Current perspective

Neural control of the cardiovascular system during exercise

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The objective of this review was to give an overview on the current knowledge on the neural mechanisms of cardiovascular regulation during exercise. Evidence derived mainly from human studies which supports the contribution of the different control mechanisms, namely the central command, the reflex drive from active muscles and the arterial baroreflex, with the attendant modifications in autonomic nervous system activity, in determining the cardiovascular responses to exercise are discussed, along with some controversial issues and evolving concepts in exercise physiology. In particular, data that show how the various neural mechanisms involved in cardiovascular regulation during exercise are differently modulated by factors related to the muscular activity being performed, such as the type and intensity of exercise and the size of the active muscle masses are presented, stressing the plasticity of the neural network. Finally, clinical implications pertaining to neural cardiovascular regulation and exercise are advanced.

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Physical exercise is characterized by increases in arterial blood pressure (AP), heart rate (HR) and cardiac output. The appropriate cardiovascular responses to exercise are largely accomplished by changes in autonomic nervous system activity acting in concert with local release of vasoactive substances in the exercising muscles. Thus, blood flow and metabolic requirements are coupled. That is, there is a decrease in the activity of the parasympathetic nervous system and an overall increase in the activity of the sympathetic nervous system to the heart and blood vessels.

Three main mechanisms have been proposed as playing a role in cardiovascular neural regulation during exercise, a diagram of which is shown in figure 1. In the first mechanism, activation of regions of the brain responsible for the recruitment of skeletal muscle motor units would concomitantly activate neuronal circuits within the medulla thus establishing changes in parasympathetic and sympathetic efferent activity that determine the cardiovascular responses during skeletal muscle contraction. This mechanism has been termed "central command"[2]. In the second mechanism, neural signals following stimulation of mechano- and/or chemosensitive receptors in the contracting muscles would reflexly activate the cardiovascular control areas in the medulla. This has been referred to as the "exercise pressor reflex" or the "muscle metaboreflex"[3,4]. The third mechanism involves the arterial baroreceptor reflex[5]. Results from human studies have clearly indicated that both the central command and the reflex neural mechanisms play an important role in determining the cardiovascular responses to exercise.

In this review, evidence derived mainly from human studies which supports the role of each of these neural mechanisms in regulating the cardiovascular responses to exercise will be presented along with some controversial issues and evolving concepts in exercise physiology.

Role of central command

The central command hypothesis suggests that motor outflow from the cerebral cortex during exercise interacts with the central neuron pools that regulate the cardiovascular responses to exercise. The notion of a centrally generated neural command signal originated from the observations that, at the onset of exercise, HR (and ventilation as well) increases almost immediately[6] and

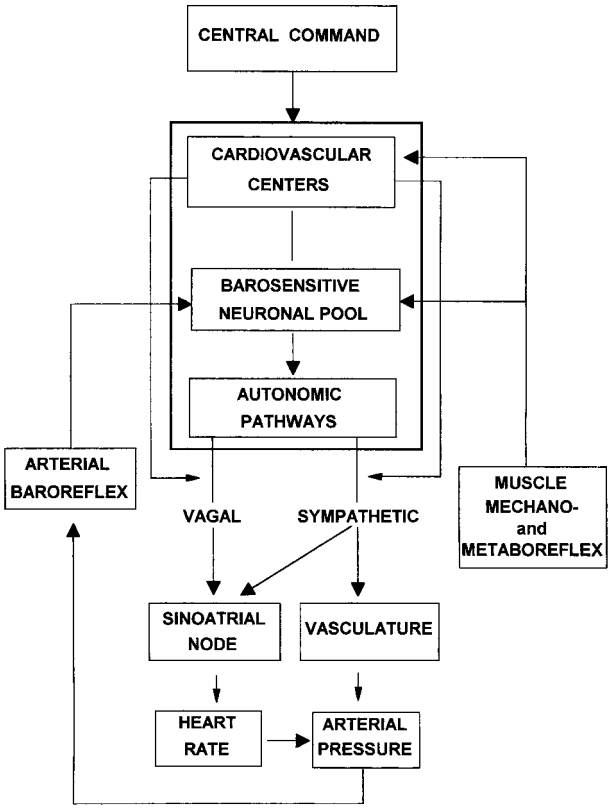

Figure 1. *Schematic diagram illustrating the main neural mechanisms of cardiovascular regulation during exercise. In addition to the mechanisms depicted in this scheme, stimulation via sympathetic and vagal afferents of cardiac receptors by exercise-induced changes in arterial blood pressure, contractility and in the loading conditions of the heart, may also exert important modulatory effects, particularly on the baroreflex control of heart rate*[1].

that the tachycardic response to electrically induced exercise, that is, central command inoperative, developed more slowly than that to voluntary exercise[7]. Although the involvement of the central command in the cardiovascular responses to exercise could appear intuitive, experimental evidence supporting its role is indirect.

One model used to isolate the effect of central command has been that of studying the cardiovascular responses to exercise during neuromuscular blockade. According to this approach, if descending impulses originating from the cerebral cortex ("cortical irradiation"[7]) actually activate the somatomotor and cardiovascular systems simultaneously, then an unsuccessful attempt to contract paralyzed muscles should nevertheless be accompanied by cardiovascular responses. Freyschuss[8] observed that attempted static contraction during total neuromuscular blockade by succinylcholine still produced an increase in HR and AP. However, this increase was only about one-half of that occurring during static contraction performed before neuromuscular blockade. In view of the fact that during total blockade the muscle does not contract and that consequently there is no metabolic and/or mechanical reflex signal originating from muscles, the rise in HR and AP in this setting should be ascribed to the central command. The contribution of the central command to the cardiovascular responses to exercise has also been supported by experiments involving partial neuromuscular blockade. During partial neuromuscular blockade which reduced the maximal voluntary contraction (MVC) force by 50%, static exercise performed at the same absolute force resulted in a greater increase in AP than during the control (unblocked) exercise[9,10]. Similar results had been obtained during dynamic exercise[11]. Because partial paralysis by neuromuscular blockade induces muscular weakness, a greater intended effort and central command signal would be required to maintain a given absolute force of muscle contraction (as indicated by an increase in electromyographic activity[9]), and this would result in greater cardiovascular responses. However, in the different studies[9,10] it has been pointed out[12] that the HR response to experimental partial neuromuscular blockade has proved to be less consistent than the AP response. This may be due to the different contribution to HR responses exerted by the various mechanisms involved in neural cardiovascular regulation during exercise.

Other evidence on the role of central command derived from studies in patients who, because of sensory neuropathy, lost neural feedback from the active muscles but retained some motor function. In these patients, both isometric and dynamic exercise still resulted in an increase in AP and HR[13,14]. Finally, reduction or enhancement of the level of the central motor command signal at a constant force during static exercise by facilitating or inhibiting motor neurons with the application of high frequency (HF) vibration to the tendon from a contracting or an antagonist muscle, resulted in reduced and enhanced HR and AP responses respectively. That is, the magnitude of the cardiovascular responses was in accordance with the predicted level of the putative central command signal rather than with the developed tension[2].

Anyway, crucial for the full development of cardiovascular responses to centrally generated motor command is a functional spinal cord. When paraplegic subjects with complete transection of the spinal cord at levels T-8 to T-12 attempted to contract their paralyzed leg muscles, no cardiovascular response was observed. In the same patients, attempted contractions of an arm, temporarily paralyzed by local anesthesia, elicited significant increases in HR and AP[15]. Thus, spinal transection abolished the cardiovascular responses to a central command signal to the legs, whereas paralysis of the arm by peripheral blockade did not abolish the cardiovascular response to such a signal. Hence, a spinal feedback loop is an important part of the central motor and cardiovascular command processes, being involved in the generation and/or modulation (or both) of the command signal[15].

In summary, the findings reported above suggest that central command alone may increase HR and AP, although they do not inform us how central command

is integrated with the other mechanisms in producing the cardiovascular responses to exercise when all the mechanisms are intact.

Reflexes from active muscles: mechano- and metaboreflexes

Skeletal muscles contain group III (myelinated) and group IV (unmyelinated) afferents, the free nerve endings of which reside within the interstitium of the muscles. They are stimulated by the mechanical and metabolic activities of the muscles: group III fibers would be more sensitive to mechanical (i.e. muscle tension) stimuli, whereas group IV would be more sensitive to local chemical stimuli, i.e., the metabolic by-products of muscle contraction[16,17], although both tend to be polymodal, responding to either mechanical or chemical stimuli[18]. It is worthy of note that injection of chemical factors involved in the processes of functional hyperemia into the femoral artery produces reflex cardiovascular (and respiratory) responses[19] very similar to those induced by muscle contractions following electrical stimulation of the femoral nerve in several animal species[20,21].

Evidence of the involvement of muscle mechanoreflexes in the cardiovascular responses to exercise in man derives mainly from studies showing that electrically induced muscle contractions, that is absence of central command and muscle metaboreflexes, were able to induce increases in HR and AP[22-24] the latency and magnitude of which were similar to those induced by voluntary exercise of the same (low) intensity. Theoretically, muscle mechanoreceptors might be activated by each contraction during dynamic exercise. The muscle mechanoreflex may also contribute to the rise in HR and AP at the onset of static contractions, but less so during sustained static exercise, since mechanoreceptor discharge quickly returns towards control levels[16].

Much more is known about the role of the muscle metaboreflex in human cardiovascular regulation during exercise. When blood flow and oxygen delivery to contracting muscles are insufficient for the rate of metabolism, chemical products of muscle metabolism accumulate within the muscle and stimulate group III and IV afferents. Activation of these afferents elicits the reflex increase in sympathetic nerve activity and blood pressure, termed muscle metaboreflex. The chemical substances responsible for activation of the muscle metaboreflex have not been defined at all. However, some events associated with lactic acid production seem crucial for activation of this reflex, since in patients with myophosphorylase deficiency (McArdle's disease), muscle sympathetic nerve activity (MSNA) did not increase during static exercise[25].

One basic approach taken to demonstrate the contribution of the muscle metaboreflex during exercise has been that of studying AP, HR and MSNA during post-exercise arrested circulation to the exercising limb by means of a pneumatic cuff. With this technique, the blood flow to the exercising limb is arrested shortly before cessation of exercise. In this way metabolites produced during contractions are entrapped within the muscles and maintain the chemical activation of muscle metaboreceptors in the post-exercise recovery period until relief of ischemia; concomitantly the volitional component of exercise (i.e. the central command) is abolished. Hence, the responses that are maintained during muscle ischemia are considered to be due only to the muscle metaboreflex.

Static exercise followed by post-exercise muscle ischemia has provided the most expedient model to investigate the role of the muscle metaboreflex, since during this type of muscular activity blood flow is hampered during the whole period of contraction and the release of metabolites within the contracting muscles is more readily observed[4,26].

Static exercise induces increases in AP, HR and MSNA[27-30], the magnitude of which is related to the relative intensity of contraction. During muscle ischemia following static exercise, AP and MSNA are kept elevated above resting levels[28,30-32], and may even increase over exercise levels: persistence of elevated AP and MSNA as long as post-exercise vascular occlusion is maintained is the unquestionable evidence of the involvement of the muscle metaboreflex.

Integration of the different mechanisms in the cardiovascular responses to exercise

Various combinations of central cortical influences and muscle afferent reflexes have been considered responsible for the increases in AP on the one hand, and for the increase in HR on the other. Until recently, the prevailing view was that during exercise the rise in AP occurs mainly via an increase in sympathetic activity to blood vessels due to muscle metaboreflex activation, whereas the increase in HR occurs mainly through a decrease in parasympathetic activity to the sinus node due to central command[12]. This general view derived mainly from the observation that during post-exercise muscle ischemia (only metaboreflex activity and no central command and/or mechanoreflexes) the increases in AP, vascular resistance and MSNA to resting muscles are kept elevated above resting values whereas HR fully recovers[28,30,31,33]. However, after administration of a beta-adrenergic blocking drug, the HR response to static exercise was reduced[34,35], suggesting involvement of the sympathetic nervous system in HR regulation, although the mechanism underlying the sympathetic contribution (i.e. central vs reflex) was not determined. In addition, enhancement of muscle metaboreflex engagement, by reducing blood flow to active muscle with occluding cuffs during rather than after exercise, resulted in greater HR and AP responses in comparison with intensity-matched exercise performed under free

flow conditions[32,36]. Experiments performed in the conscious dog by O'Leary[4] provided more direct evidence that sympathetic activation originating from the muscle metaboreflex contributes substantially to increase HR during exercise, inasmuch as parasympathetic blockade with atropine did not affect the increase in AP and HR occurring during exercise, but prevented the fall in HR during post-exercise muscle ischemia. The contribution of the muscle metaboreflex to HR regulation via sympathetic activation has recently been confirmed in humans by Iellamo et al.[37] by means of power spectral analysis of HR variability. Sustained static contraction at 30% of the MVC induced an increase in the R-R interval low frequency (LF) oscillatory power that, by reflecting enhanced sympathetic modulation of the sino-atrial node[38-41], indicated a significant contribution of this autonomic division to HR regulation during static exercise. During post-exercise muscle ischemia, the R-R interval returned to control values, whereas AP remained significantly elevated above rest levels. However, LF power still remained significantly elevated until the relief of circulatory occlusion (Fig. 2)[37], after which it returned to control values, indicating the muscle metaboreflex as the effective stimulus in maintaining the LF power during post-exercise muscle ischemia elevated. These data strongly suggest that the muscle metaboreflex contributes to HR regulation during static exercise via sympathetic excitation that is maintained during post-exercise muscle ischemia, similarly to what occurs for the peripheral vasculature, despite the concomitant recovery of HR that can be explained by a baroreflex mechanism. In fact, during exercise, baroreflex sensitivity (BRS) was significantly reduced but it was restored during post-exercise muscle ischemia (Fig. 3)[37]. The restoration of BRS back to resting levels at the time when AP was maintained elevated by the muscle metaboreflex could explain, through a vagally-mediated baroreflex mechanism, the return of HR towards resting levels despite maintained sympathetic activation. In this setting, the increased parasympathetic outflow induced by the arterial baroreflex can overpower the tachycardic effect of the metaboreflex-induced cardiac sympathetic activation[42]. The experimental approach used in this study[37] allowed a distinctive insight into the integrated reflex neural regulation of HR during exercise by using non-perturbative techniques and without artificially isolating the influence of the different neural pathways. This could be of relevance particularly when multiple control mechanisms are integrated in producing the net responses, as during exercise.

These data challenge the concept of a differential control of HR (central command via vagal withdrawal) and AP (muscle metaboreflex via a sympathetic vasoconstriction) during static exercise and also the exclusiveness of removal of central command as the unique cause of HR recovery during post-exercise muscle ischemia. On the other hand, even the concept that central command raises HR only via vagal withdrawal playing a very small, if any, role in producing the increase in sympathetic activity to skeletal muscle vasculature needs to be reconsidered. Indeed, attempted static handgrip (SHG) during partial neuromuscular blockade (i.e. enhanced central command) resulted in no or very small changes in MSNA in comparison with actual SHG of mild to moderate intensity (up to 30% of the MVC)[10,25] and MSNA increased during involuntary but fell during voluntary static contraction, each performed at 20% of the MVC[28]. Similarly, MSNA did not increase during mild rhythmic (dynamic) handgrip, but it did so when the exercise was performed during arrested forearm

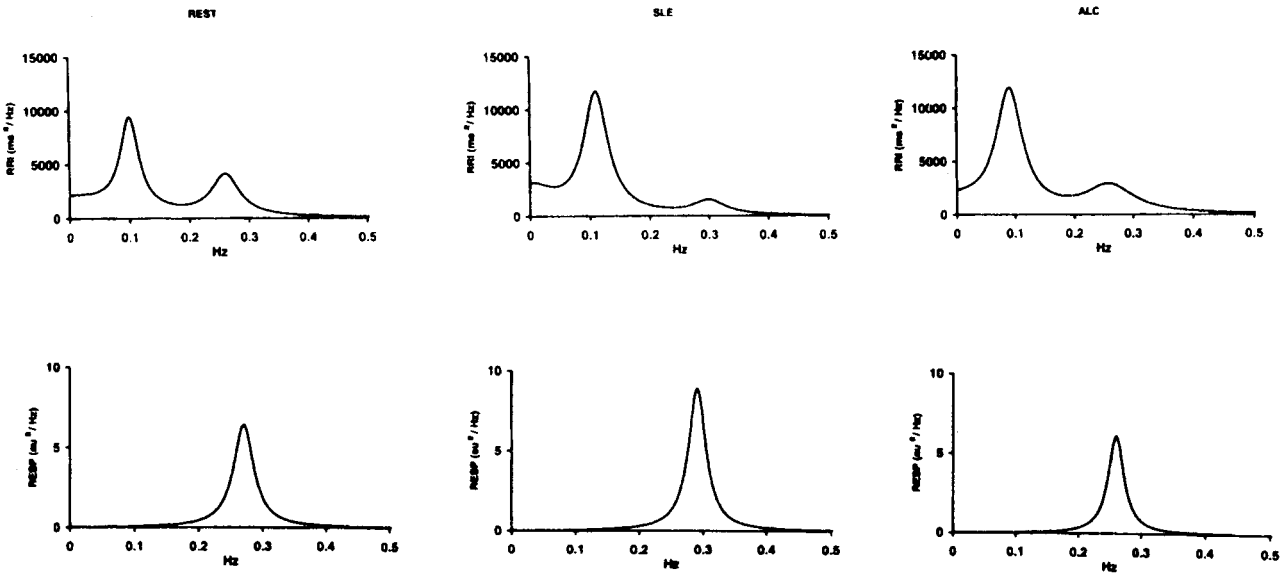

Figure 2. *An example of spectral analysis of the R-R interval (RRI) and of the respiratory (RESP) variations during rest, static leg extension (SLE) and post-exercise arrested leg circulation (ALC). The oscillatory components centered around 0.1 Hz on the autospectra identify the low frequency power linked to sympathetic modulation of the sino-atrial node. au = arbitrary units. From Iellamo et al.[37].*

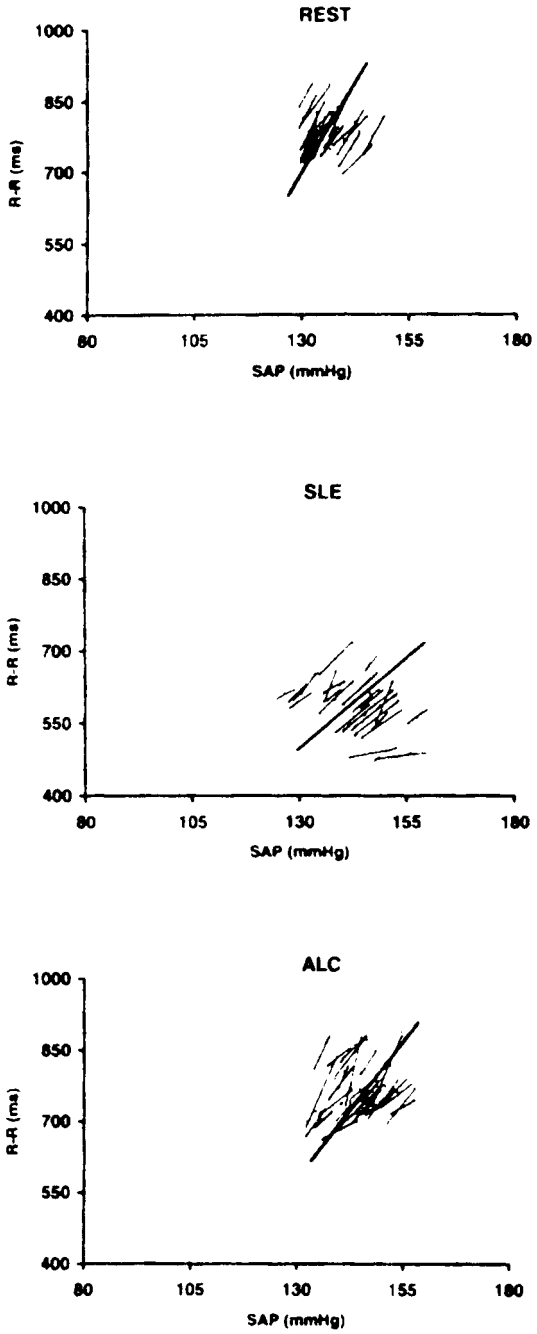

Figure 3. *An example of spontaneous baroreflexes during rest* (top panel), *static leg extension* (middle panel) *and post-exercise arrested leg circulation* (bottom panel). *The* thin lines *represent the regression lines for each sequence; the* thick lines *represent their mean slopes. SAP = systolic arterial pressure. Other abbreviations as in figure 2. From Iellamo et al.*[37].

circulation[36]. However, intermittent SHG at 75% of the MVC induced marked sympathetic activation, which did not differ from that observed during partial neuromuscular blockade (i.e. enhanced central command), despite a reduction in handgrip force and thus in muscle afferent activation[43]. Thus, central command is capable of increasing sympathetic outflow to skeletal muscle blood vessels, at least at high exercise intensity.

A very recent study by Winchester et al.[44] in patients with Brown-Séquard syndrome, provided one of the most compelling demonstrations of the involvement of both central and reflex mechanisms in the cardiovascular responses to exercise. In these patients, hemisection of the spinal cord leaves one side of the body with sensory loss and normal motor function and the other side with reduced motor function and normal sensation. As such, this human model is unique for studying the influence of central command and reflex drive from muscles while avoiding the possible limitations involving experiments with partial neuromuscular blockade or autonomic blocking drugs[5,37]. In these patients, both voluntary and electrically stimulated static knee extension of either the leg with motor deficit and intact sensitivity or that with intact motor function and sensory deficit elicited increases in HR and AP, with the exception of electrical stimulation of the leg with sensory deficit (i.e. no activation of central command and diminished input from muscle afferents).

In summary, all the findings reported above clearly point to the concept that the neural mechanisms of cardiovascular regulation are not mutually exclusive and that the control systems are redundant[45]. In short, the cardiovascular control mechanisms, with the attendant modifications in autonomic nervous system activity, could always find a strategy for raising AP, HR and cardiac output during exercise when at least one mechanism is available, stressing the plasticity of the neural network.

However, there is evidence that in subjects with all mechanisms intact, the various mechanisms may not be completely redundant, but that the relative contribution they afford may vary, depending on the modulatory effects exerted by the factors associated with the muscular activity being performed, such as the type (static vs dynamic) and intensity of exercise and the size of the active muscle masses. Indeed, Iellamo et al.[46] have recently shown that the relative contribution of the muscle metaboreflex to the cardiovascular (and respiratory) responses to static exercise is influenced by the combined effects of muscle mass and contraction intensity. Comparison of cardiorespiratory responses to static leg extension (SLE) and SHG (i.e. different muscle masses) both performed at 30% of the MVC revealed that the increases in AP and HR, as well as in ventilation, were significantly greater during SLE than during SHG, with the difference in the AP response being maintained during post-exercise muscle ischemia. The part of the pressor response that was maintained during post-exercise muscle ischemia, that is, by the muscle metaboreflex, was significantly greater after SLE-30 than SHG-30, amounting to 88 vs 68% of the overall AP response attained during the respective exercise periods (Fig. 4)[47]. In line with these findings, Seals[47,48] reported a greater increase in AP and MSNA during two- vs one-arm SHG at 30% of the MVC, with the difference being maintained during post-exercise circulatory occlusion. Gandevia and Hobbs[49] also observed that the pressor responses to post-handgrip circulatory occlusion increased in paral-

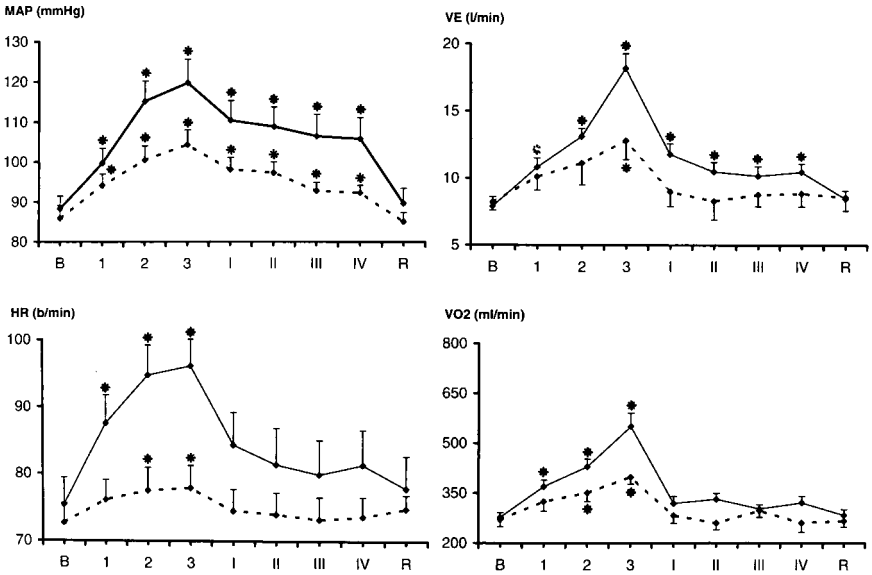

Figure 4. *Mean arterial pressure (MAP), heart rate (HR), ventilation (VE), and oxygen consumption (VO_2) during each minute of exercise* (arabic numerals) *and during post-exercise circulatory occlusion* (roman numerals) *in static leg extension at 30% of the maximal voluntary contraction trial* (solid lines) *and in static handgrip at 30% of the maximal voluntary contraction trial* (broken lines). *B = baseline resting values; R = recovery values. * p < 0.05 vs rest. From Iellamo et al.[46], with permission from the American Physiological Society.*

lel with the intensity of contraction. Thus, it appears that during static exercise the relative contribution of the muscle metaboreflex is related to the amount of metabolites released during contraction, which, in turn, is determined by the intensity of contraction and the size of the active muscle masses[46-50]. Consistent with this interpretation is the observation that electrically induced contractions of leg[51] but not arm muscles[28] produced the normal HR response to voluntary contraction.

The crucial role of muscular factors in modulating the contribution of the reflex drive from muscles vs central influences is also supported by the differences in HR regulating mechanisms during dynamic as opposed to static exercise. At variance with the static exercise studies reviewed above, neuromuscular blockade experiments performed during dynamic (bicycle) exercise have indicated that central command plays a minor role in raising HR in this type of exercise. The HR was lower in case of maximal dynamic exercise performed during neuromuscular blockade than during control exercise. Furthermore, the HR was not significantly different during partial neuromuscular blockade as compared to control exercise at a given oxygen uptake. Both these findings are suggestive of a predominant role of the reflex component in regulating HR[52]. That the contribution of the various regulatory mechanisms attending dynamic exercise could partially differ from that associated with static exercise, is not surprising, owing, among others, to differences in peripheral and central hemodynamics[5,26]. For example, the release of metabolites within the contracting muscles is more readily observed during static exercise than during the unrestricted flow conditions of dynamic exercise. During dynamic exercise, blood flow is unobstructed in the relaxation phase whereas in case of static exercise blood flow is hampered during the whole period of contraction. Moreover, at variance with dynamic exercise, during static exercise the muscle pump is absent. Thus, results from one form of exercise cannot at all be extrapolated to the other form. In accordance with this concept, significant differences have been reported in the cardiorespiratory responses to dynamic vs static exercise performed at the same contraction intensity by the same muscle mass[53].

The importance of the muscular factors in influencing the neural mechanisms of cardiovascular regulation during exercise is further emphasized by their modulatory effects on baroreflex circulatory control.

Arterial baroreflex

Under resting conditions an increase in AP usually induces a decrease in HR through a baroreceptive reflex mechanism. During muscular exercise the increase in AP is accompanied by a concomitant increase in HR which significantly contributes to the rise in blood pressure. This leads to the conclusion that the arterial baroreflex is somehow modified during exercise. However, whether and how the baroreflex control mechanism is altered is a controversial issue in human exercise physiology[54].

Two hypotheses have been advanced to explain baroreflex control of AP and HR. One hypothesis is that the sensitivity (or gain) of the reflex, that is, the change in systemic AP and HR per unit increase in blood pressure at the baroreceptor level, is reduced during exercise. This reduction in sensitivity would mean that any baroreflex opposition to an increase in AP and

HR would be lessened, thus permitting concomitant increases in AP and HR. According to the other hypothesis, the baroreflex would be "reset" to operate at the higher blood pressure of exercise, without a change in sensitivity. In this scheme, once the baroreflex had been reset, the central neuron pool that integrates the baroreflex receives input signals from the baroreceptors which are interpreted as hypotensive relative to the higher operating pressure, and acts to increase HR and cardiac output and, in turn, AP initially through vagal withdrawal and thereafter by means of increased sympathetic activity to the heart and blood vessels. The concept of "resetting" would imply that it is the baroreflex that stimulates the increase in AP and HR, whilst maintaining the capability of opposing any extreme rise in AP[5,12].

Whereas there is substantial agreement that the baroreflex response curve for AP is reset to a higher operating point during exercise, more controversial is the issue of arterial baroreflex control of HR. Although a number of studies reported reduced BRS during various types of exercise, at least just as many provided direct or indirect evidence of a resetting of the integrated baroreflex function curve with no attenuation in BRS.

Earlier studies using either single intensity, prolonged carotid baroreceptor stimulation[55-57] or the phenylephrine bolus technique[58] reported a decrease in BRS during SHG. On the contrary, recent studies employing either graded intensity, brief carotid baroreceptor stimulation[59,60] or the spontaneous baroreflex method[61], have shown that moderate intensity static contraction of small muscle groups, such as handgrip at 20-30% of the MVC, induces a rightward shift of the baroreflex stimulus-response curve along the pressure axis, with an unchanged BRS. These findings have been interpreted as evidence of a resetting of the baroreflex function curve to a new higher operating point.

However, the issue of baroreflex control of HR, as other aspects of neural cardiovascular regulation, is rather complex, and the results obtained during handgrip, often used as a convenient model of muscular activity, should not be generalized to other combinations of exercise modality, intensity and/or size of active muscle mass. In accordance with this concept, we observed[46] that SLE and SHG, both performed at the same relative intensity, differently influenced the integrated baroreflex control of the sinus node: SLE resulted in decreased BRS, whereas SHG did not modify BRS. Interestingly, in the same study SLE performed at 15% of the MVC showed cardiovascular and baroreflex responses which overlap with those obtained during SHG. Thus, baroreflex control of the sinus node appears to depend on the combined effects of both the muscle mass and contraction intensity.

Again, it is important to point out that the above findings could be pertinent to static exercise only, and that they cannot be extended to dynamic exercise, since the mechanisms regulating this type of exercise may be different from those associated with static exercise. However, some similarities with static exercise also exist.

Iellamo et al.[24] reported that mild intensity, dynamic one-legged knee extension did not alter BRS, but resulted in an apparent rightward shift in the regression line relating AP to pulse interval, a finding suggestive of baroreflex "resetting", similarly to what had been observed during SHG[61]. However, during bicycle exercise incremented to exhaustion, we observed a progressive flattening and rightward shift of the baroreflex slope as the workload increased[62], such that at the higher workloads baroreflex buffering of AP changes by means of fast changes in HR was drastically reduced. These findings, together with those previously reported for static exercise, indicate that the size of the active muscle mass and the intensity of muscular activity exert important modulatory effects on the baroreflex control of HR. Earlier studies by the Oxford group[58,63] also reported reduced BRS during graded, steady-state bicycle exercise in response to bolus injection of vasoactive drugs. However, in contrast with the above studies, many papers have suggested a resetting of the baroreflex without a change in sensitivity during constant load dynamic exercise from 25 up to 75% of peak oxygen consumption[64-68].

The reasons for these discrepant findings and conclusions have been attributed mainly to differences in the method of analysis of the chronotropic response, that is, the use of the R-R interval vs HR, and/or to differences among methods of baroreflex activation.

Because the R-R interval is inversely related to HR, for any change in HR, the corresponding change in the R-R interval decreases as the initial HR increases as during exercise, and thus it has been argued that BRS could appear reduced at a time when the HR response (in terms of b/min) would be unchanged. On the other hand, the use of the R-R interval rather than HR would seem more appropriate for studying the reflex neural control of the sinus node, because the relationship between the frequency of stimulation of vagal efferent nerves and R-R interval responses is linear, whereas that between HR and vagal stimulation is hyperbolic[69]. It is also noteworthy that the R-R interval may be a better index of neurotransmitter concentration at the sino-atrial node. This is important because neurotransmitters are considered as factors that influence the frequency of discharge of the pacemaker cells by decreasing or increasing the time necessary for the membrane potential to reach the firing threshold during diastole[70]. Anyway, the attribution of the diversity in the conclusions on baroreflex control of the sinus node during exercise to the use of different methods of analysis may hold only in part. In fact, the spontaneous baroreflex method, which permits analysis of BRS either in terms of HR or of the R-R interval using the same primary data, has clearly shown that BRS decreases during SLE[37] and high intensity bicycle exercise[62], both in terms of HR and of the R-R interval.

This argumentation introduces the other issue of contention, that is the methods of baroreflex testing during exercise[70]. Studies employing the rapid neck suction/pressure method have been quite consistent in suggesting that the arterial baroreflex is reset during exercise[66-68], whereas studies employing the spontaneous baroreflex method and the phenylephrine bolus injection have suggested that BRS may even be reduced during some exercise conditions[37,46,58,62,63].

All the above techniques have inherent advantages and limitations. The spontaneous baroreflex method is based on the analysis of the continuous physiological linkage between beat-by-beat spontaneous fluctuations in systolic arterial pressure and the R-R or pulse interval[72]. The main advantage of this technique is that it permits dynamic assessment of the baroreceptor-cardiac vagal reflex responses, relying on a natural stimulus of physiological magnitude, that is, spontaneous AP increases and decreases, at the current, prevailing levels of blood pressure without having to induce any pharmacological or mechanical disturbance external to the cardiovascular system. In this context, it is of note that studies which employed a different, nevertheless dynamic and unobtrusive baroreflex testing methodology relying on the analysis of reciprocal fluctuations in AP and the R-R interval, also reported a decrease in BRS during bicycle exercise[73,74] but a maintained BRS during light intensity dynamic handgrip[75], thus acknowledging the variable and complex nature of autonomic adjustments to exercise and their strong dependence on the intensity of effort and the size of the active muscle mass. Apparently, just as for other techniques[58,73], the most important limitation of the spontaneous baroreflex method is its inadequacy for analyzing the full stimulus-response curve of the arterial baroreflex (i.e., threshold, saturation and linear operational range of the reflex). However, in all the studies performed so far [24,37,46,61,62,76], independent of whether BRS was reduced or not, there was no significant difference in the BRS response to hypertensive and hypotensive stimuli (i.e. increasing and decreasing blood pressure ramps). This makes it likely that the method, by its own nature of working at the current, prevailing levels of AP and HR, reflects the baroreflex modulation of the sinus node along the linear region of the baroreflex stimulus-response curve.

As to the rapid neck suction/pressure method, the main advantage of this technique is that it permits analysis of the full stimulus-response curve of the arterial baroreflex. On the other hand, it explores the carotid baroreceptor-cardiac reflex only, and the reflex responses to carotid baroreceptor stimulation could be partially counteracted by directionally opposite afferent information from aortic baroreceptors. BRS values obtained with this technique have consistently been reported to amount to ~50% of those obtained with all other available techniques. Another limitation of the neck chamber technique is the incomplete transmission of the chamber pressure to the carotid sinus[77]. Overestimation of pressure transmission and, thus, of carotid transmural pressure may lead to overestimation of the calculated baroreflex gain.

The interested reader is referred to specific reviews[78,79] for a more comprehensive discussion of these different baroreflex-testing methodologies which share the common characteristic of reflecting baroreceptor-cardiac responses which are mainly vagally mediated. Interestingly, new models that might add further insights into the baroreflex control of HR during exercise have been developed very recently[1,80]. These models take into account the effects of a number of factors normally engaged by exercise (e.g., changes in respiration and feed-forward mechanisms) that could influence the estimate of the baroreflex gain.

It has been argued that the variable controlled by the arterial baroreceptors is arterial pressure, and hence that the important point is whether exercise alters baroreflex control of AP[71]. However, HR is an important component of blood pressure rise and one that is controlled by the baroreflex, the other being the vasomotor tone; the two components may be differently influenced in case of stress such as during exercise[5,81]. On the other hand, inferences on baroreflex control of AP in humans have been drawn only by means of the rapid (~5 s) neck suction/pressure technique, making it likely that AP responses to baroreceptor stimulation are mainly due to changes in HR (i.e. cardiac output) and much less to changes in peripheral vascular resistance[5,59,71]. Hence, studying the cardiac component of the baroreflex can be regarded as a valid, although incomplete, means of evaluating baroreflex function during exercise.

Effects of central command and muscle reflexes on the baroreceptor reflex. Another issue of current interest closely linked to the previous one, is how the arterial baroreflex is modulated by central command and the reflex drive from muscles. Rowell et al.[5,82] suggested that neural input from central command acts on the central neuron pool receiving baroreceptor afferents to reset the arterial baroreflex from the onset of exercise. This hypothesis would be supported by the study of Di Carlo and Bishop[83] who reported a greater increase in HR and renal sympathetic nerve activity from the onset of dynamic exercise in rabbits in which nitroglycerin was infused to attenuate the rise in AP. Recent studies from this laboratory[24,61] suggest that in addition to central command, even the muscle metaboreflex would be an adequate stimulus for resetting of the arterial baroreflex. We observed that the rightward shift in the baroreflex function curve with unchanged slope occurring during SHG was maintained during post-exercise muscle ischemia, when the pulse interval returned to control values whereas the AP was kept elevated by the muscle metaboreflex. This finding has been interpreted as an indication that, with progression of exercise necessary for accumulation of metabolites in the active muscles, the muscle metaboreflex could have played a role analogous to that of

central command. Similarly, Papelier et al.[68] also reported an unchanged linear slope for the relationship between carotid transmural pressure and HR (but not for AP) during both dynamic exercise and post-exercise muscle ischemia. The hypothesis that neural input from the muscle metaboreflex could shift the arterial baroreflex to a higher operating pressure derives from observations made not only after exercise with maintained stimulation of muscle chemosensitive receptors, but also from experiments with muscle metaboreflex activation during exercise. Iellamo et al.[24] have compared the effect of mild intensity, voluntary dynamic knee exercise under free- and arrested-flow conditions on the integrated baroreflex modulation of HR to that observed following intensity-matched electrically induced exercise. Voluntary exercise, during which both central command and mechanoreceptor stimulation were surely operative, did not alter BRS but resulted in an apparent rightward shift towards the prevailing pressures in the regression line relating systolic arterial pressure to pulse interval. During electrically induced exercise under arrested-flow conditions, during which both mechano- and chemosensitive receptors were activated (as indicated by the greater AP and HR responses) in the absence of central command, arterial baroreflex behavior paralleled that observed during voluntary exercise. On the contrary, electrically induced exercise under free-flow conditions, a situation in which mechanoreceptors should be stimulated mainly at the intensity at which the exercise was performed, resulted in a significant decrease in BRS. On this basis, it was suggested that in humans the central command and reflex drive from the contracting muscle differently modulate the baroreflex control of the sinus node, and that both the central command and the muscle metaboreflex are capable of shifting, i.e. resetting, the arterial baroreflex to a higher operating pressure, overwhelming the influence possibly exerted by mechanoreceptor stimulation.

Once again, subsequent studies have indicated that this interpretation cannot be generalized but it should be regarded as contingent to the intensity of exercise and the size of active muscles. This concept is exemplified by the results observed during static contractions by different muscle masses and at varying intensities and during whole-body dynamic exercise. Whereas both SHG at 30% of the MVC and SLE at 15% of the MVC resulted in unchanged BRS with a rightward shift of the baroreflex stimulus-response curve that was maintained during post-exercise muscle ischemia, SLE at 30% of the MVC resulted in a significant decrease in BRS, that was restored during post-exercise muscle ischemia, at the time when central command was absent and the muscle metaboreflex was still active. These findings prompted us to suggest that central command may act on the central neuron pool that integrates the baroreflex also by decreasing the gain of the integrated baroreceptor-cardiac reflex. This depends on the conditions of higher contraction intensity and larger size of active muscle masses that entail greater increases in HR and cardiac output and, in turn, in AP. In addition to central command, activation of positive feedback reflex mechanisms, which have been shown to interact dynamically with the negative feedback baroreflex mechanisms in the neural regulation of the cardiovascular system, could also contribute to the observed decrease in BRS[84-87].

As to the role played by muscle mechanoreflexes in modulating the arterial baroreflex, relatively little is known. The few animal studies performed so far have provided conflicting results. Potts and Mitchell[88] reported in anesthetized dogs that stimulation of mechanically sensitive muscle receptors resets the carotid baroreflex. On the contrary, McWilliam et al.[89,90] found in decerebrate cats that electrical stimulation of group III and IV afferent fibers and electrically induced hind limb contractions attenuated the prolongation of the R-R interval in response to carotid sinus pressure elevations just after the onset of contractions. Our observations in humans[24] of decreased BRS during electrically induced exercise under free-flow conditions would be consistent with the latter reports. Clearly, any implication of muscle mechanoreflexes in the modulation of the arterial baroreflex would regard mainly dynamic exercise, during which they may be activated with each contraction. On the other hand, during static exercise they would be active only transiently, at the onset of contraction. The question of whether muscle mechanoreceptor stimulation might contribute to the decrease in BRS reported during heavy dynamic exercise in some human studies described above, remains speculative.

In summary, the baroreflex control of HR seems far from being invariant during exercise, but would be differently influenced by a number of factors related to the muscular activity being performed, with the ultimate aim of achieving the most adequate cardiovascular regulation for the best performance in any particular exercise condition.

Clinical implications

Investigating the neural mechanisms that regulate the cardiovascular responses to exercise has a clinical relevance that goes beyond pure physiology. Specifically, cardiovascular disorders that impair perfusion of the exercising muscles may alter the metaboreflex mechanism.

The most immediate example is represented by patients with unilateral intermittent claudication. When these patients performed rhythmic exercise using the poorly perfused leg, the increase in AP was greater than when exercise was performed with the normally perfused leg before the onset of ischemic pain[91]. More recently, considerable evidence indicated that in patients with chronic heart failure the muscle metaboreflex mechanism is altered, possibly playing a role in the pathophysiology and clinical manifestations of this complex patho-

logical condition[92]. This would be a consequence not only of a reduction in blood flow, but also of altered skeletal muscle morphology and metabolism, even unrelated to blood flow reduction[93]. However, the way (e.g. enhancement vs attenuation) and extent to which heart failure alters the muscle metaboreflex are still to be defined[94-98], and further investigations in this area are clearly warranted.

Another area of great clinical relevance pertaining to exercise and cardiovascular neural regulation is represented by physical training. Physical training has been shown to produce beneficial effects in many cardiovascular disorders and to improve the prognosis after myocardial infarction. It is now recommended as a major component of cardiovascular therapy[99]. Part of these beneficial effects could be ascribed to adaptive changes in neural cardiovascular regulation. Endurance physical training has been shown to reduce sympathetic and concomitantly to enhance vagal modulation of HR, as reflected by a decrease in the LF and an increase in the HF spectral components respectively of HR variability[38,39] in hypertensive patients[74]. This was accompanied by an increase in BRS that is typically depressed in these patients, thus confirming the enhanced vagal contribution to HR regulation induced by physical activity. Similarly, a shift from sympathetic towards enhanced vagal activity after training (e.g. increase in HF and decrease in LF components of HR variability with reduced whole-body norepinephrine spillover) has also been reported in patients with chronic heart failure[100], implying an improvement in the autonomic control of the circulation known to be altered in chronic heart failure syndrome. Finally, physical training positively influences cardiac autonomic function in patients with coronary artery disease. In such patients, interventions that could enhance vagal modulation of HR while concomitantly reducing sympathetic activity are of paramount importance in conferring protection against arrhythmias during myocardial ischemia or infarction[101,102]. In addition, a recent large prospective study has indicated that a depressed BRS and a reduced HR variability (expressed as the standard deviation of the R-R intervals - SDRR, and interpreted as a measure of the tonic vagal control of the heart) have an independent prognostic value for cardiac mortality and cardiac events after myocardial infarction[103]. Physical training has been shown to improve these indirect markers of cardiac autonomic activity. Malfatto et al.[104] reported an increase in the SDRR which was associated with an increase in the HF and a decrease in the LF components of HR variability. Similar results have been observed by Leitch et al.[105]. We have recently reported a marked increase in BRS after physical training in a relatively large population of patients with coronary artery disease with and without a previous myocardial infarction[106]. Overall, the above findings clearly indicate that physical training is capable of influencing cardiac autonomic modulation in a direction that is associated with cardioprotective effects. However, the exact mechanisms through which this occurs are still to be defined. They may involve adaptations in the peripheral and central neural pathways, although modifications in the responsiveness of the heart might also contribute[107].

Conclusions

The objective of this review was to give an overview on the current knowledge on the neural mechanisms of cardiovascular regulation during exercise. Throughout this article, particular emphasis has been given to the modulatory effects exerted by muscular factors, i.e. the type and intensity of exercise and the size of the active muscle masses, on the contribution afforded by the different control mechanisms to the cardiovascular responses to exercise. The existence of some redundancy of the control mechanisms has also been outlined, stressing the plasticity of the neural network.

However, even though our knowledge on the neural control of the circulation during exercise has greatly increased, the neural control of the circulation is very complex, being influenced by reflex afferent inputs, even of opposite signs[84-87], from many receptor areas and by central integration of multiple afferent signals[108]. Much is still unknown as to the way the different mechanisms are integrated in producing the net cardiovascular responses and the way and extent to which these mechanisms are altered by cardiovascular diseases and exercise therapy.

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