Recent Advances in Baroreflex Control of Blood Pressure during Exercise in Humans: An Overview

PETER B. RAVEN

Department of Integrative Physiology, University of North Texas Health Science Center, Fort Worth, TX

ABSTRACT

RAVEN, P. B. Recent Advances in Baroreflex Control of Blood Pressure during Exercise in Humans: An Overview. *Med. Sci. Sports Exerc.*, Vol. 40, No. 12, pp. 2033–2036, 2008. This article provides an overview of the history behind the physiological concepts defining the role of the arterial baroreflexes and their regulation of arterial blood pressure during dynamic exercise. Initially, the case is made as to "why the arterial baroreflexes must be involved with blood pressure regulation during exercise." Subsequently, the historical animal and human experiments performed from the late 19th century to the present day describing how the two major neural mechanisms "central command" and "exercise pressor reflex" and their involvement in "resetting" are reviewed. These historical experiments have resulted in the development of a hypothetical model identifying the major factors involved in baroreflex resetting, and these factors are described. The four manuscripts presented in these proceedings address a new set of questions. These new questions address the importance of the baroreflex control of muscle sympathetic nerve activity and vasomotor tone in the regulation of blood flow, not only in the systemic vasculature but also in the cerebral and cutaneous vasculatures. **Key Words:** CAROTID BAROREFLEX, CENTRAL COMMAND, EXERCISE PRESSOR REFLEX, VASCULAR CONTROL, CEREBRAL BLOOD FLOW, CUTANEOUS CIRCULATION

Quadriceps muscle blood flow during maximal exercise has been reported to achieve a flow of 2.5 $L \cdot kg^{-1} \cdot min^{-1}$ (1,27,28,32), and in high-fit endurance-trained subjects, thigh muscle flows have reached values of 4 $L \cdot kg^{-1} \cdot min^{-1}$ (29). If during whole-body maximal exercise the active muscle mass requiring a maximal flow of 2.5 $L \cdot kg^{-1} \cdot min^{-1}$ was 36 kg (51% of a 70-kg human), the required cardiac output would need to be 90 $L \cdot min^{-1}$. Such a cardiac output value is far in excess of any measured for endurance-trained athletes, including cross-country skiers or rowers. Clearly, during whole-body maximal exercise, the increase in vascular conductance of the active muscles is restrained from achieving its maximal conductance (3). Without this restraint, the heart's pumping capacity would be overwhelmed and arterial blood pressure would fall. A fundamental question is "what is the source of this restraint?" One suggested mechanism by which this restraint is maintained involves the arterial baroreflex regulation of arterial blood pressure.

In 1863, Marey (13) in his book *The Physiology of the Circulation of the Blood* described the reflex nature of the arterial baroreflex control of the circulation at rest. However, one of the earliest (1913) observations made regarding the cardiovascular response to dynamic exercise was that both the heart rate and the arterial blood pressure increased (12). The lack of a reflex bradycardia as the blood pressure increased during exercise suggested that the arterial baroreflex was "switched off." Due to the rapid nature of the heart rate and the blood pressure response to the onset of exercise, the "switch off" mechanism was thought to be a neural mechanism (12). In the late 1800s, two neural mechanisms of cardiovascular regulation during exercise were suggested, these being i) the "exercise pressor reflex" by Zuntz and Geppert in 1886 (43) and ii) the "central command" by Johansson in 1895 (10). Due to the primacy of activation of the cardiovascular system in conjunction with the skeletal muscle activation of exercise, these two neural mechanisms received the bulk of investigative attention from the 1890s to the 1990s and due to their importance in the neural control of the circulation during exercise remain a focus of our attention today. Comprehensive reviews of this

Address for correspondence: Peter B. Raven, Ph.D., Department of Integrative Physiology, University of North Texas Health Science Center, 3500 Camp Bowie Boulevard, Fort Worth, TX, 76107; E-mail:praven@hsc.unt.edu.

Submitted for publication December 2007.
Accepted for publication January 2008.

0195-9131/08/4012-2033/0
MEDICINE & SCIENCE IN SPORTS & EXERCISE®

DOI: 10.1249/MSS.0b013e318180bc41

work can be found in the *Handbook of Physiology* (33) and in past JB Wolfe lecture proceedings published in the *Medicine & Science in Sports & Exercise®* (17,30) as well as in a classic monograph supplement issue of *Circulation* (16).

Another explanation for the parallel increase in heart rate and blood pressure at the beginning of exercise was the possibility that the arterial baroreflex was "reset" to allow the arterial blood pressure to increase and to enable an increase in perfusion pressure of the active muscles, thereby providing an increase in oxygen delivery. In support of this concept, Bevegard and Shepherd in 1966 (2) performed the first experiment in humans during dynamic exercise utilizing a newly developed neck pressure and neck suction system of Ernsting and Parry (6). The data identified that the arterial baroreflex control of heart rate and blood pressure remained during exercise and suggested that resetting had occurred. Despite this finding, the concept of a "switch off" remained, but in 1976, Coote and Dodd (4) used decerebrate unanesthetized cats in which they stimulated the exercise pressor reflex and identified arterial baroreflex resetting. Subsequently, in the early 1980s, Donald et al. performed a series of chronically instrumented animal experiments using a technically difficult surgical isolation of one carotid sinus with and without selective section of the aortic depressor nerve during treadmill exercise (5,15,38,40). The data obtained clearly demonstrated that the arterial baroreflexes were reset during exercise. These studies were referenced by Sagawa (34) in the *Handbook of Physiology* and provided a basis, along with their own work, for Rowell and O'leary's (31) proposed model of arterial baroreflex resetting during exercise, which incorporated the activation of "central command" and the "exercise pressor reflex." In 1992, Dicarlo and Bishop (5) identified in an exercising conscious rabbit that the resetting of the arterial baroreflex occurred simultaneously with the onset of exercise.

Subsequently, a series of human (18,23,25) and animal experiments (19,24) have established that the arterial baroreflex is "reset" to regulate the prevailing blood pressure during progressive increases in work intensity. In addition, in several experiments, it was identified that arterial baroreflex control of the vasculature was the principal mechanism by which blood pressure was controlled during exercise (7,20). Furthermore, by selective stimulation or attenuating activation of the "central command" (8,9,14,22,26) and the "exercise pressor reflex" (8,14,36,37) and by interpreting the results on the background of experiments that eliminated the "central command" and the "exercise pressor reflex" (39, 42), the roles of each neural mechanism in affecting arterial baroreflex resetting have begun to be elucidated.

A hypothetical model of arterial baroreflex resetting incorporating the answers to the historical questions and identifying some of the new questions (questions 1–4) that are addressed in these proceedings of the 2007 ACSM symposium is presented in Figure 1.

Question 1: How does activation of the muscle metaboreflex affect arterial baroreflex control of muscle sympathetic nerve activity?

Ichinose et al., in their manuscript presentation entitled "Baroreflex and Muscle Metaboreflex: Control of Muscle Sympathetic Nerve Activity," provide substantive evidence that establishes that activation of the muscle metaboreceptors during rhythmic and static isometric muscle contractions increases the sensitivity of the baroreflex control of the muscle sympathetic nerve activity in a time-dependent manner.

Question 2: Does the arterial baroreflex control of the peripheral vasculature have any role in regulating the cerebral vasculature during exercise?

Over the past 40 yr, William P. Morgan et al. have established the field "The Psychobiology of Exercise" and identified the role of an individual's "perception of effort" as greatly influencing their cardiovascular response to exercise (41). This influence appears to modulate central command's control of the autonomic nervous system. Over the past 30 yr, Secher et al. (35) have identified the increase in brain metabolism and blood flow that occurs during exercise. Ogoh, in his manuscript entitled "Autonomic Control of Cerebral Circulation: Exercise," establishes the case for there being reflex control of the cerebral circulation. The review addresses the fact that steady-state measures of cerebral blood flow are inadequate in measuring the challenges to cerebral autoregulation (CA) during dynamic changes in arterial pressure. In addition, the challenge to CA that is imposed by moderate to heavy dynamic exercise intensities, when the pulse pressure exceeds the defined CA range, indicates the presence of sympathetic control of the cerebral vasculature.

Question 3: How does the arterial baroreflex regulate the peripheral vasculature?

Fadel, in his manuscript entitled "Arterial Baroreflex Control of the Peripheral Vasculature in Humans: Rest and Exercise," provides a historical review of the experiments that have identified the arterial–vasomotor arm of the reflex as the major control mechanism for the regulation of blood pressure during exercise. Furthermore, the review documents the importance of "functional sympatholysis" in establishing the balance that exists in the active muscle between the required vasodilation for increased delivery of oxygen and the required vasoconstriction for the regulation of perfusion pressure.

Question 4: Does the arterial baroreflex have any control of the cutaneous circulation during heat stress?

Crandall, in his manuscript entitled "Heat Stress and Baroreflex Regulation of Blood Pressure," addresses the

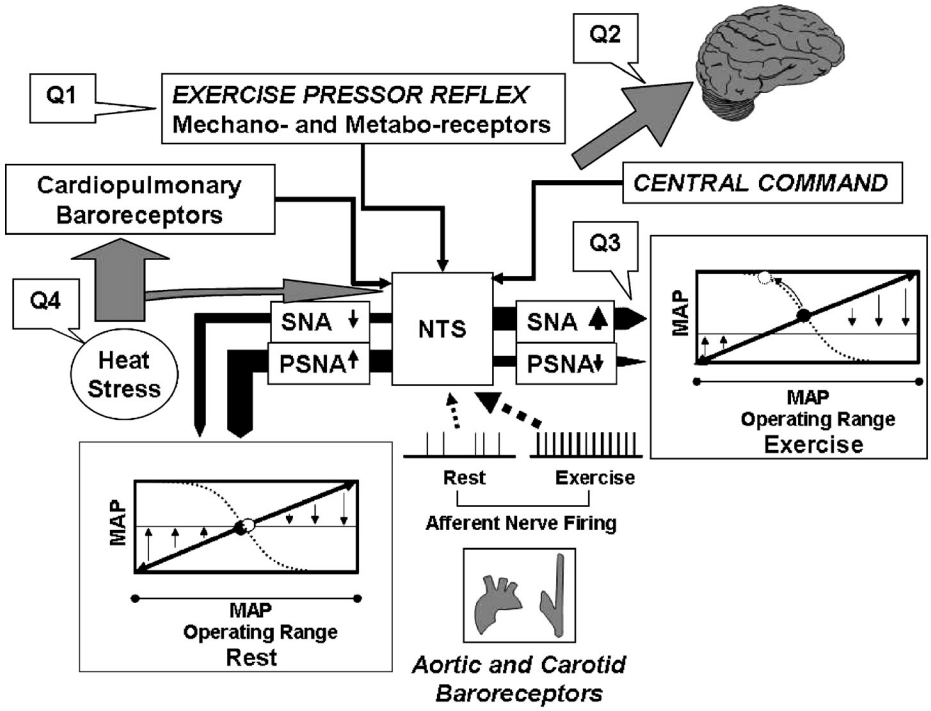

FIGURE 1—A hypothetical model of the neural integration associated with the resetting of the vasomotor arm of the arterial baroreflex that occurs from rest to exercise. The inset boxes labeled Rest and Exercise identify the outcome of the central resetting that occurs within the nucleus tractus solitarii (NTS). The primary determinant of this resetting is the feedforward control arising from an activated central command, with modulatory feedback control arising from the exercise pressor reflex as well as input from the cardiopulmonary baroreceptors reflecting central blood volume status. The central resetting appears to reestablish the operating range of the reflex at the exercise intensity-related increase in arterial baroreceptor afferent neural traffic, which is reflective of the increase in arterial blood pressure. This resetting and relocation of the operating point (○) away from the centering point (•) to a position of reduced gain results from the integration within the NTS and subsequent modulation of efferent sympathetic and parasympathetic neural control to the vasculature and the heart, respectively. The relocation of the operating point places the cardiac baroreflex in a more optimal position via a mechanism of vagal withdrawal to counteract hypertensive stimuli during exercise, as indicated by the arrows within the inset boxes. However, the operating point of the vascular baroreflex is established by the central blood volume and the input from the cardiopulmonary baroreceptors to the NTS. MAP indicated mean arterial pressure; SNA, sympathetic nerve activity; PSNA, parasympathetic nerve activity. The questions addressed in these proceedings are identified as Q1–Q4. This figure has been modified from the original Figure 6 published in Raven et al. Arterial baroreflex resetting during exercise: a current perspective. *Exp Physiol*. 2006;91(1):37–49 and is published with permission from Wiley-Blackwell Publishing Ltd.

challenge to the blood pressure control systems that must be present when the human performs exercise in the heat. The external environmental heat load causes an increase in body temperature, and because the human is only 25% efficient, 75% of the energy required to perform dynamic exercise is added to the body as a heat load. Crandall explores the integrative mechanisms of "how the exercise blood pressure is maintained while the redistribution of the blood to the cutaneous circulation to dissipate the heat occurs."

SUMMARY

Since the 1960s, the answer to the question as to whether the reflex is "switched off" or "reset" establishes that it has been "reset." However, there remain many unanswered integrative physiological questions as to the role of the arterial baroreflex during dynamic and static exercise. These proceedings of the ACSM symposium address only a few of the unanswered questions. Indeed, until recently, the role of the arterial baroreflex control of the cerebral and cutaneous circulations was not being addressed. Furthermore, the recent finding that the central blood volume modulated the "operating point" around which the arterial baroreflex was regulating the arterial pressure (21) identified a significant, yet controversial, role for the cardiopulmonary baroreceptors in blood pressure control, especially during orthostasis, exercise in the heat, microgravity, hypergravity, and supine and upright exercise.

As noted by Joyner (11), all of these fundamental questions have been and are being addressed in healthy subjects. The question as to how the arterial and cardiopulmonary baroreflexes operate in patients with cardiovascular disease that are prescribed exercise has not been addressed. Furthermore, Joyner (11) goes on to suggest that it may be time for us to investigate manipulation of one or more populations of the baroreceptors during exercise as a strategy to improve cardiovascular function and exercise tolerance of the cardiovascular impaired patient.

The results of this review article do not constitute endorsement by ACSM and were supported in part by NIH grant no. HL045547.

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An exaggerated blood pressure response during an acute dynamic exercise bout (defined as an increase in systolic blood pressure from rest of >10 mmHg per metabolic equivalent or a diastolic blood pressure change of >10 mmHg at any workload) [1] has been considered as an indicator of cardiovascular risk [2â€“6].Â The techniques currently applied for studying sympathetic activity in humans are (i) regional norepinephrine spilloverÂ Figure 2: Alterations in the control of blood pressure during exercise in obese individuals: the baroreflex is less sensitive to stimulation (i.e., exercise) and the metaboreflex is blunted.Â Differences in the reported results regarding blood flow during exercise in obese individuals could be BASIC SCIENCES: Symposium: Recent Advances in Baroreflex Control of Blood Pressure during Exercise in Humans. Free. Abstract.Â Quadriceps muscle blood flow during maximal exercise has been reported to achieve a flow of 2.5 LÂ·kgâˆ’1Â·minâˆ’1 (1,27,28,32), and in high-fit endurance-trained subjects, thigh muscle flows have reached values of 4 LÂ·kgâˆ’1Â·minâˆ’1 (29). If during whole-body maximal exercise the active muscle mass requiring amaximal flow of 2.5 LÂ·kgâˆ’1Â·minâˆ’1 was 36 kg (51% of a 70-kg human), the required cardiac output would need to be 90 LÂ·minâˆ’1.Â Role of central command in carotid baroreflex resetting in humans during static exercise. J Physiol. 2002;543:349-64.