1995.

Bryant, K.H., R.M. Welch-O'Connor, I.P. Reese, X. Shi, and P.B. Raven. Activated intramuscular receptors (IMR) inhibit human carotid baroreflex (CBR) function. *The Texas Regional Chapter of the American College of Sports Medicine* , 1996.

Smith S.A., K.M. Gallagher, R.G. Querry, K.H. Bryant, and P.B. Raven. Interaction of muscle ergoreceptors with central command during progressive workload dynamic exercise to maximum in humans. *The Texas Regional Chapter of the American College of Sports Medicine*, 1996.

Querry R.G., K.M. Gallagher, I.P. Reese, K.H. Bryant, and P.B. Raven. Comparison of non-invasive vs. invasive measurements of arterial blood pressure during dynamic exercise to fatigue. *The Texas Regional chapter of the American College of Sports Medicine,* 1996. Also: *Medicine and Science in Sport and Exercise*. 28(5) S170:, May, 1996.

K.M. Gallagher, S.A. Smith, K.H. Bryant, R.G. Querry, V.M. Burgos, X. Shi, and P.B. Raven. Interaction of muscle mechano- and metaboreceptors in regulating blood pressure during dynamic exercise. *American Physiological Society: Intersociety Conference*. Vancouver, B.C.Canada, 1996.

K.M. Gallagher, K.H. Bryant, R.G. Querry, S.A. Smith, and P.B. Raven. Oxygen extraction compensates for reductions in blood flow during steady-state dynamic exercise. *American Heart Association. 1996.*

Bryant, K.H., R. Boushel, S. Strange, B. Saltine, and P.B. Raven. Carotid arterial baroreflex function in relation to active skeletal muscle mass. *The FASEB Journal,* 1997. Also: *Texas Regional Chapter of the American College of Sports Medicine* , 1997.

Presentations

Texas Wesleyan University - Carotid Baroreflex Function during Exercise, April 1997.

University of Texas at Arlington - Carotid Baroreflex Function in Relation to Active Skeletal Muscle Mass; and Graduate Opportunity and Experience, February, 1997.

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LIST OF ABBREVIATIONS

ANOVA	analysis of variance
CBR	carotid baroreflex
CBV	central blood volume
CP	centering point
CSP	carotid sinus pressure
CVP	central venous pressure
ECG	electrocardiogram
EMG	electromyographic activity
HR	heart rate
HTL	hypothalamic locomotor region
IV	intravenous
LBF	leg blood flow
MAP	mean arterial pressure
NP / NS	neck pressure / neck suction technique
OP	operating point
%	percent
Qc	cardiac output

RPE	rating of perceived exertion
RSNA	renal sympathetic nerve activity
SV	stroke volume
TPR	total peripheral resistance
VLM	ventral lateral medulla
$\dot{V}O_2$	oxygen uptake
$\dot{V}O_{2\ max}$	maximal oxygen uptake
$\dot{V}O_{2\ peak}$	peak oxygen uptake

CHAPTER 1

INTRODUCTION

The primary question which stimulated the investigations described in this dissertation stems from the observation of an interesting phenomenon which occurs during prolonged dynamic exercise of a moderate to high intensity. Following the initial response to the onset of dynamic exercise, prolonged exercise at a constant workload is characterized by the redistribution of blood volume to the cutaneous circulation in response to thermoregulatory demands resulting in a progressive decrease in central blood volume (CBV), central venous pressure (CVP), and total peripheral resistance (TPR) (5). This redistribution consequently results in a progressive decrease in stroke volume (SV) and mean arterial pressure (MAP) and a concomittant, compensatory increase in heart rate (HR), a phenomenon which has been termed *cardiovascular drift*. However, despite the use of whole body surface cooling or saline infusion during prolonged exercise to return central blood volume to pre-cardiovascular drift values, HR continues to increase and a slight downward drift in MAP remains (13,24). These data raise the question as to whether there is a loss of baroreflex regulation of arterial blood pressure during prolonged dynamic exercise. However, data exists in both animal (1,10) and human (15,20) models which support the continued modulation of arterial blood

pressure by the arterial baroreflexes during dynamic exercise and which suggest that the baroreflex may be reset to operate around the prevailing blood pressure elicited by the exercise. This dissertation is intended to demonstrate that the carotid baroreflex is reset during prolonged dynamic exercise in direct relation to the activation of central command with no decrement in reflex gain, or sensitivity, and further to elucidate the mechanisms involved in the resetting of the reflex with particular attention to the roles of central command and the muscle metaboreflex (25).

BACKGROUND

Prolonged Exercise - Cardiovascular Drift

In 1967, Ekelund (5) reported that prolonged (one hour) of constant load dynamic leg exercise on a cycle ergometer at 65% of maximal aerobic capacity ($\dot{V}O_{2max}$) resulted in a progressive decrease in arterial and pulmonary artery pressures between 10 and 60 minutes of exercise. In addition, stroke volume fell as cardiac filling volume decreased, and heart rate (HR) increased as a compensatory response resulting in the maintenance of a constant cardiac output. This phenomenon, which has been termed "cardiovascular drift", is illustrated in Figure 1.

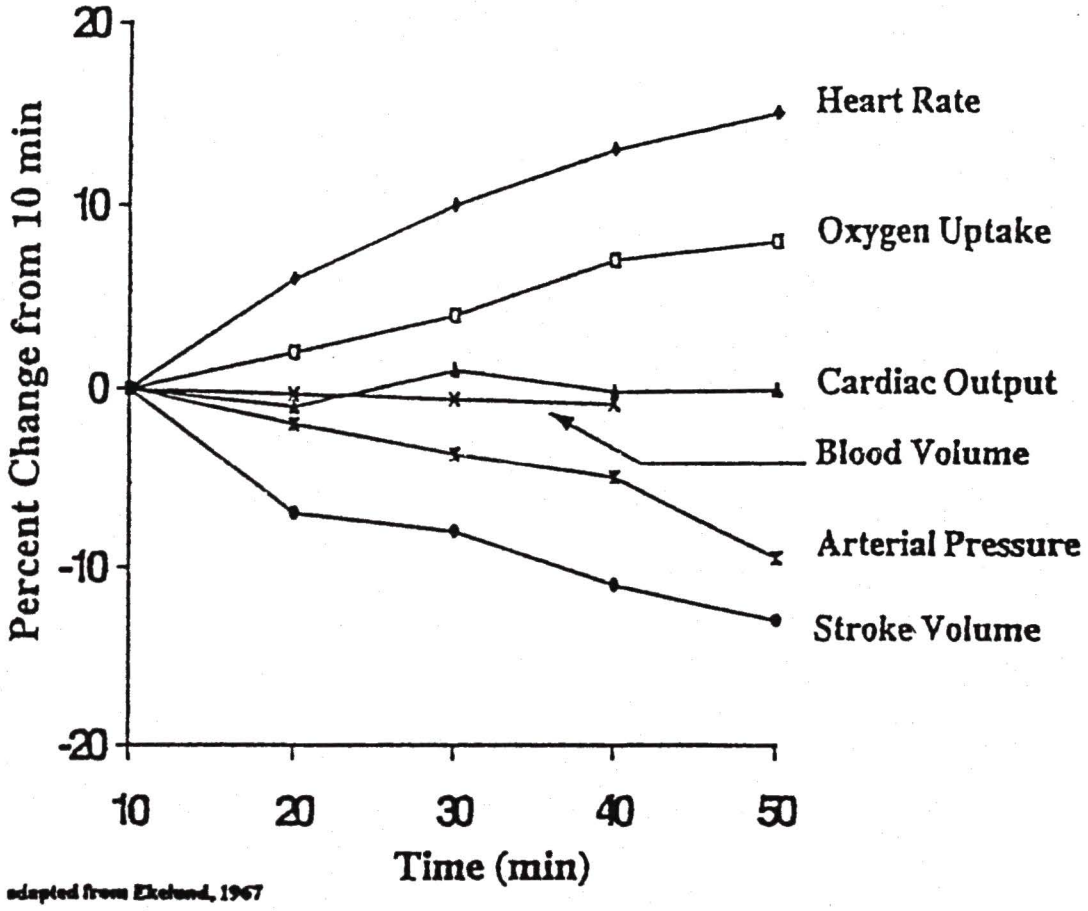


Figure 1. An illustration of "cardiovascular drift" during 65% $\dot{V}O_{2max}$ leg cycling exercise. All values are reported as percent change from 10 minutes of exercise. Adapted from Ekelund et al (5).

Rowell et al (24), Gliner et al (6), and Raven and Stevens (22) in their review have reported that cardiovascular drift is related to thermoregulation by showing that the fall in MAP during prolonged exercise was exacerbated by the addition of heat stress to the exercise protocol. In addition, in their 1969 investigation, Rowell et al. (24) demonstrated that by cooling the skin during prolonged exercise, in order to correct the thermoregulatory redistribution of circulating blood volume to the cutaneous circulation, central venous pressure (CVP) and SV were maintained and the compensatory increase in HR was reduced. In addition, much of the downward drift in MAP was eliminated, presumably through the counteraction of the decrease in total peripheral resistance (TPR) associated with the thermoregulatory redistribution of circulating blood volume to the cutaneous circulation. However, despite this measure there remained a slight progressive decrease in arterial pressure and a progressive increase in HR and oxygen uptake ($\dot{V}O_2$) between 10 and 60 minutes of exercise. In addition, maintenance of central venous pressure (CVP) during prolonged exercise (50 min) via saline infusion has been shown by Nose et. al (1990) to result in the maintenance of plasma volume with no effect on the increase in HR when the ambient temperature was 22°C and only minor effects on the increase in HR in a heated room of 30°C (13), see Figure 2. These data indicate that thermoregulatory blood volume redistribution is an important component of cardiovascular drift but also raise the question as to whether baroreflex control of blood pressure is diminished or fatigued during prolonged exercise.

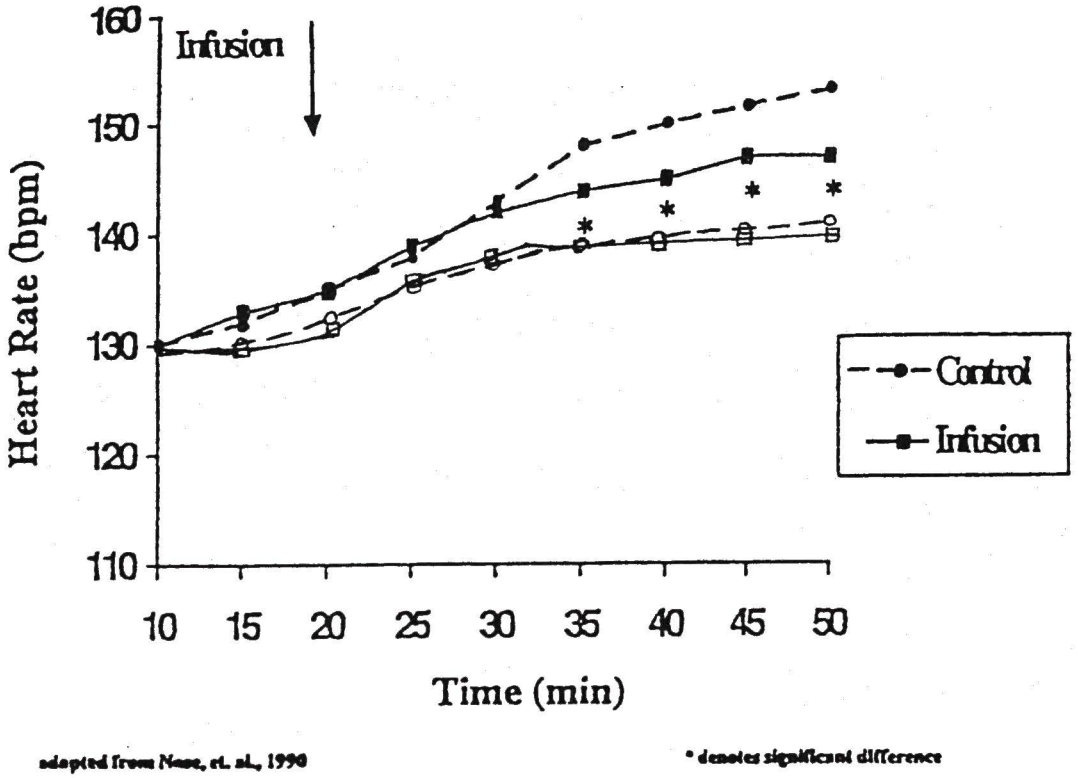
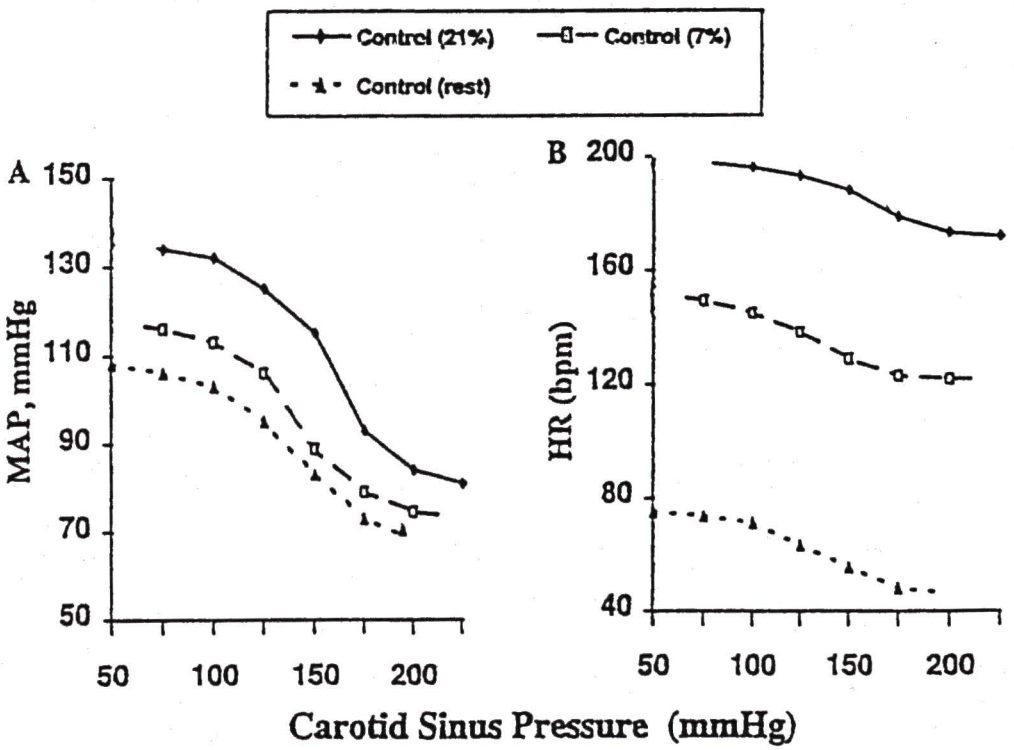


Figure 2. Increases in heart rate during prolonged exercise with and without saline infusion. Closed symbols indicate an ambient temperature of 22°C and open symbols indicate an ambient temperature of 30°C. Adapted from Nose et al (13).

Carotid Baroreflex

The role of the arterial baroreflex in the regulation of arterial blood pressure during dynamic exercise has been controversial for many years. However, data from both animal (1,10) and human (15,20) studies provide strong evidence for continued modulation of arterial blood pressure by the arterial baroreflex during dynamic exercise without a decrement in reflex sensitivity.

Canine model. Melcher and Donald (10) have demonstrated a functioning carotid baroreflex in dynamically exercising dogs using surgical isolation and independent perfusion of the carotid sinus baroreceptors. Pressures within the carotid sinus were changed independently of the systemic circulation and stimulus-response curves for HR and MAP were generated, see Figure 3. The results of this investigation indicated that the carotid baroreflex was indeed functional during dynamic exercise in dogs and that the reflex function curve had undergone an upward shift in threshold and saturation with no change in the maximal gain of the reflex.



adapted from Melcher and Donald, 1981

Figure 3. Alterations in the A.) carotid-vasomotor and B.) carotid-cardiac baroreflex stimulus-response relationship in exercising canines. Note: no change in reflex gain or sensitivity with increasing exercise intensity. Adapted from Melcher and Donald (10).

Human model. In humans, the CBR can be investigated non-invasively through the use of the neck pressure / neck suction technique. This technique, which was developed in the 1950's and has gone through several modifications (28), involves the use of a malleable lead chamber which is secured to the anterior two-thirds of the subject's neck. Pressure and suction pulses ranging from +40 to -80 torr are created within the chamber via vaccuum motors attached by flexible tubing to the lead collar. These pulses are transmitted through the tissue of the neck to the carotid sinus region of the carotid arteries causing distortions which stimulate the carotid arterial baroreceptors. Potts et al (20) have recently modified the technique such that reliable CBR stimulus-response relationships can be constructed during dynamic exercise. These modifications include the administration of very brief pulses (five seconds) to the carotid sinus region in order to increase the selectivity of the protocol by minimizing compensation by the aortic baroreceptors for the reflex arterial pressure responses to the CBR stimuli. In addition, Potts et al (20) triggered the neck pressure and suction pulses during a voluntary end-expiratory breath hold performed by the subject. This modification was undertaken to eliminate the confounding effects of respiratory sinus arrythmia on the cardiac responses to the carotid sinus stimuli. The HR and MAP responses

can be plotted against the estimated carotid sinus pressure, as calculated from the pre-stimulus MAP minus the neck chamber pressure, producing a sigmoid-shaped stimulus-response curve. The individual CBR stimulus-response curves can then be analyzed using the logistic function described by Kent et al (8) which incorporates the equation shown in Figure 4. Several parameters are derived from the model including reflex threshold, saturation, and maximal gain. Baroreflex threshold is described as the minimum carotid sinus pressure that elicits a reflex change in HR or MAP. Similarly, baroreflex saturation is described as the maximum carotid sinus pressure that elicits a reflex change in HR or MAP. Estimations of CBR threshold and saturation are based on the calculation of the third derivative of the equation described in Figure 4, and defines the points at which the sigmoidal shaped CBR stimulus-response curve becomes linear. Baroreflex maximal gain, derived from the first derivative of Eq. 1, was defined as the reflex gain value located at the centering point of the reflex. The operating point of each baroreflex stimulus-response curve was defined by the pre-stimulus MAP for each condition and the centering point refers to the point on the relationship from which an increase or decrease in carotid sinus pressure results in an equal response, generally also the point of maximal gain. Figure 4 illustrates these parameters on a schematic representation of a CBR stimulus-response curve.

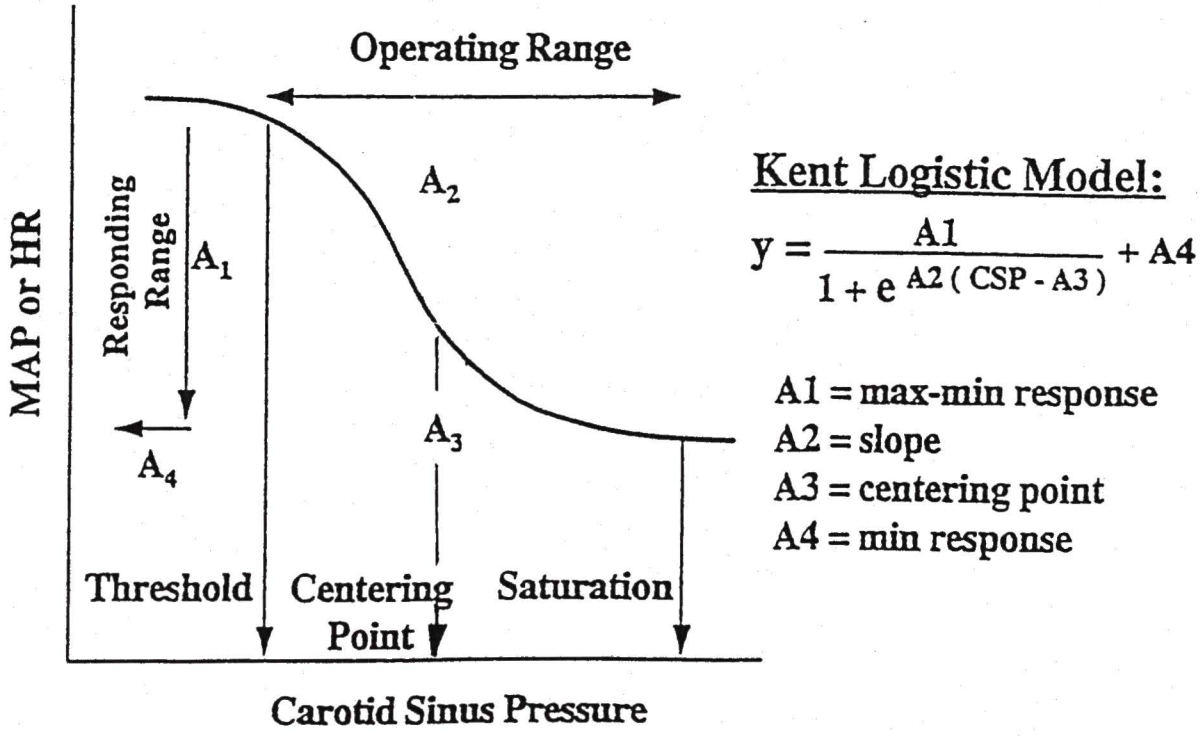


Figure 4. Schematic illustration of a carotid baroreflex stimulus-response curve and Kent model (8) logistic equation.

The investigations of Potts et al (20) demonstrated that CBR function was classically reset from rest to the higher mean arterial pressure (MAP) of exercise at 10-20 minutes of 25% $\dot{V}O_{2peak}$ and 50% $\dot{V}O_{2peak}$ steady-state exercise (20). In addition, their modeling of the baroreflex function curves indicate that the operating point (i.e. the pre-stimulus MAP) of the reflex was relocated from rest to exercise to operate at a location near the threshold of the reflex and above the centering point of the baroreflex stimulus-response relationship (20), see Figure 5 below.

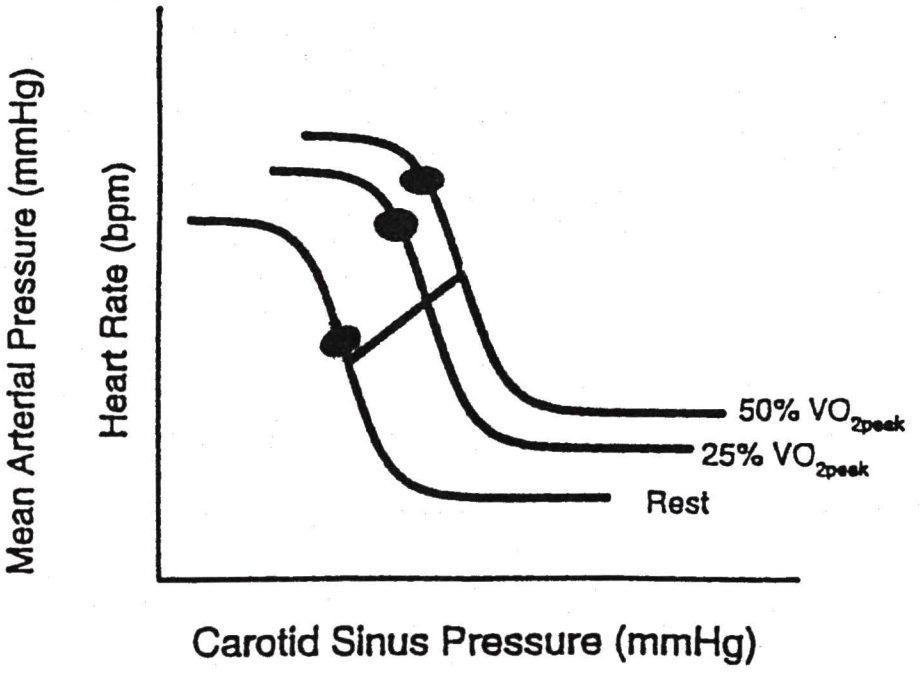


Figure 5. Schematic illustration of carotid baroreflex resetting upward and rightward from rest to two levels of dynamic exercise. Note: no decrement in reflex gain, or sensitiviy. ● represents the location of the reflex operating point, i.e. pre-stimulus mean arterial pressure, in relation to the reflex centering point as represented by the solid line. Adapted from Potts et al (20).

These findings have been confirmed by the work of Papelier et al (15) who similarly demonstrated an intensity dependent upward resetting of the CBR stimulus-response curve during mild to severe dynamic exercise. The stimulus and modelling techniques used in Papellier et al's investigation did not allow the calculation of reflex threshold and saturation, however the slope of the stimulus-response relationship indicated no change in the gain or sensitivity of the reflex with increasing exercise intensity to approximately 75% $\dot{V}O_{2max}$.

Mechanisms of Carotid Baroreflex Resetting.

These demonstrations of CBR resetting with dynamic exercise support the idea of a continued modulation of arterial pressure during dynamic exercise by the CBR. In addition, the modeling of the relocation of the baroreflex operating point by Potts et al (20) indicate that the baroreflex is in an optimal position to respond to hypertensive stimuli. However, the question is raised as to what mechanism(s) evince the resetting of the reflex.

The mechanism or mechanisms responsible for the acute resetting of the carotid arterial baroreflex during dynamic exercise have been postulated and theorized, however few investigations have been documented which test these theories (1,16). Rowell and O'Leary (25) have outlined how two possible effector mechanisms may shift or reset the carotid baroreflex prior to or as a result of exercise. Central command, the feed-forward mechanism which is proposed to initiate the recruitment of motor fibers for the performance of exercise, may exert a parallel influence on the cardiovascular system by immediately shifting the baroreflex rightward. Therefore reflex vagal withdrawal and sympathetic nervous system activation in response to the location of the operating point pressure relative to the shifted stimulus-response relationship result in the on-response of the cardiovascular system to exercise (25). Alternatively or additionally, the activation of the muscle metabo- and mechano- reflexes, which comprise the exercise pressor reflex, during exercise may result in an upward shift in the baroreflex stimulus-response curve without an alteration in operating point position such that only the efferent, or response, arm of the stimulus-response relationship is affected (25). Figure 6 schematically illustrates the theory of Rowell and

O'Leary (25) on the possible roles of central command and the exercise pressor reflex in resetting the CBR with exercise.

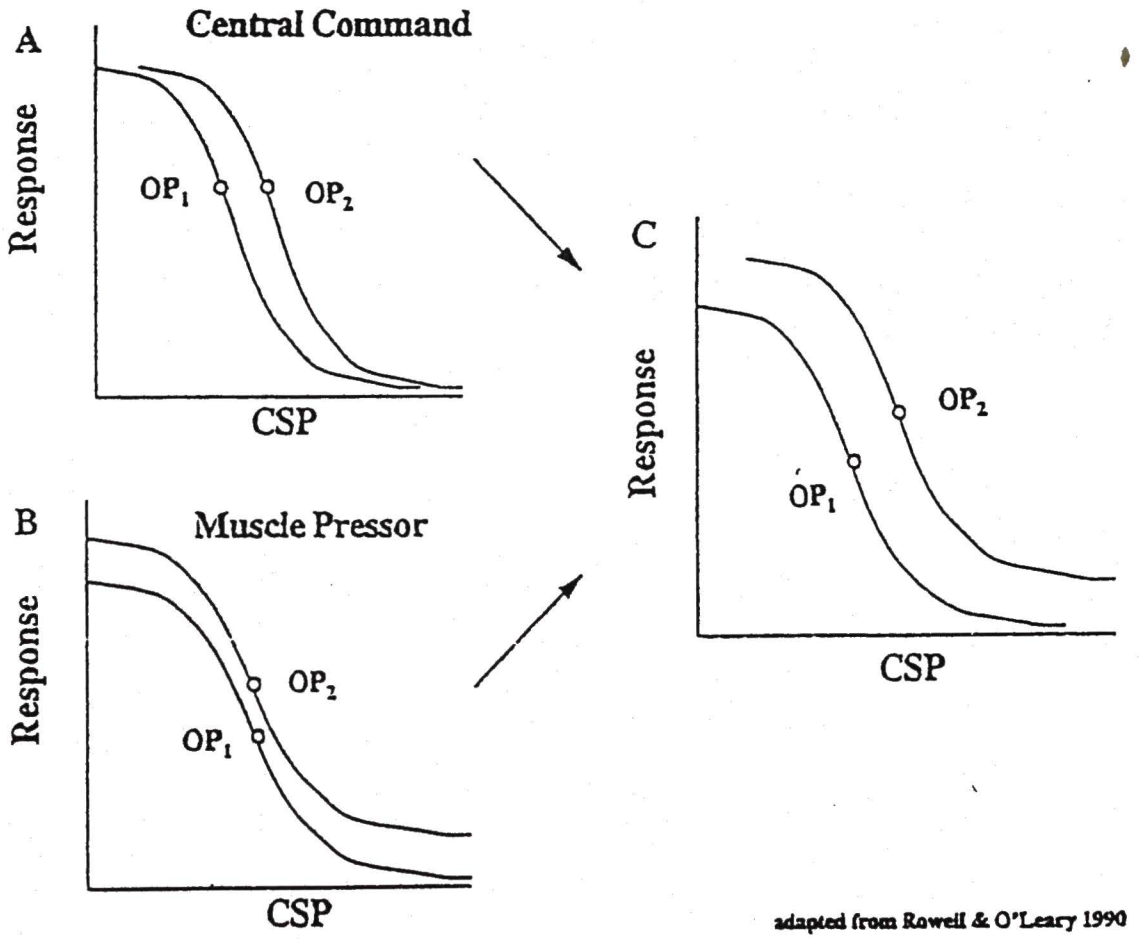
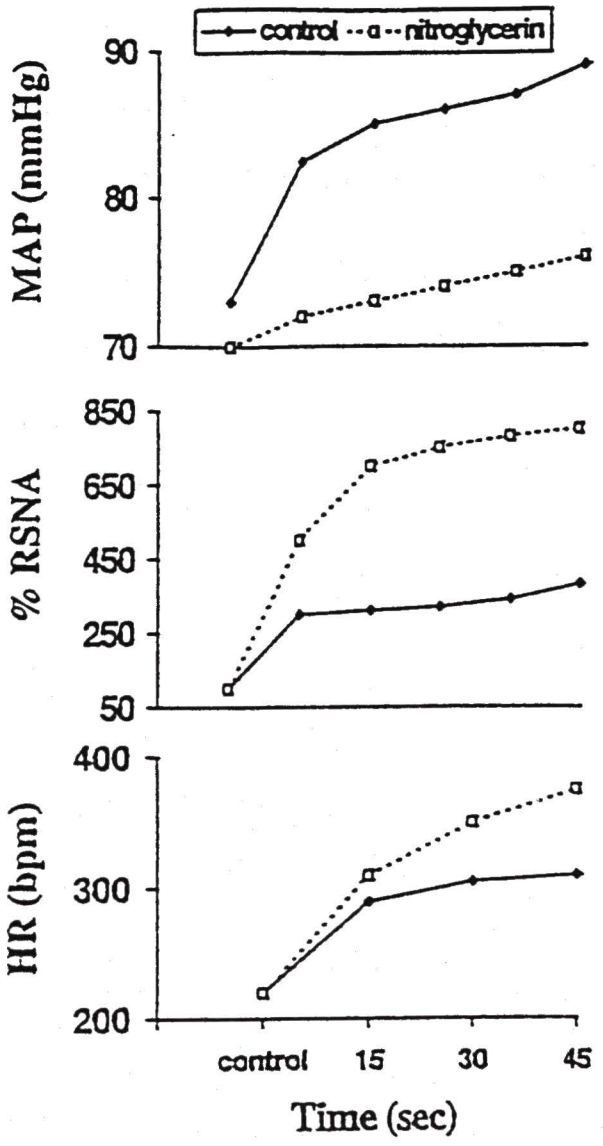


Figure 6. Schematic illustration of the theory of baroreflex resetting proposed by Rowell and O'Leary (25). In panel A, central command is shown to reset the baroreflex to operate around a higher arterial pressure through action on the neuron pool which receives baroreceptor afferents. In panel B, the muscle pressor reflex resets the curve upward through sympathetic nervous system activation resulting in an augmentation of the efferent, or response arm, of the baroreflex. Adapted from Rowell and O'Leary (25).

Note that Rowell and O'Leary use the term operating point (OP) to demonstrate the shifts in the baroreflex stimulus-response relationships with exercise. The position of this point in the center of the reflex and at the point of maximal gain for all curves redefines the point as the reflex centering point (CP). Furthermore, modeling of the baroreflex operating point, defined as the pre-stimulus arterial pressure, demonstrate that the OP is shifted away from the CP and toward the threshold of the baroreflex in relation to exercise intensity (20), an idea which is not illustrated in the figure above.

Central Command. "Central command" is the term applied to the descending, cortically-originated signals which are thought to affect in parallel the recruitment of skeletal muscle motor fiber units and the cardiovascular system through feed-forward control (4,11,21). As electrical and chemical stimulation of the hypothalamic locomotor (HTL) region of the brain elicits both skeletal locomotor and cardiovascular system responses, this area is the putative site of origination of central command, see review by Mitchell at al (11). In addition, alterations in the discharge properties of neurons in the ventral lateral medulla (VLM) demonstrated by Nolan et al (12) via HTL stimulation and electrically induced muscle contraction, indicate that central command and muscle reflexes may affect baroreflex function through an integration of the three systems at this brainstem site (21). It has been proposed that central command activation would directly effect the neuron pool in this area resulting in the resetting of the CBR to operate around a higher arterial pressure associated with exercise (25).

DiCarlo and Bishop (1) have examined the time course of the resetting of the arterial baroreflex in rabbits exercising on a treadmill with and without the infusion of nitroglycerin to counteract the increase in arterial pressure normally seen with exercise, see Figure 7. During exercise with nitroglycerin infusion, increases in HR and renal sympathetic nerve activity (RSNA) with exercise were immediately augmented indicating that the baroreflex had been repositioned to perceive the lack of rise in arterial pressure as a hypotensive stimuli. The time course of the resetting of the reflex which occurred immediately at the onset of exercise suggests that a negative feedback error signal was not necessary to provoke reflex resetting. The DiCarlo and Bishop investigation also demonstrated that an intact CBR was required in order for central command to elicit a HR increase with exercise (1).



adapted from Dicarlo & Bishop, 1992

Figure 7. Illustration of response to exercise with and without nitroglycerin infusion. Panel A depicts the effect of nitroglycerin infusion on arterial pressure (MAP). Panel B and C depict the resultant effects on renal sympathetic nerve activity (RSNA) and heart rate (HR). Note immediacy of RSNA and HR response to the lack of increase in MAP. Adapted from DiCarlo and Bishop (1).

Additionally, Ebert et al (2) have shown that the anticipation of static exercise in humans results in an alteration in carotid-cardiac and carotid-vasomotor responses to neck pressure and neck suction stimuli. Furthermore, the CBR resetting documented by Potts et al (22) occured in direct relation to the intensity of exercise and the related increases in several known indices of central command such as HR and $\dot{V}O_2$. These findings question the role of the exercise pressor reflex in baroreflex resetting at the onset of exercise and support the role of a quicker acting feed-forward type mechanism such as "central command".

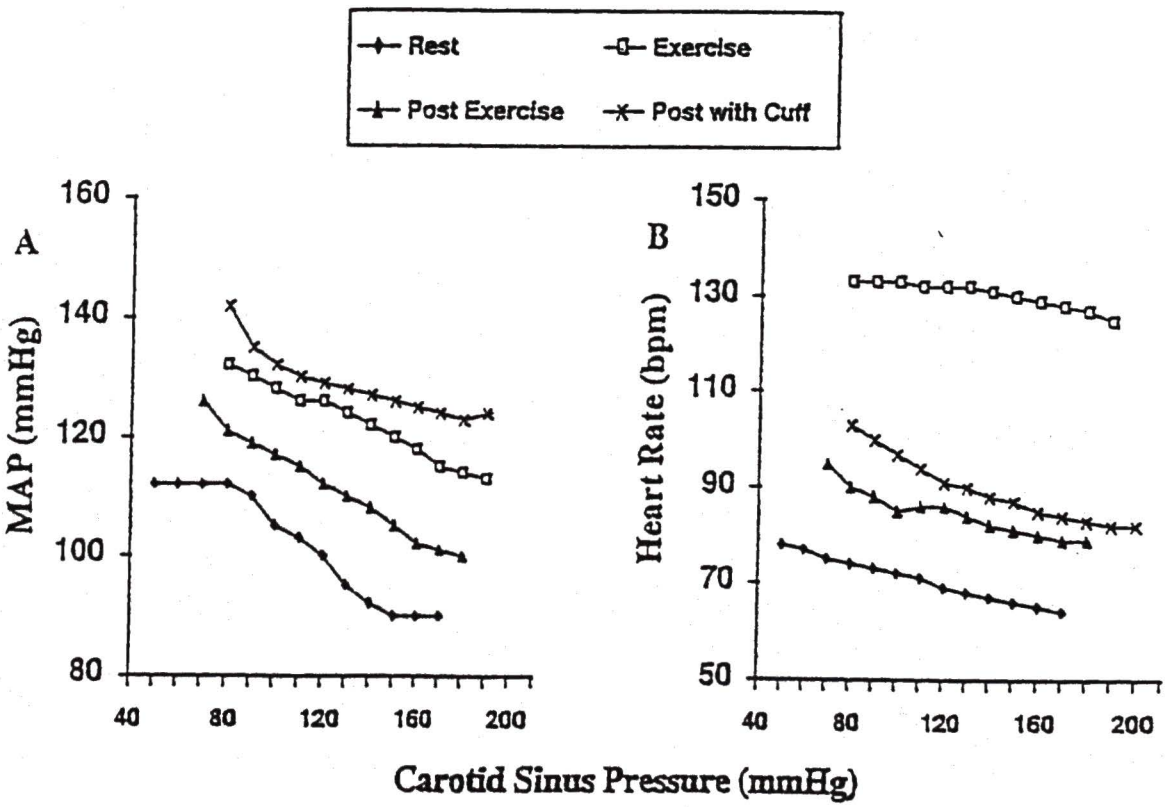
Muscle Metaboreflex. The muscle metaboreflex component of the exercise pressor reflex originates in skeletal muscle through the activation of chemically sensitive receptors, in the form of unencapsulated nerve endings, which cause discharge primarily in Group IV afferent fibers (11). These signals may be integrated with central command and baroreflex neurons in the VLM area of the brainstem as discussed previously (11,21). However, the primary effect of the activation of the muscle pressor reflex on the baroreflex stimulus-response relationship is thought to be through an increase in sympathetic nervous system activity resulting in an upward shift of the relationship along the efferent or reponse arm of the baroreflex (23,25).

Sherrif et al (27) have shown that the reflex response to muscle metaboreflex activation is attenuated by arterial baroreflex activation. Conversely, McWilliam et al (9) demonstrated an apparent attenuation of the reflex bradycardia response to increases in

carotid sinus pressure during electrical stimulation of the ventral roots containing ascending metaboreflex afferent fibers (L7-S2 ventral roots) of decerebrate cats, indicating the existence of an antagonistic relationship between these two control systems. More recently however, Potts et al (19) have questioned the interpretation of the data of McWilliam et al (9) through the demonstration that the effect of muscle reflex activation on the function of the arterial baroreflex may be to shift, or reset, the reflex rather than diminish the reflex sensitivity. This suggestion is in concordance with the hypothesis proposed by Rowell and O'Leary (25). In Potts et al (19), HR, arterial pressure, and renal sympathetic nerve activity responses to ramped increases in carotid sinus pressure (CSP) were recorded in the dog model with and without simultaneous electrical stimulation of L7-S1 ventral roots. The response of each cardiovascular variable was shifted rightward or to a higher pressure during contraction, however, calculation of the maximal gain or sensitivity of the reflex, e.g. change in HR divided by change in CSP, found no decrement in reflex sensitivity (ref. 19 and personal communication). Based on this finding the attenuation of the bradycardia response to increases in carotid sinus pressure seen in the experiments of McWilliam et al (9) may have been due to the location of the stimulus relative to the reset baroreflex stimulus-response relationship, i.e., the stimulus now falls closer to the threshold of the reflex resulting in a relatively diminished response. These data suggest that rather than attenuate baroreflex function, activation of the exercise pressor reflex may reset the baroreflex to operate at a higher level of blood pressure.

In addition, Papelier et al (16) investigated the effect of a post-exercise activation of

the muscle metaboreflex on CBR function by supra-systolic thigh cuff inflation initiated twenty seconds before the end of a 7 minute, 150 watt leg cycling exercise bout, see Figure 8. Comparisons of neck pressure / neck suction carotid baroreflex stimulus-response curves at rest, during exercise and after one minute of control and flow occluded recovery demonstrated that the carotid-vasomotor stimulus-response relationship undergoes a significant vertical shift with post-exercise leg blood flow occlusion as compared to the control post-exercise condition. The lack of this effect on the carotid-cardiac baroreflex has been attributed to the proposed differences in metaboreflex activation on cardiac and vasomotor function (14).



adapted from Papelier, et. al.

Figure 8. Effect of post-exercise supra-systolic thigh cuff inflation on carotid baroreflex function. The carotid-vasomotor stimulus-response relationship is shifted upward with thigh cuff inflation post exercise as compared to the return toward the resting curve seen post exercise without cuff inflation. Note: response is restricted to the carotid-vasomotor baroreflex. Adapted from Papelier et al (16).

It should be noted, however, that the physiologic significance of this information must be tempered by the idea that the muscle metaboreflex may not be tonically active during moderate exercise (23,29), although the muscle mechanoreflex may exert a more constant influence on the modulation of arterial blood pressure by the CBR.

SPECIFIC AIMS

Two primary objectives emerge from the questions posed in the background section of this dissertation. These are: a) to further support the existing data which indicate that the CBR is functional without a decrement in reflex gain or sensitivity during a wide range of dynamic exercise intensities including exercise at $\dot{V}O_{2\ max}$ and b) to examine the roles of central command and the muscle pressor reflex in the resetting of the CBR with dynamic exercise. Based on the background data discussed I specifically propose that central command is the primary mechanism by which the CBR is reset at the onset of dynamic exercise through feed-forward control. However, additional, feed-back modulation can be

exerted by the exercise pressor reflex upon the development of mechanical or chemical error signals in the exercising muscle. In order to investigate this proposal I submit the following specific aims:

I. To test the hypothesis that the resetting of the carotid baroreflex during prolonged exercise occurs in direct relation to a progressive increase in central command activity with motor fiber recruitment upon fatigue and is independent of the global hemodynamic responses to thermoregulation.

II. To test the hypothesis that the resetting of the carotid baroreflex occurs in direct relation to exercise intensity through a wide range of intensities including exercise at maximal oxygen uptake and that reflex resetting can be influenced by the type of exercise being performed in relation to the potential for activation of the exercise pressor reflex.

EXPERIMENTAL DESIGN

Two individual experiments were designed to investigate specific aims I and II. These experiments are discussed in detail in the following chapters, however a brief description of the rationale and experimental design for each follow:

Prolonged exercise. In order to uncouple the global hemodynamic responses to prolonged exercise from the effects of increases in central command, volunteer subjects performed one hour of dynamic leg cycling exercise at 65% of maximal aerobic capacity

($\dot{V}O_{2max}$) with: i) no intervention; and ii) maintenance of cardiac filling volume via continuous infusion of a 6% dextran in saline solution to counteract thermoregulatory blood volume redistribution. At 10 and 50 minutes of exercise, CBR stimulus-response curves were generated using a variable pressure neck collar as previously described by Potts et al (20). We anticipated that maintenance of cardiac filling volume would oppose the compensatory component of the increase in HR (compensating for the fall in SV) during the exercise bout, however, the portion of the increase in HR which is related to the progressive increase in central command as motor fibers fatigue and more are recruited (26) would remain. Furthermore,we anticipated that increases in other indices of central command such as $\dot{V}O_2$ and ratings of perceived exertion (RPE) would be similar during the two exercise bouts and that this increase in central command would be reflected by an augmented resetting of the CBR at 50 minutes of exercise as compared to 10 minutes under both exercise conditions. In addition, although the infusion of dextran in saline counteracts the fall in SV during prolonged exercise by maintaining central filling volume, the decrease in TPR due to cutaneous vasodilation would remain. Therefore we anticipated that some degree of diminution of MAP would occur and would proceed uncorrected due to the location of the operating point of arterial pressure in relation to the progressively reset CBR.

Exercise type and intensity. The second investigation was designed to demonstrate the effects of exercise type and intensity on the regulation of arterial blood pressure during exercise through baroreflex resetting. Therefore, CBR stimulus-response relationships were

compared during dynamic exercise at a wide range of exercise intensities (50% $\dot{V}O_{2max}$ to maximal exercise) using the modification of the neck pressure/neck suction (NP/NS) technique developed by Potts et al (20). We anticipated that increases in exercise intensity to maximal exercise would result in increases in several indices of central command such as HR and $\dot{V}O_2$ as well as an augmentation of the magnitude of the lateral shift in the CBR stimulus-response curve (with the operating point being shifted further toward or below the threshold of the reflex) relative to the activation of central command. In addition, arm exercise as compared to leg exercise performed at the same absolute $\dot{V}O_2$ results in higher heart rates (17,18) and ratings of perceived exertion (18). Also, lactate accumulation in the venous system has been reported to occur earlier and the removal of the lactate to be less efficient during arm exercise. Therefore we anticipated that the performance of combined arm and leg exercise would elicit an augmented shift in the carotid-vasomotor (16) stimulus-response relationship compared to leg exercise alone at the same intensity relative to leg exercise due to a disproportionate activation of the muscle metaboreflex in combination with the heightened activation of central command.

METHODS

Although the methodology for each investigation is described within the following chapters it is applicable to discuss here alterations that were made in the neck pressure / neck suction technique developed by Potts et al (20) for use in the present investigations. In order

to accommodate the high workloads being used in the present experiments, the neck pressure / suction technique was altered such that the subjects were allowed to breathe freely during each five second carotid sinus stimulus, in contrast to the end expiratory breath hold maneuver previously used at rest and during the lighter exercise workloads of Potts et al (20). Based on data from Eckberg et al, 1980 (3), which demonstrated that at a breathing frequency of 24 breaths/minute, no difference existed between the responses to neck collar stimuli during inspiration and expiration, we predicted that by choosing the peak HR and MAP response to each stimulus, CBR stimulus-response curves could be modeled at high exercise workloads with appropriate repeatability. In addition, the time required to construct a stimulus-response curve during exercise was reduced to a maximum of 10 to 12 minutes, therefore minimizing the confounding effects of cardiovascular drift on CBR function.

REFERENCES

1. **DiCarlo, S.E., and V.S.Bishop**. Onset of exercise shifts operating point of arterial baroreflex to higher pressures. *Am. J. Physiol.* 262 *(Heart Circ. Physiol.* 31*)*: H302-H307, 1992.

2. **Ebert, T.J.** Baroreflex responsiveness is maintained during isometric exercise in humans. *J. Appl. Physiol.* 61(2):797-803, 1986.

3. **Eckberg, D.L., Y.T. Kifle, and V.L. Roberts**. Phase relationship between normal human respiration and baroreflex responsiveness. *J. Physiol. (Lond.)* 304:489-502, 1980.

4. **Eldridge, F.L., D.E. Millhorn, J.P. Kiley and T.G. Waldrop**. Stimulation by central command of locomotion, respiration and circulation during exercise. *Resp. Physiol.* 59: 313-337, 1985.

5. **Ekelund, L.G. Circulatory and respiratory adaptation during prolonged exercise.** *Acta Physiol. Scand.* 70 **(***Suppl.* 292): 1-38, 1967.

6. **Gliner, J.A., P.B. Raven, S.M. Horath, B.L. Drinkwater and J.C. Sutton.** Man's physiologic response to long term work during thermal and positional stress. *J. Appl. Physiol.* 39: 628-632, 1975.

7. **Hobbs, S.F.** Central command during exercise: parallel activation of the cardiovascular and motor systems by descending command signals. *In Circulation, Neurobiology, and Behavior.* Eds. O.A.Smith, R.A. Galosy, and S.M.Wiess. Elsevier, New York. pp. 217-231, 1982.

8. **Kent, B.B., J.W. Drane, B. Blumenstein, and J.W. Manning**. A mathematical model to assess changes in the baroreceptor reflex. *Cardiol.* 57:295-310, 1970.

9. **McWillam, P.N. and T. Yang.** Inhibition of cardiac vagal component of baroreflex by group III and IV afferents. *Am. J. Physiol.* 260 *(Heart Circ. Physiol.* 29*)*: H730-H734, 1991.

10. **Melcher, A., and D.E. Donald**. Maintained ability of carotid sinus baroreflex to regulate arterial pressure during exercise. *Am. J. Physiol.* 241 *(Heart Circ. Physiol.* 10*)*:H838-H849, 1981

11. **Mitchell, J.H.** Neural control of the circulation during exercise. *Med. Sci. Sports Exerc.* 22:141-154,1990.

12. **Nolan, P.C., J.A. Pawelczyk, and T.G. Waldrop**. Neurons in the ventrolateral medulla receive input from descending "central command" and feedback from contracting muscles. *Physiologist* 35: 240, 1992.

13. **Nose, H., G. Mack, X. Shi, K. Morimoto, and E.R. Nadel.** Effect of saline infusion during exercise on circulatory and thermal regulations. *J. Appl. Physiol.* 69: 609-616, 1990.

14. **O'Leary, D.S.** Autonomic mechanisms of muscle metaboreflex control of heart rate. *J. Appl. Physiol.* 74:1798-1754, 1993.

15. **Papelier, Y., P. Escourrou, J.P. Gauthier, and L.B. Rowell.** Carotid baroreflex control of heart rate and blood pressure in men during dynamic exercise. *J. Appl. Physiol.* 77(2):502-506, 1994.

16. **Papelier, Y.P., P. Escourrou, F. Helloco, and L.B. Rowell.** Muscle chemoreflex alters carotid sinus baroreflex response in humans. *J. Appl. Physiol.* 82(2): 577-583, 1997.

17. **Pendergast, D.R.** Cardiovascular, respiratory, and metabolic responses to upper body exercise. Med. Sci. Sports Exerc. 21(5)S: S121-s12, 1989.

18. **Pivarnik, J.M., T.R. Grafner, and E.S. Elkins**. Metabolic, thermoregulatory, and psychophysiological responses during arm and leg exercise. *Med. Sci. Sports Exerc.* 20(1): 1-5, 1988.

19. **Potts, J.T., G.A. Hand, J. Li, and J.H. Mitchell**. Functional significance of varied levels of carotid sinus baroreceptor and hindlimb muscle afferent input on reflex cardiovascular responses. *Physiologist* 39(5) Abstract 8.1, pA-16, 1996.

20. **Potts, J.T., X.Shi, and P.B.Raven**. Carotid baroreflex responsiveness during dynamic exercise in man. *Am. J. Physiol.* 265 *(Heart Circ. Physiol.* 34*)* : H1928-H1938, 1993.

21. **Raven, P.B., J.T. Potts, and X. Shi**. Baroreflex regulation of blood pressure during dynamic exercise. In: *Exercise and Sports Science Reviews.* Vol. 25, Ed. J.O.

Holloszy. Publ. Williams & Wilkins, Baltimore, MD, pp365-389.

22. **Raven, P.B. and G.H.J. Stevens.** Cardiovascular function and prolonged exercise. In: *Perspectives in Exercise Science and Sports Medicine: Prolonged Exercise*. Ed. R. Maree, Benchmark Press. Indianapolis, pp.43-74, 1989.

23. **Rowell, L.B., P.R. Freund, and S.F. Hobb**. Cardiovascular responses to muscle ischemia in humans. *Circ. Res.* 48(6): I37-I47, 1981.

24. **Rowell, L.B., J.A. Murray, G.L.Brengelmann, and K.K.Kraning, II.** Human cardiovascular adjustments to rapid changes in skin temperature during exercise. *Circ. Res.* 24:711-724, 1969.

25. **Rowell, L.B. and D.S. O'Leary.** Reflex control of the circulation during exercise: chemoreflexes and mechanoreflexes. *J. Appl. Physiol.* 69(2): 407-418, 1990.

26. **Saltin, B.** Muscle fiber recruitment and metabolism in prolonged exhaustive dynamic exercise. *In: Human Muscle Fatigue: Physiological Mechanisms*, Ed. R. Porter and J Whelan. London: Pitman, 1981, p 41-58.

27. **Sheriff, D.D., D.S. O'Leary, A.M. Scher, and L.B. Rowell.** Baroreflex attenuates pressor response to graded muscle ischemia in exercising dogs. *Am. J. Physiol* 258 *(Heart Circ. Physiol.* 27*)*:H305-H310, 1990.

28. **Sprenkle, J.M., D.L. Eckberg, R.L. Goble, J.J. Schelhom and H.C. Halliday.** Device for rapid quantification of human carotid baroreceptor-cardiac reflex responses. *J. Appl. Physiol.* 80:727-732, 1986.

29. **Williamson, J.W., C.G. Crandall, J.T. Potts, and P.B. Raven**. Blood pressure responses to dynamic exercise with lower-body postitive pressure. *Med. Sci. Sports Exerc.* 26(6): 701-708, 1994.

CHAPTER II

CAROTID BAROREFLEX FUNCTION DURING PROLONGED EXERCISE

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ABSTRACT

CAROTID BAROREFLEX FUNCTION DURING PROLONGED EXERCISE. K.H. Bryant, K.M. Gallagher, S.A. Smith, R.Q. Querry, R.M. Welch-O'Connor and P.B. Raven

The present investigation was designed to uncouple the hemodynamic physiologic effects of thermoregulation from the effects of a progressively increasing central command activation during prolonged exercise. Volunteer subjects performed two one hour bouts of leg cycling exercise with a) no intervention and b) continuous infusion of a dextran solution to maintain central venous pressure during the exercise. Volume infusion resulted in a significant reduction in the decrement in stroke volume and mean arterial pressure (MAP) seen in the control exercise bout. However, indices of central command such as heart rate and oxygen uptake rose to a similar extent during both exercise conditions. In addition, the carotid baroreflex (CBR) stimulus-response relationship as measured using the neck pressure neck suction technique was reset from rest to 10 minutes of exercise and further from 10 to 50 minutes of exercise in both exercise conditions with the operating point being shifted toward the reflex threshold. Therefore, progressive resetting renders the reflex ineffectual in counteracting the downward drift in MAP which occurs during prolonged exercise.

INDEX OF TERMS:

Threshold, Saturation, Operating Point, Central Command

INTRODUCTION

Although the hemodynamic responses associated with prolonged exercise have been documented, the mechanisms involved in blood pressure regulation during prolonged exercise have not been fully elucidated. Following the initial response to the onset of dynamic exercise, prolonged exercise at a constant workload is characterized by the redistribution of blood volume to the cutaneous circulation in response to thermoregulatory demands resulting in a progressive decrease in central blood volume (CBV), central venous pressure (CVP), and total peripheral resistance (TPR) (5). This redistribution consequently results in a progressive decrease in stroke volume (SV) and mean arterial pressure (MAP) and a concomittant increase in heart rate (HR), a phenomenon which has been termed *cardiovascular drift*. The increase in HR occurs progressively as a compensatory response to the decrease in central filling volume and stroke volume and results in the maintenance of cardiac output (Qc). However, despite the use of whole body surface cooling or saline infusion during prolonged exercise to return central blood volume to pre-cardiovascular drift values, HR continues to increase and a slight downward drift in MAP remains (12,19). These data raise the question as to whether there is a loss of baroreflex regulation of arterial blood pressure during prolonged dynamic exercise.

Potts et al (16) have previously demonstrated that at the onset of low to moderate

intensity exercise the carotid baroreflex (CBR) was classically reset in direct relation to the intensity of exercise and that the operating point (i.e. pre-stimulus MAP) was relocated toward the threshold of the reflex. We propose that the mechanism of resetting of the carotid baroreflex at the onset of dynamic exercise is a result of the activation of the feed forward mechanism, "central command". Furthermore, with prolongation of the exercise at a constant workload, further increases in central command reflected by progressive motor fiber recruitment, and increases in HR, oxygen uptake ($\dot{V}O_2$) and electromyographic (EMG) activity of the exercising skeletal muscle will result in a continual upward resetting of the CBR. In addition, we propose that with exercise at a greater intensity than the 50% of maximal oxygen uptake ($\dot{V}O_2max$) used by Potts et al (16), the operating point would be further shifted to a pressure below the threshold pressure of the reflex. We hypothesize that as prolonged steady-state exercise continues and cardiovascular drift becomes manifest, MAP would fall below the operating range of the progressively reset CBR which, therefore, would become ineffectual in correcting the downward drift in MAP. Hence, the objective of the present investigation was to demonstrate that the apparent loss of arterial blood pressure regulation seen during prolonged constant load dynamic exercise can be attributed to a progressive resetting of the CBR in relation to increases in central command and that the resetting is independent of the central blood volume displacement which occurs in response to the thermoregulatory stress incurred during prolonged moderate to high intensity dynamic exercise.

METHODS AND PROCEDURES

In order to uncouple the effects of increases in central command from the global hemodynamic responses to prolonged exercise, volunteer subjects performed one hour of dynamic leg cycling exercise at 65% of maximal aerobic capacity ($\dot{V}O_{2max}$) with: i) no intervention; and ii) maintenance of cardiac filling volume via continuous infusion of a 6% dextran in saline solution. At 10 and 50 minutes of exercise, CBR stimulus-response curves were generated using a variable pressure neck collar as previously demonstrated in our laboratory (16). We anticipated that maintenance of cardiac filling volume would oppose the compensatory component of the increase in HR (compensating for the fall in SV) during the exercise bout, however, the central command related increases in HR would remain. In addition, although the infusion of dextran in saline counteracts the fall in SV by maintaining central filling volume, the decrease in TPR due to cutaneous vasodilation during the exercise would remain. Therefore we anticipated that some degree of diminution of MAP would occur and would proceed uncorrected due to the relocation of the operating arterial pressure in relation to the progressively reset CBR.

Subjects

Eight healthy subjects (aged 27.9 ± 1.6 yr.) gave written informed consent for participation in this investigation as approved by the Internal Review Board of the University

of North Texas Health Science Center at Fort Worth. All subjects were free of known cardiovascular and pulmonary disorders and were not taking any prescribed medications. Subject data are summarized in Table 1.

INSERT TABLE 1 HERE

Protocol

At least two days prior to participating in the experimental protocol, each subject performed a graded exercise test for the determination of maximal oxygen uptake ($\dot{V}O_{2max}$) during semi-recumbent leg cycling exercise. On the experimental day, each subject performed two one hour bouts of constant load dynamic leg cycling exercise at approximately 65%$\dot{V}O_{2max}$ in the semi-recumbent position, consisting of either constant load leg cycling exercise with no intervention or constant load leg cycling with continuous intravenous infusion of a 6% dextran in saline solution. The infusion rate of the dextran solution was varied such that central venous pressure (CVP)did not fall below the pressure value recorded at ten minutes of exercise. The exercise bouts were performed in a 24°C, 40-60% relative humidity environment and were separated by a rest period of sufficient length (at least three hours) to return heart rate (HR) and mean arterial pressure (MAP) to approximate baseline

values. Carotid baroreflex stimulus-response curves were constructed at rest, following attainment of steady-state exercise (after approximately 10 minutes of constant load exercise) and during the last 10 to 12 minutes of each experimental exercise bout, using a modification of the neck pressure/neck suction (NP/NS) protocol previously developed by Potts et al (16). For the experimental bouts with infusion of dextran in saline, the infusions were begun following the first exercise NP/NS protocol (i.e. at 20 minutes of exercise) and were maintained throughout the exercise bout at an infusion rate which would maintain CVP at the level no lower than that attained immediately prior to the execution of the first exercise NP/NS protocol. During each exercise bout, HR, $\dot{V}O_2$, MAP and central venous pressure (CVP) were continuously monitored and recorded. In addition, at ten minute intervals cardiac output and ratings of perceived exertion (RPE) were assessed. Venous blood samples were also drawn periodically for the measurement of venous hemoglobin, hematocrit, oxygen content, oxygen saturation and lactate and catacholamine (norepinephrine and epinephrine) concentrations. The concentration of atrial natriuetic peptide was also assessed in the blood samples to discern the effects of the infusion of the dextran solution on the volume sensitive cardiopulmonary baroreflex.

Measurements

Maximal exercise test and oxygen uptake measures. Subjects determined acceptable by physical examination performed a graded exercise test for the determination of maximal

oxygen uptake ($\dot{V}O_{2max}$). The subjects exercised in the 70° semi-recumbent back supported posture at progressively increasing workloads on a constant load cycle ergometer until they reached volitional fatigue. During the test, measurements included the rate of oxygen uptake ($\dot{V}O_2$) using breath-by-breath open circuit spirometry and continuous ECG monitoring using a 12-lead monitoring system. Subjects returned to the laboratory no less than two days following maximal exercise testing for performance of the experimental exercise bouts.

Cardiovascular variables Heart rate and oxygen uptake were continuously monitored via electrocardiogram (ECG) and a customized breath-by-breath mouthpiece apparatus. Cardiac output was measured at ten minute intervals using the acetylene rebreathe method (23) with stroke volume being calculated from the division of cardiac output by heart rate. Arterial blood pressure and CVP were measured directly via catheters inserted by a consulting physician into the radial artery and brachial vein of each subject. Placement of the dual lumen CVP catheter at the 4th intercostal space was confirmed with the use of fluoroscopy. Both pressures were monitored using disposable pressure transducers interfaced with pressure monitors. Pressure transducers were calibrated and established at zero reference pressure at the mid-axillary and third intercostal space before and after the experiment and catheters were appropriately connected to an IV bag for saline flush. Mean, systolic and diastolic blood pressure along with CVP and HR were recorded beat-by-beat on-line using a personal computer (Gateway 2000) and customized software. Oxygen uptake ($\dot{V}O_2$) was similarly recorded breath-by-breath using a personal computer (Dell Optiplex GXi) and customized

software. In addition, venous blood samples, taken from the second port of the dual lumen CVP catheter, and ratings of percieved exertion (RPE), supplied by the subject, were recorded at ten minute intervals.

Venous Blood Samples. Venous blood samples were drawn from the second port of the dual lumen CVP catheter at rest, at 10, 20, 50, and 60 minutes of exercise, and following ten minutes of recovery from the exercise. These samples were subjected to hematocrit analysis (microcentifuge). In addition, the hemoglobin concentration (g/dl), oxygen saturation (%) and oxygen content (ml/dl) of each sample was measured and recorded (IL 282 Co-Oximeter). Also, the concentration of lactate in the venous blood samples was recorded (YSI 2300 Stat). Finally, the plasma concentration (pmol/ml) of the catacholamines, epinephrine and norepinephrine, were analyzed in each of these samples via isocratic high pressure liquid chromatography (HPLC), whereas the plasma concentration (pmol/ml) of atrial natriuretic peptide (ANP) was measured using a radio-immuno assay kit (Penninsula Laboratories).

Carotid Baroreflex (CBR) Function. CBR function during exercise was analyzed using the neck pressure / neck suction technique (22) in which a malleable lead-chambered collar was secured with velcro straps to the anterior 2/3 of the subject's neck. Variable pressure vacuum pumps were used to generate pressure within the collar thereby delivering perturbations ranging from +40 to -80 Torr (20 Torr increments) directly to the carotid sinus region of the subject's neck. Randomized pressure or suction pulses were delivered to the neck precisely 50ms after the R wave of the ECG for a duration of 5 seconds each. The HR

and MAP responses to each of three trials at each generated neck pressure or suction level were used to construct baroreflex stimulus-response curves. The curves were then individually modeled using a four parameter logistic function utilizing a non-linear least-square regression algorithm (8). This modeling technique produced a sigmoidal shaped stimulus-response curve of "best-fit" for each data set. These procedures have been developed in our laboratory and published (16) however, several changes were made in the technique to accommodate the high workloads being used in the present experiments. The NP/NS technique was altered such that subjects were allowed to breathe freely during the five second carotid sinus stimuli (in contrast to the end expiratory breath hold maneuver previously used at rest and during lighter exercise workloads). Based on data from Eckberg et al, 1980 (3) which demonstrated that at a breathing frequency of 24 breaths/minute, no difference existed between the responses to neck collar stimuli during inspiration and expiration, we predicted that by choosing the peak HR and MAP response to each stimulus, CBR stimulus-response curves could be modeled at high exercise workloads with appropriate repeatability. In addition, the time required to construct a stimulus-response curve during exercise was reduced to a maximum of 10 to 12 minutes to minimize the confounding effects of cardiovascular drift on CBR function. Prior to the investigation of the effects of active skeletal muscle mass on CBR function the repeatability of the modified NP/NS technique was established, see Figure 5 and Table 2.

Analysis

The individual CBR stimulus-response curves were analyzed using the logistic function described by Kent et al (8) which incorporates the equation below.

$$HR \text{ or } MAP = A1 * \{1 + e^{[A2(CSP-A3)]}\}-1 + A4 \qquad (Eq.\ 1)$$

where:

CSP = carotid sinus pressure; MAP + or - neck chamber pressure;

A1 = range of response of dependent variable (max-min);

A2 = gain coefficient;

A3 = CSP required to elicit equal pressor and depressor responses (centering point);

A4 = minimum HR or MAP response.

Baroreflex threshold was described as the minimum carotid sinus pressure that elicited a reflex change in HR or MAP. Similarly, baroreflex saturation was described as the maximum carotid sinus pressure that elicited a reflex change in HR or MAP. Estimations of CBR threshold and saturation were based on the calculation of the third derivative of Eq. 1, which defined the points at which the sigmoidal shaped CBR stimulus-response curve became linear. These values were obtained in order to evaluate lateral shifts in the CBR stimulus-response relationship with exercise. Baroreflex maximal gain, derived from the first derivative of Eq. 1, was defined as the reflex gain value located at the centering point of the reflex. The

operating point of each baroreflex stimulus-response curve was defined as the pre-stimulus HR and MAP for each condition. The resulting values were compared using one way analysis of variance (ANOVA) with repeated measures across conditions. Student-Newman-Keuls post-hoc pairwise comparisons were used to further analyze group mean differences. Statistical significance was set at a p value of <0.05 .

RESULTS

Cardiovascular variables

The maintenance of a consistent thermal stress between the two exercise conditions was of primary importance to our investigation. Accordingly, the increases in body temperature during the hour of exercise (approximately 2°C) as measured at the tympanic membrane at ten minute intervals were not significantly different between the two exercise conditions at any time of measurement. The alterations in several cardiovascular variables recorded during the exercise bouts are reported below as percent change from the measurement taken at 10 minutes of exercise. The absolute measurement value for each of these variables recorded at 10 minutes of exercise are listed in Table 3.

One hour of exercise in the control condition resulted in a significant fall in central venous pressure (CVP) as shown in Figure 1 (linear regression equation: $y = -0.029x + 3.11$). In addition, stroke volume (SV), total peripheral resistance (TPR) and mean arterial pressure (MAP) declined significantly with exercise time, 15.17 ± 2.21, 11.59 ± 1.30, and 13.35 ± 1.66 percent (%) respectively, see Figure 2. Figure 2 also illustrates that HR rose significantly

throughout the exercise protocol (12.54 ± 2.16 %) and that as a result cardiac output was maintained over this period, i.e. no significant differences were found in Qc from 10 to 60 minutes of exercise. Conversely, when infusion of a dextran solution was begun at 20 minutes of exercise and maintained throughout the exercise period (mean infusion volume 419 ± 45 ml) CVP increased slightly during the exercise bout (linear regression equations: from 10 to 20 minutes of exercise y = -0.018x + 3.89); from 20 through 60 minutes of exercise y = 0.053x + 3.32), see Figure 1. Volume infusion resulted in the maintenance of SV during the exercise bout, i.e. no significant differences were found in SV from 10 to 60 minutes of exercise, however, TPR continued to fall to a statistically similar extent as during the control condition, see Figure 2. As a result, a significant decrement was seen in MAP with exercise time however, by minute 50 this decrement was significantly less than in the control condition (total MAP decrease of 6.71 ± 1.83 %) as shown in Figure 2. In addition, HR rose to the same extent as in the control condition as a function of exercise time (12.27 ± 1.98 %) and Qc also increased significantly over the hour of exercise (9.35 ± 2.24 %) due to the maintenance of SV,see Figure 2. Figure 2 also illustrates a significant increase in the arterio-venous oxygen difference (A-V O_2 diff.) from 10 to 60 minutes of the control exercise bout (12.11 ± 2.67 %) which was absent during exercise with volume infusion. The difference between the A-V O_2 diff. of the control versus the infusion exercise bouts, which was statistically significant at 60 minutes of exercise, was presumed to be due to the effect of the increase in flow (Q_c) on oxygen extraction. However, despite a significant difference in oxygen carrying capacity at 60 minutes (control - 20.41 ± .96 ml/dl vs. infusion - 18.54 ± .92

ml/dl, p = 0.012) the resultant difference in percent oxygen extraction was not significant (0.96 ± .052 % vs. 0.92 ± .069 %, p=.65).

INSERT FIGURE 1 HERE

INSERT FIGURE 2 HERE

Indices of Central Command

All indices of central command measured in the current investigation were statistically similar between the two exercise bouts, as clearly illustrated in Figure 3. HR rose 12.54 ± 2.16 % in the control condition and 12.27 ± 1.98 % in the volume infusion experiment. Ratings of perceived exertion also rose significantly with exercise time in the control and volume infusion bouts, 34.89 ± 4.44 and 32.02 ± 4.68 %, respectively. In addition, oxygen uptake ($\dot{V}O_2$) was seen to drift upwards similarly during both exercise bouts. Percent change in this measurement was calculated from 20 minutes rather than 10 minutes due to an increase in $\dot{V}O_2$ at the ten minute value due to anticipation of the impending neck pressure / neck suction protocol, which was administered between 10 and 20 minutes of exercise.

INSERT FIGURE 3 HERE

Blood Measurements

Venous blood samples were drawn during the resting period prior to each exercise bout, at 10, 20, 50 and 60 minutes of exercise and following 10 minutes of recovery from the exercise. The infusion of an average of 419 ± 45 ml of dextran solution significantly reduced the measured hematocrit at 50 and 60 minutes of exercise, as well as during recovery, as compared to exercise under the control condition. Accordingly, hemoglobin content (g/dl) was also significantly less in these blood samples. The infusion did not significantly affect the oxygen saturation nor the oxygen content of the venous blood, although a trend existed for an increased venous oxygen saturation during exercise with volume infusion. This trend corresponded to a trend for a decreased A-V O_2 difference during volume infusion, as Qc was higher during this condition compared to control. In addition, the plasma concentrations of epinephrine and norepinephrine were similar during the two exercise conditions, as was the concentration of atrial natriuretic peptide (ANP) indicating that the cardiopulmonary baroreceptors were not affected by this degree of volume infusion. Finally, measures of lactic acid (mmol/L) indicated that the concentration of this metabolite was significantly higher at 10 and 20 minutes of control exercise compared to the exercise with volume infusion. As infusion of the dextran in saline infusion had not begun at this time, we submit that this discrepancy may be an effect of order as the volume infusion exercise bouts were consistently performed following several hours of recovery from the control exercise bouts. This order was necessary to prevent the confounding effects of increased blood volume on the hemodynamic resposes to exercise in the control condition because the experiment was

designed to be undertaken in one experimental day in order to minimize the invasive procedures experienced by the volunteer subjects. Figure 4 illustrates the absolute measurements of each of the variables discussed above.

INSERT FIGURE 4 HERE

Repeatability of Baroreflex Stimulus-Response Curves:

Prior to beginning the prolonged exercise investigation, we demonstrated that carotid baroreflex stimulus-response curves can be generated using the modified neck pressure / neck suction protocol with high repeatability in subjects performing leg cycling exercise at workloads greater than that demonstrated by Potts et al (19), i.e. 50% $\dot{V}O_{2max}$. Figure 5 below represents the mean and standard errors of the heart rate responses (carotid-cardiac baroreflex) to several levels of carotid sinus stimulation (ranging from -80 to +40 torr) generated following 10 minutes of dynamic leg cycling exercise at 68% $\dot{V}O_{2max}$ in one subject during four separate bouts of exercise. The gain, threshold and saturation values for each of the four individual carotid baroreflex stimulus-response curves are listed below in Table 2.

INSERT FIGURE 5 HERE

INSERT TABLE 2 HERE

Carotid Baroreflex in Prolongd Exercise

i) Carotid-cardiac baroreflex

Modelling of the carotid-cardiac baroreflex stimulus-response relationship demonstrated that the reflex was significantly shifted rightward on the carotid sinus pressure axis from rest to 10 minutes of exercise and also from 10 to 50 minutes of exercise in both exercise conditions. Figure 6 panel A, B, and C illustrate each shift in the carotid-cardiac baroreflex threshold, centering point and saturation. Panel D illustrates that no reflex shift was accompanied by a decrement in reflex gain. Panel E illustrates the operating point pressure at rest, 10 minutes and 50 minutes of exercise. The operating point of the carotid-cardiac baroreflex was also significantly relocated from rest, at which time there was no significant difference between the operating point and centering point pressures, to 10 minutes of exercise and further from 10 to 50 minutes of exercise. These shifts occured away from the reflex centering point and toward the threshold of the reflex such that there was no significant difference between the operating point and threshold pressures at 50 minutes of exercise, see figure 6, panel F.

INSERT FIGURE 6 HERE

ii) Carotid-vasomotor baroreflex

We were unable to obtain threshold, saturation and gain values for the carotid-vasomotor stimulus-response relationships elicited by the neck pressure / neck suction protocol due to the inability to attain convergence in the modelling procedure. Figure 7 illustrates the mean responses of the eight subjects to each level of carotid sinus perturbation for rest, 10 and 50 minutes of exercise in both exercise conditions. The inability to adequately model these responses to the logistic equation of Kent et al (8) may be explained by the differential effects of prolonged exercise on the activation of the exercise pressor reflex of individual subjects. This reflex is thought to have a modulatory effect predominantly on the efferent, or response, arm of the vasomotor component of the carotid baroreflex via the activation of the sympathetic nervous system (15,20).

INSERT FIGURE 7

DISCUSSION

Prolonged Exercise - Cardiovascular Drift

In 1967, Ekelund (5) reported that prolonged (one hour) constant load dynamic leg exercise on a cycle ergometer at 65% of maximal aerobic capacity ($\dot{V}O_{2max}$) resulted in a progressive decrease in arterial and pulmonary artery pressures between 10 and 60 minutes

of exercise. In addition, stroke volume fell as cardiac filling volume decreased, and heart rate (HR) increased as a compensatory response resulting in the maintenance of a constant cardiac output (Qc). This phenomenon has been termed "cardiovascular drift". Later Gliner et al (6) demonstrated that cardiovascular drift was exacerbated by the lengthening of exercise time and more importantly by the addition of heat stress to the exercise protocol.

In 1969, Rowell et al. (19) demonstrated that by cooling the skin during prolonged exercise much of the downward drift in MAP was eliminated, presumably through the counteraction of the decrease in total peripheral resistance (TPR) associated with the thermoregulatory redistribution of circulating blood volume to the cutaneous circulation. However, despite the use of skin cooling there remained a slight progressive decrease in arterial pressure and a progressive increase in HR and oxygen uptake ($\dot{V}O_2$) between 10 to 60 minutes of exercise. Furthermore, Nose et al (1990) have demonstrated that when central venous pressure (CVP) was maintained during prolonged exercise (50 min) via saline infusion, plasma volume was maintained, however, there were only minor effects on the increase in HR (12).

In the present investigation, one hour of leg cycling exercise at 65% $\dot{V}O_{2max}$ elicited the cardiovascular and hemodynamic responses that have been previously documented for prolonged moderate to high intensity dynamic exercise (5,19), see Figure 2. The progressive decrease in MAP seen during prolonged exercise following the initial increase at exercise onset has been attributed to a redistribution of circulating blood volume to the cutaneous

circulation in response to thermoregulatory demands (19). Accordingly, our data illustrates that central venous pressure (CVP) decreased significantly from 10 to 60 minutes of exercise presumably due to a greater percentage of cardiac output being distributed to the cutaneous circulation. This fall in central blood volume resulted in a decreased cardiac filling volume which was reflected by a concomittant reduction in SV and a compensatory increase in HR. When CVP, and thus SV, were maintained via a continuous infusion of a 6% dextran in saline solution during the prolonged exercise protocol, a progressive decrement in MAP remained (6.71 ± 1.83 %), albeit to a lesser degree than in the control condition, presumably due to the fall in total peripheral resistance (11.59 ± 1.30 %) corresponding to cutaneous vasodilation. Interestingly, no significant difference existed in the rise in HR between the two exercise conditions. Cardiac output (Qc) was relatively constant throughout the control exercise condition, however, due to the maintenance of central blood volume and SV, Qc increased appreciably during the volume infusion condition (9.35 ± 2.24 %) in relation to the increase in HR, see Figure 2. These data in conjunction with that of previous investigations (6,12,19) indicate that thermoregulatory blood volume redistribution was an important component of the cardiovascular drift. However these data also raise the question as to whether baroreflex control of blood pressure was diminished or fatigued during the prolonged exercise, particularly in the light of a maintained increase in HR despite the countermeasures used in the present and previous investigations (12,19).

Carotid Baroreflex

The role of the arterial baroreflexes in the regulation of arterial blood pressure during dynamic exercise has been controversial for many years. However, data from both animal (1,9) and human (14,16) studies provide strong evidence for continued modulation of arterial blood pressure by the carotid baroreflex during dynamic exercise without a decrement in reflex sensitivity. Melcher and Donald (9) have demonstrated a functioning carotid baroreflex in dynamically exercising dogs using surgical isolation and independent perfusion of the carotid sinus baroreceptors. Pressures within the carotid sinus were changed independently of the systemic circulation and stimulus-response curves for HR and MAP were generated. The results of Melcher and Donald (9) indicated that the carotid baroreflex was indeed functional during dynamic exercise and that the reflex function curve had undergone an upward shift in threshold and saturation with no change in the maximal gain of the reflex.

In humans,Potts et al (16) have recently demonstrated that CBR function was classically reset from rest to the higher mean arterial pressure (MAP) of exercise at 10-20 minutes of 25%$\dot{V}O_{2peak}$ and 50% $\dot{V}O_{2peak}$ steady-state exercise (16). These findings have been confirmed by the work of Papelier et al (14) who similarly demonstrated an intensity dependent upward resetting of the CBR stimulus-response curve during mild to severe dynamic exercise with no change in reflex gain. However, Potts et al (16) also found from their modeling of the baroreflex function curves that the operating point (i.e. the pre-stimulus MAP) of the baroreflex was relocated from rest to exercise to operate at a location near the

threshold of the reflex and above the centering point of the baroreflex stimulus-response relationship (16). In addition, DiCarlo and Bishop (1) have examined the time course of the resetting of the arterial baroreflex in exercising rabbits and have demonstrated an immediate resetting of the reflex at the onset of exercise and suggest that a feed-back error signal was not necessary to provoke reflex resetting. This finding opposes the role of the exercise pressor reflex in baroreflex resetting at the onset of exercise and supports the role of a quicker acting feed-forward type mechanism such as "central command". Central command is the neural control system thought to originate in the hypothalamic locomotor region of the brain and to affect in parallel the recruitment of skeletal muscle motor fiber units and the cardiovascular system through an integration in the ventrolateral medulla (10,17). Additionally, DiCarlo and Bishop have also demonstrated that an intact CBR was required in order for central command to elicit a HR increase with exercise (1).

In the present investigation, the construction of CBR stimulus-response curves during the control exercise bouts indicated that the baroreflex was indeed classically reset from the resting condition to the onset of the exercise bout as well as being further reset by the prolongation of the bout to one hour, see Figure 6. The carotid-vasomotor baroreflex could not be modelled, however the data summarized in figure 7 illustrates that the reflex appears to be reset in a manner similar to the carotid-cardiac baroreflex. The data also demonstrate that these shifts occurred without a significant change in the maximal gain, or sensitivity, of the reflex from rest throughout the exercise protocol. The rightward shift of the carotid-cardiac baroreflex threshold and saturation values occured in direct relation to the increases

seen in the idices of central command (i.e. HR, $\dot{V}O_2$, and RPE). In fact, the increase in HR and the rightward shift in reflex threshold both approximated a change of 12.5 percent from 10 to 60 minutes of exercise. In the dextran solution infusion experiments in which CVP was maintained and even increased during the hour of exercise, the threshold and saturation pressures of the carotid-cardiac baroreflex relationships were similarly reset, see figure 6. Again, the data indicates that there was no significant difference in reflex gain during this protocol. Interestingly, the maintenance of CVP and thus SV had no significant effect on the upward drift in HR during the exercise bout. In addition, $\dot{V}O_2$ drifted upward to an equal extent as during the control condition. Taken together, these data indicate that central command activation was similar in the two exercise conditions. Accordingly, the rightward shifts in the reflex threshold and saturation values were also directly related to the rise in HR, $\dot{V}O_2$, and RPE. Again, both HR and the reflex threshold increased approximately 12.3 and 12.5 percent respectively during the hour of exercise.

Based on these data, we propose that prolongation of moderate to high intensity exercise at a constant workload, resulted in a progressive increase in central command evidenced by increases in HR and $\dot{V}O_2$, (10) due to motor unit recruitment (7,21) and which was reflected by a progressive upward resetting of the CBR. The operating point of the carotid-cardiac baroreflex in the present investigation was relocated away from the centering point and toward the threshold of the baroreflex in direct relation to exercise time and thus central command activation. Therefore, as the thermoregulatory stress related to prolonged

steady-state exercise developed in the control condition and cardiovascular drift became manifest, MAP would have fallen below the operating range of the reset carotid baroreflex rendering it ineffectual in correcting the downward drift in MAP. The same resetting occured in the volume infusion exercise bouts presumably resulting with the same scenario of drift in MAP, only to a lesser degree than in the control condition due to the maintenance of CVP and SV.

CONCLUSION

The present investigation was successful in uncoupling the global hemodynamic responses to the thermal stress associated with prolonged exercise from the effects of a progressively increasing central command activation in response to muscular fatigue. The results support our hypothesis: that central command is the primary mechanism by which the carotid arterial baroreflex is reset during dynamic exercise. This resetting results in an augmentation of the capacity of the reflex to respond to hypertension, however it renders the reflex ineffectual in counteracting a fall in arterial pressure such as occurs during prolonged exercise with the manifestation of cardiovascular drift.

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REFERENCES

1. **DiCarlo, S.E., and V.S. Bishop**. Onset of exercise shifts operating point of arterial baroreflex to higher pressures. *Am. J. Physiol.* 262 *(Heart Circ. Physiol.* 31*)*: H302-H307, 1992.

2. **Ebert, T.J.** Baroreflex responsiveness is maintained during isometric exercise in humans. *J. Appl. Physiol.* 61(2):797-803, 1986.

3. **Eckberg, D.L., Y.T. Kifle, and V.L. Roberts**. Phase relationship between normal human respiration and baroreflex responsiveness. *J. Physiol. (Lond.)* 304:489-502, 1980.

4. **Eldridge, F.L., D.E. Millhorn, J.P. Kiley and T.G. Waldrop**. Stimulation by central command of locomotion, respiration and circulation during exercise. *Resp. Physiol.* 59: 313-337, 1985.

5. **Ekelund, L.G.** Circulatory and respiratory adaptation during prolonged exercise. *Acta Physiol. Scand.* 70 (*Suppl.* 292): 1-38, 1967.

6. **Gliner, J.A., P.B. Raven, S.M. Horath, B.L. Drinkwater and J.C. Sutton.** Man's physiologic response to long term work during thermal and positional stress. *J. Appl. Physiol.* 39: 628-632, 1975.

7. **Hobbs, S.F.** Central command during exercise: parallel activation of the cardiovascular and motor systems by descending command signals. *In Circulation, Neurobiology, and Behavior.* Eds. O.A.Smith, R.A. Galosy, and S.M.Wiess. Elsevier, New York, 1982. pp. 217-231.

8. **Kent, B.B., J.W. Drane, B. Blumenstein, and J.W. Manning**. A mathematical model to assess changes in the baroreceptor reflex. *Cardiol.* 57:295-310, 1970.

9. **Melcher, A., and D.E. Donald**. Maintained ability of carotid sinus baroreflex to regulate arterial pressure during exercise. *Am. J. Physiol.* 241 *(Heart Circ. Physiol.* 10*)*:H838-H849, 1981.

10. **Mitchell, J.H.** Neural control of the circulation during exercise. *Med. Sci. Sports Exerc.* 22:141-154,1990.

11. **Nolan, P.C., J.A. Pawelczyk, and T.G. Waldrop**. Neurons in the ventrolateral medulla receive input from descending "central command" and feedback from contracting muscles. *Physiologist* 35: 240, 1992.

12. **Nose, H., G. Mack, X. Shi, K. Morimoto, and E.R. Nadel.** Effect of saline infusion during exercise on circulatory and thermal regulations. *J. Appl. Physiol.* 69: 609-616, 1990.

13. **O'Leary, D.S.** Autonomic mechanisms of muscle metaboreflex control of heart rate. *J. Appl. Physiol.* 74:1798-1754, 1993.

14. **Papelier, Y., P. Escourrou, J.P. Gauthier, and L.B. Rowell.** Carotid baroreflex control of heart rate and blood pressure in men during dynamic exercise. *J. Appl.*

Physiol. 77(2):502-506, 1994.

15. **Papelier, Y.P., P. Escourrou, F. Helloco, and L.B. Rowell.** Muscle chemoreflex alters carotid sinus baroreflex response in humans. *J. Appl. Physiol.* 82(2): 577-583, 1997.

16. **Potts, J.T., X.Shi, and P.B.Raven**. Carotid baroreflex responsiveness during dynamic exercise in man. *Am. J. Physiol.* 265 *(Heart Circ. Physiol.* 34*)* : H1928-H1938, 1993.

17. **Raven, P.B., J.T. Potts, and X. Shi**. Baroreflex regulation of blood pressure during dynamic exercise. In: *Exercise and Sports Science Reviews.* Vol. 25, Ed. J.O. Holloszy. Publ. Williams & Wilkins, Baltimore, MD, 1997. pp365-389.

18. **Raven, P.B. and G.H.J. Stevens.** Cardiovascular function and prolonged exercise. In: *Perspectives in Exercise Science and Sports Medicine: Prolonged Exercise*. Ed. R. Maree, Benchmark Press. Indianapolis, 1989. pp.43-74.

19. **Rowell, L.B., J.A. Murray, G.L.Brengelmann, and K.K.Kraning, II.** Human cardiovascular adjustments to rapid changes in skin temperature during exercise. *Circ. Res.* 24:711-724, 1969.

20. **Rowell, L.B. and D.S. O'Leary.** Reflex control of the circulation during exercise: chemoreflexes and mechanoreflexes. *J. Appl. Physiol.* 69(2): 407-418, 1990.

21. **Saltin, B.** Muscle fiber recruitment and metabolism in prolonged exhaustive dynamic exercise. *In: Human Muscle Fatigue: Physiological Mechanisms*, Ed. R. Porter and J Whelan. London: Pitman, 1981, p 41-58.

22. **Sprenkle, J.M., D.L. Eckberg, R.L. Goble, J.J. Schelhom and H.C. Halliday.** Device for rapid quantification of human carotid baroreceptor-cardiac reflex responses. *J. Appl. Physiol.* 80:727-732, 1986.

23. **Triebwasser, J.H., R.L. Johnson, R.P. Burpo, J.L. Campbell, W.L. Reardon, and C.G. Blomqvist.** Noninvasive determination of cardiac output by a modified acetylene rebreathing procedure utilizing mass spectrometer measurements. *Aviat. Space Environ. Med.* 48: 203-209, 1977.

TABLE 1. Subject information

Age (yr)	Height (cm)	Weight (kg)	$\dot{V}O_{2max}$ (ml/min/kg)
27.9 ± 1.6	177.8 ± 1.7	75.1 ± 2.2	48.3 ± 3.6

Mean ± standard error; $\dot{V}O_{2max}$, maximal oxygen uptake during leg cycling

TABLE 2. Derived variables for the CBR stimulus response relationships depicted in Fig. 5.

	Gain	**Threshold, mmHg**	**Saturtion, mmHg**
Trial 1	-0.15	99.5	165.7
Trial 2	-0.14	84.6	162.6
Trial 3	-0.14	87.8	166.8
Trial 4	-0.15	96.6	160.7
mean±SE	-.14±004	92.4±4.3	163.9±2.8
CV, %	2.6	4.6	1.7
95% C.I.	0.004	6.9	4.4

CV, coefficient of variation [(SE/mean) X 100], 95%CI, 95 percent confidence interval

TABLE 3. Absolute measurements of cardiovascular variables at ten minutes of exercise

	Control	Volume Infusion
Heart Rate (bpm)	141.2±2.4	145.5±2.6
Central Venous Pressure (mmHg)	3.1±0.7	3.8±0.6
Total Peripheral Resistance ( )	5.4±0.9	5.9±.3
Stroke Volume (ml/beat)	128.5±7.6	121.7±8.4
Mean Arterial Pressure (mmHg)	106.5±4.5	103.6±2.1
Cardiac Output (L)	18.1±1.1	17.6±1.1
Arterial-Venous Oxygen Difference ()	0.12±0.008	0.12±0.009

Figure Legends

Figure 1. An illustration of the linear regression of central venous pressure (CVP) during the hour of exercise in the control (———) and volume infusion (- - - - -) exercise conditions. During the control exercise condition, the linear regression equation for CVP was $y = -0.029x + 3.11$. Prior to the infusion of the dextran solution, the linear regression equation for the volume infusion exercise condition also indicated a decrement in CVP ($y = -0.018x + 3.89$), however, during the infusion (minutes 20-60) CVP increased as indicated by the slope of the linear regression equation: $y = 0.053x + 3.32$.

Figure 2. An illustration of the alterations in several cardiovascular variables during the control and volume infusion exercise conditions. All values are presented as percent change from the value attained at 10 minutes of exercise. A-V O_2, arterio-venous oxygen difference; HR, heart rate; MAP, mean arterial pressure; Q_c, cardiac output; SV, stroke volume; TPR, total peripheral resistance. * indicates significant difference between exercise condition. ANOVA, $p < 0.05$.

Figure 3. An illustration of the alterations in several indices of central command during the control and volume infusion exercise conditions. HR and RPE are presented as percent change from the value attained at 10 minutes of exercise. $\dot{V}O_2$ is presented at percent change

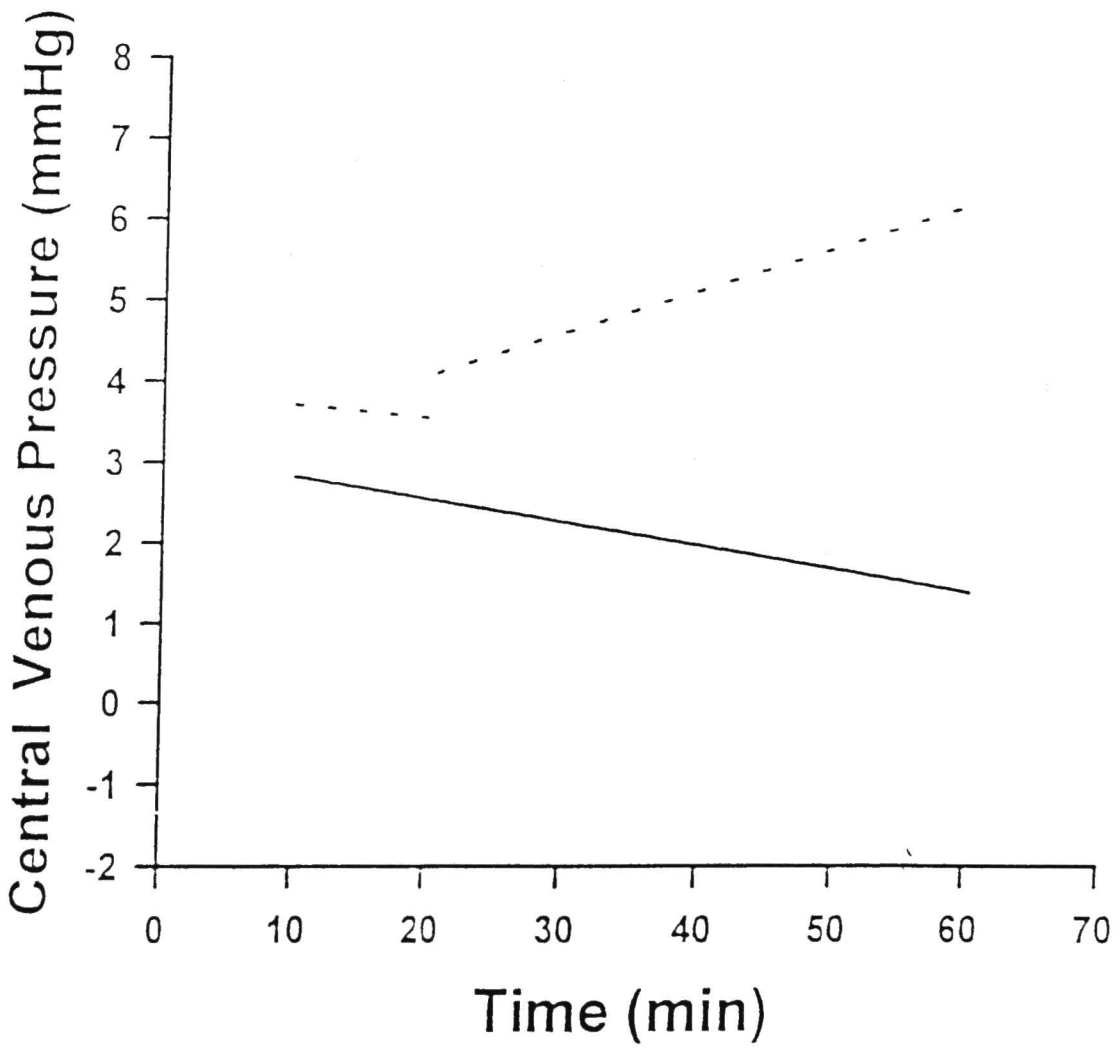
from 20 minutes of exercise. HR, heart rate; $\dot{V}O_2$, oxygen uptake; RPE, rating of perceived exertion. No significant differences existed between exercise condition. ANOVA, $p < 0.05$

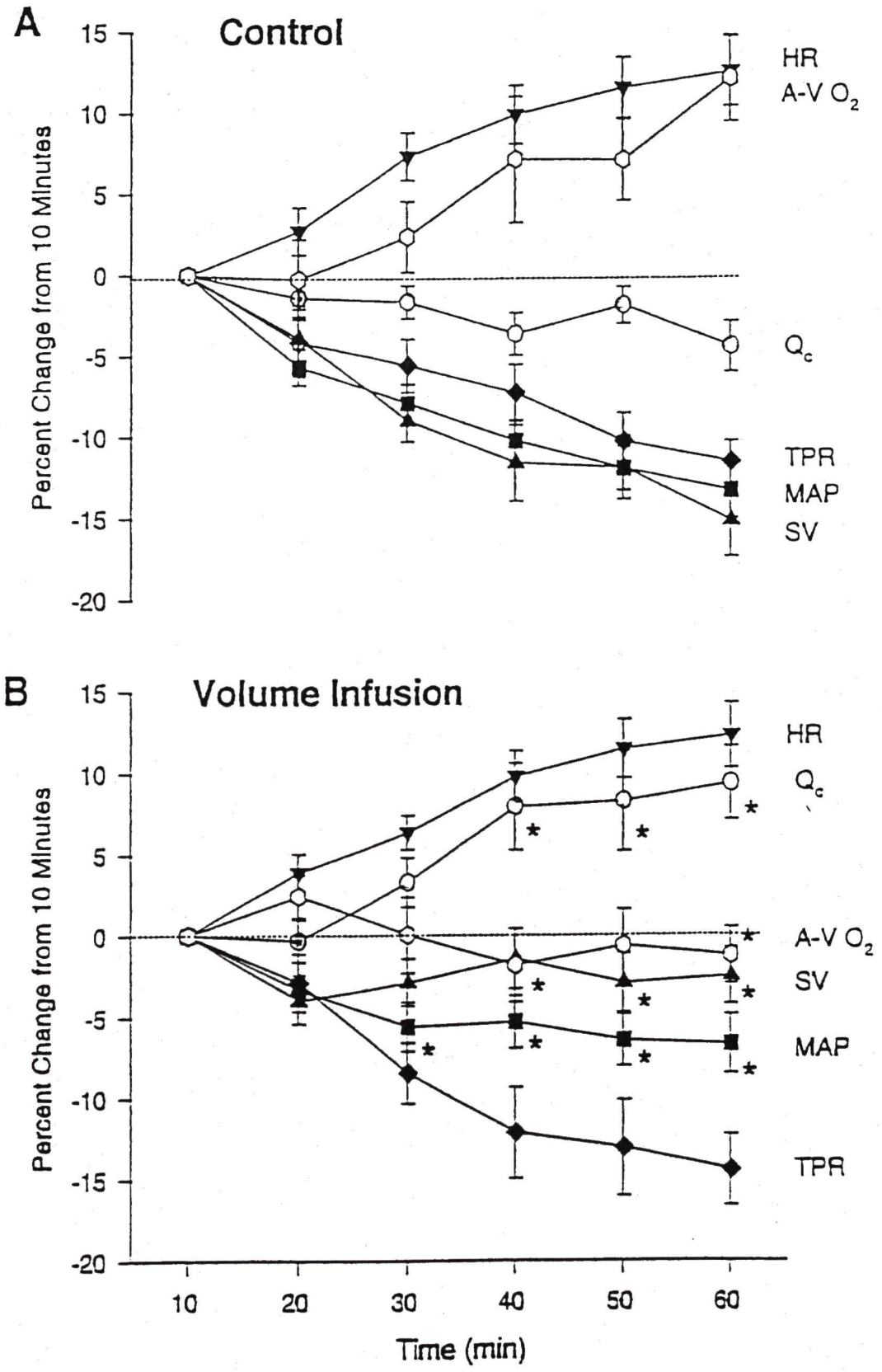
Figure 4. Illustration of the measurements of hematocrit, hemoglobin, atrial natriuretic peptide, epinephrine, norepinephrine, oxygen saturation, oxygen content and lactate in the venous blood samples drawn at rest, 10, 20, 50, 60 minutes of exercise and following 10 minutes of recovery from the exercise. * indicates significant difference between exercise condition. ANOVA, $p < 0.05$.

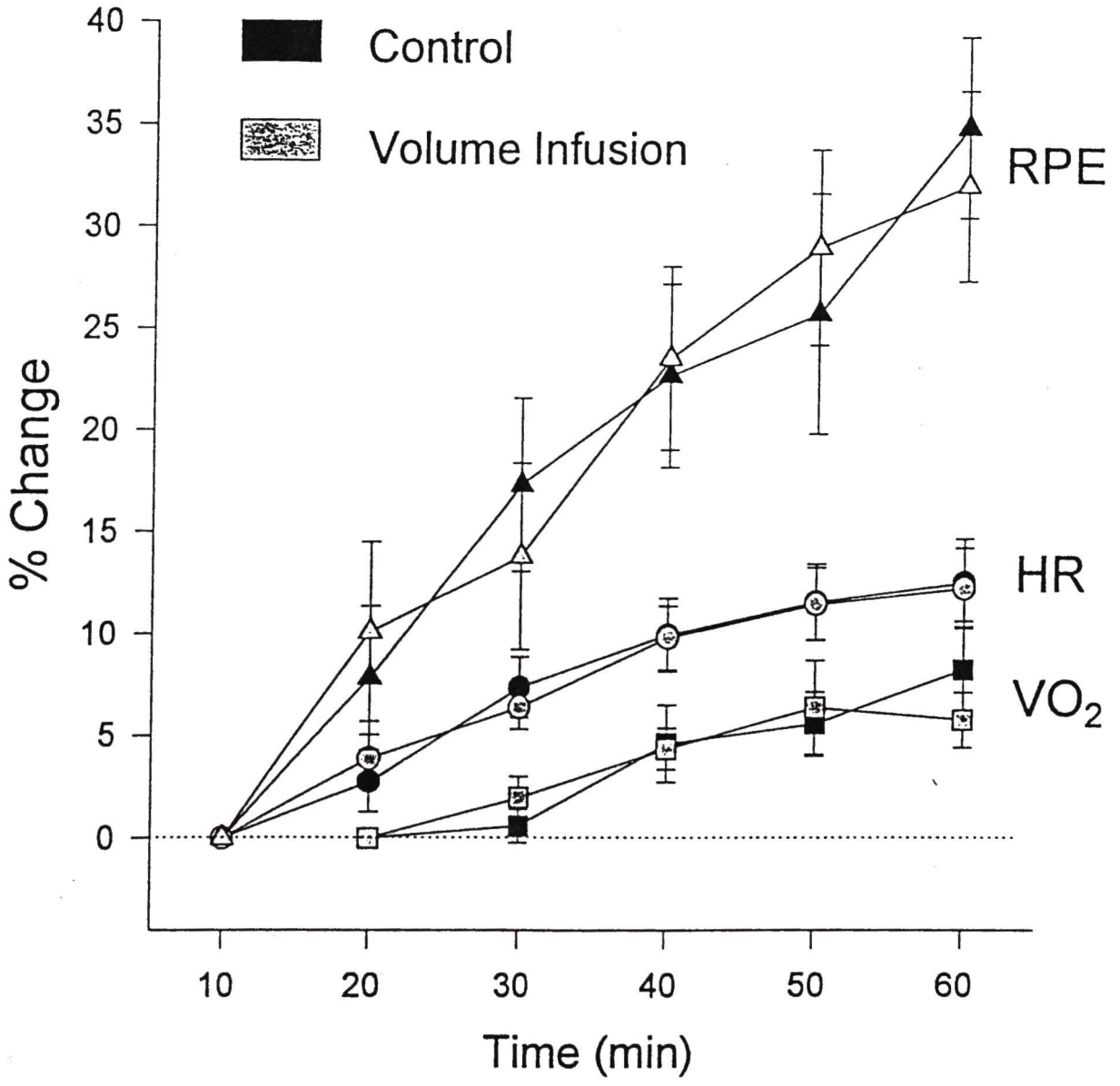
Figure 5. A representation of the logistic model of the mean HR responses to four individual carotid baroreflex stimulus-response curves each generated in the same subject during four separate 68% $\dot{V}O_{2max}$ exercise bouts . Suction / pressure pulses were administered at -80, -60, -40, -20, +20, and +40 Torr following 10 minutes of exercise. The maximal gain, threshold, and saturation for each stimulus-response curve are in listed in Table 2.

Figure 6. An illustration of the alterations in the carotid-cardiac baroreflex A) threshold, B) centering point, C) saturation, D) maximal gain, and E) operating point. Panel F demonstrates the movement of the operating point from its postion at rest near the centering point of the reflex to its position at 50 minutes of exercise near the threshold of the reflex. * indicates significant difference from the previous measurement time. ANOVA, $p < 0.05$.

Figure 7. An illustration of the mean response of the carotid-vasomotor baroreflex to the carotid sinus stimuli ranging from +40 to -80 torr. Panal A represents the control exercise condition, whereas Panel B represents the volume infusion exercise condition. Although modelling of these relationships was not possible, the position of the reflex centering point (black bar) indicate that the carotid-vasomotor baroreflex may be reset rightward with increasing exercise time in a similar manner to the carotid-cardiac baroreflex. Note that centering point was not calulated by the Kent Model procedure but was estimated to be the median carotid sinus pressure for the operating range of the carotid-vasomotor baroreflex.


Central Venous Pressure (mmHg)
8
7
6
5
4
3
2
1
0
-1
-2
0
10
20
30
40
50
60
70
Time (min)


A
Control
Percent Change from 10 Minutes
15
10
5
0
-5
-10
-15
-20
HR
A-V O2
Qc
TPR
MAP
SV
B
Volume Infusion
Percent Change from 10 Minutes
HR
Qc
A-V O2
SV
MAP
TPR
10
20
30
40
50
60
Time (min)


Control
Volume Infusion
RPE
HR
VO2
% Change
Time (min)
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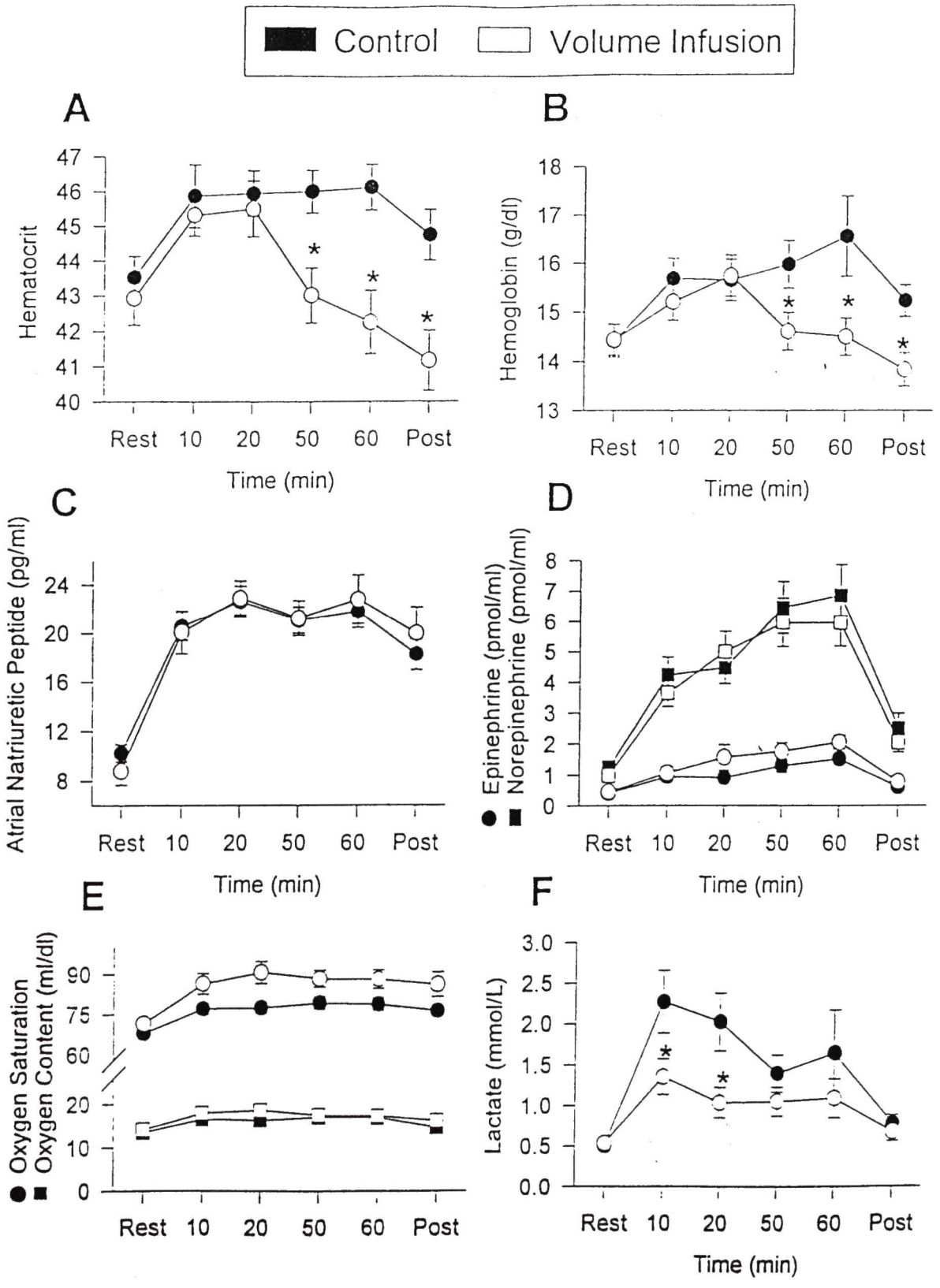
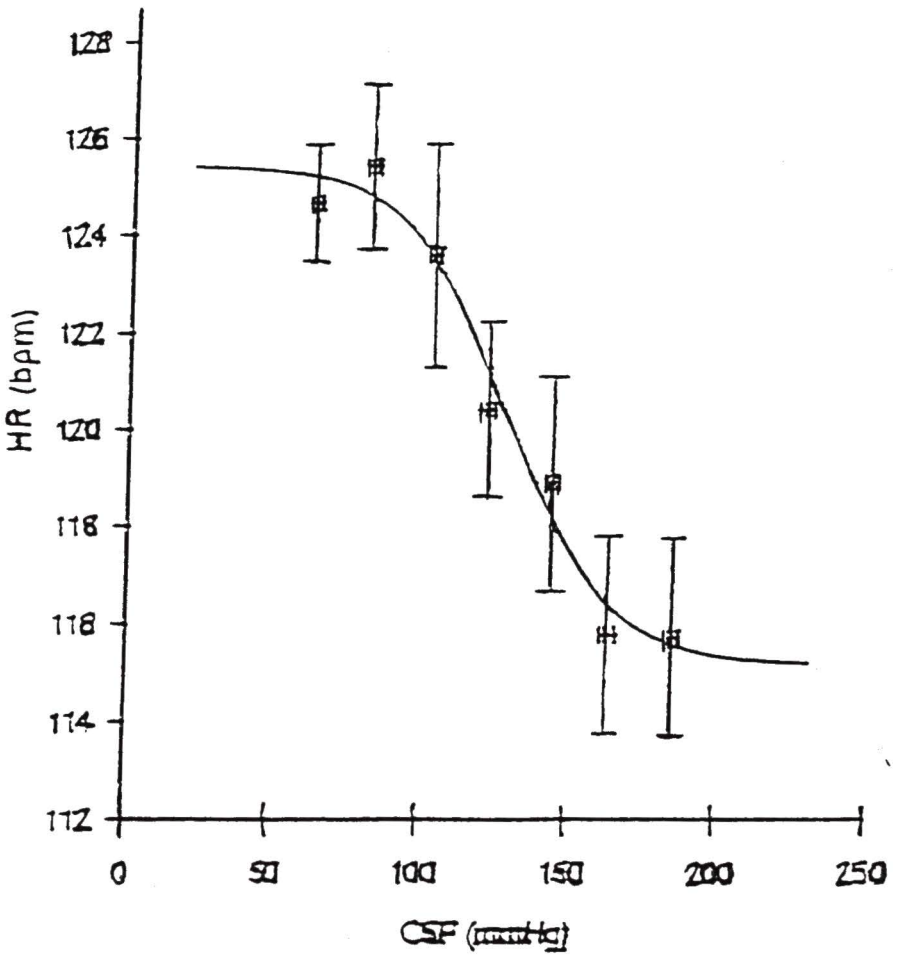
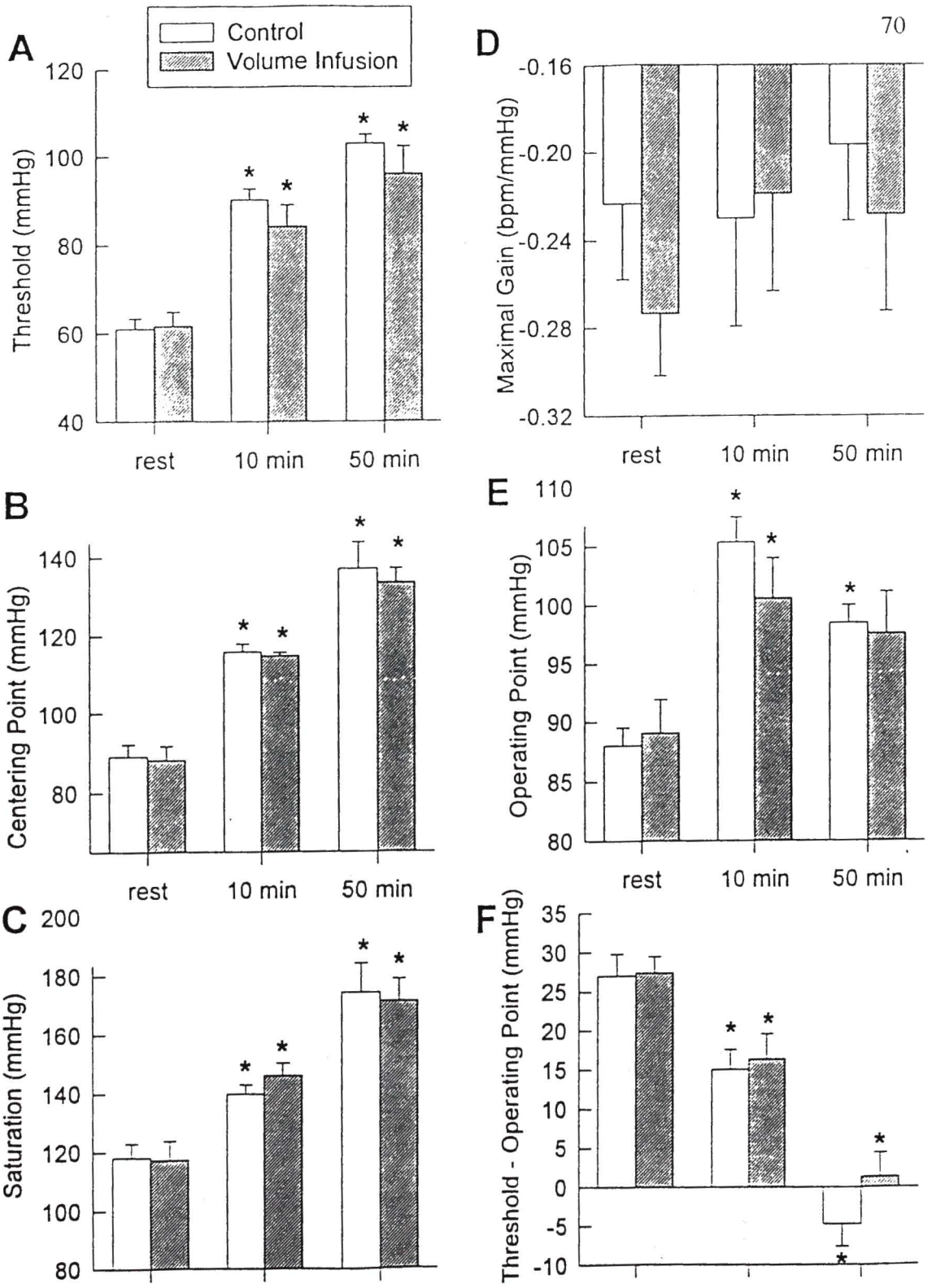
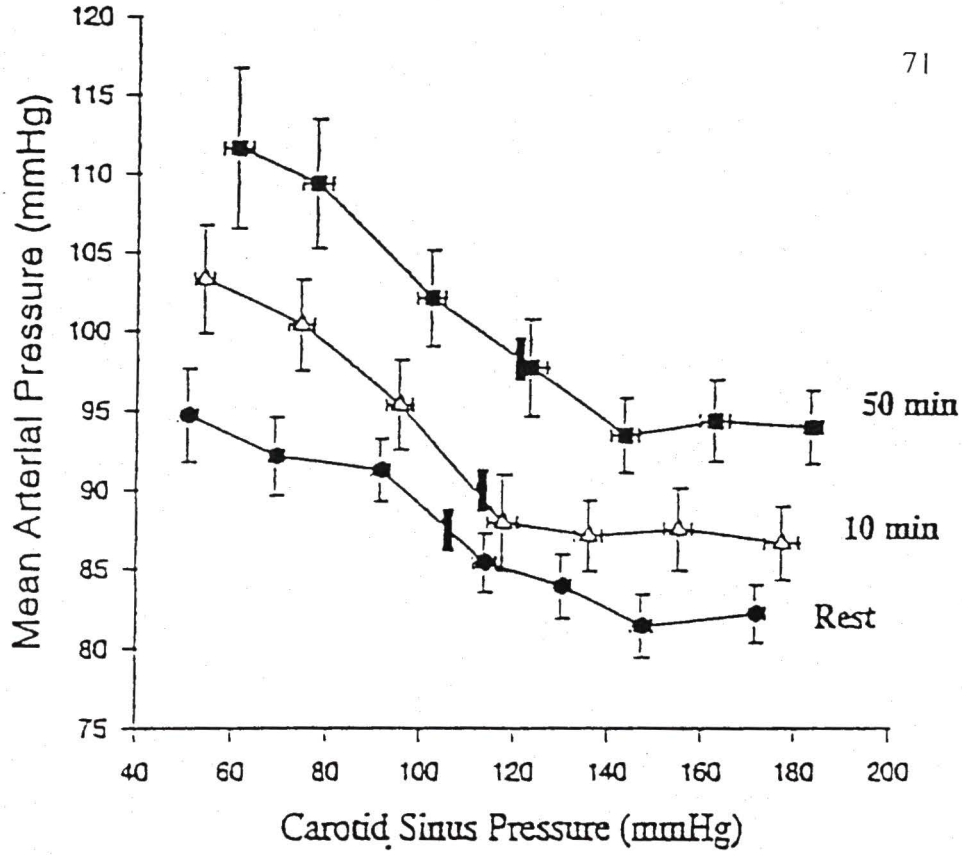
35
30
25
20
15
10
5
0
10
20
30
40
50
60


Control
Volume Infusion
A
Hematocrit
47
46
45
44
43
42
41
40
Rest 10 20 50 60 Post
Time (min)
B
Hemoglobin (g/dl)
18
17
16
15
14
13
Rest 10 20 50 60 Post
Time (min)
C
Atrial Natriuretic Peptide (pg/ml)
24
20
16
12
8
Rest 10 20 50 60 Post
Time (min)
D
Epinephrine (pmol/ml)
Norepinephrine (pmol/ml)
8
7
6
5
4
3
2
1
0
Rest 10 20 50 60 Post
Time (min)
E
Oxygen Saturation
Oxygen Content (ml/dl)
90
75
60
20
10
0
Rest 10 20 50 60 Post
F
Lactate (mmol/L)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Rest 10 20 50 60 Post
Time (min)

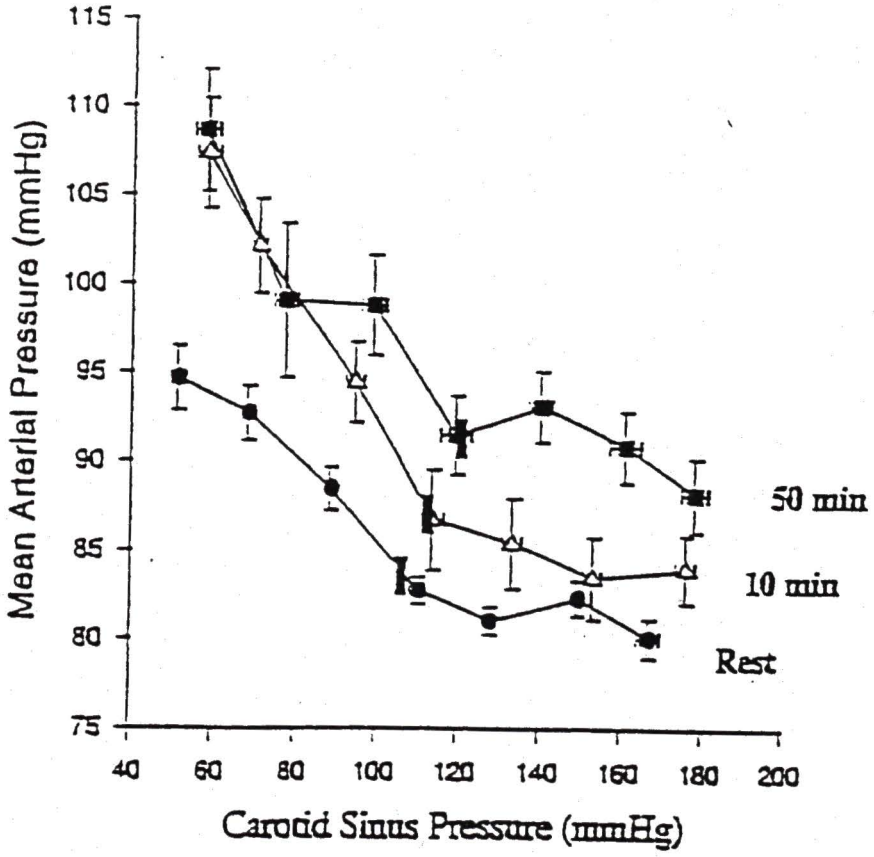

128
126
124
122
120
118
116
114
112
HR (bpm)
0
50
100
150
200
250
CSF (mmHg)


A
Control
Volume Infusion
Threshold (mmHg)
120
100
80
60
40
rest
10 min
50 min
B
Centering Point (mmHg)
140
120
100
80
rest
10 min
50 min
C
Saturation (mmHg)
200
180
160
140
120
100
80
D
Maximal Gain (bpm/mmHg)
-0.16
-0.20
-0.24
-0.28
-0.32
rest
10 min
50 min
E
Operating Point (mmHg)
110
105
100
95
90
85
80
rest
10 min
50 min
F
Threshold - Operating Point (mmHg)
35
30
25
20
15
10
5
0
-5
-10

A


Mean Arterial Pressure (mmHg)
120
115
110
105
100
95
90
85
80
75
40
60
80
100
120
140
160
180
200
Carotid Sinus Pressure (mmHg)
50 min
10 min
Rest

B


Mean Arterial Pressure (mmHg)
115
110
105
100
95
90
85
80
75
40
60
80
100
120
140
160
180
200
Carotid Sinus Pressure (mmHg)
50 min
10 min
Rest

TRANSITION

The results of the previous investigation support our primary hypothesis: that central command is the primary mechanism by which the carotid arterial baroreflex is reset during dynamic exercise. However, the question remains as to what contribution the activation of the exercise pressor reflex during exercise may have on the resetting of the carotid baroreflex. It has been postulated that activation of the muscle metaboreflex may result in an upward shift in the carotid-vasomotor baroreflex stimulus-response relationship without an alteration in the operating point position such that only the efferent, or response, arm of the stimulus-response relationship is affected. Therefore the second investigation was designed to demonstrate the effects of exercise type and intensity on the regulation of arterial blood pressure during exercise through baroreflex resetting. Using the neck pressure/neck suction technique, CBR stimulus-response relationships were compared during dynamic exercise ranging in intensity from 50% $\dot{V}O_{2max}$ to maximal exercise. In addition, exercise was performed with either leg exercise alone or combined with arm exercise. We anticipated that the magnitude of baroreflex resetting would be related to exercise intensity and thus the activation of central command and that arm exercise would elicit an augmented shift in the carotid-vasomotor stimulus-response relationship as compared to leg exercise alone due to a disproportionate activation of the muscle metaboreflex in combination with a heightened central command activation.

CHAPTER III

RESETTING OF THE CAROTID ARTERIAL BAROREFLEX DURING DYNAMIC EXERCISE IN HUMANS

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ABSTRACT

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Carotid baroreflex (CBR) stimulus-response relationships were compared in humans using the neck pressure/neck suction technique during a wide range of dynamic exercise intensities performed by leg exercise alone or combined with arm exercise. Increases in indices of central command as well as the magnitude of CBR resetting occurred relative to exercise intensity and thus the activation of central command. In addition, the performance of the combined exercise resulted in an augmented resetting of the carotid-vasomotor baroreflex compared to leg exercise alone presumably due to a disproportionate activation of the muscle metaboreflex and a heightened central command activation. We propose that CBR resetting at the onset of dynamic exercise is primarily the result of the activation of central command, a phenomenon that is directly related to exercise intensity, i.e., activation of an appropriate number of motor fibers in order to execute the exercise. However, we do not discount the potential effect of the exercise pressor reflex on the regulation of arterial blood pressure by the CBR under certain circumstances.

INDEX OF TERMS:

Threshold, Saturation, Operating Point, Central Command, Exercise Pressor Reflex

INTRODUCTION

Stimulated by the controversy concerning the functional role of the arterial baroreflexes in the regulation of arterial blood pressure during dynamic exercise, recent investigations have shown in humans that at the onset of low to moderate intensity leg cycling exercise the carotid baroreflex (CBR) was classically reset: i.e., the open-loop stimulus-response relationship was shifted to operate around the prevailing arterial blood pressure of the exercise without an alteration in the maximal gain or sensitivity of the reflex (14, 19). The resetting of the reflex occurred in direct relation to the intensity of exercise (14, 19). In addition, the operating point (i.e., pre-stimulus arterial pressure) was shown to be relocated away from the centering point and toward the threshold of the reflex (19). This relocation of the operating point was also in direct relation to the exercise intensity, thus facilitating the reflex response to hypertensive stimuli during exercise. Potential candidates for the resetting of the carotid baroreflex include the feed-forward centrally originated signals which activate in parallel the cardiovascular and somatomotor responses to exercise (central command) and the feedback reflexes which originate in the active skeletal musculature due to chemical and mechanical error signals defined as the exercise pressor reflex (24).

We propose that the immediate resetting of the CBR at the onset of dynamic exercise is primarily the result of the activation of central command, a phenomenon that is directly related to exercise intensity, i.e., activation of an appropriate number of motor fibers in order

to execute the exercise. Therefore an increase in exercise intensity will result in increases in several indices of central command such as heart rate (HR) and oxygen uptake ($\dot{V}O_2$) and will be reflected by an augmented resetting of the CBR as evidenced by a lateral shift in the CBR stimulus-response relationship such that the reflex operates around the exercise induced increase in blood pressure. However, although the muscle metaboreflex may not be tonically active during dynamic exercise at all exercise intensities (22, 30), we do not discount the potential effect of the mechanoreceptor activation of the exercise pressor reflex on the regulation of arterial blood pressure by the CBR at all exercise intensities.

The present investigation was designed to demonstrate the effects of exercise type and intensity on the regulation of arterial blood pressure during exercise through baroreflex resetting. Therefore, CBR stimulus-response relationships were compared during dynamic exercise at a wide range of exercise intensities (50% $\dot{V}O_{2max}$ to maximal exercise) using a modification of the neck pressure/neck suction (NP/NS) technique developed by Potts et al (19). We anticipated that increases in exercise intensity to maximal exercise would result in increases in several indices of central command such as HR and $\dot{V}O_2$ as well as an augmentation of the magnitude of the lateral shift in the CBR stimulus-response curve (with the operating point being shifted further toward or below the threshold of the reflex) relative to the activation of central command. In addition, we anticipated that the performance of combined arm and leg exercise would elicit an augmented shift in the carotid-vasomotor stimulus-response relationship relative to leg exercise alone at the same exercise intensity due

to a disproportionate activation of the muscle metaboreflex in combination with a heightened central command activation.

METHODS AND PROCEDURES

Subjects

Seven healthy men (aged 25.4 ± 0.75 yr.) gave written informed consent for this investigation as approved by the Ethics Committee of the University of Copenhagen. All subjects were free of known cardiovascular and pulmonary disorders and were not taking any prescribed medications. Subject data are summarized in Table 1.

INSERT TABLE 1 HERE

Protocol

Each subject performed two graded exercise tests at least two days prior to participating in the experiment. The primary test was a maximal exercise test for the determination of maximal oxygen uptake ($\dot{V}O_{2max}$) during upright, seated, back supported leg cycling exercise. The second test involved the measurement of oxygen uptake ($\dot{V}O_2$) during arm ergometry performed at several graded exercise workloads in order to determine the arm exercise workload which would elicit a $\dot{V}O_2$ of approximately 25% of the leg cycling $\dot{V}O_{2max}$. On the experimental day, each subject performed four 10 to 15 minute bouts of

constant load dynamic exercise in a 20°C, 40-60% relative humidity environment in the same body position used during the preliminary exercise tests. Each exercise bout was separated by a rest period of sufficient length to return heart rate (HR) and mean arterial pressure (MAP) to baseline values. Exercise Bout 1 consisted of leg cycling exercise at 50% of the predetermined leg cycling $\dot{V}O_{2max}$ ("50%L"). Exercise Bout 2 consisted of leg cycling at the same workload with the addition of arm cranking exercise at a workload eliciting 25% of the leg cycling $\dot{V}O_{2max}$ such that the whole body $\dot{V}O_2$ approximated 75% of leg $\dot{V}O_{2max}$ ("75%L+A"). Exercise Bout 3 consisted of leg cycling alone at a workload eliciting the same $\dot{V}O_2$ as was attained during the exercise Bout 2 combined exercise ("75%L"). Finally, exercise Bout 4 consisted of leg cycling at the same workload as in Bout 3 with the addition of arm cranking exercise at a workload eliciting 25% of the leg cycling $\dot{V}O_{2max}$ such that the whole body $\dot{V}O_2$ approximated leg $\dot{V}O_{2max}$ ("Max L+A"). Figure 1 illustrates the apparatus and experimental protocol used in the investigation and Table 2 lists the absolute $\dot{V}O_2$ measures and wattages for each level of exercise. During each exercise bout, HR, $\dot{V}O_2$ and MAP were continuously monitored and recorded. At rest and following attainment of steady-state exercise in each experimental exercise bout, CBR stimulus-response curves were constructed using a modification of the neck pressure/neck suction protocol previously developed by Potts et al (19).

INSERT FIGURE 1 HERE

INSERT TABLE 2 HERE

Measurements

Maximal exercise test and oxygen uptake measures. Subjects determined acceptable by physical examination performed two graded exercise tests for the determination of oxygen uptake ($\dot{V}O_2$). The test for leg $\dot{V}O_{2max}$ was performed in the upright posture on a constant load cycle ergometer. The arm ergometry exercise test was performed in the seated position with a constant load cycle ergometer which was modified for arm ergometry. During each test, the subject exercised to volitional fatigue and measurements included the rate of oxygen uptake ($\dot{V}O_2$) using breath-by-breath open circuit spirometry and continuous ECG monitoring using a 12-lead monitoring system. Subjects returned to the laboratory no less than two days following maximal exercise testing for performance of the experimental exercise bouts.

Heart rate and Arterial blood pressure. Heart rate was continuously monitored via electrocardiogram (ECG). Arterial blood pressure was measured directly via a catheter placed into the right femoral artery by a consulting physician. The pressure was monitored using disposable pressure transducers interfaced with pressure monitors. Pressure transducers were calibrated and established at zero reference pressure at the mid-axillary and third

intercostal space before and after the experiment and catheters were appropriately connected to an IV bag for saline flush. Mean, systolic and diastolic blood pressure along with HR, were recorded beat-by-beat on-line by using a personal computer (Zitech Pro, Pentium 90) and customized software.

Carotid Baroreflex (CBR)Function. CBR function during exercise was analyzed via the use of a malleable lead-chambered collar which was secured with velcro straps to the anterior 2/3 of the subject's neck. Variable pressure vacuum pumps were used to generate pressure within the collar thereby delivering perturbations ranging from +40 to -80 Torr (20 Torr increments) directly to the carotid sinus region of the subject's neck. Randomized pressure or suction pulses were delivered to the neck precisely 50ms after the R wave of the ECG for a duration of 5 seconds each. The HR and MAP responses to each of three trials at each generated neck pressure or suction level were used to construct baroreflex stimulus-response curves. The curves were then individually modeled using a four parameter logistic function utilizing a non-linear least-square regression algorithm (6). This modeling technique produced a sigmoidal shaped stimulus-response curve of "best-fit" for each data set. These procedures have been developed and published in our laboratory (19) however, several changes were made in the technique to accommodate the high workloads being used in the present experiments. The neck pressure / suction technique was altered such that subjects were allowed to breathe freely during the 5 second carotid sinus stimuli (in contrast to the end expiratory breath hold maneuver previously used at rest and during lighter exercise workloads (14)). Based on data from Eckberg et al, 1980 (3) which demonstrated that at a breathing

frequency of 24 breaths/minute, no difference existed between the responses to neck collar stimuli during inspiration and expiration, we predicted that by choosing the peak HR and MAP response to each stimulus, CBR stimulus-response curves could be modeled at high exercise workloads with appropriate repeatability. In addition, the time required to construct a stimulus-response curve during exercise was reduced to a maximum of 10 to 12 minutes to lessen exercise time and minimize the confounding effects of cardiovascular drift on CBR function. Prior to the investigation of the effects of active skeletal muscle mass on CBR function, the repeatability of the modified neck pressure / neck suction technique was established, see Figure 2 and Table 3 below.

Analysis

The individual CBR stimulus-response curves were analyzed using the logistic function described by Kent et al (5) which incorporates the equation below.

$$HR \text{ or } MAP = A1 * \{1 + e^{[A2(CSP-A3)]}\}^{-1} + A4 \qquad (Eq.1)$$

where:

CSP = carotid sinus pressure; MAP + or - neck chamber pressure;

A1 = range of response of dependent variable (max-min);

A2 = gain coefficient;

A3 = CSP required to elicit equal pressor and depressor responses (centering point);

A4 = minimum HR or MAP response.

Baroreflex threshold was described as the minimum carotid sinus pressure that elicits a reflex change in HR or MAP. Similarly, baroreflex saturation was described as the maximum carotid sinus pressure that elicits a reflex change in HR or MAP. Estimations of CBR threshold and saturation are based on the calculation of the third derivative of Eq. 1, which defines the points at which the sigmoidal shaped CBR stimulus-response curve becomes linear. These values were attained in order to evaluate lateral shifts in the CBR stimulus-response relationship with exercise. Baroreflex maximal gain, derived from the first derivative of Eq. 1, was defined as the reflex gain value located at the centering point of the reflex. The operating point of each baroreflex stimulus-response curve was defined by the pre-stimulus HR and MAP for each condition. The HR and MAP response values on the y-axis to the corresponding threshold and saturation pressures on the x-axis were also determined for each curve in order to assess vertical shifts in the CBR stimulus-response relationship with exercise. This value was determined by adding the range of response of the dependent variable (A1) to the minimum HR or MAP response (A4). The resulting values were compared using one way analysis of variance (ANOVA) with repeated measures across condition. Student-Newman-Keuls post pairwise comparisons were used to further analyze group mean differences. Statistical significance was accepted at a p value of <0.05 .

RESULTS

Repeatability of Baroreflex Stimulus-Response Curves:

We have demonstrated that carotid baroreflex stimulus-response curves can

be generated using the modified neck pressure / neck suction (NP/NS) protocol with high repeatability in subjects performing leg cycling exercise at workloads greater than that demonstrated by Potts et al (19), i.e., 50% $\dot{V}O_{2max}$. Figure 2 below represents the mean and standard errors of the heart rate responses (carotid-cardiac baroreflex) to several levels of carotid sinus stimulation (ranging from -80 to +40 torr) generated following 10 minutes of dynamic leg cycling exercise at 68% $\dot{V}O_{2max}$ in one subject during four separate bouts of exercise. The gain, threshold and saturation values for each of the four individual carotid baroreflex stimulus-response curves are listed below in Table 3.

INSERT FIGURE 2 HERE

INSERT TABLE 3 HERE

Carotid-cardiac baroreflex response to dynamic exercise:

No significant differences were seen in the carotid-cardiac baroreflex maximal gain, or sensitivity, at any exercise intensity. However, significant lateral shifts were seen in the threshold and saturation values of the carotid-cardiac baroreflex with increasing exercise intensity, see table 4. These shifts occurred regardless of the type of exercise being performed, i.e., 'Leg only' or combined 'Leg + Arm' exercise with the exception of the comparison

between the CBR threshold values during the '75% Leg + Arm' and 'Max Leg + Arm' exercise bouts. Failure to achieve significance between these bouts appears to be primarily related to the large standard error of the mean values of saturation seen in both bouts. However as the shift between these bouts was near significance at $p<0.07$, the results of this investigation indicate that the carotid baroreflex was classically reset (i.e., a shift in reflex threshold and saturation without a concomitant change in reflex maximal gain) from rest to $\dot{V}O_{2max}$. The examination of vertical shifts in threshold and saturation (i.e., the y-axis coordinate or HR response to the corresponding threshold or saturation pressure value) between all exercise bouts revealed similar results, see Table 4. The HR response at the threshold and saturation values for the '75% Leg only' vs. '75% Leg + Arm' exercise bouts were not significantly different based on one way repeated measures ANOVA. However, due to the observation that for each individual the combined exercise bout appeared to elicit greater lateral and vertical shifts from the previous workload, i.e., '50% Leg only', the data were further analyzed using 'a priori' paired t-tests. Using this statistical method, the HR response values at threshold and saturation for the carotid-cardiac baroreflex stimulus-response relationships during '75% Leg only' and '75% Leg + Arm' exercise were again statistically similar indicating no vertical shifting of the carotid-cardiac baroreflex relationship during the combined exercise bout.

INSERT TABLE 4 HERE

Table 4 describes the lateral (threshold and saturation pressure values) and vertical (corresponding HR values) shifts in the threshold and saturation values for the carotid-cardiac baroreflex stimulus-response relationships to the various exercise protocols used in this investigation. These data also demonstrate the lack of a significant difference in reflex maximal gain among the exercise bouts. In addition, the operating point of the carotid-cardiac baroreflex stimulus-response relationship was significantly shifted away from the centering point of the reflex and toward the reflex threshold in relation to exercise intensity. No significant difference was found between the position of the operating points of the leg only and combined arm and leg exercise bouts at 75% $\dot{V}O_{2max}$, see Figure 3.

INSERT FIGURE 3 HERE

Carotid-vasomotor baroreflex response to dynamic exercise:

The carotid-vasomotor baroreflex stimulus-response relationships of only four subjects were statistically analyzed due to an inability to model the baroreflex function curves for each exercise bout on the remaining subjects. Although rhythmic variation in MAP recordings due to the effect of the movement of the exercising legs on the intravascular pressure transducer can hinder modeling of carotid-vasomotor stimulus-response curves, a primary difficulty in the present investigation lay in obtaining reliable threshold values for these curves which would imply that stronger neck pressure or a more prolonged stimuli are required to achieve

maximal reflex vasomotor responses during these exercise types and intensities. Modeling of reflex curves derived during 'Leg + Arm' exercise bouts were particularly difficult. This finding may be related to the alterations Papelier et al (15) documented in the shape of the baroreflex function curve during activation of the muscle chemoreflex such that decreases in carotid sinus pressure below the operating point of the reflex (neck pressure) resulted in a progressive increase in the reflex MAP response. Therefore, the data from only four subjects of the total seven were used in order that a one-way repeated measures ANOVA could be used across all conditions for each subject, however, achievement of statistical significance with this limited subject number indicates the strength of the data of this investigation.

No significant differences were seen in the carotid-vasomotor baroreflex maximal gain, or sensitivity at any exercise intensity. However, significant lateral and vertical shifts (i.e., the y-axis coordinate or MAP response to the corresponding threshold or saturation pressure value) were seen in the threshold and saturation values of the carotid-vasomotor baroreflex with increasing exercise intensity, with the exception of vertical shifts from rest to '50% Leg only' exercise, see Table 5. These shifts occurred regardless of the type of exercise being performed, i.e., 'Leg Only' or combined 'Leg + Arm' exercise. Although the threshold and saturation values of the 75% Leg only and Leg + Arm exercise bouts were statistically similar when compared using repeated measures ANOVA, a priori analysis using paired t-tests indicated that when group variance is disregarded, the differences between these values are highly significant: lateral threshold shift ($p= 0.012$), vertical shift in MAP response at threshold ($p= 0.0044$), lateral saturation shift ($p=0.0015$), vertical shift in MAP response at

saturation (p=0.026).

INSERT TABLE 5 HERE

Similar to the carotid-cardiac stimulus-response curves, the operating point was significantly shifted away from the centering point and toward the threshold of the reflex at each exercise intensity. No significant difference was found between the position of the operating points of the leg only and combined exercise bouts at 75% $\dot{V}O_{2max}$, see Figure 4.

INSERT FIGURE 4 HERE

DISCUSSION

The primary findings of this investigation indicate that the carotid baroreflex was classically reset; i.e., a shift in reflex threshold and saturation occurred without an alteration in maximal gain or sensitivity, in relation to the intensity of exercise throughout a wide range of exercise intensities including $\dot{V}O_{2max}$. This conclusion supports the investigations of Melcher and Donald (9) in the dog model, as well as Potts et al (19) and Papelier et al (14) in the exercising human, each of which also demonstrated a reset but a functional and equally sensitive baroreflex during exercise as compared to the resting condition. As in the investigation by Potts et al (19), the operating point of the baroreflex, i.e., pre-stimulus MAP,

was shown to be relocated away from the centering point and toward the threshold of the baroreflex stimulus-response relationship also in relation to the intensity of the exercise. However, the present investigation demonstrates that the shift in operating point continues to occur in conjunction with baroreflex resetting throughout increasing exercise intensities up to $\dot{V}O_{2max}$. By utilizing a wider range of exercise intensities and modes of exercise, the present investigation further elucidates the mechanism(s) responsible for acute baroreflex resetting during dynamic exercise. All resetting occurred in direct relation not only to the intensity of exercise but to increases in HR and $\dot{V}O_2$, two important indices of central command. Therefore, this data supports our proposal of a primary role of central command in baroreflex resetting with exercise. In addition, combined arm and leg work elicited augmented shifts in the carotid-vasomotor baroreflex relative to leg exercise alone thus indicating an additional role for the exercise pressor reflex in baroreflex resetting under certain conditions. See Figure 5 for a schematic illustration of the carotid baroreflex resetting seen in the present investigation.

INSERT FIGURE 5 HERE

Role of the Carotid Baroreflex during Exercise

The role of the arterial baroreflex in the regulation of arterial blood pressure during dynamic exercise has been controversial for many years. However, data from both animal (1,

9) and human (14, 19) studies provide strong evidence for continued modulation of arterial blood pressure by the arterial baroreflex during dynamic exercise without a decrement in reflex sensitivity. Melcher and Donald (6) demonstrated a functioning carotid baroreflex in dynamically exercising dogs using surgical isolation and independent perfusion of the carotid sinus baroreceptors. Pressures within the carotid sinus were changed independently of the systemic circulation and stimulus-response curves for HR and MAP were generated. The results of this investigation indicated that the carotid baroreflex was indeed functional during dynamic exercise and that the reflex function curve had undergone an upward shift in threshold and saturation with no change in the maximal gain of the reflex.

Over time the technique of using variable neck pressure and neck suction to selectively stimulate the carotid baroreceptors has been altered. Potts et al (19) have developed a variation in this technique which was highly reproducible, was not confounded by interaction with extracarotid baroreceptor reflexes or respiratory activity, and was not affected by alterations in baseline HR. This technique involved the application of a series of five second periods of neck pressure or suction to the carotid sinus region of the subject's neck during an end expiratory breath hold. Using this methodology, Potts et al (19) recently demonstrated that CBR function was classically reset to higher mean arterial pressures (MAP) at 10-20 minutes of 25% $\dot{V}O_{2peak}$ and 50% $\dot{V}O_{2peak}$ steady-state exercise (19). In addition, their modeling of the baroreflex function curves indicated that the operating point (i.e., the pre-stimulus MAP) was relocated from rest to exercise to operate at a location near the threshold

of the reflex and above the centering point of the CBR function curve (19). These findings have been confirmed by the work of Papelier et al (14) who similarly demonstrated an intensity dependent upward resetting of the CBR stimulus-response curve during mild to severe dynamic exercise with no change in reflex gain. The results of the current investigation further support the findings of continued modulation of arterial blood pressure during dynamic exercise by the carotid baroreflex without diminution of reflex sensitivity or gain (1,9,14,19). The upward and rightward shift in the carotid arterial baroreflex stimulus-response curve and the relocation of the operating point of the curve toward the threshold of the reflex render the reflex in a position to respond to changes in systemic arterial pressure from the prevailing pressure of the steady-state dynamic exercise with a particular augmentation in the capacity to respond to hypertension.

Resetting of the Carotid Baroreflex during Exercise

The mechanism or mechanisms responsible for the acute resetting of the carotid arterial baroreflex during dynamic exercise have been postulated and theorized, however few investigations have been documented which test these theories (1, 15). Rowell and O'Leary (24) have outlined how two possible effector mechanisms may shift or reset the carotid baroreflex prior to or as a result of exercise. Central command, the feed-forward mechanism, which is proposed to initiate the recruitment of motor fibers for the performance of exercise, may exert a parallel influence on the cardiovascular system by immediately shifting the baroreflex rightward such that reflex vagal withdrawal and sympathetic nervous system

activation in response to the position of the operating point of the reflex on the shifted stimulus-response curve results in the on-response of the cardiovascular system to exercise (24). Alternatively or additionally, the activation of muscle metabo- and mechano- reflexes during exercise may result in an upward shift in the baroreflex stimulus-response curve without an alteration in operating point position such that only the efferent, or response, arm of the stimulus-response relationship is affected (24). Refer to Figure 5 for a schematic illustration of the carotid arterial baroreflex resetting seen in the present investigation.

Central Command. "Central command" is the term applied to the descending, cortically-originated signals which are thought to affect in parallel the recruitment of skeletal muscle motor fiber units and the cardiovascular system through feed-forward control (4, 10, 20). As electrical and chemical stimulation of the hypothalamic locomotor (HTL) region of the brain elicits both skeletal locomotor and cardiovascular system responses, this area is the putative site of origination of central command, see review by Mitchell et al (10). In addition, alterations in the discharge properties of neurons in the ventral lateral medulla (VLM) demonstrated by Nolan et al (12) via HTL stimulation and electrically induced muscle contraction, indicate that central command and muscle reflexes may affect baroreflex function through an integration of the three systems at this brainstem site (20).

DiCarlo and Bishop (1) have examined the time course of the resetting of the arterial baroreflex in exercising rabbits and have demonstrated an immediate resetting of the reflex at the onset of exercise which suggests that a negative feedback error signal was not necessary to provoke reflex resetting. Additionally, Ebert et al (2) have shown that the

anticipation of static exercise in humans results in an alteration in carotid-cardiac and carotid-vasomotor responses to neck pressure and neck suction stimuli. These findings question the role of the exercise pressor reflex in baroreflex resetting at the onset of exercise and supports the role of a quicker acting feed-forward type mechanism such as "central command". Additionally, DiCarlo and Bishop have also demonstrated that an intact CBR was required in order for central command to elicit a HR increase with exercise (1).

Muscle Metaboreflex. The muscle metaboreflex originates in skeletal muscle through activation of chemically sensitive receptors, in the form of unencapsulated nerve endings, and causes discharge primarily in Group IV afferent fibers (10). These signals may be integrated with central command and baroreflex neurons in the VLM area of the brainstem as discussed previously (10, 20). Sherrif et al (27) have shown that the reflex response to muscle metaboreflex activation is attenuated by arterial baroreflex activation, and conversely, McWilliam and Yang (8) demonstrated an apparent attenuation of the reflex bradycardia response to increases in carotid sinus pressure during electrical stimulation of the ventral roots containing ascending metaboreflex afferent fibers (L7-S2 ventral roots) of decerebrate cats. More recently however, Potts et al (18) have questioned the interpretation of the data of McWilliam and Yang (8) through the demonstration that the effect of muscle reflex activation on the function of the arterial baroreflex may be to shift, or reset, the reflex rather than diminish the reflex sensitivity. In Potts et al (18), HR, arterial pressure, and renal sympathetic nerve activity responses to ramped increases in carotid sinus pressure (CSP)were recorded in the dog model with and without simultaneous electrical stimulation of L7-S1

ventral roots. The response of each cardiovascular variable was shifted rightward or to a higher pressure during contraction, however, calculation of the maximal gain or sensitivity of the reflex, e.g. change in HR divided by change in CSP, revealed no decrement in reflex sensitivity (ref. 18 and personal communication). Based on this finding, the attenuation of the bradycardia response to an elevation in CSP seen in the experiments of McWilliam and Yang (8) may be due to the location of the stimulus relative to the reset baroreflex stimulus-response relationship, i.e., the stimulus now falls closer to the threshold of the reflex resulting in a relatively diminished response. These data suggest that rather than attenuate baroreflex function, activation of the exercise pressor reflex may reset the baroreflex to operate at a higher level of blood pressure. In addition, Papelier et al (15) investigated the effect of a post-exercise activation of the muscle metaboreflex on CBR function by supra-systolic thigh cuff inflation initiated twenty seconds before the end of a 7 minute, 150 watt leg cycling exercise bout. Comparisons of neck pressure / neck suction carotid baroreflex stimulus-response curves at rest, during exercise and during control and flow occluded recovery demonstrated that the carotid-vasomotor stimulus-response relationship undergoes a significant vertical shift with post-exercise leg blood flow occlusion as compared to the control post-exercise condition. It should be noted, however, that the physiologic significance of this information must be tempered by the idea that the muscle metaboreflex may not be tonically active during moderate exercise (22, 30).

Leg Only vs. Leg + Arm exercise

The addition of arm exercise to leg exercise presents a complex physiologic picture. Not

only does arm work elicit different chemical, thermal, and perceptive responses to exercise than leg work, the additional muscle mass must receive an adequate proportion of cardiac output to sustain the exercise (16,17,26). The question of how cardiac output is distributed to exercising muscle during high intensity dynamic exercise was raised by Secher et al, in 1976 (26). These investigators found that the addition of arm cranking exercise to leg cycling exercise resulted in an increase in HR and $\dot{V}O_2$ without a concomitant increase in MAP or pulse pressure. The increases in HR and $\dot{V}O_2$ elicited by the increase in muscle mass are consistent with our proposal, however, we would predict that a rise in MAP would be seen with the addition of arm exercise to leg exercise. Unfortunately, the pressure data of Secher et al's investigation (26) was only reported in 5 to 10 minute increments, and furthermore suggests that a transient increase in MAP may have occurred prior to a return of pressure to a value approximating the value for leg exercise alone. The authors also noted that leg vascular resistance was increased and leg blood flow decreased during the addition of arm exercise in both non-active and active leg tissues. Therefore, for a maintenance of (or return to) a relatively similar MAP between the two exercise bouts, arm vasodilation and leg vasoconstriction must have been balanced in conjunction with the observed modest rise in cardiac output. The question of the origin of the signal for increased leg vascular resistance in the face of the exercise demand can possibly be explained by our reflex resetting model. An augmented central command activation with increased active muscle mass (addition of arm cranking exercise to leg cycling exercise, i.e., increased numbers of active motor fibers)

will result in an upward and rightward shift in the carotid baroreflex stimulus-response curve. If, after a transient rise, MAP returned to a value similar to that observed during leg exercise alone as in Secher et al's investigation (26), it would then lie nearer to the threshold of the reset baroreflex function curve producing a hypotensive stimuli which would result in an activation of the efferent sympathetic limb of the autonomic nervous system (vasoconstriction).

In order to discern whether the baroreflex regulated muscle vasomotion in active muscle during high intensity dynamic exercise, Strange et at (29) measured the HR, MAP, and leg blood flow (LBF) responses to 30 second trains of intra-beat pulsatile neck suction (-50 mmHg) during both moderate and high intensity exercise bouts. At moderate work intensities, neck suction produced reflex decreases in HR, MAP, and leg blood flow with corresponding increases in leg vascular conductance. However, at the highest work intensity, 88% $\dot{V}O_{2max}$, leg blood flow and MAP again fell in response to neck suction, however, no increase in leg conductance was seen. The authors attributed the lack of baroreflex regulation of leg vascular conductance during the highest submaximal level of exercise to several possible explanations including: insufficient intensity of exercise to require vasoconstriction in active muscle in order to maintain MAP and increased opposition of carotid baroreflex vasomotor control by the aortic baroreflex or muscle mechanoreflex during high intensity exercise.

We offer an additional explanation for the apparent lack of carotid baroreflex

responsiveness to pulsatile neck suction during high intensity exercise. Based on the results of the present investigation, at an exercise intensity of 88% $\dot{V}O_{2max}$, the carotid arterial baroreflex would have been reset upward and rightward at the onset of the exercise, and the operating point of the reflex would have been relocated away from the centering point and toward the reflex threshold pressure. Therefore, a moderate hypertensive stimulus would produce less of a reflex response than if the operating point were located on a portion of the stimulus-response relationship with a higher reflex gain. In addition, at an exercise intensity of 88% $\dot{V}O_{2max}$, the interbeat interval (R to R interval) approaches or becomes shorter than the neural latency of the baroreflex arc, reported to vary between 200 and 500 ms (28) for the carotid-cardiac baroreflex and one to two orders of magnitude larger for the sympathetic branch of the baroreflex responsible for vasomotor tone (21). Therefore, the stimulus used in Strange et al's experiment (29) may have been of insufficient length to facilitate complete activation of the carotid-vasomotor baroreflex. This in combination with the position of the pre-stimulus pressure (operating point) on a less responsive portion of the baroreflex stimulus-response relationship may account for the lack of change in leg vascular conductance at the higher workloads.

Cardiovascular and metabolic responses to arm exercise. Exercise performed at the same absolute $\dot{V}O_2$ results in higher heart rates (16, 17) and ratings of perceived exertion (17) when the exercise is performed with the arms (upper body) as compared to the legs (lower

body). As these variables are indices of central command, this is indicative of an increased level of central command activation during arm exercise as compared to leg exercise. In addition, lactate accumulation in the venous system has been reported to occur earlier during arm exercise and the removal of this lactate to be less efficient resulting in an augmented metabolic stress (16). Therefore arm exercise is presumably associated with increased central command as well as metaboreflex activation as compared to leg exercise at a similar absolute $\dot{V}O_2$. The type and extent of carotid baroreflex resetting seen in the present investigation when comparing Leg only to combined Leg+Arm exercise at 75%$\dot{V}O_{2max}$ is consistent with the hypothesis proposed by Rowell and O'Leary (24) in that the augmented resetting during the combined exercise bout was comprised of both a lateral and vertical component. Interestingly, the upward shift was only seen in the carotid-vasomotor component of the carotid baroreflex, as was reported in the investigation by Papelier et al (15). The lack of this effect on the carotid-cardiac baroreflex has been attributed to the proposed differences in metaboreflex activation on cardiac and vasomotor function (13). This difference is presumably due to the disproportionate effect of muscle metaboreflex activation of the sympathetic nervous system on a constant background of mechanoreceptor activation. In addition, at the HR elicited by 75% $\dot{V}O_{2max}$ exercise, the majority of the parasympathetic influence on HR had been withdrawn and as baroreflex control of heart rate is primarily modulated via the parasympathetic nervous system the absence of an effect of the muscle metaboreflex activation was not unexpected.

CONCLUSION

In summary, the results of this investigation support the concept of continued regulation of arterial blood pressure during exercise by the carotid baroreflex. The carotid-cardiac and carotid-vasomotor reflexes were reset upward and rightward in direct relation to the intensity of exercise with a concomitant shift of the reflex operating point away from the centering point and toward the threshold of the reflex. This resetting positions the reflex to respond to changes in systemic arterial pressure from the prevailing pressure of the steady-state dynamic exercise with a particular augmentation in the capacity to respond to hypertension. The results also support the role of central command as the primary mechanism responsible for the resetting of the baroreflex with an additional effect by the exercise pressor reflex to augment resetting under relevant circumstances. Figure 5 illustrates schematically the resetting of the carotid-cardiac and carotid-vasomotor baroreflexes seen in this investigation.

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REFERENCES

1. **DiCarlo, S.E., and V.S.Bishop**. Onset of exercise shifts operating point of arterial baroreflex to higher pressures. *Am. J. Physiol.* 262 *(Heart Circ. Physiol.* 31*)*: H302-H307, 1992.

2. **Ebert, T.J.** Baroreflex responsiveness is maintained during isometric exercise in humans. *J. Appl. Physiol.* 61(2):797-803, 1986.

3. **Eckberg, D.L., Y.T. Kifle, and V.L. Roberts**. Phase relationship between normal human respiration and baroreflex responsiveness. *J. Physiol. (Lond.)* 304:489-502, 1980.

4. **Eldridge, F.L., D.E. Millhorn, J.P. Kiley and T.G. Waldrop**. Stimulation by central command of locomotion, respiration and circulation during exercise. *Resp. Physiol.* 59: 313-337, 1985.

5. **Hobbs, S.F.** Central command during exercise: parallel activation of the cardiovascular and motor systems by descending command signals. *In Circulation, Neurobiology, and Behavior.* Eds. O.A.Smith, R.A. Galosy, and S.M.Wiess. Elsevier, New York. pp. 217-231, 1982.

6. **Kent, B.B., J.W. Drane, B. Blumenstein, and J.W. Manning**. A mathematical model to assess changes in the baroreceptor reflex. *Cardiol.* 57:295-310, 1970.

7. **Lewis, S.F., P.G. Snell, W.F. Taylor, M. Hamra, R.M. Graham, W.A. Pettinger and C. G. Blomqvist**. Role of muscle mass and mode of contraction in circulatory responses to exercise. *J. Appl. Physiol.* 58(1): 146-151, 1985.

8. **McWillam, P.N. and T. Yang.** Inhibition of cardiac vagal component of baroreflex by group III and IV afferents. *Am. J. Physiol.* 260 *(Heart Circ. Physiol.* 29*)*: H730-H734, 1991.

9. **Melcher, A., and D.E. Donald**. Maintained ability of carotid sinus baroreflex to regulate arterial pressure during exercise. *Am. J. Physiol.* 241 *(Heart Circ. Physiol.* 10*)*:H838-H849, 1981

10. **Mitchell, J.H.** Neural control of the circulation during exercise. *Med. Sci. Sports Exerc.* 22:141-154,1990.

11. **Mitchell, J.H., B. Schibye, F.C. Payne III, and B. Saltin.** Response of arterial blood pressure to static exercise in relation to muscle mass, force development, and electromyographic activity. Circ. Res. 48(6):I70-I75, 1981.

12. **Nolan, P.C., J.A. Pawelczyk, and T.G. Waldrop**. Neurons in the ventrolateral medulla receive input from descending "central command" and feedback from contracting muscles. *Physiologist* 35: 240, 1992

13. **O'Leary, D.S.** Autonomic mechanisms of muscle metaboreflex control of heart rate. *J. Appl. Physiol.* 74:1798-1754, 1993.

14. **Papelier, Y., P. Escourrou, J.P. Gauthier, and L.B. Rowell.** Carotid barorelflex control of heart rate and blood pressure in men during dynamic exercise. *J. Appl.*

Physiol. 77(2):502-506, 1994.

15. **Papelier, Y.P., P. Escourrou, F. Helloco, and L.B. Rowell.** Muscle chemoreflex alters carotid sinus baroreflex response in humans. *J. Appl. Physiol.* 82(2): 577-583, 1997.

16. **Pendergast, D.R.** Cardiovascular, respiratory, and metabolic responses to upper body exercise. Med. Sci. Sports Exerc. 21(5)S: S121-s12, 1989.

17. **Pivarnik, J.M., T.R. Grafner, and E.S. Elkins**. Metabolic, thermoregulatory, and psychophysiological responses during arm and leg exercise. *Med. Sci. Sports Exerc.* 20(1): 1-5, 1988.

18. **Potts, J.T., G.A. Hand, J. Li, and J.H. Mitchell**. Functional significance of varied levels of carotid sinus baroreceptor and hindlimb muscle afferent input on reflex cardiovascular responses. *Physiologist* 39(5) Abstract 8.1, pA-16, 1996.

19. **Potts, J.T., X.Shi, and P.B.Raven**. Carotid baroreflex responsiveness during dynamic exercise in man. *Am. J. Physiol.* 265 *(Heart Circ. Physiol.* 34*)* : H1928-H1938, 1993.

20. **Raven, P.B., J.T. Potts, and X. Shi**. Baroreflex regulation of blood pressure during dynamic exercise. In: *Exercise and Sports Science Reviews.* Vol. 25, Ed. J.O. Holloszy. Publ. Williams & Wilkins, Baltimore, MD, pp365-389.

21. **Rowell, L.B.** Blood pressure regulation during exercise. *Ann. Med.* 23:229-333, 1991.

22. **Rowell, L.B., P.R. Freund, and S.F. Hobb**. Cardiovascular responses to muscle ischemia in humans. *Circ. Res.* 48(6): I37-I47, 1981.

23. **Rowell, L.B., J.A. Murray, G.L.Brengelmann, and K.K.Kraning, II.** Human cardiovascular adjustments to rapid changes in skin temperature during exercise. *Circ. Res.* 24:711-724, 1969.

24. **Rowell, L.B. and D.S. O'Leary.** Reflex control of the circulation during exercise: chemoreflexes and mechanoreflexes. *J. Appl. Physiol.* 69(2): 407-418, 1990.

25. **Saltin, B.** Muscle fiber recruitment and metabolism in prolonged exhaustive dynamic exercise. *In: Human Muscle Fatigue: Physiological Mechanisms*, Ed. R. Porter and J Whelan. London: Pitman, 1981, p 41-58.

26. **Secher, N.H., J.P. Clausen, K. Klausen, I Noer, and J. Trap-Jensen**. Central and regional effects of adding arm exercise to leg exercise. *Acta Physiol. Scand.* 100: 288-297, 1977.

27. **Sheriff, D.D., D.S. O'Leary, A.M. Scher, and L.B. Rowell.** Baroreflex attenuates pressor response to graded muscle ischemia in exercising dogs. *Am. J. Physiol* 258 *(Heart Circ. Physiol.* 27*)*:H305-H310, 1990.

28. **Sprenkle, J.M., D.L. Eckberg, R.L. Goble, J.J. Schelhom and H.C. Halliday.** Device for rapid quantification of human carotid baroreceptor-cardiac reflex responses. *J. Appl. Physiol.* 80:727-732, 1986.

29. **Strange, S., L.B. Rowell, N.J. Christensen, and B. Saltin**. Cardiovascular responses to carotid simus baroreceptor stimulation during moderate to severe

exercise in man. *Acta Physiol. Scand.* 138: 145-153, 1990.

30. **Williamson, J.W., C.G. Crandall, J.T. Potts, and P.B. Raven**. Blood pressure responses to dynamic exercise with lower-body postitive pressure. *Med. Sci. Sports Exerc.* 26(6): 701-708, 1994.

TABLE 1. Subject information

Age (yr)	Height (cm)	Weight (kg)	$\dot{V}O_{2max}$ (ml/min/kg)
25.4 ± 0.7	182.6 ± 2.0	84.6 ± 3.9	45.7 ± 2.6

Mean ± standard error; $\dot{V}O_{2max}$, maximal oxygen uptake during leg cycling

TABLE 2. Absolute $\dot{V}O_2$ and watts for each exercise stage

	50%L	75%L	75%L+A	Max L+A
$\dot{V}O_2$(L/min)	1.7±0.1	2.6±0.3	2.7±0.8	3.8±0.2
Watts	137.8±8.1	208.8±8.1	212.0±22.5	264.8±15.3

Mean ± standard error; % indicates percent of VO_{2max}, maximal oxygen uptake during leg cycling; L indicates leg only exercise, L+A indicates combined leg and arm exercise

TABLE 3. Derived variables for the CBR stimulus response relationships depected in Fig. 1

	Gain	**Threshold, mmHg**	**Saturtion, mmHg**
Trial 1	-0.15	99.5	165.7
Trial 2	-0.14	84.6	162.6
Trial 3	-0.14	87.8	166.8
Trial 4	-0.15	96.6	160.7
mean±SE	-.15±004	92.4±4.3	163.9±2.8
CV, %	2.6	4.6	1.7
95% C.I.	0.004	6.9	4.4

CV, coefficient of variation [(SE/mean) X 100], 95%CI, 95 percent confidence interval

TABLE 4. Derived variables for the carotid-cardiac baroreflex stimulus-response relationship

Condition	Threshold (mmHg)	HR at Threshold (bpm)	Saturation (mmHg)	HR at Saturation (bpm)	Gain (bpm/mmHg)
Rest	66.1±8.6	77.0±5.5	131.3±11.0	57.4±1.7	-0.33±0.07
50%L	80.5±8.0*	126.3±3.2*	143.4±8.0*	116.7±2.9*	-0.24±0.05
75%L+A	100.1±11.4*	161.1±1.7*	161.3±6.2*	156.9±2.1*	-0.23±0.05
75%L	94.4±7.9†	170.9±6.6†	154.7±8.5†	160.9±6.3†	-0.22±0.03
Max L+A	109.8±11.6*†$_{p=.07}$	189.1±4.9*†	173.0±9.3*†	172.5±9.3*†	-0.26±0.04

Mean ± standard error; % indicates percent of VO_{2max}, maximal oxygen uptake during leg cycling; L indicates leg only exercise, L+A indicates combined leg and arm exercise; * indicates significance from previous state; † indicates significance from last similar stage, i.e., L vs. L or L+A vs. L+A; statistical analysis performed using ANOVA; $p<0.05$.

Threshold and saturation values in mmHg represent the position of the stimulus-response relationship relative to the x-axis of the reflex function curve whereas threshold and saturation values in bpm indicate the position of the curve relative to the y-axis.

TABLE 5. Derived variables for the carotid-vasomotor baroreflex stimulus-response relationship

Condition	Threshold (mmHg)	Hr at Threshold (mmHg)	Saturation (mmHg)	HR at Saturation (mmHg)	Gain (mmHg/mmHg)
Rest	57.7±7.1	94.6±6.9	109.8±6.6	71.1±7.9	-0.50±.063
50%L	73.7±4.9*	97.7±6.7	128.8±7.5*	77.5±6.6	-0.47±.036
75%L+A	96.4±5.3*	113.4±8.7*	156.4±5.3*	94.1±8.9	-0.45±.066
75%L	93.1±5.1†$^{\chi}$	107.2±9.3†$^{\chi}$	146.2±5.8†$^{\chi}$	87.3±7.7†$^{\chi}$	-0.50±.068
Max L+A	112.0±5.2*†	130.4±7.1*†	172.3±3.2*†	110.0±5.5*†	-0.53±.068

Mean ± standard error; % indicates percent of VO_{2max}, maximal oxygen uptake during leg cycling; L indicates leg only exercise, L+A indicates combined leg and arm exercise; * indicates significane from previous stage; † indicates significance from last similar stage, i.e., L vs. L or L+A vs. L+A; $^{\chi}$ indicates significance between 75% L+A and 75% L as analyzed using an 'a priori' paired t-test; all other statistical analysis performed using ANOVA; $p<0.05$.

Threshold and saturation values in mmHg represent the position of the stimulus-response relationship relative to the x-axis of the reflex function curve whereas threshold and saturation values in bpm indicate the position of the curve relative to the y-axis.

Figure Legends

Figure 1. An illustration of: a) the apparatus used in the experimental procedures and prelimary exercise testing; b) the experimental protocol for each individual bout of exercise; and c) the type and intensity of exercise for each of the four exercise bouts.

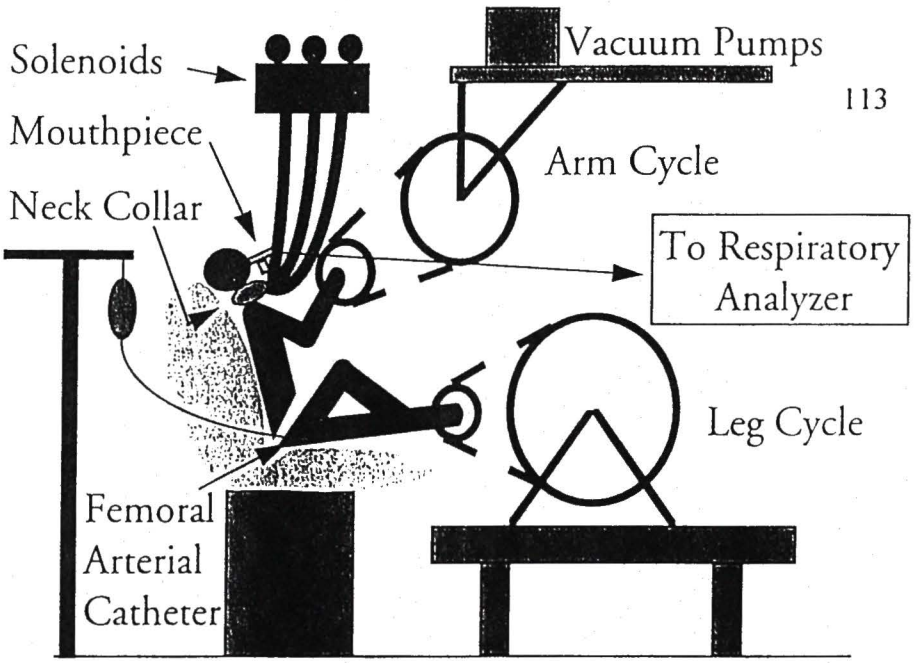
Figure 2. A representation of the logistic model of the mean HR responses to four individual carotid baroreflex stimulus-response curves each generated in the same subject during four separate 68% $\dot{V}O_{2max}$ exercise bouts . Suction / pressure pulses were administered at -80, -60, -40, -20, +20, and +40 Torr following 10 minutes of exercise. The maximal gain, threshold, and saturation for each stimulus-response curve are in listed in Table 3.

Figure 3. A summary of the shift of the operating point away from the centering point of the carotid-cardiac baroreflex stimulus-response relationship. All shifts are leftward. * indicates a significant shift relative to the previous workload and $^{\chi}$ indicates significance from the last similar stage, i.e. Leg only or Leg + Arm exercise bouts, at a significance level of $p < 0.05$.

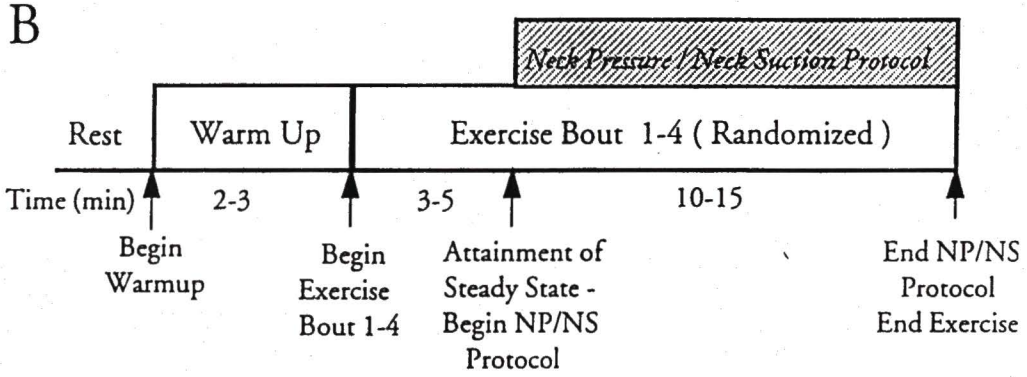
Figure 4. A summary of the shift of the operating point away from the centering point of the carotid-vasomotor baroreflex stimulus-response relationship. All shifts are leftward. * indicates a significant shift relative to the previous workload and $^{\chi}$ indicates significance from the last similar stage, i.e. Leg only or Leg + Arm exercise bouts, at a significance level of $p < 0.05$.

Figure 5. A schematic illustration of carotid aterial baroreflex resetting during dynamic exercise. Panel A: Shifts in carotid-cardiac baroreflex. Panel B: Shifts in carotid-vasomotor baroreflex. Note the effect of combined arm and leg exercise versus leg exercise alone on baroreflex stimulus response relationship. ● denotes reflex operating point, i.e. pre-stimulus mean arterial pressure, and ——— indicates the position of the reflex centering point.

A

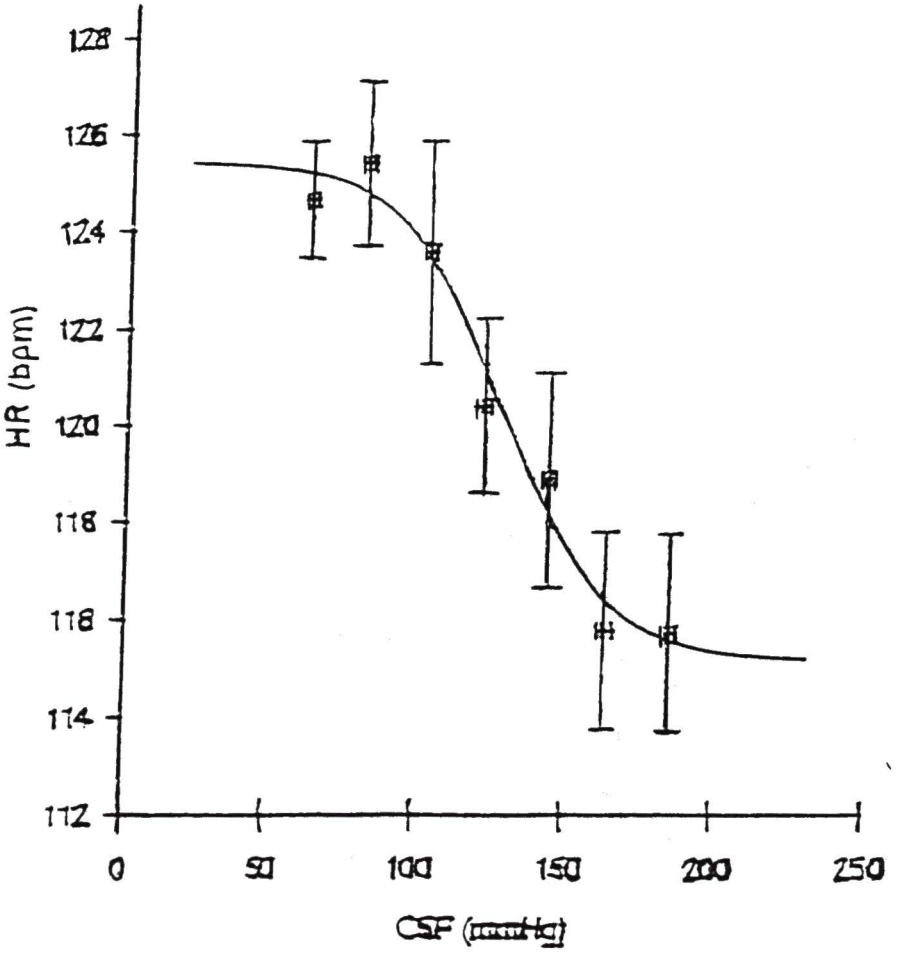


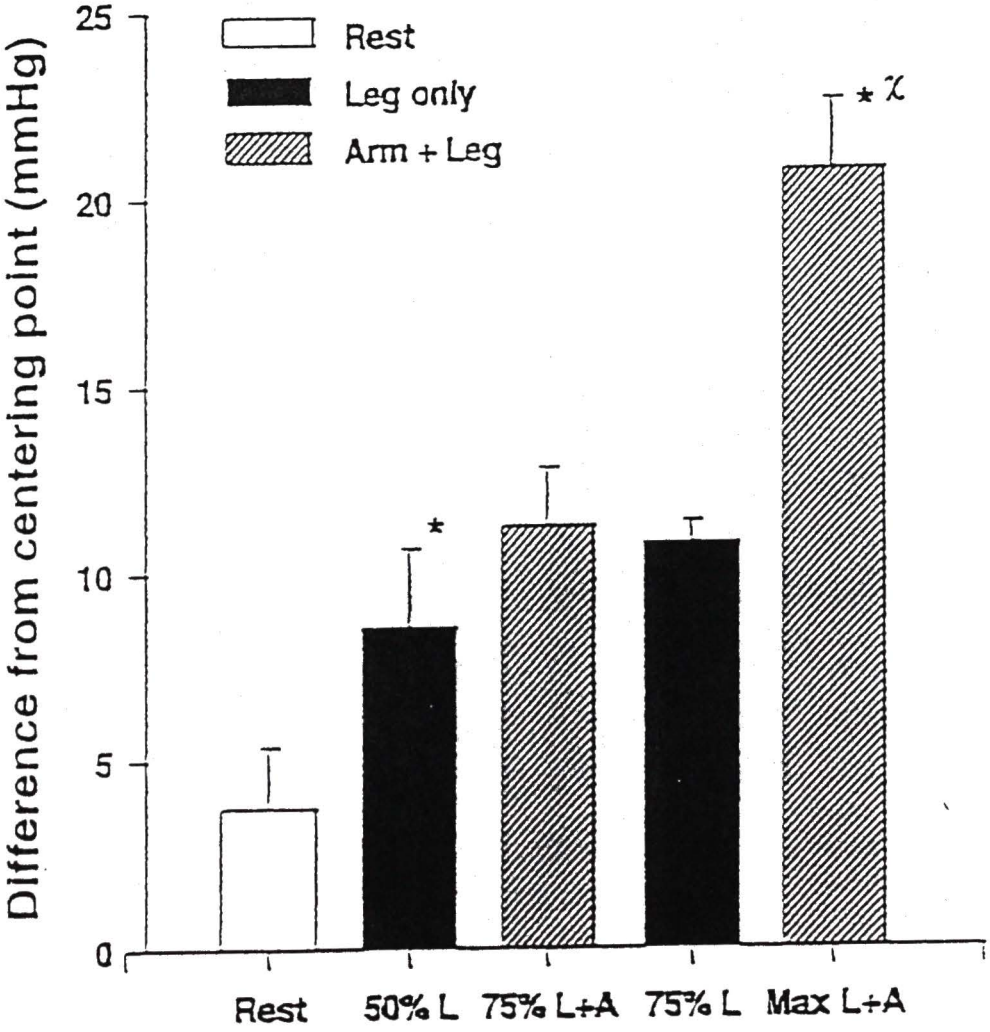
B

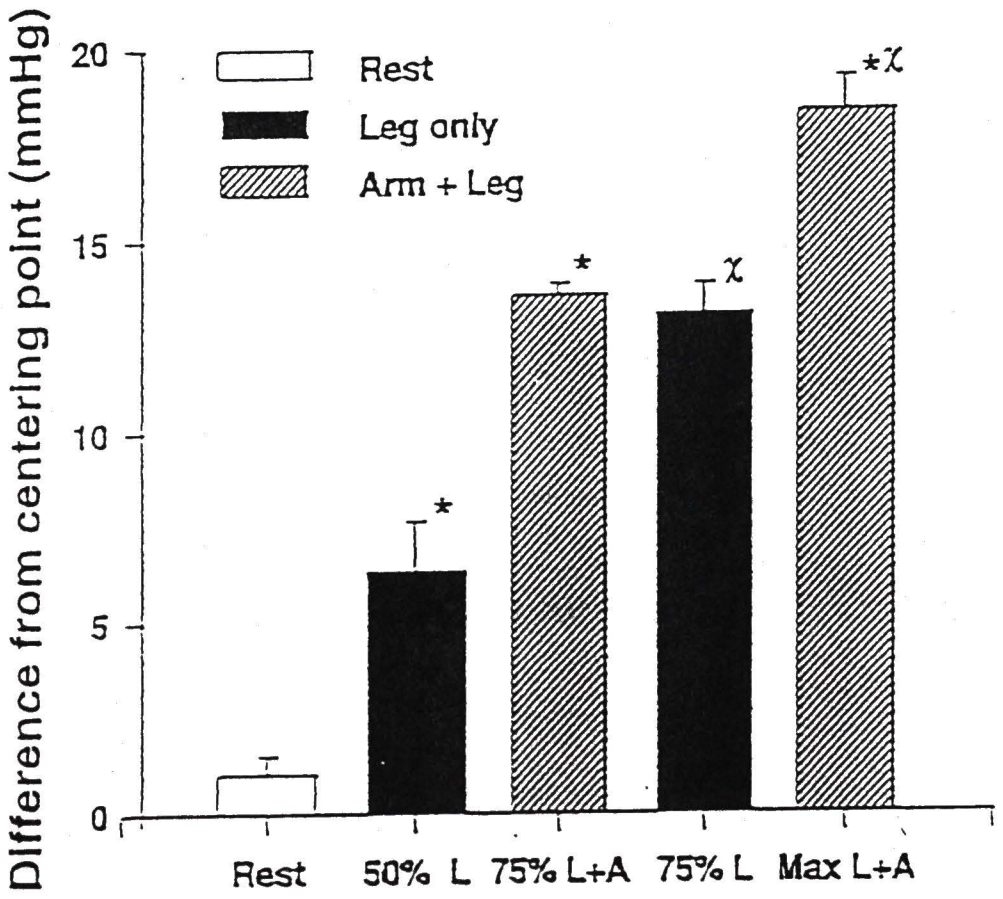


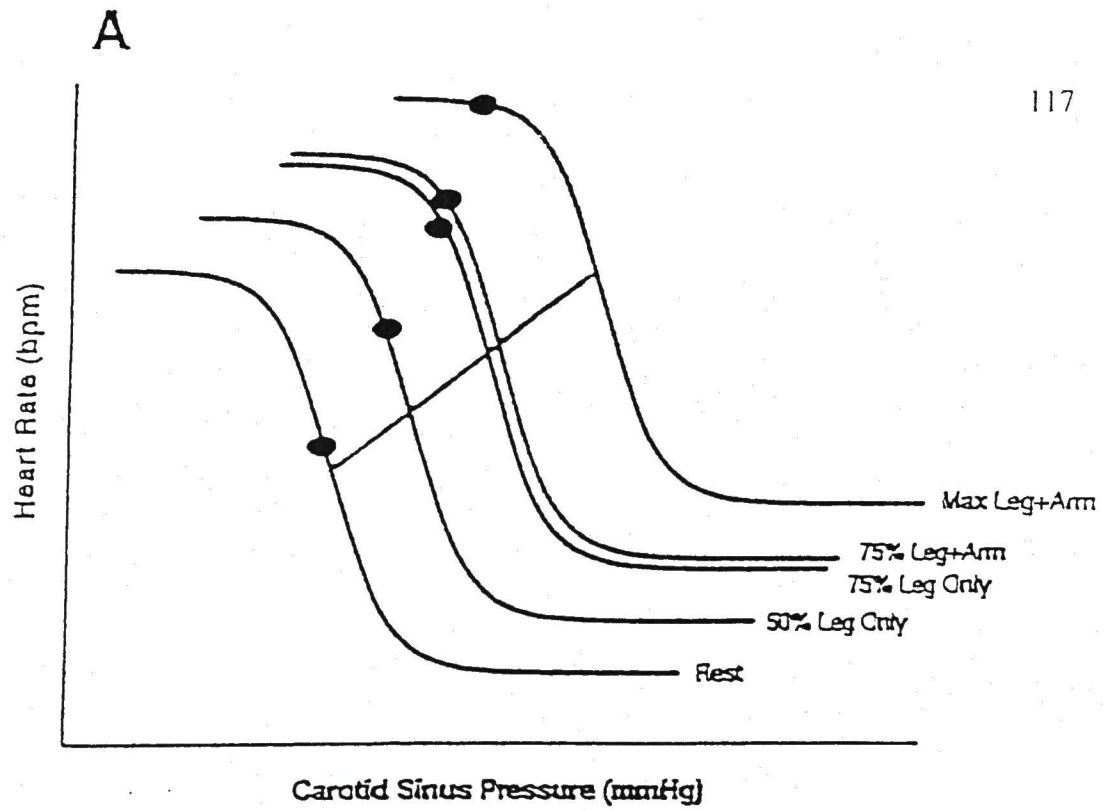
C

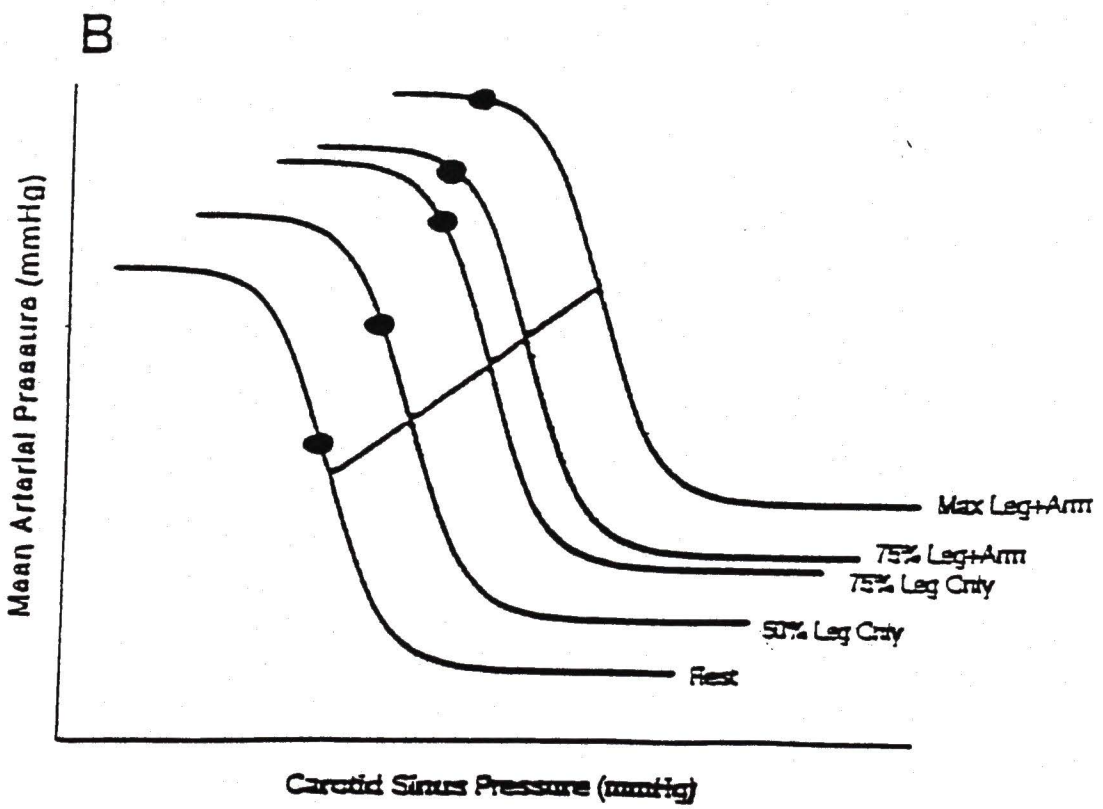
Bout	*Type*	*Total Oxygen Uptake*
1	Leg Only	50% VO_{2max}
2	Leg & Arm	75% VO_{2max}
3	Leg Only	75% VO_{2max}
4	Leg & Arm	VO_2 Max


128
126
124
122
120
118
116
114
112
HR (bpm)
0
50
100
150
200
250
CSF (mmHg)


Rest
Leg only
Arm + Leg
Difference from centering point (mmHg)
25
20
15
10
5
0
*
* χ
Rest
50% L
75% L+A
75% L
Max L+A


Difference from centering point (mmHg)
20
15
10
5
0
Rest
Leg only
Arm + Leg
*
*
χ
*χ
Rest
50% L
75% L+A
75% L
Max L+A


A
Heart Rate (bpm)
Max Leg+Arm
75% Leg+Arm
75% Leg Only
50% Leg Only
Rest
Carotid Sinus Pressure (mmHg)


B
Mean Arterial Pressure (mmHg)
Max Leg+Arm
75% Leg+Arm
75% Leg Only
50% Leg Only
Rest
Carotid Sinus Pressure (mmHg)

CONCLUSION

The results of the two investigations described herein support the concept of the continued regulation of arterial blood pressure during exercise by the carotid baroreflex (CBR). The primary investigation demonstrated that the downward drift in mean arterial pressure seen during prolonged exercise was not due to a decrement in baroreflex function, but due to the progressive resetting of the CBR such that the arterial pressure changes occurred nearer to the threshold of the reflex where it is unresponsive to hypotensive stimuli. This resetting occurred in direct relation to the activation of central command as reflected by increases in heart rate, oxygen uptake and ratings of perceived exertion despite the continuous infusion of a dextran solution during the exercise to counteract the effects of thermoregulatory blood volume redistribution.

The second investigation demonstrated that increases in exercise intensity also resulted in CBR resetting, with the concomitant shift of the reflex operating point toward threshold, in relation to the activation of central command. In addition, the comparison of baroreflex function during combined arm and leg exercise versus leg exercise alone indicated that activation of the muscle metaboreflex can augment baroreflex resetting during exercise. Therefore, this research supports the role of central command as the primary mechanism responsible for the resetting of the CBR during dynamic exercise with an additional effect of the exercise pressor reflex to augment reflex resetting under relevant circumstances.

SUGGESTIONS FOR FUTURE RESEARCH

Below is a list of several potential investigations designed to further support the research presented in this dissertation and to build upon the concepts summarized above. The investigations described below are intended: a) to further support the concept that the resetting of the carotid baroreflex during prolonged exercise is independent of the global hemodynamic responses to thermoregulation and b) to further examine the roles of central command and the exercise pressor reflex in the resetting of the carotid baroreflex during dynamic exercise.

I. To further test the hypothesis that the resetting of the carotid baroreflex during prolonged exercise occurs independently of the global hemodynamic responses to thermoregulation, an experiment could be designed with a protocol similar to that described in Chapter II, however the use of dextran infusion to counteract cardiovascular drift would be replaced by the use of whole body surface cooling. Whole body surface cooling during the prolonged exercise bout would not only maintain central blood volume, and thereby stoke volume, as in the dextran infusion experiments, but would also oppose the vasodilation of the cutaneous circulation thereby maintaining another important component of arterial blood pressure, total peripheral resistance. Therefore, I would anticipate that whole body surface cooling would result in a more pronounced diminution of the fall in mean arterial pressure seen during cardiovascular drift, however as occurred in the investigation presented in Chapter II, indices of central command such as heart rate, oxygen uptake, and ratings of perceived exertion would rise during the prolonged exercise condition to a similar extent as occurred during the control exercise condition. In addition, an examination of carotid baroreflex function would indicate that the reflex had been progressively reset during the prolonged exercise bouts regardless of exercise condition.

II. A second experiment which would support the findings of the investigation presented in Chapter II focuses on the concept that the resetting of the carotid baroreflex during prolonged exercise occurs in direct relation to a progressive increase in central command activity with motor fiber recruitment upon muscular fatigue. As exercise training is known to cause biochemical alterations which produce resistance to muscular fatigue, I would anticipate that endurance trained athletes would experience less fatigue during a prolonged exercise bout than would non-trained subjects. Therefore, as the trained subjects would not require a significant level of motor fiber recruitment to maintain a given exercise intensity over a prolonged period, there would be a measurable difference in the rise in central command activity experienced by these two subject populations as reflected by progressively increasing discrepancies in heart rate, oxygen uptake, and ratings of perceived exertion between the two groups. In addition, based on the results of the investigation presented in Chapter II, I would anticipate that an examination of carotid baroreflex function would indicate that the endurance trained subjects did not experience progressive baroreflex resetting during the prolonged exercise protocol due to the lack of rise in central command activity.

III. Several experiments could also be designed to support the results of the investigation presented in Chapter III. For example, a series of exercise bouts could be performed under conditions which minimize or augment the contributions of the exercise pressor reflex and/or central command activation to the function of the carotid baroreflex during exercise. These conditions include: a) dynamic cycling exercise performed via the timed electrical stimulation of the agonist and antagonist musculature of the leg to eliminate the need for the activation of motor fiber units by central command; b) dynamic and/or static exercise performed volitionally by the subject during partial neuromuscular blockade (e.g. tubocurarine

administration) in order to increase the level of central command activation needed to produce a given exercise intensity or force; c) dynamic cycling exercise performed volitionally by the subject during the simultaneous application of lower body positive pressure or the inflation of thigh blood flow occlusion cuffs resulting in an augmented stimulation of the exercise pressor reflex; and d) dynamic or static exercise performed by subjects who have been given epidural anesthesia to reduce muscle strength and thus increase the central command activation necessary to perform a given exercise intensity or force and to simultaneously block afferent feedback from the exercising musculature thereby decreasing the exercise pressor reflex.