Review article

Neural mechanisms of cardiovascular regulation during exercise

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Abstract

This brief review addresses current hypotheses concerning the reflex control of circulation during exercise in humans. In particular, the specific objective of this review is to describe how time and frequency domain analysis of blood pressure and heart rate variability signals permitted to gain new insights onto reflex mechanisms of cardiovascular regulation during exercise, without the need of perturbing the cardiovascular system from the outside, utilizing fully noninvasive approaches and avoiding artificially isolating the influence of the different neural pathways involved in the control of the cardiovascular system.

Throughout the article, particular emphasis is given to the complexity and plasticity of the neural control of the circulation during exercise, by presenting data that show how the reflex mechanisms involved in cardiovascular regulation, namely, the arterial baroreflex and the muscle metaboreflex, may be differently modulated in relation to the muscular activity being performed, such as the type of exercise, the intensity of exercise and the size of active muscle masses. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

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.

Three mechanisms have been described as playing a role in cardiovascular neural regulation during exercise. In the first mechanism, activation of regions of the brain responsible for the recruitment of skeletal muscle motor units concomitantly activates neuronal circuits within the medulla, establishing changes in parasympathetic and sympathetic efferent activity that determine the cardiovascular responses during skeletal muscle contraction. This mechanism has been termed "Central Command" (Goodwin et al., 1972). In the second mechanism, neural signals arising from stimulation of chemosensitive receptors in the contracting muscles would activate reflexly the cardiovascular control areas in the medulla, and this has been called the "exercise pressor reflex" or the "muscle metaboreflex" (Mitchell, 1985; O'Leary, 1993). The third mechanism involves the arterial baroreceptor reflex (Rowell, 1993).

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 and that there is some redundancy of the control systems (Mitchell, 1990).

This brief review addresses current hypotheses concerning the reflex control of circulation during exercise in humans. In particular, the specific objective of this review is to describe how time and frequency domain analysis of blood pressure and heart rate variability signals permitted to gain new insights onto reflex mechanisms of cardiovascular regulation during exercise, without the need of perturbing the cardiovascular system from the outside and utilizing fully noninvasive approaches. For more detailed discussion of cardiovascular control during exercise, the reader is referred to other more complete and extensive reviews (Mitchell and Schmidt, 1983; Rowell et al., 1996).

2. Muscle metaboreflex

Group III and IV myelinated and unmyelinated somatic fibers constitute the afferent arm of this reflex (McCloskey and Mitchell, 1972; Kaufman et al., 1988). When blood flow and oxygen delivery to contracting muscles is insufficient for the rate of metabolism, chemical products of muscle metabolism accumulate within the muscle and

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stimulate group III and IV afferents. Activation of these afferents elicits the reflex increase in sympathetic nerve activity and blood pressure, termed exercise pressor reflex or muscle metaboreflex.

One basic approach taken to demonstrate the contribution of the muscle metaboreflex during exercise has been that of studying AP, HR and (muscle) sympathetic nerve activity (MSNA) during postexercise muscle ischemia. 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 postexercise recovery period until release 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 as produced by the muscle metaboreflex.

Static exercise followed by postexercise muscle ischemia has provided the most expedient model to investigate the role of the muscle metaboreflex, inasmuch as during this type of muscular activity, the blood flow is hampered during the whole period of contraction and the release of metabolites within the contracting muscles is more readily observed (Asmussen, 1981; Rowell, 1993).

Static exercise induces increases in AP, HR and MSNA (Mitchell et al., 1980; Mark et al., 1985; Seals, 1988; Wallin et al., 1989), the magnitude of which is related to the relative intensity of contraction. Various combinations of central cortical influences and reflexes from stimulation of chemosensitive muscle afferents have been considered responsible on one hand for the increases in AP, and on the other hand for the increase in HR.

Until recently, the current view was that during static 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 (Rowell and O'Leary, 1990). This general view came mainly from the observation that during postexercise muscle ischemia (only metaboreflex active and no central command), the increases in AP, vascular resistance and MSNA to resting muscles are kept elevated above rest, whereas HR fully recovers (Mark et al., 1985; Wallin et al., 1989; Iellamo et al., 1994). However, experiments performed in the conscious dog by O'Leary (1993) provided evidence that sympathetic activation originating from the muscle metaboreflex contributes substantially to HR raise 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 postexercise muscle ischemia. The hypothesis advanced by O'Leary was that the fall in HR during postexercise muscle ischemia despite a maintained increase in sympathetic outflow was caused by a sudden rise of parasympathetic

activity at the cessation of exercise, due to the loss of central command or to arterial baroreflex mechanisms, that overpowered the sympathetic activation.

We have recently addressed the issue of the muscle metaboreflex contribution to HR regulation in humans by assessing power spectral analysis of HR variability during static leg exercise (Iellamo et al., 1999a). In the power-spectrum analysis of short-term fluctuations of R–R interval, two main components can be identified, in low (LF, ~0.1 Hz) and high (HF, ~0.25 Hz) frequency bands, which are predominantly linked to a relative increase in sympathetic and parasympathetic activity, respectively (Pomeranz et al., 1985; Pagani et al., 1986, 1997; Cooley et al., 1998; Malliani, 2000). By applying this methodology, we observed, as others did (Taylor et al., 1995), a decrease in the HF component of the R–R interval spectra during exercise, that would reflect the well-known decrease in parasympathetic outflow to sinus node occurring during exercise. Concomitant with the decrease in the HF oscillations, there was an increase in the R–R interval LF oscillatory power that, by reflecting an enhanced sympathetic modulation to the sinoatrial node, would indicate a significant contribution of this autonomic division to HR regulation during static exercise. During postexercise muscle ischemia, R–R interval returned to control, whereas AP remained significantly elevated above rest. However, while HF power also returned to rest, LF power still remained significantly elevated until the release of circulatory occlusion (Fig. 1), after which it returned to control, indicating the muscle metaboreflex as the effective stimulus in maintaining elevated the LF power during postexercise muscle ischemia. Overall, these data strongly suggest that the muscle metaboreflex contributes to HR regulation during static exercise via a sympathetic excitation that is maintained during postexercise muscle ischemia, similar to what occurs for the peripheral vasculature, despite the 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 postexercise muscle ischemia (Fig. 2). The restoration to the level at rest of BRS 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 the 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 (Levy, 1971; Stramba-Basiale et al., 1991). Clearly, also the loss of central command at the cessation of exercise, with the attendant increase in parasympathetic activity, may contribute to HR recovery. However, the observation of an HR recovery with a maintained pressor response during muscle ischemia following electrically induced contractions (Bull et al., 1989) supports the concept that removal of central command on cessation of exercise is not invari-
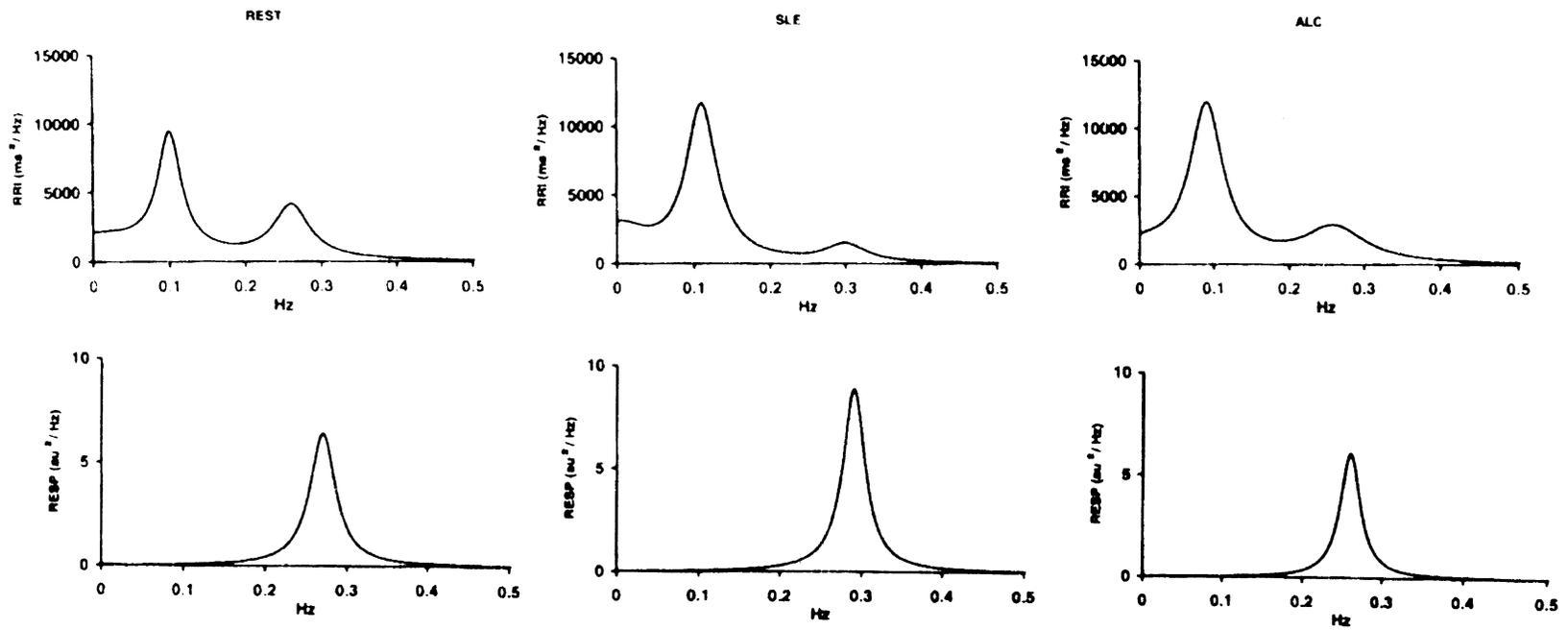
Fig. 1. Example of spectral analysis of R–R interval (RRI) and respiratory (RESP) variabilities during rest, static leg extension (SLE) and postexercise arrested leg circulation (ALC). au indicates arbitrary units (from Iellamo et al., 1999a).
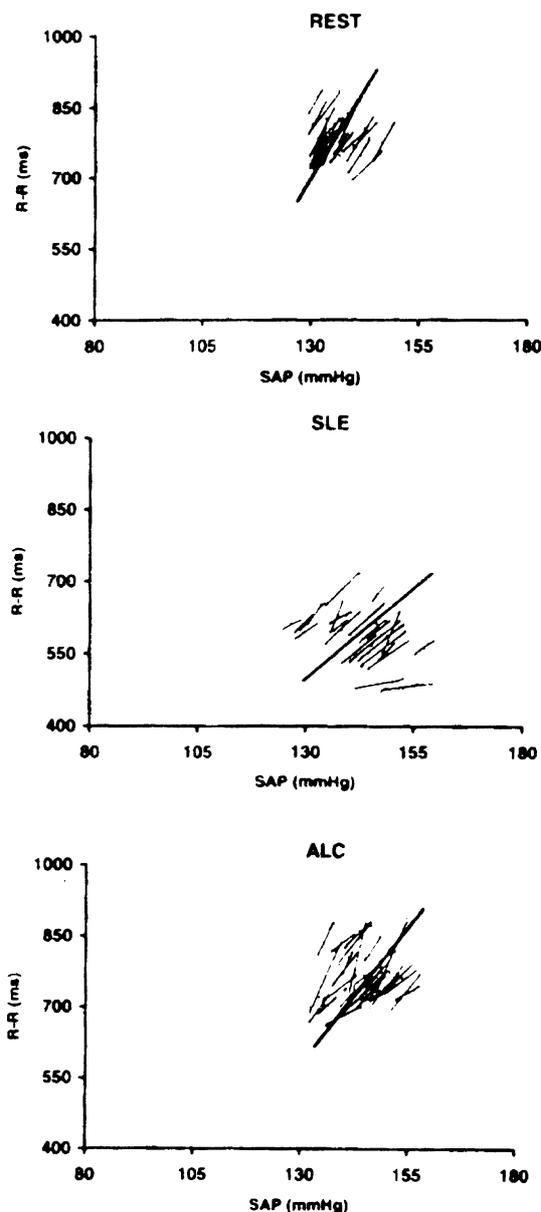
Fig. 2. Example of spontaneous baroreflex during rest (top panel), static leg extension (middle panel) and postexercise arrested leg circulation (bottom panel). Thin lines, regression lines for each sequence; thick lines, their mean slopes (from Iellamo et al., 1999a).

even be able to raise muscle blood flow by increasing cardiac output in addition to increasing blood pressure by vasoconstriction; that is, it would not only be a flow-sensitive, pressure-raising reflex but also a flow-sensitive, flow-raising reflex. Indeed, recent studies in conscious running dogs have indicated that the muscle metaboreflex may increase ventricular performance and cardiac output (Sheriff et al., 1998; O'Leary and Augustyniak, 1998).

3. 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 is an important component in blood pressure rise. This phenomenon has raised the question on how arterial baroreflex is altered by exercise to allow this deviation from normal baroreflex physiology to occur. However, whether and how arterial baroreflex is altered is a controversial issue in human exercise physiology.

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 baroreceptors level, would be reduced during exercise. This reduction in baroreflex 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. In the other hypothesis, the baroreflex would be "reset" to operate at the higher BP of exercise, without a change in sensitivity. In this scheme, once the baroreflex had been reset, the central nervous system perceives hypotension relative to the higher operating pressure, and acts to increase HR and cardiac output and, in turn AP, initially through a vagal withdrawal and thereafter through a sympathetic vasoconstriction. The concept of "resetting" would imply that it is the baroreflex that becomes the stimulus to increase AP and HR, maintaining the capability to oppose any extreme raise in AP (Rowell and O'Leary, 1990; Rowell, 1993).

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 a reduced BRS during exercise, at least as many provided direct or indirect evidence of a resetting of the integrated baroreflex function curve with no attenuation in BRS.

In the recent years, the issue of arterial baroreflex modulation of sinus node during exercise has been systematically addressed in our laboratory by utilizing a technique that is based on the analysis of the continuous physiological linkage between beat-by-beat spontaneous

ably the cause of HR recovery during postexercise muscle ischemia.

Overall, 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 postexercise muscle ischemia, stressing the plasticity of the neural network.

The contribution of the muscle metaboreflex to HR regulation during exercise has important physiological implications. It might convey the idea that this reflex may

fluctuations in systolic arterial pressure (SAP) and R–R interval (Bertinieri et al., 1988; Parati et al., 1988), and that has been called "the spontaneous baroreflex method" (Iellamo et al., 1994). With this method, the beat-by-beat time series of systolic arterial pressure and R–R interval are scanned by a computer to identify sequences of three or more spontaneous consecutive beats in which SAP and R–R (or pulse) interval change in the same direction (either increasing or decreasing). A linear regression is applied to each individual sequence and the mean slope of the SAP/R–R interval relationship, obtained by averaging all slopes computed within a given test period, is calculated and taken as a measure of the BRS for that period. This method provides an index of BRS around the current, prevailing level of AP and HR and furnished reproducible results during many laboratory tests, including muscular exercise (Iellamo et al., 1996). It can be employed in a fully noninvasive way, by recording beat-by-beat arterial blood pressure with the widely used plethysmographic method of the unloaded arterial wall (Finapres device).

By applying this methodology, Iellamo et al. (1994) observed that moderate intensity static contraction of small muscle groups, such as handgrip performed at 30% of maximal voluntary contraction (MVC), caused a rightward shift in the regression line relating SAP to pulse interval (PI) along the pressure axis, with an unchanged slope indicating an unaltered BRS (Fig. 3). Notably, a rightward shift of the baroreflex stimulus–response relationship during handgrip has also been reported by Ebert (1986) and Spaak et al. (1998), employing the rapid neck suction/pressure technique. These findings have been interpreted as an evidence for a resetting of the baroreflex function curve to a new higher operating point. On the contrary, earlier studies employing either single, rather than graded, intensity carotid baroreceptors stimulation (Ludbrook et

al., 1978; Mancia et al., 1978; Eckberg and Wallin, 1987) or the vasoactive drugs technique (Cunningham et al., 1972) reported a decreased BRS during static handgrip.

However, the issue of baroreflex control of HR, as other aspects of the 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. All these factors can differently affect the peripheral and central hemodynamics and, in turn, the contribution afforded by the neural mechanisms involved in cardiovascular regulation.

Indeed, comparison of cardiorespiratory responses to static leg extension (SLE) and static handgrip (SHG) (i.e. different muscle masses), both performed at 30% of MVC (Iellamo et al., 1999b), 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 AP response being maintained during postexercise muscle ischemia. Concomitant with these responses, it was found that SLE resulted in a decrease in the gain of the integrated baroreflex control of sinus node, whereas SHG left BRS unaffected, confirming the results obtained in separate studies (Iellamo et al., 1994, 1999a). As previously recalled, this decrease in BRS would imply a lessened baroreflex opposition to exertional tachycardia and led us to hypothesize that the decrease in BRS observed during SLE could have been involved, in part, in the greater HR response to the large vs. small mass static exercise, thus contributing, in addition to a greater engagement of muscle metaboreflex, to the augmented pressor response. The significant relationship we observed between the magnitude of PI response and the magnitude of BRS decrease would support (although it does not definitely prove) this suggestion. Interestingly, in the same study, SLE performed at 15% of MVC showing cardiovascular and baroreflex responses superimposable to those obtained during SHG. Thus, the baroreflex control of sinus node appears to be affected by the combined effects of both the muscle mass and contraction intensity. Here again, it could be argued that the above findings could be pertinent to static exercise only and could not be generalized to dynamic exercise, since the regulatory mechanisms attending dynamic exercise may be different from those associated with static exercise (see Asmussen, 1981; Rowell, 1993). Control may also differ between small and large masses, e.g. whole body, dynamic exercise during which hemodynamics and humoral mechanisms are rather different.

According to this concept, we observed that the integrated spontaneous baroreflex modulation of HR is differently affected by dynamic exercise of different intensity and size of active muscle mass. However, some similarities with static exercise also exist. We (Iellamo et al., 1997) reported that mild intensity, dynamic one-legged knee extension, did not alter BRS, but resulted in an
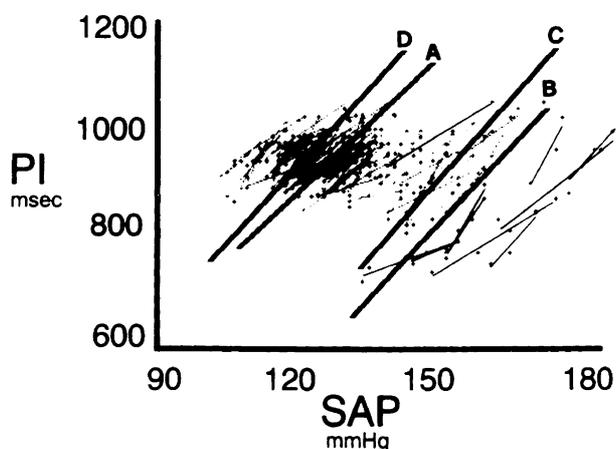

Fig. 3. Example of spontaneous baroreflex during static handgrip at 30% MVC. Heavy lines indicated by letters A, B, C and D represent mean slope at rest and during handgrip, post-exercise muscle ischemia and recovery, respectively (from Iellamo et al., 1994, with permission from the American Physiological Society).

apparent rightward shift in the regression line relating SAP to PI, a finding suggestive of baroreflex "resetting", similar to what we had observed during static handgrip. However, during incremental bicycle exercise to exhaustion, we observed a progressive flattening and rightward shift of the spontaneous baroreflex slope as the workload increased (Iellamo et al., 1998). These findings together with those previously reported for static exercise are consistent in indicating that the size of active muscle mass and the intensity of muscular activity exert important modulatory effects on baroreflex control of HR.

Earlier studies by the Oxford group (Bristow et al., 1971a,b; Cunningham et al., 1972; Pickering et al., 1972) also reported a reduced BRS during graded, steady-state bicycle exercise in response to bolus injection of vasoactive drugs. However, in contrast with the above studies, many recent 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 V_{O_2} (Bevergard and Shepherd, 1966; Robinson et al., 1966; Potts et al., 1993; Papelier et al., 1994, 1997).

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

Because R–R interval is the inverse of HR, for any change in HR, the corresponding change in R–R interval becomes less as the initial HR becomes higher, as during exercise, and thus it has been argued that BRS could appear reduced at a time when HR response (in terms of beats/min) would be unchanged. On the other hand, the use of 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 the relationship between heart rate and vagal stimulation is hyperbolic (Parker et al., 1984). As pointed out by Bristow et al. (1971a,b), valid comparison across acute experimental conditions may be made between the slopes of straight lines but comparison of the slopes of hyperbolas could be less valid. Also of note, R–R interval may be a better index of neurotransmitter concentration at the sinoatrial node, and this is important because the neurotransmitters are considered as affecting the frequency of discharge of the pacemaker cells by shortening or lengthening the time taken by the membrane potential to reach the firing level during diastole (Bristow et al., 1971a,b). Anyway, the use of different methods of analysis as explanation for the different conclusions on baroreflex control of sinus node during exercise may hold only in part. In fact, the spontaneous baroreflex method, which permits to analyze BRS either in terms of HR or R–R interval directly on the same primary data, has clearly shown that BRS undergoes a reduction during static leg extension (Iellamo et al., 1999a,b) and high

intensity bicycle exercise (Iellamo et al., 1998), both in terms of HR and R–R interval.

This argumentation introduces the other issue of contention, that is, the methods of baroreflex testing during exercise (O'Leary, 1996). Most of the studies so far performed in humans have employed the rapid neck suction/pressure method, the bolus injections of vasoactive drugs and the spontaneous baroreflex method. Studies employing the rapid neck suction/pressure method have been quite consistent in suggesting that the arterial baroreflex is reset during exercise (Potts et al., 1993; Papelier et al., 1994, 1997), whereas studies employing the spontaneous baroreflex method have suggested that BRS may be even reduced during some exercise conditions (Iellamo et al., 1998, 1999a). All the above techniques have inherent advantages and limitations, and the reader is referred to the original papers or specific reviews (Sleight, 1992; Parati et al., 2000) for a comprehensive discussion of the different baroreflex testing methodologies. What is important to outline here, is that all these techniques share the common characteristic of reflecting HR responses to rapid, transient changes in AP that are mainly vagally mediated, not enabling us to investigate the slower sympathetic component of the baroreflex (O'Leary, 1996), and that it has not been established which method should be considered the "gold standard" (Rudas et al., 1999).

Since this review is focused mainly on the spontaneous baroreflex method, some comment on this relatively new technique may be proper. The uniqueness of the spontaneous baroreflex method is that it permits to assess the baroreceptor-cardiac vagal reflex responses dynamically, relying on a natural stimulus of physiological magnitude, that is, spontaneous SAP increases and decreases, at the current, prevailing levels of blood pressure without having to induce any pharmacological or mechanical disturbance from outside the cardiovascular system. It makes it possible to appreciate that the baroreflex is operating in response to both activating and deactivating stimuli (i.e. increasing and decreasing blood pressure ramps) during exercise in a manner analogous to the resting state. Finally, it allows to take into account the wide intraindividual variability of the baroreflex gain (Parati et al., 1988; Iellamo et al., 1996) when calculating BRS, an aspect of particular relevance during short-lasting experimental investigations. The method has some inherent limitations. Apparently, the most important would be its inadequacy to analyze the full stimulus–response curve of the arterial baroreflex (i.e. threshold, saturation and linear operational range of the reflex), as it would be possible with the rapid neck suction/pressure method, that, on the other hand, explores the carotid baroreceptor-cardiac reflex only. If one assumes that the stimulus–response curve of the arterial baroreflex in humans has the same sigmoid shape observed in other species (Sagawa, 1983), then it could be contended that the decrease in BRS we reported during some exercise conditions might have resulted from a shift

to a nonlinear region of the baroreflex stimulus–response relationship. This possibility cannot be totally discounted. However, in this context, it is worth noting that in all the studies we performed under a variety of stimuli, it is to say different types of exercises (Iellamo et al., 1994, 1997, 1999a,b), mental arithmetic and active orthostatism (Iellamo et al., 1996), short-term and prolonged head down tilt (unpublished), which involve wide range of hemodynamic conditions and background neural activity, we always found no significant differences in BRS in response to activating and deactivating stimuli (i.e. $+RR/+SAP$ and $-RR/-SAP$ sequences), independent of whether BRS were reduced or not. This consistent finding makes it likely that our subjects were operating on the linear portion of their SAP to R–R interval relationship, and also suggests 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.

It has been argued that the variable sensed and controlled by the arterial baroreflex is arterial pressure, and hence the important point is whether exercise alters baroreflex control of AP (O'Leary, 1996). 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 affected during stresses such as exercise (Ferguson et al., 1985; Rowell, 1993). On the other hand, inferences on baroreflex control of AP in humans have been drawn only with the neck chamber technique. When neck suction/pressure is applied rapidly (~ 5 s), the blood pressure response could be primarily due to vagally mediated changes in HR (i.e. cardiac output) and much less to changes in peripheral vascular resistance, because the technique does not allow sufficient time for the full activation of the slower sympathetic component of the baroreflex, which may take 10–15 s or longer (Bath et al., 1981; Ebert, 1983, 1986; Rowell, 1993; O'Leary, 1996). In the intact circulation, more prolonged stimulation of carotid sinus baroreceptors carries the drawback to be associated with directionally opposite afferent information from aortic baroreceptors, which may affect the observed results (Mancia et al., 1977; Ferguson et al., 1985; Sleight, 1992). Hence, studying the cardiac component of the baroreflex can be regarded as a valid, although incomplete, means to evaluate baroreflex functioning during exercise.

4. Effects of central command and muscle reflexes on the baroreceptor reflex

Another issue of current interest is how the arterial baroreflex is modulated by the central command and the reflex drive from muscles. Rowell (1993) and Rowell et al. (1996) 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 (1992) 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 BP. Recent studies from our laboratory (Iellamo et al., 1994, 1997) suggest that in addition to the central command, the muscle metaboreflex would also be an adequate stimulus to reset the arterial baroreflex. We observed that the rightward shift in the baroreflex function curve with unchanged slope occurring during static handgrip was maintained during postexercise muscle ischemia (letter C in Fig. 3), when PI returned to control while AP was kept elevated by the muscle metaboreflex. This finding has been interpreted as indicating that the muscle metaboreflex could have played a role analogous to that of central command as the exercise progressed in time, owing to the time required for accumulation of metabolites in the active muscles. Similarly, Papelier et al. (1997) also reported an unchanged linear slope for the relationship between carotid transmural pressure and HR (but not for AP) both during dynamic exercise and postexercise muscle ischemia. The possibility that neural input from the muscle metaboreflex could shift the arterial baroreflex to higher operating pressure comes from observations made not only after exercise with maintained stimulation of muscle chemosensitive receptors, but also from experiments with muscle metaboreflex activation obtained during exercise. Iellamo et al. (1997) have recently compared the effect of mild intensity, voluntary dynamic knee exercise with intensity-matched electrically induced exercise under free-flow and arrested flow conditions on the integrated baroreflex modulation of HR. Voluntary exercise, during which both central command and mechanoreceptors stimulation were surely operative, did not alter BRS but resulted in an apparent rightward shift in the regression line relating SAP to PI toward the prevailing pressures (Fig. 4, middle panel). During electrically induced exercise under arrested-flow, during which both mechano- and chemosensitive receptors were activated (as indicated by the greater AP and HR responses), whereas central command was absent, arterial baroreflex behavior paralleled that observed during voluntary exercise (Fig. 4, bottom panel). On the contrary, electrically induced exercise under free-flow conditions, a situation in which mechanoreceptors mainly should be stimulated at the intensity at which the exercise was performed, resulted in a significant decrease in BRS (Fig. 4, top panel). On this basis, it was suggested that in humans, the central command and reflex drive from contracting muscle differently modulate the baroreflex control of the sinus node, and that both the central command and the muscle metaboreflex are able of shifting to higher operating pressure, i.e. resetting, the arterial baroreflex, overwhelming the influence possibly exerted by mechanoreceptor stimulation.

Once again, subsequent studies have indicated that this interpretation cannot be generalized but it should be re-
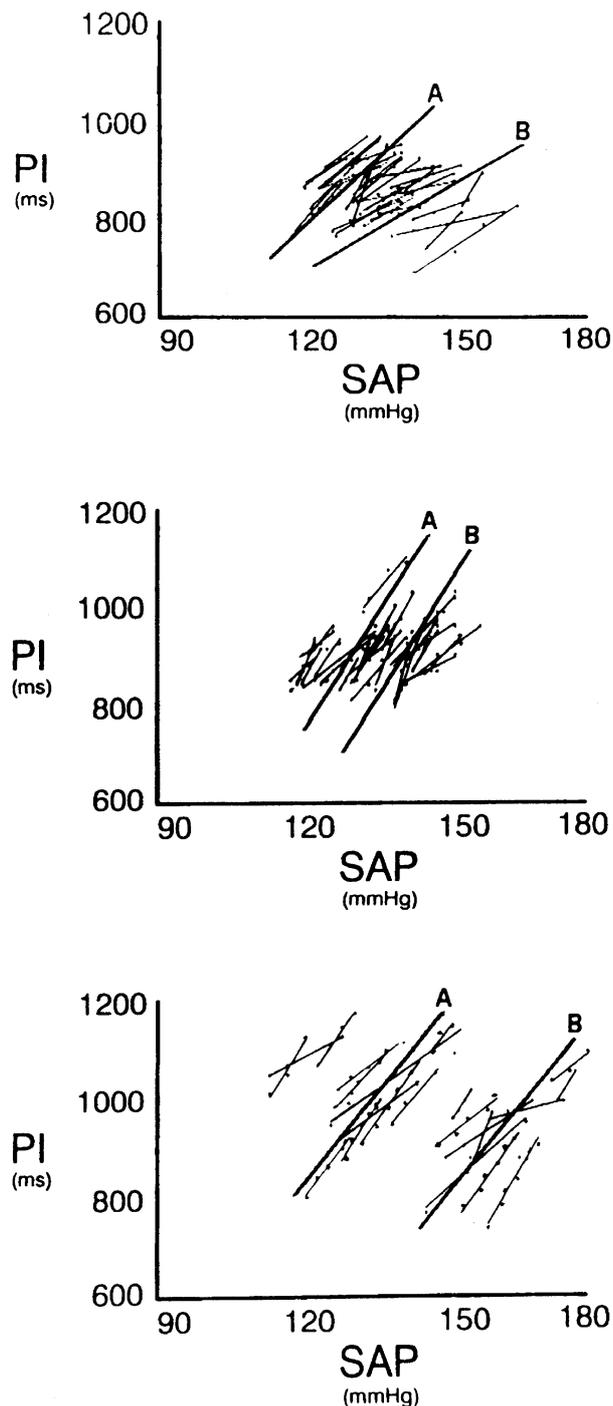
Fig. 4. Example of spontaneous baroreflex during voluntary and electrically induced dynamic knee extension. Heavy lines indicated by letters A and B represent mean slope at rest and during exercises, respectively. Top panel illustrates electrically induced exercise under free-flow conditions, middle panel illustrates voluntary exercise and bottom panel illustrates electrically induced exercise under arrested-flow conditions (from Iellamo et al., 1997, with permission from the American Physiological Society).

garded as contingent on the intensity of exercise and the size of active muscles. This concept is exemplified by our findings with static contractions of different muscle mass and intensities and whole body dynamic exercise. Whereas

both SHG and SLE at 15% MVC resulted in unchanged BRS with a rightward shift of the baroreflex stimulus–response curve that was maintained during postexercise muscle ischemia, SLE at 30% MVC resulted in a significant decrease in BRS that was restored during postexercise muscle ischemia, at the time when central command was absent, whereas 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, and this depends on the condition of higher contraction intensity and larger size of active muscle masses that involve greater increases in HR and cardiac output and, in turn, of AP.

As to the role played by muscle mechanoreflexes in modulating the arterial baroreflex, relatively little is known. The few animal studies have provided conflicting results. Potts and Mitchell (1998) reported in anesthetized dogs that stimulation of mechanically sensitive muscle receptors resets the carotid baroreflex. On the contrary, McWilliam and Yang (1991) and McWilliam et al. (1991) found in decerebrate cats that electrical stimulation of group III and IV afferent fibers and electrically induced hindlimb contractions attenuated the prolongation of R–R interval in response to carotid sinus pressure elevations just after the onset of contractions. Our observations in humans of a 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 (Pickar et al., 1994), whereas they would be only transiently active, at the onset of contraction, during static exercise. The question of whether muscle mechanoreceptors stimulation might contribute to the decrease in BRS reported during heavy dynamic exercise in some human studies described above remains speculative.

5. Conclusions

The objective of this review was to describe how time and frequency domain analysis of arterial pressure and heart rate variability signals could be a valuable tool to investigate the reflex mechanisms of cardiovascular regulation during exercise in a fully noninvasive way.

This experimental approach allowed a distinctive insight into the integrated reflex neural regulation of HR during exercise by having used nonperturbational techniques and by avoiding artificially isolating the influence of the different neural pathways. This could be of relevance particularly when multiple (redundant) control mechanisms are integrated in producing the net responses, as during exercise. Throughout the article, particular emphasis has been given to the plasticity of the neural control

of HR during exercise. Modulation of HR is rather complex, being affected by afferent inputs from many receptor areas and central integration of converging multiple afferent signals (Malliani, 2000). It would be amazing if such a complex control system would always work in the same manner, for example through a resetting or an inhibition of the arterial baroreflex, during every kind of muscular activity, despite the markedly different hemodynamic, humoral and metabolic conditions occurring during exercises differing in type, intensity, duration and size of active muscle masses.

I believe that the findings reported in this review support the above concept and represent barriers against rigid and univocal interpretations of the neural control of the circulation during exercise.

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