Final Report
Grant Award NASA-NAG5-4688

Solicitation:       NRA 96-OLMSA-01 359
Task Type:          Ground Based Research
Subdiscipline:      Space Physiology and Countermeasures
Title:              Carotid Baroreflex Function During Prolonged Exercise
Period:             June 1, 1997 to May 31, 2000
                    One year No Cost Extension May 31, 2001
                    Funding Total $301,896

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Abstract:

Astronauts are often required to work (exercise) at moderate to high intensities for extended periods while
performing extra-vehicular activities (EVA). Although the physiologic responses associated with prolonged
exercise have been documented, the mechanisms involved in blood pressure regulation under these conditions
have not yet been fully elucidated. An understanding of this issue is pertinent to the ability of humans to perform
work in microgravity and complies with the emphasis of NASA’s Space Physiology and Countermeasures
Program.

Prolonged exercise and a constant workload is known to result in a progressive decrease in mean arterial pressure
(MAP) concomitant with a decrease in stroke volume and a compensatory increase in heart rate. The continuous
decrease in MAP during the exercise, which is related to the thermoregulatory redistribution of circulating blood
volume to the cutaneous circulation, raises the question as to whether there is a loss of baroreflex regulation of
arterial blood pressure. We propose that with prolongation of the exercise to 60 minutes, progressive increases
in central command reflect a progressive upward resetting of the carotid baroreflex (CBR) such that the operating
point of the CBR is shifted to a pressure below the threshold of the reflex rendering it ineffectual in correcting
the downward drift in MAP. In order to test this hypothesis, experiments have been designed to uncouple the
global hemodynamic response to prolonged exercise from the central command mediated response via: (i)
continuous maintenance of cardiac filling volume by intravenous infusion of a dextran solution; and (ii) whole
body surface cooling to counteract thermoregulatory cutaneous vasodilation. As the type of work (exercise)
performed by astronauts is inherently arm and upper body dependent, we will also examine the physiologic
responses to prolonged leg cycling and arm ergometry exercise in the supine positions with and without lower
body negative pressure (-10 torr) to mimic spaceflight-related decreases in cardiac filling volumes.
Revised Work Tasks - #9601-359

Title: “Carotid Baroreflex Function during Prolonged Exercise”

Specific Aim 1. Eight volunteer subjects will perform four 1-hour bouts of 65% VO$_{2peak}$ arm or leg exercise in a thermoneutral environment.

Experiment 1
a. One hour of leg exercise with carotid baroreflex function determined at rest; at 10 min and 50 minutes of exercise.
b. Three hours of rest after (1a) followed by another one hour of leg exercises while central venous pressure is maintained constant by dextran infusion. Carotid baroreflex function determined at rest, at 10 min and 50 minutes of exercise.

Experiment 2
Arm and leg exercise used to increase the active muscle mass from rest to 50%, 75%, and 100% of VO$_{2peak}$ Carotid baroreflex function determined at each steady state work load.

Experiment 3
a. One hour of arm exercise with carotid baroreflex function determined at rest, 10 min and 50 minutes of exercise.
b. Three hours of rest after (2a) followed by another one-hour arm exercise with reduced CVP by applying -10 torr LBNP with carotid baroreflex function determined at rest, at 10 minutes and 50 minutes of exercise.

Modination of Experiment 3 was designed to address a number of questions related to:

(i) arm exercise
(ii) endurance exercise training and
(iii) aortic baroreflex control of heart rate and sympathetic nerve activity

Outcomes:


The present investigation was designed to uncouple the hemodynamic physiological effects of thermoregulation for the effects of a progressively increasing central command activation during prolonged exercise. Subjects performed two 1-h bouts of leg cycling exercise with 1) no intervention and 2) continuous infusion of a dextran solution to maintain central venous pressure constant at the 10-min pressure. Volume infusion resulted in a significant reduction in the decrement in mean arterial pressure seen in the control exercise bout (6.7 ± 1.8 vs. 11.6 ± 1.3 mmHg, respectively). However, indexes of central command such as heart rate and ratings of perceived exertion rose to a similar extent during both exercise conditions. In addition, the carotid-cardiac baroreflex stimulus-response relationship, as measured by using the neck pressure-neck suction technique, was reset from rest to 10 min of exercise and was further reset from 10 to 50 min of exercise in both exercise conditions, with the operating point being shifted toward the reflex threshold. We conclude that the progressive resetting of the carotid baroreflex and the shift of the reflex operating point render the carotid-cardiac reflex affectual in counteracting the continued decrement in mean arterial pressure that occurs during the prolonged exercise.
Lay Interpretation: When aerobically fit humans undergo prolonged, greater than one hour of intense exercise (greater than 50% of their maximal oxygen uptake capacity) their regulation of arterial blood pressure is compromised. This phenomenon is caused by muscular fatigue beginning at approximately 20 minutes of the exercise which results in central nervous system directed recruitment of non-fatigued muscle fibers to maintain the work output. This increased central nervous system activation results in a progressive resetting of the arterial baroreflex function, which is unable to correct the fall in blood pressure.

The importance of this finding to NASA is that their long term space walks (EVAs) in which they are working with their arms to the point of fatigue may place the astronaut in an at risk situation for hypotension. This situation may occur if a sudden gravitational stress is placed on them, such as returning to an artificial gravity environment. Also, if the astronaut is required to work for long periods of time in an artificial gravity environment at greater than 50% maximal oxygen uptake, a similar problem may arise.

Experiment 2. Norton, 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.* 87(1):332-338, 1999. Recent investigations have demonstrated that at the onset of low-to-moderate-intensity leg cycling exercise (L) the carotid baroreflex (CBR) was classically reset in direct relation to the intensity of exercise. On the basis of these data, we proposed that the CBR would also be classically reset at the onset of moderate-to-maximal-intensity L exercise. Therefore, CBR stimulus-response relationships were compared in seven male volunteers by using the neck pressure-neck suction technique during dynamic exercise that ranged in intensity from 50 to 100% of maximal oxygen uptake (VO₂max). L exercise alone was performed at 50 and 75% VO₂max, and L exercise combined with arm (A) exercise (L+A) was performed at 75 and 100% VO₂max. O₂ consumption and heart rate (HR) increased in direct relation with the increases in exercise intensity. The threshold and saturation pressures of the carotid-cardiac reflex at 100% VO₂max were >75% VO₂max, which were in turn >50% VO₂max (P<0.05), without a change in the maximal reflex gain (Gmax). In addition, the HR response value at threshold and saturation at 75% VO₂max was >50% VO₂max (P<0.05) and 100% VO₂max was >75% VO₂max (P<0.07). Similar changes were observed for the carotid-vasomotor reflex. In addition, as exercise intensity increased, the operating point (the prestimulus blood pressure) of the CBR was significantly relocated further from the centering point (Gₘₐₓ) of the stimulus-response curve and was at threshold during 100% VO₂max. These findings identify the continuous classic rightward and upward resetting of the CBR, without a change in Gₘₐₓ, during increases in dynamic exercise intensity to maximal effort.

Lay Interpretation: The findings of the above experiment for the first time demonstrated that as the intensity of the exercise increases, whether it be arm or leg exercise, the regulation of arterial blood pressure by the arterial baroreflexes are reset to regulate the blood pressure at the prevailing blood pressure of the exercise, which is directly related to the amount of active muscle mass and the intensity of the exercise. Another finding of this investigation is that the reset baroreflex is set to defend against hypertension and not hypotension.

The relevance to NASA is that it has now been established that blood pressure regulation by the arterial baroreflexes are normal regardless of work intensity. However, if during work a hypergravity stress or a return of normal gravity (as in an artificial gravity) situation produces a hypotensive challenge the arterial baroreflex will be less able to respond. This maybe an important avenue of investigation for NASA with the future development of the human powered centrifuge and the short arm centrifuge.

Ancillary Investigations to Experiments 1 and 2.

Ancillary Study 1.
Smith, S.A., K.M. Gallagher, K.H. Norton, R.G. Querry, R.M. Welch-O’Connor and P.B. Raven. Ventilatory responses to dynamic exercise elicited by intramuscular sensors. Sci. Sports Exerc., Vol. 31, No. pp. 277-286, 1999. Purpose: Eight subjects, aged 27.0 ± 1.6 yr, performed incremental workload cycling to investigate the contribution of skeletal muscle mechano- and metaboreceptors to ventilatory control during dynamic exercise. Methods: Each subject performed four bout of exercise: exercise with no intervention (CON); exercise with bilateral thigh cuffs inflated to 90 mmHg (CUFF); exercise with application of lower-body positive pressure (LBPP) to 45 torr (PP); and exercise with 90 mmHg thigh cuff inflation and 45 torr LBPP (CUFF + PP). Ventilatory responses and pulmonary gas exchanges variables were collected breath-by-breath with concomitant measurement of leg intramuscular pressure. Results: Ventilation (\(V\)) was significantly elevated from CON during PP and CUFF + PP at workloads corresponding to ≥ 60% CON peak oxygen uptake (\(V_{\text{O}_2,\text{max}}\)), and during CUFF at workloads ≥ 80% CON \(V_{\text{O}_2,\text{peak}}\), \(P < 0.05\). The \(V_{\text{O}_2}\) at which ventilatory threshold occurred was significantly reduced from CON (2.17 ± 0.28 L·min\(^{-1}\)) to 1.60 ± 0.19 L·min\(^{-1}\), 1.45 ± 0.15 L·min\(^{-1}\), and 1.15 ± 0.11 L·min\(^{-1}\) during CUFF, PP, and CUFF + PP, respectively. The slope of the liner regression describing the VE/CO\(_2\) output relationship was increased from CON by approximately 22% during CUFF, 40% during PP, and 41% during CUFF + PP. Conclusions: As intramuscular pressure was significantly elevated immediately upon application of LBPP during PP and CUFF + PP without a concomitant increase in \(V_{\text{O}_2}\), it seems unlikely that LBPP-induced increases in \(V_{\text{O}_2}\) can be attributed to activation of the mechanoreflex. These findings suggest that LBPP-induced reductions in perfusion pressure and decreases in venous outflow resulting from inflation of bilateral thigh cuffs may generate a metabolite sensitive intramuscular ventilatory stimulus.

Lay Interpretation: The findings of this investigation identified that a population of sensory receptors within the exercising muscle sense the metabolic milieu of the muscle and increases ventilation by a feedback to the central nervous system’s ventilatory control center. A workload of approximately 100 watts appears to be critical before the selective activation of ventilation occurs. The intramuscular stimulus for ventilation appears related to an increased concentration of metabolites trapped by using lower body positive pressure or venous occlusion cuffs. This is important to NASA in that the anti-gravity suit when inflated acts like a positive pressure squeezing on the active muscles. This will require an increase in ventilatory capacity of the suit when working in a pressurized anti-gravity suit.

Ancillary Study 2.


1. This investigation was designed to determine the contribution of the exercise pressor reflex to the resetting of the carotid baroreflex during exercise.
2. Ten subjects performed 3.5 min of static one-legged exercise (20% maximal voluntary contraction) and 7 min dynamic cycling (20% maximal oxygen uptake) under two conditions: control (no intervention) and with the application of medical anti-shock (MAS) trousers inflated to 100 mmHg (to activate the exercise pressor reflex). Carotid baroreflex function was determined at rest and during exercise using a rapid neck pressure/neck suction technique. During exercise, the application of MAS trousers (MAS condition) increased mean arterial pressure (MAP), plasma noradrenaline concentration (dynamic exercise only) and perceived exertion (dynamic exercise only) when compared to control (\(P < 0.05\)). No effect of the MAS condition was evident at rest. The MAS
condition had no effect on heart rate (HR), plasma lactate and adrenaline concentrations or oxygen uptake at rest and during exercise. The carotid baroreflex stimulus-response curve was reset upward on the response arm and rightward to a higher operating pressure by control exercise without alterations in gain. Activation of the exercise pressor reflex by MAS trousers further reset carotid baroreflex control of MAP, as indicted by the upward and rightward relocation of the curve. However, carotid baroreflex control of HR was only shifted rightward to higher operating pressures by MAS trousers. The sensitivity of the carotid baroreflex was unaltered by exercise pressor reflex activation.

4. These findings suggest that during dynamic and static exercise the exercise pressor reflex is capable of actively resetting carotid baroreflex control of mean arterial pressure; however, it would appear only to modulate carotid baroreflex control of heart rate.

Lay Interpretation: These data identify the role of the intramuscular mechanoreceptor in the resetting of the arterial baroreflex in the regulation of blood pressure during exercise. By selectively activating the intramuscular mechanoreceptors by squeezing on the leg with positive pressure during exercise the carotid baroreflex was reset to a higher operating pressure and indicated the redundancy of the neural control mechanisms that regulate blood pressure.

Similar to above studies the importance to NASA is the identification that the anti-gravity positive pressure suit utilizes a neural activation mechanism as well as a volume redistribution mechanism in protecting arterial blood pressure.

Ancillary Study 3.

adel, P.J., S. Ogoh, D.E. Watenpaugh, W. Wasmund, A. Olivencia-Yurvati, M.L. Smith and P. B. Raven. Carotid baroreflex regulation of sympathetic nerve activity during dynamic exercise in humans. *Am J Physiol Heart Circ Physiol* 280:H1383-H1390, 2001. We sought to determine whether carotid baroreflex (CBR) control of muscle sympathetic nerve activity (MSNA) was altered during dynamic exercise. In five men and three women, 23.8 ± 0.7 (SE) yr of age, CBR function was evaluated at rest and during 20 min of arm cycling at 50% peak O₂ uptake using 5- periods of neck pressure and neck suction. From rest to steady-state arm cycling, mean arterial pressure (MAP) was significantly increased from 90.0 ± 2.7 to 118.7 ± 3.6 mmHg and MSNA burst frequency (micro neurography at the peroneal nerve) was elevated by 51 ± 14% (P<0.01). However, despite the marked increases in MAP and MSNA during exercise, CBR-∆%MSNA responses elicited by the application of various levels of neck pressure and neck suction ranging from +45 to -80 Torr were not significantly different from those at rest. Furthermore, estimated baroreflex sensitivity for the control of MSNA at rest was the same as during exercise (P=0.74) across the range of neck chamber pressures. thus CBR control of sympathetic nerve activity appears to be preserved during moderate-intensity dynamic exercise.

Lay Interpretation: The findings of this investigation clearly and for the first time identify that the carotid baroreflex control of muscle sympathetic nerve activity is in direct relation to its control of arterial blood pressure both at rest and during exercise. Importantly, the findings also confirm our previous contention that the arterial baroreflex control of vasomotor function (control of blood vessels) was reset from rest to exercise similar to the arterial baroreflex control of the heart.

The importance of this work to NASA is that it clearly demonstrates that arterial baroreflex regulation of blood pressure is similar both at rest and exercise for both the cardiac and the vasomotor reflex.

Experiment 3.
Differential baroreflex control of heart rate: Endurance exercise fitness


In order to characterize the stimulus-response relationships of the arterial, aortic, and carotid baroreflexes in mediating cardiac chronotropic function, we measured heart rate (HR) responses elicited by acute changes in mean arterial pressure (MAP) and carotid sinus pressure (CSP) in 11 healthy individuals. Arterial (aortic + carotid) baroreflex control of HR was quantified using ramped changes in MAP induced by bolus injection of phenylephrine (PE) and sodium nitroprusside (SN). To assess aortic cardiac responses, neck pressure (NP) and suction (NS) were applied during PE and SN administration, respectively, to counter alterations in CSP thereby isolating the aortic baroreflex. Graded levels of NP and NS were delivered to the carotid sinus using a customized neck collar device to assess the carotid cardiac baroreflex, independent of drug infusion. The operating characteristics of each reflex were determined from the logistic function of the elicited HR response to the induced change in MAP. The arterial pressures at which the threshold was located on the stimulus response curves determined for the arterial, aortic and carotid baroreflexes were not significantly different (72 ± 4 mmHg, respectively, P > 0.05). Similarly, the MAP at which the saturation of the reflex responses were elicited did not differ among the baroreflex arcs examined (98 ± 3, 99 ± 2, and 102 ± 3 mmHg, respectively). These data suggest that the baroreceptor populations studied operate over the same range of arterial pressures. This finding indicates each baroreflex functions as both an important anti-hypotensive and anti-hypertensive mechanism. In addition, this investigation describes a model of aortic baroreflex function in normal healthy humans, which may prove useful in identifying the origin of baroreflex dysfunction in disease and training induced conditions.

Smith, S.A., R.G. Querry, P.J. Fadel, R.M. Welch-O’Connor, A. Olivencia-Yurvati, X. Shi, and P.B. Raven. Differential baroreflex control of heart rate in sedentary and aerobically fit individuals. Med. Sci. Sports Exerc., Vol. 32, No. 8 pp. 1419-1430, 2000. Purpose: We compared arterial, aortic and carotid cardiac baroreflex sensitivity in eight average fit (maximal oxygen uptake, VO₂max = 42.2 ± 1.9 mL·kg⁻¹·min⁻¹) healthy young adults. Methods: Arterial and aortic (ABR) baroreflex functions were assessed utilizing hypo- and hypertension challenges induced by graded bolus injections of sodium nitroprusside (SN) and phenylephrine (PE), respectively. Carotid baroreflex (CBR) sensitivity was determined using ramped 5-s pulses of both pressure and suction delivered to the carotid sinus via a neck chamber collar, independent of drug administration. Results: During vasoactive drug injection, mean arterial pressure (MAP) was similarly altered in average fit (AF) and high fit (HF) groups. However, the heart rate (HR) response range of the arterial baroreflex was significantly attenuated (P < 0.05) in HF (31 ± 4 beats·min⁻¹) compared with AF individuals (46 ± 4 beats·min⁻¹). During CBR perturbation, the HF (14 ± 1 beats·min⁻¹) and AF (16 ± 1 beats·min⁻¹) response ranges were similar. The arterial baroreflex response range was significantly less than the simple sum of the CBR and ABR (HR, 38 ± 3 beats·min⁻¹ and AF, 57 ± 4 beats·min⁻¹) in both fitness groups. Conclusions: These data confirm that reductions in arterial cardiac reflex sensitivity are mediated by diminished ABR function. More importantly, these data suggest that the integrative relationship between the ABR and CBR contributing to arterial baroreflex control of HR is inhibitory in nature and not altered by exercise training.

Lay Interpretation: The findings of both these investigations confirmed our earlier work that the aortic baroreceptor cardiac reflex is the predominate arterial baroreflex regulation of cardiac function during an orthostatic and hypertensive stress. Furthermore, these present findings identified that the aerobically fit (endurance exercise trained) individual’s reduced maximal gain of the aortic heart rate reflex was specifically related to a reduced response to hypotension.
These data have significance to NASA in that an outcome of endurance exercise fitness puts the astronaut at risk for orthostatic hypotensive episodes during changes in posture.


We examined arterial baroreflex control of muscle sympathetic nerve activity (MSNA) during abrupt decreases in mean arterial pressure (MAP) and evaluated whether endurance training alters baroreflex function. Acute hypotension was induced nonpharmacologically in 14 health subjects, of which 7 were of high fitness (HF) and 7 were of average fitness (AF), by releasing a unilateral arterial thigh cuff after 9 min of resting ischemia under two conditions: control, which use aortic and carotid baroreflex (ABR and CBR, respectively) deactivation; and suction, which used ABR deactivation alone. The application of neck suction to counteract changes in carotid sinus transmural pressure during cuff release significantly attenuated the MSNA response (which increased 134 ± 32 U/14 s) compared with control (which increased 195 ± 43 U/14 s) and caused a greater decrease in MAP (19 ± 2 vs. 15 ± 2 mmHg; P < 0.05). Furthermore, during both trials the HF subjects exhibited a greater decrease in MAP compared with AF subjects despite an augmented baroreflex control of MSNA. These data indicate that the CBR contributes importantly to the MSNA response during acute systemic hypotension. Additionally we suggest that an impaired control of vascular reactivity hinders blood pressure regulation in HF subjects.

**Lay Interpretation:** Using a non-pharmacological method we identified that aerobically fit (endurance exercise trained) individuals were unable to regulate arterial blood pressure as well as untrained individuals and specifically identified the arterial baroreflex control of muscle sympathetic nerve activity and its transduction into somotor changes in systemic vascular resistance. The other major finding of this work is that the carotid and aortic baroreflex have significant roles in regulating muscle sympathetic nerve activity and similar to the heart rate control aortic baroreflex predominates in the control of muscle sympathetic nerve activity. The specific interpretation of this data is that endurance exercise training reduces the vasocontractive capacity of the arterial vessel and this may be related to alterations in endothelial smooth muscle function.

The importance of this work for NASA is that it has been shown for the control of heart rate on astronauts with a VO$_{2\text{max}}$ > 65ml O$_{2}$/kg/min will probably have an attenuated baroreflex control of vasomotor function during a hypotensive challenge. This finding suggests that high fit individuals will be prone to orthostatic intolerance.

**Educational Activity**

Although the NASA award NAG5-4668 was not specifically an educational award it may be of interest to the funding agency that monies of this award were used to support the following students in performing their research work. Performing this research work of the Award were four Ph.D. students and one DO/PhD student.

Kristin H. Norton, Ph.D. 1996 Currently Director, Blausen Medical Communications, Houston, TX
Ross G. Querry, Ph.D. 1999 Currently Post-Doc T.W.U., Dallas, TX
Scott A. Smith, Ph.D. 1999 Currently Post-Doc UTSWMC, Dallas, TX
Paul J. Fadel, Ph.D. 2001 Currently Post-Doc UTSWMC, Dallas, TX
Kevin M. Gallagher, D.O./Ph.D. 2000 Currently Resident at Parkland Hospital/UTSWMC

Kristin H. Norton, Ph.D. in 1996 also received support from a NASA-HQ-Predoctoral award #NGT-70409 for minorities as she was a 1/4 Hispanic-American.
Critical Path Roadmap

Critical Risks - Cardiovascular Alterations
Type II Impaired Cardiovascular response to orthostatic stress.

Deliverables- Scientific knowledge of underlying mechanisms
i arterial baroreflex regulation of blood pressure during upright exercise is similar to that which operates at rest. However, the greater the work intensity the greater the protection to hypertension and the less the response to hypotension.

ii Endurance exercise training increases the risk of orthostatic intolerance through both an attenuated arterial baroreflex control of heart rates and vascular resistance.

New Questions:

i. Will the cardiovascular deconditioning of space flight counteract the attenuated arterial baroreflex control of blood pressure during orthostatic stress?

ii. What is the role of endurance exercise fitness and the regulation of blood pressure during the operation of the human powered centrifuge or the short arm centrifuge.

iii. What is the optimum anti-gravity suit pressure for augmenting arterial blood pressure during work when challenged with a gravitational stress e.g. emergency egress.

List of Publications:

Peer Reviewed Manuscripts:


9. Outreach Presentations by Principal Investigator

**International:**

“Arterial Baroreflex control of the Circulation during Dynamic Exercise” at the European College of Sports Science, July 14-17, 1999, Rome, Italy.

“Baroreflex Regulation of Blood Pressure during Exercise”, October 8, 1999, Tsukuba University, Ibaraki, Japan. Sponsored by Tsukuba University.

“Baroreflex Regulation of Blood Pressure during Exercise”, October 12, 1999, Kyoto University in Kyoto, Japan. Sponsored by Kyoto University.

“Baroreflex Regulation of Blood Pressure during Exercise”, November 9, 1999, St. George’s University Medical School, London, England. Sponsored by the Dept. of Physiology, St. George’s Medical School.


**National**


“Carotid Baroreflex Control of Arterial Pressure During Dynamic Exercise of Various Intensities and Duration” Physiology Dept., University of Nebraska Medical Center, Omaha, NE. December 11, 1997. Sponsored by the Physiology Dept.


“Carotid Baroreflex Function During Prolonged Exercise”. In the Cardiovascular Session of the first Biennial space Biomedical Investigator’s Workshop, January 11-15, 1999, League City, Texas. Sponsored by USRA/and NASA/JSC

Regulation of Blood Pressure during Exercise” An established lecture in cardiovascular physiology at the Eugene Evonuk Memorial symposium at the University of Oregon, Eugene, Oregon. June 7, 1999. Sponsored by the Evonuk Memorial Fellowship Program.

“Central Command and the Arterial Baroreflex in the Symposium entitled Cerebral Cortical Involvement in the Regulation of Exercise Blood Pressure at the 47th annual meeting of the American College of Sports Medicine, Indianapolis, IN, June 1-4, 2000. Sponsored by the American College of Sports Medicine.
