Cardiovascular regulation during exercise – Contribution of peripheral reflexes

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Abstract Static and dynamic exercise is accompanied by increases in arterial blood pressure, heart rate and sympathetic nerve activity. It has been hypothesized that these cardiovascular responses are mediated by central command as well as by feedback mechanisms operating via afferent nerves (group III and IV fibers) that arise from skeletal muscles, are sensitive to mechanical (the so-called muscle mechanoreflex) and metabolic changes (the so-called muscle metaboreflex), and are modulated by arterial and cardiopulmonary baroreflexes. In this review, discussion is focused on the roles of the arterial baroreflex and muscle metaboreflex in cardiovascular regulation during exercise. In the first part of the review, brief discussion is made of the functions of these two reflexes during exercise; in the second part, their interactions are looked at in more detail. It is thought that during heavy exercise, the arterial baroreflex and the muscle metaboreflex are both activated, and interact in ways that lead to modulation of the primary cardiovascular reflex responses. Two types of interaction have been demonstrated. In the first, the arterial baroreflex acts to oppose pressor responses induced via the muscle metaboreflex. The second type of interaction involves the modulation of arterial baroreflex function during muscle metaboreflex activation. The authors offer commentary on these two types of interaction, including recent knowledge.

Keywords : blood pressure, exercise, sympathetic nervous system, integrated circulatory regulation

Overview of neural cardiovascular regulation during exercise

The physiological systems that enable close matching among central hemodynamics, blood flow to exercising muscles, and muscle metabolism are indispensable for the performance of continuous exercise. The hyperemia seen in active skeletal muscles is thought to be initially elicited by local mechanical and metabolic factors and to be modulated by neural cardiovascular regulatory mechanisms^{1,2}. Neural mechanisms also adjust the central hemodynamics to provide the required blood flow to active muscles. These neural cardiovascular regulatory mechanisms are assumed to rely on descending nervous activity from the cerebrum (central command) and on peripheral reflexes²⁻⁴. Central command is thought to be crucial for rapid cardiovascular regulation operating in parallel with, or even preceding, the start of exercise. The peripheral reflexes are a feedback system that detects changes (i.e., error signals) within an organism and acts to correct those changes. Among these, the baroreflexes (i.e., arterial and cardiopulmonary baroreflexes) and the reflexes arising from exercising skeletal muscles (i.e., the

muscle metaboreflex and mechanoreflex) are involved in regulating cardiovascular function during exercise. In this review, the focus of the discussion is on the role of the arterial baroreflex and muscle metaboreflex. It is emphasized that these reflexes work both independently and interactively to regulate cardiovascular and autonomic nervous system activity.

Arterial baroreflex function during exercise

Mechanosensitive nerve endings in the walls of the carotid sinuses and aortic arch are called arterial baroreceptors; they transduce arterial blood pressure changes (distention of the artery in the baroreceptor region) and provide neural information to the central nervous system⁵. On the basis of this afferent signaling, efferent autonomic nerve activity is modulated, and the activities of the heart and blood vessels are adjusted on a second-to-second basis in an effort to shift systemic blood pressure in the direction opposite to the one giving rise to the input stimulus^{6,7}. This reflexive feedback mechanism for control of arterial blood pressure is the so-called arterial baroreflex. The arterial baroreflex function curve, which is constructed by plotting baroreflex output responses (regulated systemic arterial blood pressure, heart rate

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[HR], efferent sympathetic nerve activity [SNA] etc.) against input stimuli to the baroreceptors (blood pressure changes in the baroreceptor regions), is sigmoidal (Fig. 1). Baroreflex-mediated feedback regulation of blood pressure continuously functions within this sigmoidal relationship as changes in input evoke corresponding changes in output to restore the input value to the desired operating point. However, exercise increases both arterial blood pressure and HR, which means the baroreflex-mediated relationship between arterial blood pressure and HR obtained at rest cannot explain the relationship during exercise. This phenomenon led to the hypothesis that the baroreflex function curve and its operating point shift rightward and upward as shown in Fig. 1; that is, the baroreflex input-output relationship is reset during exercise^{2,8)}. The increases in HR and SNA, together with a rise in arterial blood pressure, seen during exercise, can be explained by this hypothesis if the baroreflex function curve is shifted rightward and upward in accordance with increases in exercise intensity, and autonomic nerve activity is modulated such that arterial blood pressure and HR move to a new operating point on the shifted function curve. In that scenario, arterial blood pressure and HR rise together.

Muscle metaboreflex function during exercise

During isometric handgrip exercise (IHG), arterial blood pressure, HR and muscle sympathetic nerve activity (MSNA) progressively increase with prolongation of the exercise duration, as shown in Fig. 2. Then, if the exercising forearm is occluded by inflating a cuff fixed at the upper arm to supersystolic pressure just before the end of the exercise, arterial blood pressure and MSNA stay higher than under resting conditions, even after the end of the exercise. During the period of post-exercise muscle

ischemia (PEMI), central command and the muscle mechanoreflex are no longer active because the exercise has been terminated. Given this situation, it has been assumed that there are receptors within skeletal muscles that sense metabolic changes induced by muscle contraction, and that when these receptors are stimulated reflex increases in efferent SNA and arterial blood pressure occur^{3,4,9)}. This reflex is the so-called muscle metaboreflex, whereby the nerve endings of group III and IV afferents, in skeletal muscles, function as metaboreceptors^{3,4)}. These sensory neurons project to the medulla oblongata, and can be stimulated by a variety of metabolites, including lactic acid, adenosine, potassium, diprotonated phosphate, H^+ and arachidonic acid products, among others. Activation of the muscle metaboreflex has been shown to evoke increases in SNA, arterial blood pressure, HR, cardiac output (CO) and peripheral vasoconstriction, as well as secretion of various vasoactive hormones^{2,4)}. These reflex responses are all thought to act in increasing blood flow to exercising muscles and inhibiting the accumulation of metabolic byproducts.

The muscle metaboreflex is activated during exercise only when exercise intensity and duration are sufficient to cause accumulation of metabolites within active skeletal muscles. For example, studies in dogs showed that the muscle metaboreflex is not activated by mild exercise (treadmill running at 3.2-6.4 km/h with 0% grade), but becomes tonically active at exercise intensities higher than moderate (6.4 km/h with 10% grade or 9.6 km/h with 0% grade)^{10,11)}. Although the level of dynamic exercise that activates the muscle metaboreflex in humans is not known¹²⁾, during incremental cycle exercise, MSNA is markedly increased at exercise intensities higher than moderate, suggesting this reflex may be tonically active during exercise at higher-than-moderate intensities in humans, just as in dogs^{13,14)}.

Fig. 1 Schematic illustration of the arterial baroreflex function curve and its resetting during exercise.

Fig. 2 Representative raw data for heart rate (HR), arterial blood pressure and muscle sympathetic nerve activity (MSNA) at rest and during isometric handgrip exercise (IHG), post exercise muscle ischemia (PEMI) and recovery (Rec).

Interaction between the arterial baroreflex and muscle metaboreflex

Buffering effects of the arterial baroreflex on muscle metaboreflex-induced pressor responses. When arterial blood pressure rises, the arterial baroreflex acts to reduce CO and peripheral vascular resistance by inhibiting SNA and enhancing parasympathetic nerve activity to reduce the elevated blood pressure. When the muscle metaboreflex is activated, a reflex pressor response occurs, which loads the arterial baroreceptors. In this situation, the arterial baroreflex buffers the muscle metaboreflex pressor response. Sheriff et al.¹⁵⁾ provided direct evidence of this antagonistic effect of the baroreflex by comparing the muscle metaboreflex pressor response in dogs before and after arterial baroreceptor denervation. They showed that the pressor response was increased by about 200% after baroreceptor denervation, as compared to the same dogs with intact baroreceptors. More recently, Kim et al.¹⁶⁾ showed that the remarkable increase in the muscle metaboreflex pressor response in baro-denervated dogs is attributable to an increase in peripheral vascular resistance without an increase in CO, which means that in intact animals, the arterial baroreflex buffers the muscle metaboreflex pressor response by inhibiting peripheral vasoconstriction. In addition, Scherrer et al.¹⁷⁾ showed in humans that increases in HR and MSNA, during IHG at 33% of maximal voluntary contraction, was augmented in subjects receiving nitroprusside to suppress the handgrip-induced rise in blood pressure; conversely, HR and MSNA responses were suppressed in subjects receiving phenylephrine to accentuate the handgrip-induced elevation in blood pressure. Because the muscle metaboreflex is activated and contributes to the rise in HR and MSNA during IHG at 33% MVC, it is suggested that the loading state of the arterial baroreceptors influences the muscle metaboreflex-mediated cardioacceleration and sympatho-

excitation.

During PEMI, arterial blood pressure and MSNA remain higher than under resting conditions (Fig. 2). As mentioned, these muscle metaboreflex responses arise when metabolic byproducts, produced during exercise, stimulate group III and IV afferents innervating the forearm skeletal musculature. Although the increase in SNA, seen during PEMI, ought to affect both the peripheral vasculature and the heart, HR returns to the resting level (Fig. 2). In that regard, O'Leary¹⁸⁾ demonstrated that HR remains higher than at rest during PEMI in dogs administered atropine to block parasympathetic nerve activity, and suggested that the fall of HR, to the resting level during PEMI, is due to the reactivation of parasympathetic nerve activity after the end of exercise. In addition, Nishiyasu et al.¹⁹⁾ showed that both cardiac sympathetic and parasympathetic tone increase simultaneously during PEMI in humans. They suggested that the increase in cardiac parasympathetic tone might be a component of the counteraction by the arterial baroreflex against the elevation in blood pressure induced by the muscle metaboreflex. These findings suggest that maintenance of HR at the resting level during PEMI could reflect the interaction of the effects of sympathetic activation induced via the muscle metaboreflex and parasympathetic activation induced via the arterial baroreflex. Recently, Watanabe et al.²⁰⁾ showed that the HR response during PEMI varies considerably from individual to individual. When they investigated the cause of this large individual variation in the HR response, they found that PEMI-induced changes in the RR interval correlate positively with changes in an index of cardiac parasympathetic tone, as well as with changes in cardiac baroreflex sensitivity (Fig. 3). Their results indicate that individuals with greater increases in cardiac parasympathetic tone and greater cardiac baroreflex sensitivity during PEMI will likely show a greater bradycardic response to PEMI, and vice versa. In ad-

Fig. 3 Relationships between PEMI-induced changes in the R-R interval and changes in the spectral power for R-R interval variability in the high-frequency range (ΔHF power: an index of cardiac parasympathetic tone) and cardiac baroreflex sensitivity (Δ Baroreflex sensitivity). Symbols depict data from individual subjects. Lines are the regression lines.

dition, their results also suggest the possibility that the interaction between the arterial baroreflex and the muscle metaboreflex may contribute to the individual variation in cardiovascular responses seen during exercise.

Activation of the muscle metaboreflex during submaximal treadmill exercise, in dogs with reduced hindlimb blood flow, elicits a pressor response mediated primarily by an increase in CO. However, when the ability to increase CO is limited, such as in heart failure or during maximal exercise, the muscle metaboreflex increases arterial pressure through peripheral vasoconstriction^{21,22}. In addition, a recent study by Ichinose et al.²³ demonstrated that muscle metaboreflex function is virtually instantaneously shifted from increasing CO to increasing vasoconstriction when the induced rise in CO is acutely removed (Fig. 4). These results indicate that the mechanisms involved in muscle metaboreflex response are continuously dependent upon whether a rise in CO occurs. Although it is not known what causes the shift in the metaboreflex mechanism when the normal rise in CO is impaired, it is suspected that it might be due to a change in the interaction between the metaboreflex and other systems such as baroreflexes. It has been suggested that activation of the muscle metaboreflex resets the arterial baroreflex operating point and function curve to higher blood pressures and, as a result, autonomic nerve activity is modulated to elevate arterial blood pressure to a new operating pressure^{2,4,8}. As evidenced by the previously mentioned studies of Sheriff et al.¹⁵ and Kim et al.¹⁶, muscle metaboreflex activation can potentially increase arterial blood pressure far higher than the operating pressure of the arterial baroreflex. However, the baroreflex buffers the metaboreflex-induced pressor response by inhibiting peripheral vasoconstriction, so that arterial blood pressure is maintained at the baroreflex operating pressure¹⁵⁻¹⁷. When the ability to increase CO is not limited, activation of the muscle metaboreflex evokes a rise in arterial blood pressure up to the new operating pressure by increasing CO. By contrast, under conditions in which the ability to increase CO is impaired, there is no muscle metaboreflex-induced rise in arterial blood pressure via increased CO. Consequently, the arterial baroreflex would not act to inhibit peripheral vasoconstriction until the arterial blood pressure exceeded the new operating pressure. In this situation, therefore, the muscle metaboreflex could evoke peripheral vasoconstriction.

Modulation of arterial baroreflex function during activation of the muscle metaboreflex. Research carried out over the last fifteen years has shown that arterial baroreflex-mediated cardiovascular regulation is modulated during activation of the muscle metaboreflex. Papelier et al.²⁴ reported that during PEMI, the carotid sinus baroreflex showed reduced sensitivity to loading (neck suction) and enhanced sensitivity to unloading (neck pressure) for blood-pressure regulation; but the sensitivity

for HR regulation was unchanged. Recent studies using microneurographic recordings of MSNA in humans²⁵⁻²⁷ have demonstrated, more directly, that arterial baroreflex control of SNA is modulated during muscle-metaboreflex activation. The authors conducted a series of studies^{28,29} and found that during PEMI, unloading the carotid baroreflex by applying neck pressure evokes greater increases in MSNA, peripheral vasoconstriction and arterial blood pressure, than are evoked under control conditions (Fig. 5). In addition, it was also found that during PEMI, carotid baroreflex stimulation via neck suction produces less suppression of MSNA and less vasodilation and, in turn, smaller reductions in arterial blood pressure (Fig. 6). By contrast, there were no changes in HR responses to either neck pressure or neck suction. These results suggest that carotid baroreflex-mediated sympathetic vascular regulation is modulated during activation of the muscle metaboreflex, and that such alterations in baroreflex func-

Fig. 4 Representative raw data showing changes in mean arterial pressure (MAP), cardiac output (CO), vascular conductance of all non-ischemic areas (NIVC) and hindlimb blood flow (HLBF) in one animal. The muscle metaboreflex was activated by reducing HLBF in dogs during mild dynamic exercise (3.2 km/h). Activation of the muscle metaboreflex increased CO and MAP, whereas NIVC was unchanged. CO then declined to the same level observed during exercise prior to muscle metaboreflex activation via partial occlusion of the inferior and superior vena cavae. MAP dropped rapidly with the reduction in CO, but then nearly completely recovered. With removal of the muscle metaboreflex-induced rise in CO, there was a substantial increase in peripheral vasoconstriction, which maintained arterial pressure at the level seen prior to the CO reduction; that is, muscle metaboreflex function is nearly instantaneously shifted from increased CO to increased peripheral vascular resistance when the rise in CO is removed.

tion might contribute to the increase and/or maintenance of arterial blood pressure at a higher level than under resting conditions.

Time-dependent modulation of arterial baroreflex control of MSNA during isometric exercise

As an isometric contraction develops, from rest to the onset of the contraction to steady state contraction, blood pressure, HR and SNA progressively increase. These cardiovascular responses are thought to be induced by gradual activation of both central command and the muscle metaboreflex²⁻⁴). The responses are also reportedly modulated by the arterial baroreflex^{2,4}), though baroreflex-mediated cardiovascular control, especially control of

SNA during isometric exercise, is not fully understood. According to Scherrer et al.¹⁷), the arterial baroreflex more effectively buffers reflex increases in MSNA during IHG than under resting conditions. Moreover, the baroreflex is reportedly reset to function at higher arterial pressures during IHG, and its sensitivity to control MSNA is elevated²⁶). These findings suggest that arterial baroreflex control of MSNA is modulated during isometric exercise, and that time-dependent alterations in baroreflex function are a key determinant of MSNA responses during isometric exercise.

The authors also investigated the time-dependent modulation of arterial baroreflex control over MSNA that occurs during three minutes of IHG at 30% MVC³⁰). The arterial baroreflex control of MSNA was evaluated by

Fig. 5 Averaged reflex alterations in MSNA (A), leg vascular conductance (LVC: B), MAP (C), and HR (D) elicited by neck pressure under control and PEMI conditions. *Significant difference from the value obtained 3 s prior to application of neck pressure, $p < 0.05$. †Significant difference from the value obtained under control conditions, $P < 0.05$.

Fig. 6 Averaged reflex alterations in MSNA (A), leg vascular conductance (LVC: B), MAP (C) ($n = 12$), and HR (D) ($n = 12$) elicited by neck suction under control and PEMI conditions. *Significant difference from the value obtained 3 s prior to application of neck suction, $p < 0.05$. †Significant difference from the value obtained under control conditions, $P < 0.05$.

analyzing the relationship between spontaneous variations in diastolic arterial blood pressure (DAP) and MSNA during supine rest at each minute of IHG, and during PEMI. Fig. 7 shows the group average linear relationship between DAP and MSNA. During the first minute of IHG (IHG1), the linear relationship between DAP and MSNA (DAP-MSNA line) shifted rightward, without a significant vertical shift or a change in sensitivity (slope of the DAP-MSNA line). However, within the second minute of IHG (IHG2) the DAP-MSNA line shifted both rightward and upward, and the sensitivity of the MSNA control was increased. And, during the third minute of IHG (IHG3), the DAP-MSNA line shifted further rightward and upward, and the sensitivity of the arterial baroreflex control of MSNA increased further. These results show that the arterial baroreflex control of MSNA is modulated in a time-dependent manner during the course of IHG. During PEMI, the relationship between DAP and MSNA shifted back to a lower blood pressure than was observed at IHG3; but it was still slightly higher than at IHG2. In addition, the sensitivity of the MSNA control was lower than was observed at IHG3, and appeared to be comparable to that seen at IHG2.

Activation of the muscle metaboreflex was thought to account for the time-dependent upward and rightward shifts in the DAP-MSNA relationship and for the increase in the sensitivity of the MSNA control during the IHG. This idea is supported by the finding that modulation of the DAP-MSNA relationship, that occurred during IHG, persisted during the PEMI, a time when the muscle metaboreflex would be activated in the absence of both central command and the muscle mechanoreflex. Presumably, activation of the muscle metaboreflex would be delayed from the onset of IHG by time needed to accumulate metabolites in the vicinity of the metaboreceptor afferent endings, which would account for the almost 60-s lag between the onset of IHG (at around 30% MVC) and the onset of sympathetic activation^{4,31-35}. For the same reason, the metaboreflex may not be sufficiently activated at IHG1 to mediate the upward shift in the DAP-MSNA

relationship or the increase in the sensitivity of arterial baroreflex control of MSNA. Interestingly, Scherrer et al.¹⁷ showed that MSNA increases within the first minute of IHG (33% MVC) in subjects receiving nitropruside to suppress the IHG-induced rise in blood pressure; conversely, MSNA is suppressed in subjects receiving phenylephrine to accentuate the IHG-induced elevation in blood pressure. This suggests that the lack of change in MSNA, from the resting level at IHG1, is due, at least in part, to arterial baroreflex control of MSNA. The finding that the DAP-MSNA relationship is shifted rightward, without a significant vertical shift or change in sensitivity, suggests that, at IHG1, arterial baroreflex operating pressure is reset, enabling MSNA to be maintained at the resting level despite an increase in blood pressure. This rapid resetting of arterial baroreflex operating pressure might be induced by activation of central command and/or muscle mechanoreflex^{2-4,36-40}. By IHG2 and IHG3, on the other hand, the metaboreflex is sufficiently activated and involved in mediating a full response.

Our observation that modulation of arterial baroreflex control of MSNA was greater at IHG3 (i.e., resetting and an increase in sensitivity) than during PEMI indicates that mechanisms other than the muscle metaboreflex (i.e., central command and/or muscle mechanoreflex) were also affecting arterial baroreflex control of MSNA at that time. In this regard, the authors observed that ratings of perceived exertion (RPE) had nearly reached the fatigue level ($RPE = 19.0 \pm 0.3$) by IHG3. It would therefore be expected that central command is strongly activated by IHG3, and would increase MSNA⁴¹. Thus, in addition to the resetting of arterial baroreflex operating pressure, seen with even mild activation of central command ($RPE = 14.2 \pm 0.4$ at IHG1), the strong activation occurring at IHG3 could also account for the upward shift in DAP-MSNA relationship and increased sensitivity of the arterial baroreflex control of MSNA.

Modulation of the arterial baroreflex control of MSNA during incremental leg cycling

During dynamic exercise, mean arterial pressure, HR, and SNA all increase in response to a progressive increase in workload². It has been hypothesized that these cardiovascular responses are mediated by several factors: 1) central command², 2) feedback mechanisms operating via afferent nerves (group III and IV fibers) arising from the working skeletal muscles^{3,4}, and 3) arterial and cardiopulmonary baroreflexes^{2,4}. However, the arterial baroreflex-mediated regulation of SNA during dynamic exercise is not yet fully understood. Fadel et al.⁴² reported that carotid baroreflex control of MSNA remains constant during moderate-intensity arm cycling, while Keller et al.⁴³ reported it was also unchanged during mild-intensity one-legged kicking. In addition, Ogoh et al.⁴⁴ reported that arterial baroreflex control of MSNA is progressively

Fig. 7 Group average prevailing points (symbols) with the corresponding mean regression lines relating total MSNA and DAP at indicated times during the exercise protocol ($n = 13$).

reset to higher blood pressures during the transition from rest to steady state moderate arm cycling with no change in reflex sensitivity. Thus, all of these studies suggest that arterial baroreflex control of MSNA is well preserved during dynamic exercise up to moderate intensity. In contrast to the findings of the aforementioned human studies, Miki et al.⁴⁵⁾ observed that during high-intensity (~70% of the maximum oxygen consumption) treadmill exercise in rats, arterial baroreflex control over renal SNA is reset to higher blood pressures and higher SNA levels, with a significant increase in arterial baroreflex sensitivity. In addition, significant increases in the sensitivity of arterial baroreflex control over MSNA have also been observed during isometric exercise in humans; and, importantly, it was activation of the muscle metaboreflex that triggered the increase in sensitivity^{26,27,30)}. It may well be that the intensity of dynamic exercise employed in those earlier studies, in which the arterial baroreflex control of MSNA was unchanged, did not fully activate the muscle metaboreflex⁴²⁻⁴⁴⁾, and that dynamic exercise, at a workload high enough to activate the muscle metaboreflex, would increase the sensitivity of the arterial baroreflex control of MSNA in humans.

The authors investigated arterial baroreflex control over MSNA during an exercise protocol in which intensity (workload) was incrementally increased from very mild to exhausting⁴⁶⁾. The exercise had five workload levels selected as very mild (10 W), mild (82 ± 5.0 W), moderate (126 ± 10.2 W), heavy (156 ± 14.3 W) and exhausting (190 ± 21.2 W). The workload was incremented every 6 min, and the exercise at the highest intensity was continued until volitional exhaustion (5 to 7 min). Arterial baroreflex control over MSNA was then evaluated by analyzing the relationship between spontaneous beat-to-beat variations in DAP and MSNA during the rest period and at each exercise level. Fig. 8 shows the linear relationships between MSNA and DAP for a given subject. Very mild exercise

Fig. 8 Linear relationships between total MSNA and DAP in a representative subject under the indicated conditions during an incremental dynamic exercise protocol. The symbols indicate the prevailing points.

shifted the DAP-MSNA relationship to lower MSNA levels and also reduced arterial baroreflex sensitivity. Thereafter, incremental increases in exercise workload, from mild to exhausting, caused a gradual upward shift in the DAP-MSNA relationship. During moderate exercise, sensitivity of the MSNA control recovered to the resting level; and during heavy and exhausting exercise, there was a rightward and upward shift in the DAP-MSNA relationship, with a significant increase in sensitivity. The authors' findings during mild and moderate exercise are consistent with earlier studies showing that arterial baroreflex sensitivity is unchanged during moderate-intensity arm cycling^{42,44)} and mild-intensity one-legged kicking⁴³⁾. Collectively, these results suggest that the sensitivity of arterial baroreflex control over MSNA, during mild to moderate dynamic exercise, remains at the resting level, regardless of exercise mode. In addition, modulation of arterial baroreflex function, that was observed during heavy and exhausting exercise, is in agreement with the earlier report on rats showing that high-intensity treadmill exercise resets the arterial baroreflex control over renal SNA to higher blood pressures and higher SNA levels, with a significant increase in arterial baroreflex sensitivity⁴⁵⁾. Bearing in mind those earlier studies and our present results, the authors suggest that arterial baroreflex control over SNA is not uniform during dynamic exercise at different intensities.

The mechanisms responsible for the modulation of arterial baroreflex control over MSNA, seen during incremental dynamic exercise, are not known for certain, but they will likely reflect the interactions between the arterial baroreflex and other systems contributing to the regulation of SNA. Indeed, arterial baroreflex function is reportedly influenced by central command as well as by several peripheral neural inputs^{2-4, 36-40, 47)}, and it would be expected that these factors are gradually activated or modified by the increasing workload in dynamic exercise²⁾. For example, increasing afferent neural input from active skeletal muscles, reflecting the progressive rise in workload, could be involved in modulating arterial baroreflex control over MSNA. Results of earlier studies suggest that activation of the muscle metaboreflex could account for the upward and rightward shift of the DAP-MSNA relationship, and for the increase in sensitivity of the arterial baroreflex control of MSNA observed during isometric exercise^{26,30)}. As mentioned previously, although the level of dynamic exercise that activates the muscle metaboreflex in humans remains unknown, this reflex is known to be tonically active in dogs at exercise intensities higher than moderate^{10,11)}. The modulation of arterial baroreflex function during heavy and exhausting exercise, which entails resetting the MSNA control to higher blood pressures and higher MSNA levels and increases in arterial baroreflex sensitivity, is consistent with observations made during isometric exercise and PEMI^{25-27,30)}. It may be that the muscle metaboreflex is activated at heavy and

exhausting leg cycling, which in turn induces the observed modifications in arterial baroreflex function.

Summary

The arterial baroreflex plays a pivotal role in arterial blood pressure regulation at rest and during exercise. In that context, the operating pressure of the baroreflex is thought to be reset to higher levels in accordance with ongoing exercise intensity. This baroreflex resetting appears to contribute to the increases in HR, arterial blood pressure, and SNA that accompany increases in exercise intensity. When metabolites accumulate within active skeletal muscles, the resultant activation of the muscle metaboreflex increases SNA and raises arterial blood pressure. This reflex appears to contribute to the marked elevation in SNA and arterial blood pressure seen during heavy exercise, which means that both the arterial baroreflex and the muscle metaboreflex make important contributions to cardiovascular regulation during heavy exercise. Furthermore, although these two reflexes function independently, they also interact to regulate cardiovascular and autonomic nervous activity. For example, the arterial baroreflex buffers muscle metaboreflex-induced pressor responses, which, in the absence of baroreflex buffering, would be up to twice as large. In addition, during muscle metaboreflex activation, arterial baroreflex regulation of SNA is modulated in a way that helps to maintain the elevation in arterial blood pressure. These interactions, between the arterial baroreflex and muscle metaboreflex, provide important functional links between the metabolism within active muscles and central hemodynamics, and thereby contribute to regulation of the cardiovascular system during exercise.

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References

- 1) Calbet JAL, Joyner MJ. 2010. Disparity in regional and systemic circulatory capacities: do they affect the regulation of the circulation? *Acta Physiol* 199: 393-406.
- 2) Rowell LB, O'Leary DS, Kellogg DL. 1996. Integration of cardiovascular control systems in dynamic exercise. *Handbook of Physiology*. In: Rowell LB, Shepherd JT (Eds.), *Exercise: Regulation and Integration of Multiple Systems*. Sect. 12, Chapt. 17, Bethesda, American Physiology Society, 770-838.
- 3) Mitchell JH. 1990. Neural control of the circulation during exercise. *Med Sci Sports Exerc* 22: 141-154.
- 4) Rowell LB, O'Leary DS. 1990. Reflex control of the circulation during exercise: chemoreflex and mechanoreflexes. *J Appl Physiol* 69: 407-418.
- 5) Eckberg D. L. Sleight, P. 1992. *Human Baroreflexes in Health and Disease*, Oxford, UK: Clarendon, p.19-57.
- 6) Manica G, Mark L. 1983. Arterial baroreflexes in humans. In: *Handbook of Physiology*, section 2, The cardiovascular system, Peripheral Circulation and Organ Blood Flow, Bethesda, MD: American Physiological Society, sect.2, Vol.3, pt.2, p. 755-793.
- 7) Sagawa K. 1983. Baroreflex control of systemic arterial pressure and vascular beds. In: *Handbook of Physiology. The Cardiovascular System. Peripheral Circulation and Organ Blood Flow*. Bethesda, MD: American Physiological Society, sect.2, Vol.3, pt 2, p. 453-496.
- 8) Raven PB, Potts JT, Shi X. 1997. Baroreflex regulation of blood pressure during dynamic exercise. *Exerc Sport Sci Rev* 25: 365-389.
- 9) Alam M, Smirk FH. 1937. Observations in man upon a blood pressure raising reflex arising from the voluntary muscles. *J Physiol* 89: 372-383.
- 10) O'Leary DS, Sheriff DD. 1995. Is the muscle metaboreflex important in control of blood flow to ischemic active skeletal muscle? *Am J Physiol Heart Circ Physiol* 268: H980-H986.
- 11) Wyss CR, Ardell JL, Scher AM, Rowell LB. 1983. Cardiovascular responses to graded reductions in hindlimb perfusion in exercising dogs. *Am J Physiol. Heart Circ Physiol* 245: H481-H486.
- 12) Ichinose M, Delliaux S, Watanabe K, Fujii N, Nishiyasu T. 2011. Evaluation of muscle metaboreflex function through graded reduction in forearm blood flow during rhythmic handgrip exercise in humans. *Am J Physiol Heart Circ Physiol* 301: H609-616.
- 13) Saito M, Tsukanaka A, Yanagihara D, Mano T. 1993. Muscle sympathetic nerve responses to graded leg cycling. *J Appl Physiol* 75: 663-667.
- 14) Ichinose M, Saito M, Fujii N, Ogawa T, Hayashi K, Kondo N, Nishiyasu T. 2008. Modulation of the control of muscle sympathetic nerve activity during incremental leg cycling. *J Physiol* 586: 2753-2766.
- 15) Sheriff DD, O'Leary DS, Scher AM, Rowell LB. 1990. Baroreflex attenuates pressor response to graded muscle ischemia in exercising dogs. *Am J Physiol Heart Circ Physiol* 258: H305-H310.
- 16) Kim JK, Sala-Mercado JA, Rodriguez J, Scislo TJ, O'Leary DS. 2005. Arterial baroreflex alters strength and mechanisms of muscle metaboreflex during dynamic exercise. *Am J Physiol Heart Circ Physiol* 288: H1374-H1380.
- 17) Scherrer U, Pryor SL, Bertocci LA, Victor RG. 1990. Arterial baroreflex buffering of sympathetic activation during exercise-induced elevations in arterial pressure. *J Clin Invest* 86: 1855-1861.
- 18) O'Leary DS. 1993. Autonomic mechanisms of muscle metaboreflex control of heart rate. *J Appl Physiol* 74: 1748-1754.
- 19) Nishiyasu T, Tan N, Morimoto K, Nishiyasu M, Yamaguchi Y, Murakami N. 1994. Enhancement of parasympathetic cardiac activity during activation of muscle metaboreflex in hu-

- mans. *J Appl Physiol* 77: 2778-2783.
- 20) Watanabe K, Ichinose M, Fujii N, Matsumoto M, Nishiyasu T. 2010. Individual differences in the heart rate response to activation of the muscle metaboreflex in humans. *Am J Physiol Heart Circ Physiol* 299: H1708-14.
 - 21) Hammond RL, Augustyniak RA, Rossi NF, Churchill PC, Lapanowski K, O'Leary DS. 2000. Heart failure alters the strength and mechanisms of the muscle metaboreflex. *Am J Physiol Heart Circ Physiol* 278: H818-H828.
 - 22) Augustyniak RA, Collins HL, Ansoorge EJ, Rossi NF, O'Leary DS. 2001. Severe exercise alters the strength and mechanisms of the muscle metaboreflex. *Am J Physiol Heart Circ Physiol* 280: H1645-H1652.
 - 23) Ichinose M, Sala-Mercado JA, Coutsos M, Li Z, Ichinose TK, Dawe E, O'Leary DS. 2010. Modulation of cardiac output alters the mechanisms of the muscle metaboreflex pressor response. *Am J Physiol Heart Circ Physiol* 298: H245-H250.
 - 24) Papelier Y, Escourrou P, Helloco F, Rowell LB. 1997. Muscle chemoreflex alters carotid sinus baroreflex response in humans. *J Appl Physiol* 82: 577-538.
 - 25) Cui J, Wilson TE, Shibasaki M, Hodges NA, Crandall CG. 2001. Baroreflex modulation of muscle sympathetic nerve activity during posthandgrip muscle ischemia in humans. *J Appl Physiol* 91: 1679-1686.
 - 26) Kamiya A, Michikami D, Qi Fu, Niimi Y, Iwase S, Mano T, Suzumura A. 2001. Static handgrip exercise modifies arterial baroreflex control of vascular sympathetic outflow in humans. *Am J Physiol Regul Integr Comp Physiol* 281: R1134-R1139.
 - 27) Ichinose M, Saito M, Wada H, Kitano A, Kondo N, Nishiyasu T. 2004. Modulation of arterial baroreflex control of muscle sympathetic nerve activity by muscle metaboreflex in humans. *Am J Physiol Heart Circ Physiol* 286: H701-H707.
 - 28) Ichinose M, Saito M, Wada H, Kitano A, Kondo N, Nishiyasu T. 2002. Modulation of arterial baroreflex dynamic response during muscle metaboreflex activation in humans. *J Physiol* 544: 939-948.
 - 29) Ichinose M, Nishiyasu T. 2005. Muscle metaboreflex modulates the arterial baroreflex dynamic effects on peripheral vascular conductance in humans. *Am J Physiol Heart Circ Physiol* 288: H1532-1538.
 - 30) Ichinose M, Saito M, Kondo N, Nishiyasu T. 2006. Time-dependent modulation of arterial baroreflex control of muscle sympathetic nerve activity during isometric exercise in humans. *Am J Physiol Heart Circ Physiol* 290: H1419-H1426.
 - 31) Nishiyasu T, Ueno H, Nishiyasu M, Tan N, Morimoto K, Morimoto A, Deguchi T, Murakami N. 1994. Relationship between mean arterial pressure and muscle cell pH during forearm ischemia after sustained handgrip. *Acta Physiol Scand* 151: 143-148.
 - 32) Victor RG, Bertocci LA, Pryor SL, Nunnally RL. 1988. Sympathetic nerve discharge is coupled to muscle cell pH during exercise in humans. *J Clin Invest* 82: 1301-1305.
 - 33) Saito M, Mano T, Iwase S. 1989. Sympathetic nerve activity related to local fatigue sensation during static contraction. *J Appl Physiol* 67: 980-984.
 - 34) Pryor SL, Lewis SF, Haller RG, Bertocci LA, Victor RG. 1990. Impairment of sympathetic activation during static exercise in patients with muscle phosphorylase deficiency (McArdle's disease). *J Clin Invest* 85: 1444-1449, 1990.
 - 35) Seals DR, Chase PB, Taylor JA. 1988. Autonomic mediation of the pressor responses to isometric exercise in humans. *J Appl Physiol* 64: 2190-2196.
 - 36) Gallagher KM, Fadel PJ, Strömstand M, Ide K, Smith SA, Querry RG, Raven PB, Secher NH. 2001. Effects of partial neuromuscular blockade on carotid baroreflex function during exercise in humans. *J Physiol* 533: 861-870.
 - 37) Iellamo F, Legramante JM, Raimondi G, Peruzzi G. 1997. Baroreflex control of sinus node during dynamic exercise in humans: effects of central command and muscle reflexes. *Am J Physiol Heart Circ Physiol* 272: 1157-1164.
 - 38) McIlveen SA, Shawn GH, Kaufman MP. 2001. Both central command and exercise pressor reflex reset carotid sinus baroreflex. *Am J Physiol Heart Circ Physiol* 280: 1451-1463.
 - 39) Ogoh S, Wasmund WL, Keller DM, Yurvati AO, Gallagher KM, Mitchell JH, Raven PB. 2002. Role of central command in carotid baroreflex resetting in humans during static exercise. *J Physiol* 543: 349-364.
 - 40) Potts JT, Mitchell JH. 1998. Rapid resetting of carotid baroreflex by afferent input from skeletal muscle receptors. *Am J Physiol Heart Circ Physiol*, 275: H2000-H2008.
 - 41) Victor RG, Pryor SL, Secher NH, Mitchell JH. 1989. Effects of partial neuromuscular blockade on sympathetic nerve responses to static exercise in humans. *Circ Res* 65: 468-476.
 - 42) Fadel PJ, Ogoh S, Watenpugh DE, Wasmund W, Olivencia-Yurvati A, Smith ML, Raven PB. 2001. Carotid baroreflex regulation of sympathetic nerve activity during dynamic exercise in humans. *Am J Physiol Heart Circ Physiol* 280: H1383-H1390.
 - 43) Keller DM, Fadel PJ, Ogoh S, Brothers RM, Hawkins M, Olivencia-Yurvati A, Raven PB. 2004. Carotid baroreflex control of leg vasculature in exercising and non-exercising skeletal muscle in humans. *J Physiol* 561: 283-93.
 - 44) Ogoh S, Fisher JP, Raven PB, Fadel PJ. 2007. Arterial baroreflex control of muscle sympathetic nerve activity in the transition from rest to steady-state dynamic exercise in humans. *Am J Physiol Heart Circ Physiol* 293: H2202-2209.
 - 45) Miki K, Yoshimoto M, Tanimizu M. 2003. Acute shifts of baroreflex control of renal sympathetic nerve activity induced by treadmill exercise in rats. *J Physiol* 548: 313-22.
 - 46) Ichinose M, Saito M, Fujii N, Ogawa T, Hayashi K, Kondo N, Nishiyasu T. 2008. Modulation of the control of muscle sympathetic nerve activity during incremental leg cycling. *J Physiol* 586: 2753-2766.
 - 47) Charkoudian N, Martin EA, Dinunno FA, Eisenach JH, Dietz NM, Joyner MJ. 2004. Influence of increased central venous pressure on baroreflex control of sympathetic activity in humans. *Am J Physiol Heart Circ Physiol* 287: H1658-H1662.