Reflex control of the circulation during exercise: chemoreflexes and mechanoreflexes

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ROWELL, LORING B., AND DONAL S. O’LEARY. Reflex control of the circulation during exercise: chemoreflexes and mechanoreflexes. J. Appl. Physiol. 69(2): 407-418, 1990.—The overall scheme for control is as follows: central command sets basic patterns of cardiovascular effector activity, which is modulated via muscle chemo- and mechanoreflexes and arterial mechanoreflexes (baroreflexes) as appropriate error signals develop. A key question is whether the primary error corrected is a mismatch between blood flow and metabolism (a flow error that accumulates muscle metabolites that activate group III and IV chemosensitive muscle afferents) or a mismatch between cardiac output (CO) and vascular conductance [a blood pressure (BP) error] that activates the arterial baroreflex and raises BP. Reduction in muscle blood flow to a threshold for the muscle chemoreflex raises muscle metabolite concentration and reflexly raises BP by activating chemosensitive muscle afferents. In isometric exercise, sympathetic nervous activity (SNA) is increased mainly by muscle chemoreflex whereas central command raises heart rate (HR) and CO by vagal withdrawal. Cardiovascular control changes for dynamic exercise with large muscles. At exercise onset, central command increases HR by vagal withdrawal and “resets” the baroreflex to a higher BP. As long as vagal withdrawal can raise HR and CO rapidly so that BP rises quickly to its higher operating point, there is no mismatch between CO and vascular conductance (no BP error) and SNA does not increase. Increased SNA occurs at whatever HR (depending on species) exceeds the range of vagal withdrawal; the additional sympathetically mediated rise in CO needed to raise BP to its new operating point is slower and leads to a BP error. Sympathetic vasoconstriction is needed to complete the rise in BP. The baroreflex is essential for BP elevation at onset of exercise and for BP stabilization during mild exercise (subthreshold for chemoreflex), and it can oppose or magnify the chemoreflex when it is activated at higher work rates. Ultimately, when vascular conductance exceeds cardiac pumping capacity in the most severe exercise, both chemoreflex and baroreflex must maintain BP by vasoconstricting active muscle.

arterial baroreceptors; carotid sinus; aortic and arterial baroreflexes; skeletal muscle; muscle blood flow; central command; muscle metabolism; blood pressure control; cardiac output control; lactic acid; prostaglandins; muscle afferents; autonomic nervous system; sympathetic and parasympathetic; regional blood flow; muscle sympathetic nerve activity

ONE HYPOTHESIS, which deals with how cardiovascular and metabolic functions are matched during exercise, provides a structure for this review. It is, first, that central command or centrally generated somatomotor and cardiovascular motor signals set the basic patterns of effector activity at the onset of exercise. Second, this activity is modulated via chemosensitive and mechanosensitive afferent nerve fibers in the active muscle and via the mechanosensitive afferents within the carotid sinuses and aortic arch as appropriate error signals develop.

As we examine the above hypothesis, we also address
Muscle Chemosensors and Mechanosensors

Inasmuch as large fractions of mechanosensitive muscle afferents are also chemosensitive, with the converse being true as well for chemosensitive afferents (18, 19), both groups are discussed together in this section.

In 1886, Zuntz and Geppart first postulated that any mismatch between muscle blood flow (MBF) and metabolism would change the concentration of metabolites within the muscle and that this change would be detected by putative chemosensitive afferent fibers in the muscle. The efferent arm of this reflex, the sympathetic nervous system, would raise BP, which would increase MBF and reduce the concentration of accumulated metabolites. The first experimental evidence for this reflex came when Alam and Smirk occluded the circulation to an exercising muscle, which resulted in lactate accumulation and metabolic acidosis. The rise in BP was attributed to the ischemic muscle pressor reflex, which is activated by an increase in intracellular potassium concentration (22, 36). Potassium has often been proposed as a key link between metabolic activity and muscle afferent activity, but it increases the discharge of group III and IV units (78) only transiently despite maintained high interstitial potassium activity (20, 51). Arterial injection of substances normally produced by active muscles can stimulate group III and IV afferents (43).

A fraction of group III and IV afferents is activated by isometric contractions. The immediate onset and rapid recovery of group III activity are consistent with mechanoreceptor function, whereas the slower onset and more sustained activity of group IV afferents suggested a chemoreceptive function (18, 19). Ischemia augments activity of both afferents during contraction (19).

Reflex Effects of Chemical and Mechanical Activation of Muscle Afferents

Chemical and mechanical activation of group III and IV afferents raises BP, and blockade of these fibers abolishes the response; thus it is a reflex (32). The rise in BP is achieved primarily by sympathetic vasoconstriction (32, 47); the reflex effects on HR are relatively small, and this is important for the idea (see below) that vascular resistance and HR are controlled differently during exercise.

Lactic acid infusion elicits a pressor response that is not matched by equimolar infusions of HCl (46). Somehow, lactate ions potentiate the effects of H+ (46, 79). Braykinin, which releases prostaglandins, raises BP when injected arterially (72).

Activation of group III and IV afferents by passive graded increases in intramuscular pressures and tension elicited graded increments in BP (71) [muscle spindles and Golgi tendon organs, the afferent fibers of which are the large group I and II units, do not elicit cardiovascular reflexes (32, 36, 56)].

Reflex Effects of Electrically Induced Static Contractions—Putative Mediators of the Reflex

The information gained from chemical and mechanical stimulation of muscle afferents fits well with what is...
observed during isometric contractions. Release of metabolites is most readily observed when MBF is mechanically restricted, as during isometric contractions. Reduced flow not only increases interstitial concentrations of metabolites but often augments their production and local effects, especially for substances that might be diffusion limited in normal free-flow conditions.

The chemical changes best correlated with the rise in BP are the increase in muscle venous lactate and H⁺ concentrations and PCO₂ (74). However, potentiation of this pressor reflex by muscle ischemia has been closely associated with production of bradykinin by itself (71) and also prostaglandins (21, 73, 75). Both cyclooxygenase and lipoxygenase products of the prostaglandin precursor arachidonic acid sensitize group III mechanosensor afferents during contraction (44, 45). It is possible that minor tissue injury associated with the abnormal muscle contractions and force development caused by electrical stimulation contribute to the release of these substances. The role of kinins and prostaglandins during voluntary contractions is not clear (cf. 4, 38, 42, 70).

In summary, chemosensitive group III and IV muscle afferents are activated whenever MBF to active muscle is restricted so that both delivery of oxygen and washout of metabolites are reduced. So far, lactic acid is the substance most closely associated with the pressor response. In contrast, the mechanosensitive afferents appear to be sensitized by cyclooxygenase and lipoxygenase products of arachidonic acid whenever the force of contraction and restriction in MBF foster their release.

**Reflex Responses to Voluntary Isometric Exercise**

Voluntary isometric exercise has provided a tool for isolating effects of “central command” and muscle chemo- and mechanoreflexes on the circulation. Figure 1 shows schematically the rise in BP during a voluntary contraction when central command and muscle chemo and mechanoreflexes are operative. Entrapment of metabolites in the muscle by occlusion after the contraction activates only the chemoreflex (no central command and no mechanoreflexes). Efforts to make a contraction when none is possible (due to neuromuscular blockade) isolate the effects of central command. Not illustrated in Fig. 1, but discussed below, are attempts to preserve both central command and muscle contraction without feedback from muscle afferents by means of sensory nerve blockade.

**Responses during paralysis.** Partial paralysis by neuromuscular blockade leads to a stronger central command signal at any given force of muscle contraction (13), whereas muscle chemo- and mechanosensors are activated in proportion to absolute force development. Figure 1 schematically illustrates typical responses to attempted maximal contractions without significant force development (11, 13, 82). In contrast to earlier conclusions (31), this maneuver produces a small rise in directly measured muscle sympathetic nervous activity (MSNA) (see below), but it is only one-fourth of that seen during a contraction at 30% of normal maximal voluntary contraction force (MVC) (82) (Fig. 1). With partial neuromuscular blockade (50% reduction in MVC) BP rose much more during contractions at a given absolute force (13, 26) but responses were similar at any relative (%MVC) force (26). However, the HR responses are much more variable (cf. 26, 82).

The current concept is that HR is increased mainly by central command via vagal withdrawal; the response is blocked by atropine and not by propranolol (11, 82). BP is increased partly by central command and partly by the delayed rise in SNA caused by the muscle chemoreflex. This view has been both supported and opposed by recent studies from one group (cf. 16, 24, 26, 35, 82).

**Responses with sensory loss.** Patients who have retained some motor function despite neuropathy and loss of neural feedback from muscle still raise their BP and HR during voluntary isometric contractions. When the circulation is occluded at the end of contraction (Fig. 1) the maintained elevation in BP (muscle chemoreflex) is lost (7, 47).

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**Figure 1.** Schematic illustration of responses to a normal powerful isometric contraction (A) and to an attempted contraction during complete neuromuscular blockade (B). Normal rise in BP is achieved initially by central command (CC) and muscle mechanoreflexes (MR). After ~1 min, muscle chemoreflex (CR) may also contribute to rise in BP (putative time course of CR is derived from AMSNA in arbitrary units, bottom panel). Total occlusion (Occl) of limb blood flow at end of contraction prevents normal recovery (NR) of BP. BP drops ~50% (when central command ceases) and is kept elevated by chemoreflex as long as occlusion persists. HR is increased primarily by central command and vagal withdrawal with some contribution of mechanoreflexes. Muscle sympathetic nerve activity (ΔMSNA, microneurography), elicited by muscle chemoreflex, remains elevated or increases during occlusion (dashed line, normal recovery; hatched regions, variations in response). During attempted contractions, central command raises BP to ~50% of normal; HR response is more variable (hatched region) and rise in MSNA is small. Because there was no contraction, occlusion had no effects.
An experimental approach has been to create temporary sensory loss by differential blockade of the small muscle afferents, leaving the large motor fibers intact. Results (10, 24, 35) have been difficult to interpret because complete sensory blockade (i.e., complete loss of ischemic muscle pressor reflex and pain response to intramuscular KCl injection) could not be achieved with severe motor loss (10). When recovery of motor control was sufficient for large force development, the ischemic muscle pressor reflex returned, demonstrating that sensory blockade was no longer complete despite persistence of all “usual” clinical indexes of sensory blockade (10, 59). Furthermore, motor weakness may require that force be developed with the aid of additional muscle groups (24), and this complicates interpretation. Finally, it is not clear why sensory blockade at the spinal cord and peripheral nerve blockade have different effects (cf. 10, 14, 24, 35).

What stimuli elicit the pressor response? Recent use of $^{31}$P nuclear magnetic resonance spectroscopy on isometrically contracting human forearm muscles revealed that activation of SNA accompanied increments in intramuscular $\text{H}^+$ activity (SNA was unrelated to inorganic phosphate and phosphocreatine concentrations or their ratio) (68, 81). MSNA did not rise during static contractions in patients with myophosphorylase deficiency (McArdle’s disease) (41), suggesting that an event associated with muscle glycolyis and lactate production is important to reflex activation of SNA during isometric exercise (55).

Sympathetic nervous system—efferent arm of muscle chemore- and mechanoreflexes. It appears that the rise in BP during the first minute of isometric exercise is due to increased HR and cardiac output (primarily by vagal withdrawal associated with central command and possibly mechanoreflexes), whereas the remaining rise in BP is due to increased SNA (muscle chemoreflex, Fig. 1) (11, 82). The magnitude and time course of SNA are assessed from increases in regional vascular resistance, plasma norepinephrine (NE) concentration, or NE spillover and, most recently, from microencephalography (91). In the latter, multiunit recordings of postganglionic SNA (to inactive muscle only) are obtained from muscle nerve fascicles in the peroneal nerve of one inactive leg and are referred to as MSNA throughout this review. Occasionally the tibial nerve (53) and the radial nerve on the inactive forearm (90) are used. During many stresses, including isometric handgrip (90), arm and leg MSNA change in parallel. Increments in leg MSNA are well correlated with increases in calf vascular resistance (59) and plasma NE concentration (63, 89).

MSNA during isometric exercise. MSNA does not rise during the first 1–2 min of contraction (31, 53, 59, 61–63, 84), presumably because of the time required for the accumulation of metabolites and activation of the muscle chemoreflex (31); the increase in MSNA is maintained during arrest of the circulation after contraction (Fig. 1) (31, 61, 90). The rise in both BP (48) and MSNA (60) during contraction and postexercise occlusion is proportional to the mass of muscle involved. [Mechanoreflexes would be expected to cause an immediate rise in MSNA followed by rapid recovery (18, 19, 83).]

Again the rise in MSNA has been associated with rising $\text{H}^+$ activity and also with fatigue (54, 62). Nonfatiguing contractions (15% MVC) are unaccompanied by increased MSNA [the rise in BP is proportional to the rise in HR (61)]. With fatiguing contractions (25 and 35% MVC), MSNA, BP, and electromyograph (EMG) activity rise in parallel, and with successively more fatiguing contractions, their rates of rise accelerate together (53, 62). Contraction-induced ischemia triggers lactic acid production, which may progressively activate chemosensitive muscle afferents during fatiguing contractions. Also the fall in muscle pH impairs force development and requires greater motor unit recruitment [reflected by increased EMG activity (13, 15)] and greater central command to maintain force with repeated contractions (62). However, central command appears to have only small effects on MSNA (82).

Parenthetically, another experimental approach has been to elicit involuntary muscle contractions by electrical stimulation so that responses might be attributable only to muscle reflexes (no central command) (27, 36, 47, 64). However, any direct electrical activation of muscle afferents along with reversal of normal muscle recruitment patterns could affect responses.

Reflex Responses to Dynamic Exercise

Is the muscle chemoreflex elicited during dynamic exercise when MBF is not mechanically restricted? Or are these reflexes initiated only when blood flow or oxygen delivery falls below some critical level? Overall sympathetic responses to exercise in humans. As with isometric exercise, the initial increase in HR and cardiac output is due to vagal withdrawal. As work intensity increases and HR approaches 100 beats/min, SNA begins to rise; it increases HR and plasma NE concentration and vasoconstricts visceral organs (Fig. 2).

Three characteristic responses of leg MSNA during dynamic and isometric arm exercise (i.e., small muscle mass) are similar (63, 85). 1) A distinct threshold for work intensity (e.g., 33% of maximal arm exercise) exists below which no rise in MSNA occurs. MSNA begins to rise along with plasma NE when HR approaches 100 beats/min (63, 84, 85) (Fig. 2). 2) MSNA rises only after a 1- to 2-min delay (this may depend on active muscle mass and type of exercise; see below). 3) Leg MSNA remains elevated after the active forearm is occluded at the end of exercise and HR recovers normally (as in Fig. 1). Thus the temporal patterns of reduced parasympathetic outflow to the heart and augmented SNA appear at first glance to be similar for both forms of exercise [bear in mind that MSNA in Fig. 2 is measured during arm exercise (see above) and not exercise with large muscle groups]. Is this apparently uniform pattern of SNA the signature of the muscle chemoreflex?

Involvement of the muscle chemoreflex in dynamic exercise. The muscle chemoreflex appears not to provide tonically active feedback to the cardiovascular system during mild dynamic exercise. For example, cardiovascular responses persist after complete sensory blockade of the legs by epidural anesthesia when both the pressor response to muscle ischemia and pain with KCl injection were abolished (10, 48). Because of motor weakness
flow. Large reductions in terminal aortic blood flow and femoral BP were required to raise BP at T, the threshold for the reflex. The sensitivity or open-loop gain of the reflex is the rise in systemic BP (less mechanical effects of partial occlusion) divided by the fall in femoral BP below the occluder. Below threshold (at T) this gain is zero; thus the reflex is not tonically active, and a large margin for flow error exists. Above the threshold the open-loop gain is \(-2\) to \(-3\), meaning that the reflex can correct by 67–75% any deficit in muscle perfusion pressure whenever blood flow is restricted. For example, when MBF is reduced by claudication during mild exercise in atherosclerotic patients, BP rises (47, 48).

Figure 3B shows that during moderate exercise the reflex has no threshold; prevailing BP and terminal aortic flow are on the steep portion of the stimulus-response curve; i.e., the reflex is tonically active. Bear in mind that the pressor response to a chemoreflex is proportional to the mass of ischemic muscle (48) so that this estimate of gain may increase as more muscle is active in severe exercise.

The reflex was triggered in dogs when oxygen delivery—rather than blood flow per se—fell below a critical level and lactic acid was generated (66). Thus, accumulation of the pressor substances does not depend simply on flow-dependent washout of metabolites (66). As in isometric exercise, the chemoreflex was linked (in the dog) to a metabolic event that triggered lactic acid release (i.e., when MBF was restricted).

When human forearm MBF was reduced during mild arm exercise by venous occlusion at subystolic pressures, MSNA did not increase until blood flow was stopped (84), indicating that the reflex has a threshold (lactate was not measured). With heavier exercise (30% of maximum load) and with HR close to 100 beats/min, MSNA rose spontaneously after the usual delay. Subsequent partial arterial occlusion raised both BP and MSNA in a large step, revealing a similarity to the responses illustrated in Fig. 3. Also reduction of vascular transmural pressure of exercising leg muscles by lower body positive pressure (+50 mmHg) increased systolic BP and blood lactate concentration, suggesting that the accompanying full sensory blockade, no equivalent information exists for heavy exercise.

Figure 3 schematically illustrates one approach to characterization of the muscle chemoreflex in dogs (65, 66, 92). Blood flow to the hindlimbs was reduced by stepwise partial occlusion of the terminal aorta as the dogs ran at different speeds and grades on a treadmill. Figure 3A shows that during mild exercise the prevailing BP (P) and terminal aortic flow (F) are on the flat portion of a stimulus-response curve relating systemic BP to femoral arterial BP or to terminal aortic blood.

FIG. 2. Summary of human sympathetic responses to dynamic exercise. Sympathetic nerve activity (SNA) begins to increase when HR approaches 100 beats/min, i.e., when vagal withdrawal is nearly complete. SNA is directed to splanchnic and renal vasculatures, causing vasoconstriction, and even to coronary arteries (47), suggesting that SNA during exercise is diffusely directed to most organs. Dashed line shows HR at which blood lactate begins to rise and indicates that rise in SNA precedes any known metabolic error signal. SNA is also directed to inactive and active muscle (active muscle is major source of neuronal leakage of NE) and is referred to specifically as MSNA*. MSNA to inactive muscle has only been measured during exercise with small muscle groups; its relationship to HR and magnitude of rise may be different for whole body exercise. SBF and RBF, splanchic and renal blood flow, respectively; HLa, lactic acid.

FIG. 3. Schematic illustration of muscle chemoreflex. A: graded increments in resistance across an occluder on the terminal aorta of a dog during mild exercise will generate graded decrements in terminal aortic flow (TAF) that eventually are partially reversed by graded increments in systemic arterial pressure (BP). Stimulus-response curves show that reflex has a threshold (T). “Prevaling” TAF and BP (P and F, respectively) represent normal BP and TAF for a given level of exercise, and they are on flat (low-gain) portion of curves. Thus reflex is not tonically active, and BP does not rise until TAF and femoral BP fall below some critical level. B: reflex when it is tonically active during moderate exercise. Prevailing TAF and BP are on steep portion of stimulus-response curves, and there is no threshold. Dashed line, doubling of slope (gain) of chemoreflex by arterial baroreceptor denervation (DNX) (66). [Adapted from Rowell and Sheriff (47, 80).]
chemoreflex may have been activated [mechanical effects of partial occlusion on BP were undetermined (9)].

Canine muscle has high oxidative capacity, and its release of lactate may reflect a critical reduction in oxygen delivery. The same may be true when muscle perfusion is reduced in humans. However, oxidative capacity of human muscle is much lower than that of dogs, and during dynamic exercise lactate is released before any anaerobic metabolism owing to limited ability to utilize pyruvate. Plasma lactate concentration does not rise until exercise requires 50–60% of maximal O₂ uptake (VO₂max) in humans (HR ~130–140 beats/min). As Fig. 2 illustrates, SNA begins to rise (indicated by splanchnic and renal vasoconstriction and NE release) at lower levels of exercise at which the chemoreflex should not be active. Thus, another stimulus may trigger the rise in SNA (see below).

In summary, central command appears to withdraw parasympathetic activity from the heart, increasing cardiac output at the onset of exercise. SNA does not increase during mild exercise. In moderate exercise, when HR approaches 100 beats/min, SNA begins to increase immediately in some organs (but only after a 1- to 2-min delay in muscle based on MSNA recordings made during exercise with small muscle groups), and thereafter SNA to the heart and vasculature rises in proportion to relative VO₂ ( bdsmVO₂max). Plasma lactate concentration starts to rise at work rates much higher than those raising SNA. As the severity of exercise increases, total vascular conductance and cardiac output must now be matched by reflexes to maintain BP.

The second half of this review focuses on control of BP by the arterial baroreflex, and we ask how this reflex might be affected by central command and also the muscle chemoreflex. (Space limitations prevent review of recent studies of cardiopulmonary baroreflex function during exercise.)

ARTERIAL BAROREFLEX

An early idea was that, because of rapid muscle vaso-dilation at the onset of exercise, muscle vascular conductance rises more rapidly than cardiac output, causing BP to fall and elicit a baroreflex (28, 47, 86, 88). Accordingly the arterial baroreflex was thought to initiate the circulatory responses to exercise. However, whether BP initially falls or not, it rises rapidly and exceeds the preexercise level. This led some to propose that the baroreflex is "turned off" during exercise so the rise in BP and HR is unopposed. Others postulated that the reflex is "reset" to a higher operating point so that it could still provide the stimulus to raise HR, cardiac output, and SNA. The question of what resets the baroreflex remained unanswered.

During the past decade, the importance of arterial baroreflex control of the circulation during exercise has been revealed owing mainly to advances in surgical isolation and selective stimulation of these baroreceptors. This section centers on five key points. 1) Sensitivity (gain) of the reflex is similar during rest and steady-state exercise. 2) The baroreflex is essential for the rise in BP at the onset of exercise as a result of a shift of its operating point to a higher pressure. 3) The baroreflex is necessary for maintenance of stable BP during mild but not heavy exercise. 4) The baroreflex buffers the muscle chemoreflex. 5) During severe dynamic exercise, the baroreflex and/or chemoreflex must counteract mismatches between vascular conductance and cardiac output by vasoconstricting active muscle to maintain BP.

Is the Arterial Baroreflex Operative During Exercise?

The arterial baroreflex was thought not to be an important controller of the circulation during exercise because chronic denervation of baroreceptors caused no obvious deficit in BP stability or level once responses to moderate-to-heavy exercise had stabilized (28, 86). There was, however, a sudden transient drop in BP at the onset of exercise after baroreceptor denervation (2, 12, 23, 33, 87).

The "sensitivity" of the arterial baroreflex has been assessed by observing changes in electrocardiogram (ECG) R-R interval in response to transient drug-induced increases in BP. The smaller the change in R-R interval per unit increase in BP, the lower the sensitivity of the baroreflex was assumed to be. The problem with using R-R interval is that for any change in HR the corresponding change in interval becomes less as the initial HR becomes higher, as with increased severity of exercise. Consequently, sensitivity appears to diminish at a time when HR responses (in beats/min) are unaffected (28, 47). Furthermore, changes in BP stem from rapid changes in HR (in one beat by the vagus nerve) and much slower changes in vascular resistance (in seconds by sympathetic nerves); either may dominate, depending on duration of stimulus and intensity of exercise, so that neither by itself constitutes a valid index of the sensitivity of the entire reflex (28, 47, 86).

Combined cardiac and vasomotor components of the baroreflex can be assessed simultaneously whenever effects of a perturbation on systemic BP are observed; for example, application of positive or negative pressure to the neck over the carotid sinuses reflexly raises or lowers BP (8, 28). Sensitivity of the baroreflex (based on changes in BP for a given change in carotid sinus transmural pressure) is unaffected by mild-to-heavy dynamic exercise (3, 28, 33, 86) and isometric exercise (8, 28). A problem in these studies is that the responses to the carotid sinus reflex are buffered by an intact aortic baroreflex.

Carotid sinus stimulus-response curves relating systemic BP and carotid sinus pressure were generated by controlling pressure within surgically isolated sinuses in resting and exercising dogs (33). Exercise caused no alteration in the shape (slope or gain) of the stimulus-response curves (Fig. 4). The entire curve was simply shifted vertically so that systemic BP was higher at any given carotid sinus pressure (Fig. 4H); the cause of this vertical shift is discussed below. Two disadvantages of this preparation were that pressure within the isolated carotid sinus was nonpulsatile and an intact aortic baroreflex buffered the carotid sinus reflex (33) (for further discussion, see Ref. 86). Nevertheless this study and others (8, 87) provided clear evidence of maintained baroreflex sensitivity during exercise.
Baroreflex at the Onset of Exercise—Evidence for Rightward Shift in the Reflex-Operating Point (“Resetting”)

Literally, the term “resetting” describes a change in a definite preset control value or “set point.” In reality, the baroreflex has an operating point (rather than a fixed set point) that can be continuously variable over a wide range of BP (52). For brevity, we refer to a lateral shift in operating point to a new baroreflex function curve as resetting (Fig. 4A).

In dogs without an arterial baroreflex (by sinoaortic denervation) BP does not rise at the onset of exercise; rather, it falls (2, 12, 23, 33, 87). Inasmuch as the baroreflex is essential for the rise in BP, it is assumed that the reflex has been reset to a higher pressure.

Why does BP drop at the onset of exercise if central command is operative and could raise BP normally by rapidly raising HR and cardiac output (by vagal withdrawal)? One interpretation is that at the onset of exercise the baroreflex is immediately reset rightward (Fig. 4) by central command; the system then perceives hypotension relative to its new operating point and must increase HR or elicit vasoconstriction to raise BP (29, 30). Without the baroreflex, BP falls. In other words, central command could exert its influence on SNA and vagal control of HR (see below) by resetting the arterial baroreflex.

In humans, anticipation of exercise blunted both HR and BP responses to positive and negative neck pressure, suggesting that resetting of the reflex begins just before exercise starts (8). After a transient period of adjustment, the relationship between BP and carotid sinus transmural pressure shifted to the right (as in Fig. 4), suggesting resetting. However, inasmuch as neck pressure was changed every 5 s and initiation of SNA takes >5 s, the carotid sinus curves represent the mixed results of altered HR (probably dominant) plus delayed vasoconstriction.

Strong evidence for resetting of the baroreflex in nonhuman species has come from several studies (12, 29, 30, 87). For example, it was seen in aortic baroreceptor-denervated dogs with pressure in the innervated and isolated carotid sinuses held at resting levels as dogs exercised at graded intensities (87). Cardiac output and HR rose normally at high work rates, but the stepwise increments in BP were extreme (Fig. 5). After an initial fall, systemic vascular resistance fell no further with increased work rate, meaning that a powerful vasoconstrictor outflow opposed further vasodilation of active muscle. Inasmuch as cardiac output rose normally, hypertension became extreme. Apparently, as the arterial baroreflex was progressively reset, a constant carotid...
sinus pressure was interpreted centrally as a progressively increasing hypotension (12, 29, 30, 87). In an analogous study (5a) attenuation of the rise in BP with exercise by nitroglycerin infusion markedly increased renal SNA (and also raised HR), indicating an attempt by the baroreflex to raise BP. In contrast, BP did not rise in proportion to work intensity in animals with no feedback from the receptors (denervated or unloaded baroreceptors) (5, 5a, 12, 29, 30, 87).

Evidence against resetting might be inferred from the vertical shift in the carotid sinus stimulus-response curves reported previously (33) (Fig. 4B). However, this could have resulted from persistent influences from intact aortic baroreceptors and the nonpulsatile pressures used to distend the isolated carotid sinus (33). In general, a vertical shift in the baroreflex curve presumably stems from a disturbance that activates only the effenter arm of the reflex (sympathetic nervous system) and raises systemic BP without affecting the carotid sinus operating pressure. In contrast, lateral shifts in the curve (Fig. 4A) (called “resetting”) are, in theory, caused by disturbances acting on the central neuron pool that integrates the reflex. The muscle chemoreflex might be expected to cause the former, whereas central command is assumed to elicit the latter (for details, see Ref. 52).

Parenthetically, it is now clear that the arterial mechanoreceptors themselves are not simply adapting to a higher BP caused by the higher cardiac output in exercise (40). Such mechanoreceptors do adapt rapidly to a higher static pressure, making it appear as though the “reflex” now operates at that BP (i.e., as though the baroreflex were rapidly reset). This rapid resetting of the baroreceptors does not occur when the receptors are exposed to elevated pulsatile pressures (34).

Thus, one reason for the higher BP during exercise is that the arterial baroreflex appears to “seek” a higher pressure (and if BP should rise above this pressure, the rise is counteracted by the baroreflex).

ARTERIAL BAROREFLEX AND MUSCLE CHEMOREFLEX—INTEGRATION

Our principal hypothesis is that after central command resets the baroreflex and raises cardiac output by vagal withdrawal, the primary error corrected by the sympathetic nervous system is a mismatch between vascular conductance and cardiac output, a BP error. Correction of metabolic error signals is secondary and occurs at higher levels of exercise.

How Are Cardiac Output and Vascular Conductance Matched?

If the arterial baroreflex is immediately reset in proportion to exercise intensity, cardiovascular control during exercise could be explained by continuous corrections, by the baroreflex, of small changes in BP caused by disparities between cardiac output and vascular conductance. The gain of the reflex is ~2 (33, 65), meaning that any deviation in BP from the operating point is corrected by ~67%. The muscle chemoreflex appears to be similarly effective in correcting changes in muscle perfusion pressure once the threshold for the reflex is reached. If exercise is mild, either reflex can raise BP by increasing cardiac output or by vasoconstricting inactive regions, which comprise a large fraction of total vascular conductance (92). As cardiac output and vascular conductance rise with exercise intensity, vasoconstriction of inactive regions and elevation of cardiac output contribute less and less to raising BP. When maximal cardiac output is approached and active muscle constitutes 85% of total vascular conductance, BP can only be raised by vasoconstriction of active muscle.

When Are the Baroreflex and the Chemoreflex Active in Dynamic Exercise?

We propose that these two reflexes are activated at very different severities of exercise among different mammals because of their two- to threefold differences in cardiac pumping capacity per kilogram of body weight (25, 37, 47). Activation of the baroreflex and a rise in SNA will occur whenever the rise in cardiac output is not rapid enough to raise BP immediately to the higher baroreflex operating point. This proposal has three points: 1) Central command immediately resets the baroreflex to a higher operating point and withdraws vagal outflow to the heart at the onset of exercise. 2) If the rise in cardiac output resulting from this vagal withdrawal is large enough and fast enough to raise BP to the new baroreflex operating point without significant delay, there is no “BP error.” 3) When the immediate rise in cardiac output is not sufficient to raise BP close to the new operating point, SNA must increase to achieve this rise (i.e., minimize the BP error).

In mild exercise, vagal withdrawal elicits a sufficiently large and rapid increase in HR and cardiac output to raise BP to its operating point without significant delay. As a consequence, there is no need to increase SNA and most tissues reveal little or no significant vasoconstriction (47) (Fig. 2). The importance of the baroreflex is revealed in the finding that, after baroreceptor denervation, BP falls at the onset of mild exercise (12, 29, 30), remains depressed, and is unstable because all extraneous influences on BP (e.g., noise) remain unbuffered (86–88). Thus, without an active chemoreflex (owing to the low work rate) the baroreflex is needed to modulate tonic SNA to maintain stable BP. In animals with limited ability to increase cardiac output rapidly [e.g., rabbits (12, 29, 30)], BP remains below the reset operating point so that in rabbits 40% of the initial rise in BP is achieved by vasoconstriction. Without the baroreflex, vasoconstriction appears to be abolished and BP falls (12) (again the chemoreflex is inactive).

In moderate exercise, responses depend on cardiac pumping capacity and again on the ability to increase HR and cardiac output quickly by vagal withdrawal. With initiation of central command, baroreflex control of SNA is reset and vagal withdrawal raises HR and cardiac output (Fig. 4). Available evidence suggests that vagal withdrawal is independent of the baroreflex (5), whereas the additional rise in HR attributable to increased SNA appears to depend on an intact baroreflex (5a). The range over which HR can be increased by vagal withdrawal varies greatly among different mammals and, therefore, so will the need to raise SNA. Thus, depending
on the species, responses vary from substantial vasoconstriction (rabbits) (12) and relatively small vasoconstriction in humans (Fig. 2) to virtually no regional vasoconstriction in dogs (6, 80) because of their two- to threefold greater pumping capacity (25, 37). Also the high oxidative capacity of their muscles delays development of a metabolic error signal until exercise is severe. In contrast, in dogs with cardiac pumping capacity experimentally compromised, regional vasoconstriction occurs at the onset of exercise, whereas in normal dogs, this response appears not to occur until HR exceeds 160–180 beats/min, after vagal withdrawal (80). Therefore a key feature linking findings across species appears to be the extent to which cardiac output can be rapidly increased by vagal withdrawal (and central command) to the new BP operating point.

With moderate exercise employing large muscle mass in humans, the immediate rise in cardiac output through vagal withdrawal is not sufficient (i.e., when HR exceeds 100 beats/min) to compensate fully for muscle vasodilation and therefore cannot rapidly raise BP to its reset operating point; there is a BP error. Consequently, SNA to both the heart and vasculature increases, but the sympathetically mediated rise in HR is much slower than a vagally mediated rise. Therefore, vasoconstriction in splanchnic, renal (47), cutaneous (77), and both resting and active skeletal muscle (17, 47, 57, 58, 76) becomes necessary to minimize the BP error. Also, if MBF is at a level at which the chemoreflex is tonically active, additional activation of SNA may occur (see below). Skeletal muscle must eventually become the primary site of vasoconstriction inasmuch as its conductance comprises most of the total (40, 57, 58, 76). It is now clear that active muscle is the major site of NE spillover during moderate-to-heavy exercise (57, 58) and that its vasculature constricts in response to baroreflex activation (17, 39, 69). The presence of tonic vasoconstriction in active muscle during moderate exercise was recently demonstrated in humans by increasing carotid sinus transmural pressure (by neck suction at −40 mmHg). Carotid sinus hypertension reflexly reduced BP by 15 mmHg mainly by releasing the tonic vasoconstriction present in exercising legs (76).

To What Extent Is SNA Increased by the Baroreflex or the Muscle Chemoreflex During Exercise?

In humans, moderate dynamic exercise with relatively small muscle groups (e.g., arms) increases MSNA when HR approaches 100 beats/min (cardiovascular responses and lactate release are much greater during exercise with arms than with legs at a given $V_{O_2}$). It is assumed that the rise in MSNA signals the initiation of a muscle chemoreflex because of the delayed onset (1–2 min) of the response (presumably by metabolite accumulation) and its association with increased H+ activity in isometrically contracting muscle (31, 81, 85). Under these conditions, this assumption may be correct. First, there is not likely to be activation of a baroreflex by any mismatch between cardiac output and vascular conductance because the mass of vasodilated muscle is too small to cause large increases in total vascular conductance. (Note that for this reason it may not be valid to include MSNA in Fig. 2 along with responses to whole body exercise.) Second, the chemoreflex could raise BP during either isometric or dynamic exercise with small muscle groups by vasoconstricting inactive regions.

We lack crucial information. Does MSNA rise at the onset of moderate, dynamic exercise (large muscle mass) when a baroreflex error signal may develop? Is the time lag in onset of MSNA inversely proportional to active muscle mass and work rate? That is, does MSNA increase immediately at the onset of large muscle dynamic exercise (when HR exceeds 100 beats/min), as implied by its inclusion in Fig. 2? Cutaneous vasoconstriction (77), and probably splanchnic vasoconstriction (47), occurs immediately; why would MSNA rise later? Or does the rise in MSNA not occur in this setting until later, when lactic acid appears in blood? If the latter is the case, it is consistent with MSNA being activated by the chemoreflex, with possibly a separate neuron pool directing the immediate rise in SNA to skin and visceral organs (cf. 83) (i.e., does MSNA parallel SNA to other regions?). Conversely, were SNA simultaneously directed to all these regions at the onset of exercise, baroreflex initiation of SNA would appear more likely. Overall SNA (but perhaps not MSNA) rises well before any known metabolic error signal exists; lactic acid is not released into venous blood until HR reaches 130–140 beats/min (or at ~50–60% $V_{O_2,max}$) in humans (Fig. 2), and even then it probably does not signal a metabolic error.

Does the Muscle Chemoreflex Help Maintain Muscle Perfusion Pressure (and thus BP) During Dynamic Exercise?

In moderate exercise with large muscle groups, >70% of total vascular conductance is in active muscles. To maintain or raise BP by vasoconstriction would require that the muscle chemoreflex jeopardize blood flow to the organ it presumably protects (and in so doing possibly increase the metabolic error signal causing positive feedback). On the other hand, a rise in SNA to the heart and an increase in cardiac output (without vasoconstricting active muscle) would be more helpful. The muscle chemoreflex does raise cardiac output during mild-to-moderate exercise in dogs (92), but its distribution between active and inactive regions has not yet been determined. Bear in mind that the baroreflex opposes muscle chemoreflexes; however, relative gains of the two reflexes have only been determined for mild exercise (65). The strength of the chemoreflex is reduced by ~60% by the baroreflex (Fig. 3A): when unopposed, the chemoreflex can correct by 86% an error in muscle perfusion. The strength (or “gain”) of neither reflex during moderate (or heavy) exercise is known. The chemoreflex could become much more powerful as the severity of whole body exercise increases, because its strength is a function of muscle mass (48) [current gain values apply to about one-third of the muscle mass (65, 66, 92)]. Also, opposition by the baroreflex could become greater or less with increasing work rate, depending on how much the baroreflex function curve (Fig. 4) has shifted (i.e., depending on whether the operating point is on the steep (sensitive) or flat (insensitive) region of the curve).

When exercise severity approaches maximal levels, the
consequent muscle vasodilation is too rapid and too large to be accommodated by the slow mainly sympathetically mediated rise in cardiac output. A marked increase in SNA must be directed to the vasculature to raise BP to the reset level. Also the shift in muscle metabolism to glycolysis and an exponential rise in metabolite concentration (especially lactic acid) will activate chemosensitive muscle afferents. Thus the rise in SNA could be initiated and then modulated by the baroreflex and maintained with the help of the more slowly responding muscle chemoreflex, which the baroreflex may oppose more or less strongly than at lower work rates.

Maximal levels of VO₂ and MBF during exercise are limited by the cardiac pumping capacity (47). The evidence suggests that, in humans, total vascular conductance might rise enough to overwhelm cardiac output (1, 47, 49, 57, 76). Furthermore we are clearly unable to supply adequate blood flow to both skeletal muscle and skin during heavy exercise when body temperature rises (47) or to accommodate the additional muscle vasodilation in hypoxemia (47, 49).

If humans vasodilate more muscle than the heart can supply at normal BP, the mismatch between cardiac output and total vascular conductance will lower BP below its higher operating point and the baroreflex should initiate vasoconstriction. BP must be maintained by vasoconstriction of active muscle, which now comprises 80–85% of total vascular conductance. Figure 6 makes two points. First, vasoconstriction of active muscle can be elicited by the arterial baroreflex. Second, the contribution of active muscle to the rise in BP during carotid sinus hypotension increases with work intensity (39). This demonstrates (in agreement with Refs. 6, 17, and 47) that reflex-induced vasoconstriction is not overpowered by metabolic vasodilation (as once proposed). Inasmuch as active muscle is already precariously close to, or is indeed experiencing, deficient oxygen supply, a (presumably) tonically active muscle chemoreflex is activated, further causing still more vasoconstriction in the muscles (depending on the degree of opposition by the baroreflex). In fact, it was recently concluded that the vasoconstrictor stimulus originating from active leg muscles (and causing vasoconstriction in forearm muscles rendered ischemic by 10 min of circulatory occlusion) was greater than that elicited by the baroreflex during central hypovolemia (67). Rowell and Sheriff (50) proposed that the chemoreflex may not only minimize any fall in BP (in effect amplifying any baroreflex vasoconstriction in active muscle and elsewhere) but could also serve (by this vasoconstriction) to direct the same total MBF (at maximal cardiac output and MBF) to a larger working muscle mass (less MBF per kilogram of muscle to more kilograms of muscle). Until we know more about the relative strengths of these two powerful reflexes in this complex situation and also the distribution of cardiac output, we can only speculate. We believe the hypotheses put forward in this review are testable.

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