AMERICAN JOURNAL OF PHYSIOLOGY
HEART AND CIRCULATORY PHYSIOLOGY

Am J Physiol Heart Circ Physiol 325: H675–H686, 2023.
First published July 28, 2023; doi:10.1152/ajpheart.00303.2023

REVIEW

Exercise, Physical Activity, and Cardiovascular Health

Autonomic cardiovascular control during exercise

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Abstract

The cardiovascular response to exercise is largely determined by neurocirculatory control mechanisms that help to raise blood pressure and modulate vascular resistance which, in concert with regional vasodilatory mechanisms, promote blood flow to active muscle and organs. These neurocirculatory control mechanisms include a feedforward mechanism, known as central command, and three feedback mechanisms, namely, *1*) the baroreflex, *2*) the exercise pressor reflex, and *3*) the arterial chemoreflex. The hemodynamic consequences of these control mechanisms result from their influence on the autonomic nervous system and subsequent alterations in cardiac output and vascular resistance. Although stimulation of the baroreflex inhibits sympathetic outflow and facilitates parasympathetic activity, central command, the exercise pressor reflex, and the arterial chemoreflex facilitate sympathetic activation and inhibit parasympathetic drive. Despite considerable understanding of the cardiovascular consequences of each of these mechanisms in isolation, the circulatory impact of their interaction, which occurs when various control systems are simultaneously activated (e.g., during exercise at altitude), has only recently been recognized. Although aging and cardiovascular disease (e.g., heart failure, hypertension) have both been recognized to alter the hemodynamic consequences of these regulatory systems, this review is limited to provide a brief overview on the action and interaction of neurocirculatory control mechanisms in health.

autonomic nervous system; baroreflex; central command; chemoreflex; exercise pressor reflex

INTRODUCTION

To cope with the elevated metabolic demand of exercise, the circulatory system needs to adapt and ensure adequate oxygen and nutrient supply to, and removal of byproducts from, contracting skeletal muscle and active organs. The autonomic nervous system (i.e., a part of the peripheral nervous system that controls involuntary physiological responses) plays a critical role in adjusting the cardiovascular response to meet these elevated needs by modulating the activities of both parasympathetic and sympathetic nervous systems. Specifically, with the magnitude of change depending on the intensity, duration, and environmental conditions, parasympathetic (vagus) nerve activity decreases and sympathetic nerve activity increases with exercise (1). Decreases in vagus nerve activity to the sinoatrial node, left atrial tissues, and interatrial septum reduce its inhibitory effect on the heart and increase heart rate (HR) and contractility (2). Increases in sympathetic outflow further raise HR and myocardial contractility by activating β-adrenergic receptors through increases in *1*) the release of epinephrine from the adrenal glands and *2*) the release of the neurotransmitter norepinephrine from the sympathetic nerve innervating the heart. Furthermore, elevations in sympathetic outflow to arterial resistance vessels (arterioles) increase the release of the neurotransmitter norepinephrine from the sympathetic nerve endings and thereby activate α-adrenergic receptors that facilitate vasoconstriction (3). Together, exercise-induced alterations in the autonomic nervous system raise cardiac output (CO) and vasomotor tone to optimize the blood pressure response during exercise, limit perfusion of inactive tissues (e.g., liver and gastrointestinal tract), and in concert with regional vasodilatory mechanisms (4), facilitate blood flow to muscles actively involved in exercise (e.g., locomotor and respiratory muscles; 5). The exact cardiovascular responses ultimately depend on the magnitude of the changes in parasympathetic and sympathetic outflow, the associated release of neurotransmitters, and the end-organ responsiveness to these neurochemical stimuli. A detailed description of various physiological responses governed by the autonomic nervous system can be found elsewhere (6).

Two types of mechanisms determine the cardiovascular response to exercise by activating sections of the

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Submitted 24 May 2023 / Revised 11 July 2023 / Accepted 23 July 2023

medulla oblongata that regulate sympathetic and parasympathetic nerve activity (7). One category includes descending neural signals from higher brain areas that cause a parallel activation of both medullary cardiovascular control areas and cortical regions involved in regulating skeletal muscle activation (8). This feedforward control mechanism is generally referred to as "central command" (9) and is particularly important in adjusting the initial cardiovascular response at the onset of exercise where the slower responding mechanisms (see below) are not yet fully activated. The other type of control mechanism includes a variety of peripheral receptors and associated sensory neurons which project to, and act on, medullary brain nuclei (10). These "feedback mechanisms" comprise the arterial and cardiopulmonary baroreflexes, the exercise pressor reflex (EPR), and the arterial chemoreflex. Importantly, although stimulation of the arterial and cardiopulmonary baroreflexes inhibits sympathetic tone and facilitates parasympathetic activity, central command, the EPR, and the arterial chemoreflex facilitate sympathetic outflow and inhibit parasympathetic drive.

The cardiovascular effect of each individual control mechanism has frequently been investigated over the past 100+ years (11). However, research on the interdependence of these regulatory systems and their integrated impact upon the cardiovascular response to exercise is relatively scarce. This review therefore offers only a brief description of the circulatory influence of each control mechanism when studied in isolation and primarily focuses on available human data highlighting the cardiovascular consequence resulting from the interaction of two neural mechanisms. A more detailed discussion on the role of central command and various feedback mechanisms in regulating autonomic nervous system function during exercise can be found elsewhere (12). The writing will conclude with a discussion of future directions.

NEURAL MECHANISMS DETERMINING THE CARDIOVASCULAR RESPONSE TO EXERCISE

Central Command

Central command has traditionally been defined as a feedforward mechanism that involves descending neural signals from higher brain areas activating, in parallel, cortical motor and medullary cardiovascular areas (8, 9, 13–15). However, more recent work has now suggested that a centrally mediated cardiovascular response may not necessarily require activation of cortical motor regions and that even just the intent to exercise can activate specific brain regions and trigger the autonomic nervous system (15, 17). Some of the classic, and arguably most informative, studies investigating the role of central command in determining the cardiovascular response to exercise used partial or complete neuromuscular blockade (via curare or tubocurarine infusion) during exercise recruiting a small (18) or a large (14, 19–21) muscle mass. This pharmacological approach can, in a dose-dependent manner, compromise and even completely abolish the ability of the central nervous system to activate skeletal muscle. Therefore, to overcome the partial neuromuscular blockade and exercise at a given workload, neural drive (i.e., central command) to exercising muscle needs to be increased. It should, however, be considered that neuromuscular blocking agents alter the recruitment pattern of skeletal muscle and favor a predominant activation of fast-twitch fibers, likely resulting in greater intramuscular metabolic perturbation and potentially greater metabosensitive afferent feedback (20). Regardless, investigations using this, but also other [e.g., hypnosis (15, 17)], approaches offer experimental evidence suggesting that central command augments HR, CO, and mean arterial pressure (MAP) during exercise (14, 18–22). The effects on HR result, at least during small muscle mass exercise (e.g., handgrip), mainly from decreases in vagal tone and are not mediated by β-adrenergic receptors (13, 18). Furthermore, the contribution of central command to exercise-induced increases in sympathetic vasomotor outflow, assessed by direct recordings of muscle sympathetic nerve activity (MSNA) in the peroneal nerve, is negligible during mild to moderate intensities and only becomes significant, although still considerably small, at maximal efforts (18). Although the facilitating effects of central command on HR and sympathoadrenal system activity (estimated via changes in plasma catecholamines) are also seen during exercise recruiting a large muscle mass (e.g., locomotor exercise; 20–22), the impact appears to be much smaller compared with handgrip exercise. Direct evidence for the influence of central command on vagal activity and sympathetic activation of the heart and arterial resistance vessels during locomotor exercise is currently missing.

Arterial and Cardiopulmonary Baroreflexes

The arterial baroreflex is a negative feedback mechanism that evokes neurally mediated cardiovascular adjustments in response to conformational changes of mechanosensitive arterial baroreceptors (located at the aortic arch and carotid sinuses) induced by oscillation in blood pressure (23, 24). Specifically, increases in arterial wall strain (i.e., stretching) evoked by elevations in MAP facilitate the firing rate of the baroreceptors and their projection to the medulla, which reflexively increases cardiac vagal tone and decreases sympathetic outflow to the heart and arterioles. These changes decrease CO and vascular resistance, and lower MAP (25–27). Decreases in MAP reduce arterial wall strain and thus the central projection of the baroreceptors, which evokes the opposite autonomic nervous system responses and reflexively raises MAP. During exercise, arterial baroreceptors reset in direct relation to exercise intensity and operate at a higher prevailing blood pressure (28–30) without any changes in sensitivity (30–33). This resetting is achieved via inputs from central command (34), group III/IV muscle afferent feedback (33, 35), and afferent feedback from low-pressure mechanically sensitive stretch receptors located within the heart, great veins, and blood vessels of the lungs (36). In addition, while ~25% of the carotid baroreflex-mediated changes in MAP are attributed to alterations in CO at rest, augmentation in vascular resistance mediated by increases in MSNA appears to be primarily responsible for the MAP response during exercise (31, 37).

The cardiopulmonary baroreflex is a feedback mechanism that conveys afferent signals to the medullary cardiovascular

control center in response to changes in central venous pressure and volume sensed by low-pressure mechanically sensitive receptors in the heart, lungs, and great veins (38). Unloading of these cardiopulmonary receptors causes a reflexive increase in sympathetic vasoconstriction (39). During exercise, there is a reduction in MSNA below baseline during low-intensity cycling followed by a subsequent increase above baseline during higher intensities. The fall in MSNA during low-intensity exercise is thought to be due to a muscle pump-induced increase in venous return and cardiac filling pressure, which loads cardiopulmonary baroreceptors in the absence of the powerful sympathoexcitatory drive from central command and the EPR (40). This observation also supports the finding that MSNA falls below baseline during upright knee-extension exercise that coincides with a rise in central venous pressure, whereas MSNA remains unchanged during supine exercise (41). These data demonstrate that the cardiopulmonary baroreceptors exert a modulatory effect on sympathetic activity. Furthermore, the cardiopulmonary baroreflex remains capable of modulating neurally mediated cardiovascular responses during exercise but is reset to operate around an increased central venous pressure or central blood volume (42, 43).

Exercise Pressor Reflex

The EPR is a feedback mechanism triggered by intramuscular mechanical and chemical stimuli that raise the discharge of group III/IV muscle afferents, sensory neurons anatomically connected with the cardiovascular control center in the brainstem. Following the integration of these afferent signals within the nucleus tractus solitarii and the ventrolateral medulla, the autonomic nervous system responds by increasing sympathetic activity and decreasing parasympathetic activity to mediate increases in CO, vascular resistance, and MAP, and thus cope with the cardiovascular demands associated with exercise (44–48). A detailed discussion of studies documenting the significance of the EPR in regulating the cardiovascular response to exercise in humans (49) and animals (50) can be found elsewhere.

The EPR comprises a mechanosensitive (i.e., mechanoreflex) and a metabosensitive (i.e., metaboreflex) component. Although exercise typically activates both elements, previous studies have aimed at determining the functional impact of each component in isolation. For example, passive limb movement (51–53), or passive muscle stretch (54, 55), was used to activate mechanosensitive muscle afferents in humans. These studies have documented that the mechanoreflex component of the EPR can raise HR, CO, and MAP by decreasing cardiac vagal activity and increasing sympathetic activity. The metaboreflex component of the EPR has frequently been studied using postexercise circulatory occlusion (PECO; 56). This approach uses a cuff that is inflated to a suprasystolic pressure at the cessation of exercise to interrupt blood flow to the exercised limb and trap contraction-induced metabolites within the muscle to maintain firing of metabosensitive afferents. With this maneuver, several studies found that MAP and MSNA, but not HR or CO, remain elevated after exercise until the cuff is released (57–59). These observations suggest that the muscle metaboreflex may, at least when activated in isolation, not affect the balance of vagal and sympathetic drives to the heart but is capable of raising sympathetic vasomotor outflow.

More recently, the contribution of the EPR in cardiovascular response to exercise has been investigated using lumbar intrathecal fentanyl, a μ-opioid receptor agonist that attenuates feedback from group III/IV muscle afferents to the central nervous system (60, 61). When the feedback activity of these sensory neurons was pharmacologically attenuated during locomotor exercise in humans, MAP, HR, stroke volume, and CO were significantly lower compared with the identical exercise performed with an intact feedback activity (i.e., a functional EPR; 33, 62–64). These studies provided evidence reflecting the crucial role of the EPR in determining adequate cardiovascular responses to exercise in humans.

Chemoreflex

The chemoreflex is generally initiated when alterations in arterial blood gases (i.e., arterial P_{O_2} and P_{CO_2}) and pH are detected by the sensory neurons located in the carotid and aortic bodies (i.e., peripheral chemoreceptors) and the brainstem (i.e., pH-sensitive central chemoreceptors). When stimulated, these chemoreceptors convey afferent signals to the medullary cardiovascular control center, which, in turn, leads to a decreased vagal activity to the heart and an increased sympathetic drive to the heart and peripheral vessels (65–67). Indeed, hypoxia is a common scenario (e.g., high altitude) triggering the peripheral chemoreflex in humans and animals. Both acute and chronic exposure to hypoxia have, compared with normoxic conditions, been documented to increase HR and MSNA at rest (66, 68, 69) and during exercise (70–72). Moreover, evidence based on locomotor exercise now suggests that, even under normoxic conditions, the tonic activity of the peripheral chemoreflex plays, via modulating sympathetic vasomotor outflow, an important role in regulating blood flow to working skeletal muscles (73, 74). In these studies, inhibition of carotid chemoreceptor afferent signals by infusion of dopamine or hyperoxic Ringer's solution diminished α-adrenoreceptor-mediated vasoconstriction and augmented blood flow to the active limb in dogs and humans (73, 74). Taken together, although a handful of studies have suggested that the chemoreflex is capable of modulating the cardiovascular response to exercise, this area of research remains in its infancy and warrants further investigation.

INTERACTION OF NEURAL MECHANISMS

As discussed earlier, numerous studies have thoroughly described the cardiovascular consequences resulting from each of the four neurocirculatory control mechanisms, when investigated in isolation. However, since exercise alters, to a certain degree, all mechanisms simultaneously, the autonomic cardiovascular response is ultimately determined by the interaction of these control systems. Although designing and conducting studies to address the circulatory consequence of this complex interplay remains a formidable task that has yet to be accomplished, a relatively small number of human investigations offers solid, but limited, insight into

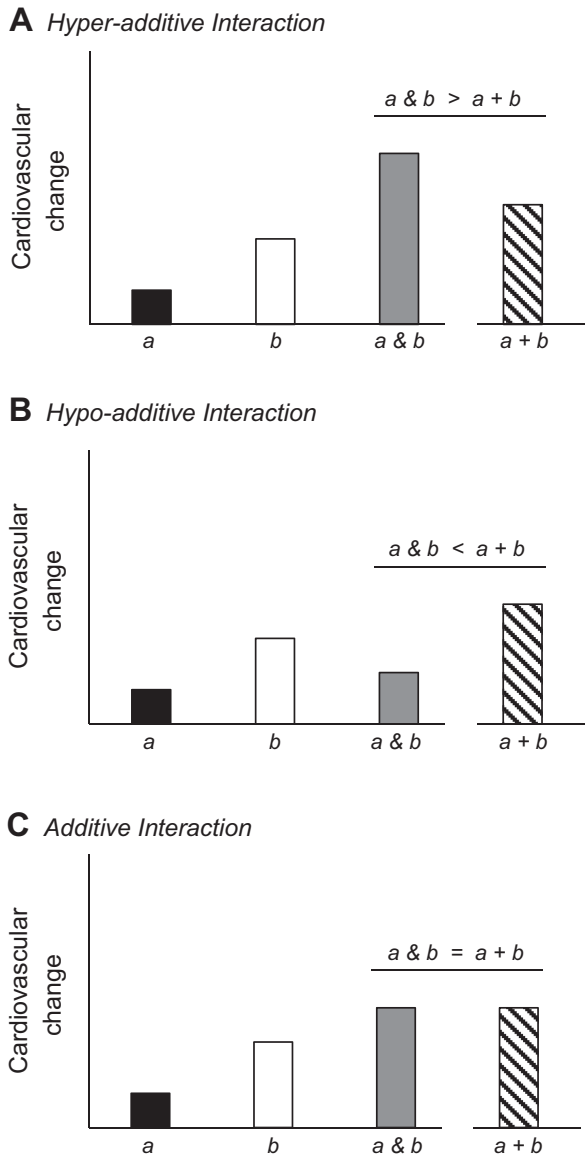

Figure 1. Graphic illustration reflecting the determination of the interaction mode of two neurocirculatory control mechanisms (*a* and *b*). Cardiovascular changes evoked by the alteration of mechanism *a* alone (black bars) and mechanism *b* alone (white bars), and by the concurrent alteration of both mechanisms (*a* & *b*, gray bars). The hatched bars ($a + b$) reflect the mathematical sum of the cardiovascular changes evoked by each mechanism alone. *A*: if the cardiovascular change observed during the concurrent alteration of the two mechanisms is greater than the summated change (a & $b > a + b$), the interaction is hyperadditive and reflects a synergistic effect. *B*: if the cardiovascular change observed during the concurrent alteration of the mechanisms is lower than the summated change (a & $b < a + b$), the interaction is hypoadditive. *C*: if the cardiovascular change observed during the concurrent alteration of the two mechanisms is equal to the summated change (a & $b = a + b$), the interaction is additive, reflecting a lack of significant interactive effect of the mechanisms.

the cardiovascular impact associated with the interaction of two control mechanisms. The following sections summarize key findings from some of these experiments.

Cardiovascular interaction effects are often determined based on a mathematical approach. Specifically, if the cardiovascular response to concurrent alteration of two neural mechanisms is greater than the sum of the changes resulting from the separate alteration of each mechanism, the interaction is considered hyperadditive, or synergistic (Fig. 1*A*). If the cardiovascular response to concurrent alteration of two neural mechanisms is less than the sum of the changes resulting from the separate alteration of each mechanism, the interaction is considered hypoadditive (Fig. 1*B*). Finally, if the cardiovascular response to concurrent alteration of two neural mechanisms is equal to the sum of the changes resulting from the separate alteration of each mechanism, the interaction is considered additive and reflective of a lack of an interactive influence (Fig. 1*C*). The following theoretical scenario is offered to highlight the practical application and relevance of this concept. For example, individual activation of the EPR may increase HR, stroke volume, and CO by 5%, 10%, and 15%, respectively, during exercise. Furthermore, individual activation of the chemoreflex may evoke different changes and increase HR, stroke volume, and CO by 10%, 5%, and 15%, respectively, during exercise. However, when both reflexes are simultaneously activated during exercise, HR, stroke volume, and CO may increase by 20%, 10%, and 30%, respectively. When compared with the sum of the responses elicited by each reflex alone, the response evoked by the simultaneous activation of both reflexes is greater for HR (i.e., 20% $>$ 15%), lower for stroke volume (i.e., 10% $<$ 15%), and similar for CO (i.e., 30% $=$ 30%). Based on the concept described earlier, this suggests that the EPR:chemoreflex interaction is hyperadditive for HR, hypoadditive for stroke volume, and simply additive for CO.

An alternative method for determining the interaction effect resulting from the concurrent alteration of two control mechanisms is to examine the influence of one neural mechanism on the sensitivity of the other neural mechanism to regulate cardiovascular responses (Fig. 2). An increase in sensitivity reflects a hyperadditive interaction, a decrease reflects a hypoadditive interaction, and no change signifies a lack of interaction. Regardless of the approach used to determine the interaction effect, it is required that the neural

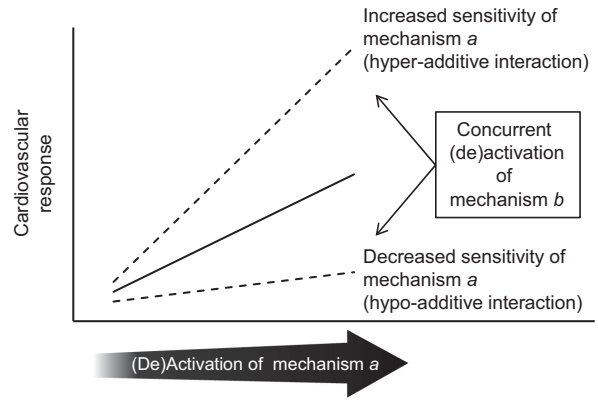

Figure 2. Graphic illustration reflecting the determination of the interaction mode of two cardiovascular control mechanisms (*a* and *b*) based on sensitivity analysis. The sensitivity of mechanism *a* in control of a cardiovascular response is established with and without concurrent alteration of mechanism *b*. When mechanism *b* is simultaneously manipulated, an increased sensitivity of mechanism *a* indicates a hyperadditive interaction, whereas a decreased sensitivity points to a hypoadditive interaction, between the two mechanisms. If the concurrent alteration of mechanism *b* elicits an unchanged sensitivity of mechanism *a*, the interaction is additive, reflecting a lack of significant interactive effect of the mechanisms.

mechanisms of interest are manipulated individually and simultaneously. This can often be achieved through a factorial experiment, for instance, implementing a two-way study design to address the interaction between two neural mechanisms.

Interaction between Central Command and the Baroreflex

To investigate the interaction between central command and the baroreflex, one can construct the stimulus-response curve of baroreflex control of HR or MAP and examine the influence of changes in central command on the gain of this stimulus-response curve (i.e., baroreflex sensitivity; 75). In this regard, a limited number of studies used the neck pressure/neck suction method to deactivate/activate the carotid baroreflex and established sigmoidal response curves for HR and MAP with changing carotid sinus pressure during voluntary exercise. Querry et al. (76) found that lidocaine-induced muscle weakening (partial axillary neural blockade) and associated increases in central command during static and rhythmic handgrip exercise, performed at 30% and 40% maximum voluntary contraction (MVC), had no effect on the sensitivity of carotid baroreflex control of HR and MAP. This suggested an additive interaction between central command and the carotid baroreflex. However, axillary blockade with lidocaine might also attenuate group III/IV afferent feedback from the exercising forearm muscle and, therefore, the EPR. As a result, the effect of central command on baroreflex sensitivity was not appropriately determined (75). To address this shortcoming, Gallagher et al. (77) augmented central command using curare, an approach that induced muscle weakness (>50% reduction in muscle strength) without affecting muscle afferent feedback during both isometric knee-extension (20% MVC) and dynamic-cycling exercises (20% of maximal oxygen uptake). These experiments confirmed the earlier findings and revealed that the sensitivity of carotid baroreflex control of HR and MAP was not affected by central command. However, the authors also observed a greater blood lactate level during exercise with curare, which was ascribed to an increased recruitment of fast-twitch muscle fibers (77). It was concluded that curare might have facilitated metabolite accumulation in the working muscle, which might have increased group III/IV muscle afferent feedback and thus the EPR. To circumvent this issue, Ogoh et al. (34) altered central command by applying tendon vibration of the agonist and antagonist muscles during isometric knee-extension and knee-flexion exercises (30% MVC). In agreement with the earlier observations, these experiments demonstrated that the sensitivity of carotid baroreflex control of HR and MAP did not change with alterations in central command during exercise (34). Collectively, these findings suggest that the interaction of central command and the carotid baroreflex is additive in terms of regulating HR and MAP responses to exercise.

Interaction between the Baroreflex and the Exercise Pressor Reflex

EPR activation during exercise results in sympathoexcitation and parasympathetic withdrawal, which increases MAP and HR (60, 62). In contrast, baroreflex activation during exercise results in sympathoinhibition and an increased vagal activity (78), which can buffer the circulatory effect of the EPR by up to ~50% and limit the degree of the EPR-mediated peripheral vasoconstriction and increases in MAP (79). To investigate how these two reflexes interact, studies have traditionally examined baroreflex sensitivity with and without concurrent stimulation of the EPR. Fisher et al. (80) constructed the stimulus-response curve of the carotid baroreceptors with neck pressure/neck suction during pre-exercise rest and during PECO following isometric handgrip exercise (35% and 45% MVC). They found no differences in the sensitivity of carotid baroreflex control of HR and MAP, suggesting an additive interaction between the carotid baroreflex and the EPR. In contrast to stimulating group III/IV muscle afferents and thus augmenting the EPR, other groups have pharmacologically reduced muscle afferent feedback from the exercising limb to examine the influence of the EPR on baroreflex sensitivity. For example, Smith et al. (81) used lumbar epidural anesthesia (1%–2% lidocaine) to attenuate the EPR during locomotor exercise (cycling at 30% peak power output and isometric single-leg knee extension at 25% MVC) and evaluated the complete stimulus-response curve of the carotid baroreflex using the neck pressure/neck suction technique. Compared with control exercise (i.e., intact muscle afferent feedback and normal EPR), they observed no changes in the sensitivity of carotid baroreflex control of HR and MAP when the EPR was attenuated during the exercise (81). These findings also suggest that the carotid baroreflex:EPR interaction is additive.

However, lumbar epidural lidocaine not only attenuates muscle afferent feedback from the legs, but also affects the motor nerve and compromises neuromuscular function (60). To compensate for the drug-induced neuromuscular impairment, central command needs to be increased to allow exercise against a given workload. Consequently, the true effect of the EPR on cardiovascular function is partially masked by the greater central command during exercise performed with the lumbar epidural anesthetic. To address this issue, Hureau et al. (33) used lumbar intrathecal fentanyl (i.e., a μ-opioid receptor agonist) to attenuate the EPR and determined the carotid baroreflex sensitivity during voluntary and electrically evoked isometric single-leg knee-extension exercise (15% MVC). Regardless of the exercise paradigm (i.e., voluntary or electrically evoked) and thus independent of central command, it was found that the EPR could reset the baroreflex operating point without altering the sensitivity of carotid baroreflex control of HR and MAP (33). These results corroborated with the studies by Fisher et al. (80) and Smith et al. (81) and indicated an additive interaction of the carotid baroreflex and the EPR for HR and MAP. Of note, the baroreflex sensitivity obtained from the neck pressure/neck suction technique only targets the carotid baroreceptors while the aortic baroreceptors are not controlled in this scenario (82).

Other studies investigating the baroreflex:EPR interaction during exercise stimulated the EPR while suppressing the arterial baroreflex in treadmill-running dogs. Sheriff et al. (78) demonstrated that the sensitivity of the EPR to control MAP was greater during exercise with denervation of arterial baroreceptors, suggesting a hyperadditive interaction (Fig. 3). In contrast, when the carotid baroreflex was unloaded via bilateral carotid artery occlusion and the EPR was augmented by

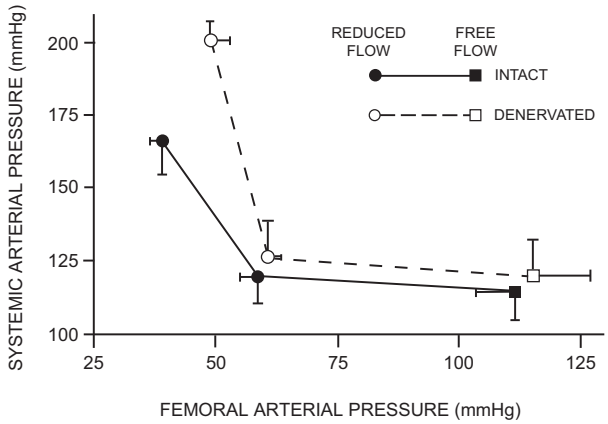

Figure 3. Graphic illustration reflecting the impact of arterial baroreceptor denervation on the exercise pressor response to graded reductions in femoral arterial pressure during steady-state treadmill running in dogs. This strategy decreases blood flow to the working hindlimb and thus augments muscle metaboreflex activity progressively, with or without deactivation of the arterial baroreflex. After the break point (femoral arterial pressure of ~60 mmHg), the gain of the pressor response to the muscle metaboreceptor stimulation, i.e., the sensitivity of the muscle metaboreflex, is twofold greater with denervated baroreceptors vs. intact baroreceptors, $P < 0.05$. Adapted from Sheriff et al. (78). Used with permission.

reducing blood flow to exercising limbs in treadmill-running dogs, Kaur et al. (83) observed an additive interaction effect for MAP and a hyperadditive effect for HR. However, bilateral carotid artery occlusion might have impeded blood flow to the carotid chemoreceptors and thus confoundingly also activated the carotid chemoreflex (84).

Similar to the work in animals, data on the baroreflex:EPR interaction in humans, through baroreflex deactivation and EPR activation, are rare and characterized by conflicting results (85, 86). For example, when using PECO following graded forearm exercise (isometric handgrip at 50% MVC for 15, 30, 45, and 60 s) to activate the metaboreflex component of the EPR in humans, Ichinose et al. (86) found that the sensitivity of muscle metaboreflex control of MAP and total peripheral resistance was not affected by carotid baroreceptor unloading via neck pressure. These observations suggest that the baroreflex:EPR interaction is additive for both MAP and vasomotor control (86). Conversely, Papelier et al. (85) unloaded the carotid baroreceptors via progressive neck pressure while activating the muscle metaboreflex in a leg using PECO after cycling exercise (performed at 150 W). They documented that muscle metaboreflex activation increased the sensitivity of the carotid baroreflex to control MAP without affecting the sensitivity of the baroreflex to control HR (85). These findings pointed toward a hyperadditive interaction in terms of the pressor response, but an additive interaction in terms of cardiac control.

In summary, although it has consistently been documented that the arterial baroreflex buffers the cardiovascular impact mediated by the EPR and that EPR activation resets the operating point of the baroreflex, our understanding of the interactive effect of these two feedback mechanisms upon the circulatory system remains uncertain. The discrepancies among the existing studies could, in part, result from the different approaches used to manipulate the reflexes and to determine their sensitivity, differences in physical activity (rest vs. exercise), and the muscle groups involved in EPR activation (arms vs. legs), and/or species differences.

Interaction between the Baroreflex and the Chemoreflex

Earlier examination of how changing arterial blood gases affects baroreflex sensitivity has offered some appreciation for the interactive influence of the arterial baroreflex and the chemoreflex upon the circulatory system. Bristow et al. (87) used vasoactive agents to manipulate blood pressure and obtain baroreflex activity (e.g., Modified Oxford technique) while activating the central chemoreflex via hypercapnia and found that the sensitivity of arterial baroreflex control of HR was not affected by the chemoreflex. Using the Modified Oxford method, Halliwill et al. (88, 89) assessed the sensitivity of arterial baroreflex control of HR and MSNA while simultaneously activating the peripheral chemoreflex with hypoxia. Although peripheral chemoreflex activation reset the baroreflex operating point for HR and MSNA to a higher blood pressure, the baroreflex sensitivity was not affected by the chemoreflex (88, 89). Thus, in terms of HR and MSNA, these studies suggest an additive interaction between the arterial baroreflex and the chemoreflex. In contrast to those findings, Gujic et al. (90) found that the baroreflex sensitivity was decreased for the control of HR, but increased for the control of MSNA, during concurrent activation of the peripheral chemoreflex via hypoxia. Recently, Janssen et al. (91) demonstrated that in the presence of an activated peripheral chemoreflex, the sensitivity of the arterial baroreflex to control HR and MSNA was decreased during arterial baroreceptor unloading (e.g., baroreflex deactivation using nitroprusside), but unaltered during arterial baroreceptor loading (e.g., baroreflex activation using phenylephrine). Therefore, in terms of HR and MSNA, the reflex interaction, resulting from simultaneous arterial baroreflex deactivation and peripheral chemoreflex activation, appears to be hypoadditive. Of note, compared with the neck pressure/neck suction method, the drug infusion approach does not allow a full stimulus-response curve to be established and only captures the operating point gain based on a portion of the linear part of this curve. If the chemoreflex activation resets/relocates the operating point of the baroreflex away from the center point (i.e., the maximal gain), this approach may lead to a misinterpretation as reduced baroreflex sensitivity (92, 93).

In contrast to the drug infusion approach to manipulate arterial baroreceptor activity, Cooper et al. (94) used the neck pressure/neck suction method and activated the chemoreflex via hypoxia at rest, and found the sensitivity of carotid baroreflex control of vasomotor tone to be reduced and the sensitivity of carotid baroreflex control of HR to be unaffected. Interestingly, when the chemoreflex was activated by hyperoxic hypercapnia, the baroreflex sensitivity of both cardiac and vasomotor control was unchanged (94). These data indicate that the interaction of the carotid baroreflex and peripheral chemoreflex is hypoadditive for vasomotor tone and additive for HR, whereas the interaction of the carotid baroreflex and central chemoreflex is additive for cardiac and vasomotor control. This suggests that the cardiovascular consequence of the interaction

between the carotid baroreflex and the chemoreflex depends on which chemoreflex (central vs. peripheral) is activated.

Interaction between the Exercise Pressor Reflex and the Chemoreflex

Previous work by Seals et al. (71) has documented a synergistic effect of hypoxia and exercise on MSNA in humans. As handgrip exercise under hypoxic conditions simultaneously activated the EPR and the peripheral chemoreflex, their findings implicate a potential interplay between the two reflexes in terms of sympathetic outflow. To examine the interactive effect of the chemoreflex and the EPR on sympathetic nervous system activity and associated cardiovascular regulation, later studies used different approaches to concurrently manipulate both reflexes. Specifically, while the chemoreflex has usually been manipulated by altering arterial blood gases, PECO has frequently been used to activate the metaboreflex component of the EPR (70, 90, 95–99) and passive muscle stretch, or passive limb movement, to selectively trigger the mechanoreflex component of the EPR (100, 101). However, the main outcomes of these studies were somewhat equivocal, which may, in part, be related to differences in inspiratory gas concentrations (e.g., hypoxia, hyperoxia, hypercapnia) and the muscle group used for exercise (e.g., arms or legs). Furthermore, despite being commonly used to study the EPR, the PECO paradigm not only neglects the interplay between mechano- and metabosensitive muscle afferents (102, 103) and the importance of central command in manifesting the EPR effect on cardiovascular responses (104, 105) but also mainly engages metabonociceptors, a subset of metabosensitive afferent fibers not active during conventional exercise (106–108). Hence, the exact nature of the interaction between the EPR and the chemoreflex and the resultant impact on the cardiovascular response to exercise remains uncertain.

To address these issues, more recent investigations used a study design that allowed the EPR and the chemoreflex to be independently and simultaneously activated during constant-load knee-extension exercise (i.e., a constant level of central command; 64, 101, 109). To manipulate the EPR, group III/IV leg muscle afferent feedback was pharmacologically blocked (lumbar intrathecal fentanyl), whereas the chemoreflex was manipulated via exposure to a hypoxic or a hypercapnic gas mixture (64). It was found that when the chemoreflex was activated by normocapnic hypoxia, the reflex interaction potentiated the sympathetically mediated cardiovascular responses, including MAP, HR, and vasoconstriction of the working muscles (Fig. 4; 64). In other words, concurrent activation of the EPR and the chemoreflex exerts a hyperadditive effect upon sympathetic outflow. However, when the chemoreflex was activated by normoxic hypercapnia, the reflex interaction was simply additive (Fig. 5; 64). Since normocapnic hypoxia primarily evokes the peripheral chemoreflex while normoxic hypercapnia can activate both central and peripheral chemoreflexes, these findings also indicate that the mode of interaction between the EPR and the chemoreflex depends on which chemoreflex (central vs. peripheral) is primarily activated. Follow-up studies then used passive exercise (e.g., passive leg movement) and hypoxia to investigate the interaction between the peripheral

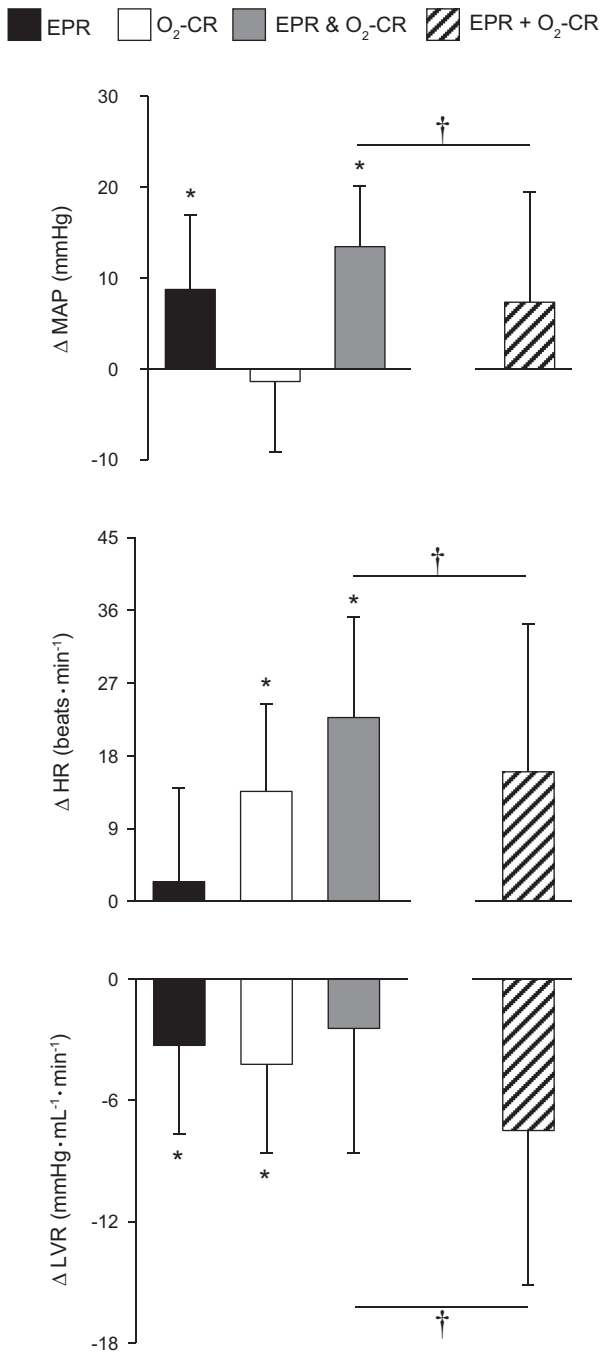

Figure 4. Cardiovascular consequences of the individual and the concurrent activation of the exercise pressor reflex (EPR) and the hypoxia-induced chemoreflex (O_2-CR) during single-leg knee-extension exercise. EPR and O_2-CR: observed cardiovascular change during coactivation of the EPR and O_2-CR; EPR + O_2-CR: sum of the cardiovascular changes elicited by each reflex alone. *$P < 0.05$, significantly different from baseline. †$P < 0.05$, significantly different between EPR and O_2-CR and EPR + O_2-CR. The EPR:O_2-CR interaction is hyperadditive for the sympathetically mediated cardiovascular responses, suggesting a potentiated sympathetic outflow when both reflexes are simultaneously activated during exercise. HR, heart rate; LVR, vascular resistance of the working leg muscles; MAP, mean arterial pressure. Adapted from Wan et al. (64). Used with permission.

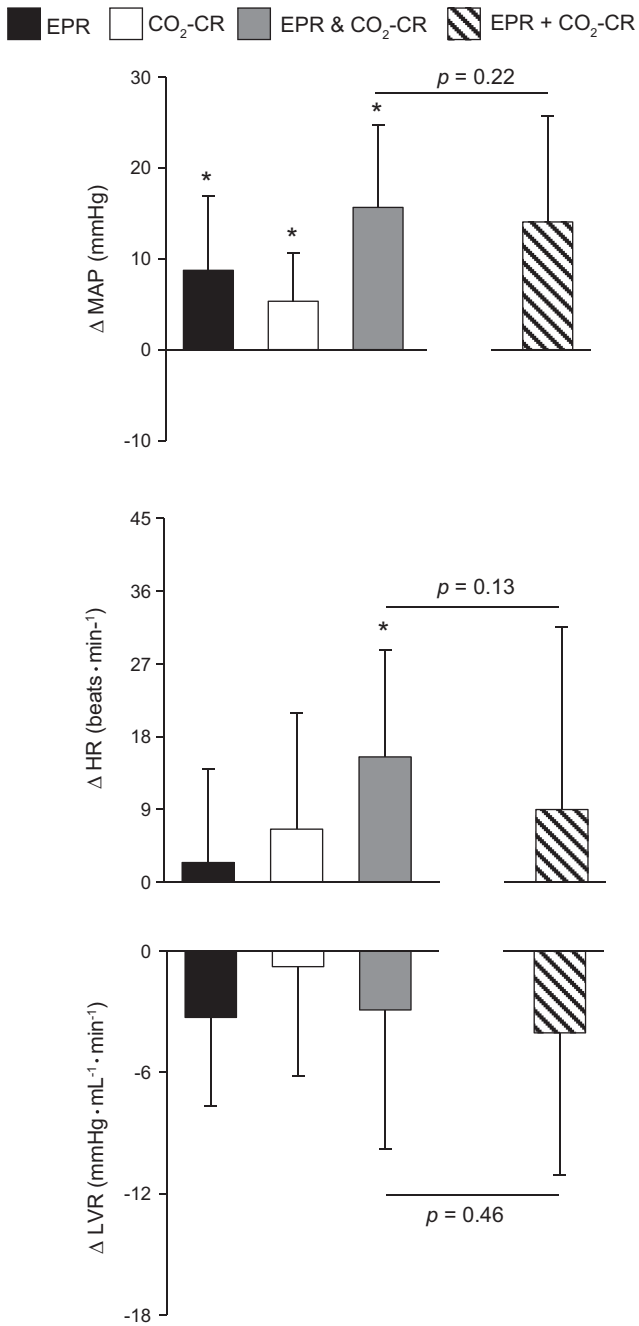

Figure 5. Cardiovascular consequences of the individual and the concurrent activation of the exercise pressor reflex (EPR) and the hypercapnia-induced chemoreflex (CO_2-CR) during single-leg knee-extension exercise. EPR & CO_2-CR: observed cardiovascular change during coactivation of the EPR and CO_2-CR; EPR + CO_2-CR: sum of the cardiovascular changes elicited by each reflex alone. *Significantly different from baseline, $P < 0.05$. No differences between EPR & CO_2-CR and EPR + CO_2-CR. The EPR:CO_2-CR interaction is simply additive for the sympathetically mediated cardiovascular responses. HR, heart rate; LVR, vascular resistance of the working leg muscles; MAP, mean arterial pressure. Adapted from Wan et al. (64). Used with permission.

chemoreflex and the mechanoreflex component of the EPR. The findings suggested that, in the absence of central command, the interaction between these two reflexes was also hyperadditive and potentiated sympathetic drive (101). Overall, it appears that the potentiated sympathetic outflow characterizing exercise in hypoxia (71) is, at least in part, due to the interaction of the EPR and the peripheral chemoreflex.

FUTURE DIRECTIONS

Since the majority of studies to date have only investigated the cardiovascular impact resulting from the interaction of two neurocirculatory control mechanisms, it is important to emphasize that exercise typically engages all four of them. To appropriately evaluate the cardiovascular influence of their interaction, future investigations need to use sophisticated study designs and manipulate the activities of the four mechanisms individually and simultaneously, e.g., a four-way factorial experiment.

It must be noted that most of the current literature related to neural interaction is based on male participants. Given the known differences in neurocirculatory control between sexes (101, 110–115), future studies need to increase the recruitment of female participants and focus on potential sex differences. Furthermore, exercise training (116), environmental stress (117), healthy aging (63), and cardiovascular disease (118) have all been documented to modulate the autonomic cardiovascular regulation during exercise. Whether these "conditions" also affect the interaction between various neurocirculatory control mechanisms and thereby contribute to the altered cardiovascular response to exercise remains unclear and warrants further investigation. Finally, exaggerated blood pressure responses to exercise have previously been documented in otherwise healthy individuals (119, 120). Although a heightened activity of the EPR (121) and the chemoreflex (122), and reduced baroreflex function (123) have all been suggested to play a role in this abnormality, the degree to which altered reflex interaction effects contribute to this dysregulation is still unknown.

CONCLUSIONS

Neurocirculatory control mechanisms regulate the cardiovascular responses to exercise through feedforward and feedback mechanisms to the medullary cardiovascular control center and associated changes in the activity of the autonomic nervous system. When activated in isolation, central command, the EPR, and the arterial chemoreflex promote sympathetic activation of the heart and arterioles and attenuate parasympathetic activity to the heart. The arterial and cardiopulmonary baroreflexes are negative feedback mechanisms evoking the opposite autonomic nervous system responses. The ultimate adjustment of the circulatory system to exercise is likely an integrated response and the consequence of multiple mechanisms operating in combination and interacting with one another. Although this review summarizes existing, but limited, evidence reflecting various interactive cardiovascular effects resulting from the simultaneous activation/deactivation of these mechanisms in humans, it is important to emphasize that considerable inconsistency exists among studies. The lack of consensus in the literature may partially result from divergent approaches used to manipulate the neural mechanisms of interest. Future investigations should also focus on the potential impact related to sex, training/environmental adaptation, aging, and disease.

GRANTS

This study was supported by National Heart, Lung, and Blood Institute Grants HL-116579 and HL-162856 and United States Veterans Affairs Rehabilitation Research and Development Grants I01RX003343 and IK2RX003670.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

H.-Y.W., K.B., and M.A. drafted manuscript; H.-Y.W., K.B., and M.A. edited and revised manuscript; H.-Y.W., K.B., and M.A. approved final version of manuscript.

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