Cardiovascular Control During Exercise: Central and Reflex Neural Mechanisms

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Both reflex neural and central command mechanisms have been postulated to explain the cardiovascular responses that occur during exercise. The 2 mechanisms appear to affect the same neural circuits and to be capable of working either in conjunction with one another or independently.

(Am J Cardiol 1985;55:34D-41D)

The cardiovascular response during exercise is matched to the intensity of physical activity. During dynamic exercise, the intensity is directly related to the oxygen demand of the active skeletal muscle and is matched by the increase in cardiac output. During static exercise, the intensity is directly related to both the active skeletal muscle mass and the percentage of maximal voluntary contraction achieved, and is matched by the increase in arterial blood pressure (BP). In the response to both dynamic and static exercise, there is increased activity of the sympathetic nervous system and decreased activity of the parasympathetic nervous system.

The neural mechanisms responsible for the changes in autonomic efferent activity to the heart and blood vessels during exercise are not completely understood. In 1895, Johansson[1] suggested that 1 or 2 distinct mechanisms of neural control might exist. Since that time 2 general theories of neural control have evolved[2] and are shown in Figure 1. In one theory[3] the cardiovascular response to exercise is thought to be due to a direct action of the central command descending from the higher motor centers on the cardiovascular control areas. In the other theory[4] the response is thought to be due to a reflex elicited by afferent neural activity from receptors in the skeletal muscle or joints acting on these control areas. As will be shown, it is probable that both mechanisms are present and that either or both can bring about the cardiovascular changes that occur during muscular exercise.

The hypothesis that cardiovascular changes during exercise are due to a reflex originating in the contracting skeletal muscle was strongly supported by the experiments of Alam and Smirk.[5,6] Asmussen et al[7] and more recently Adams et al[8] found evidence of a reflex neural mechanism during dynamic exercise when they compared the cardiovascular responses to voluntary leg exercise with those produced by direct electrical stimulation of the leg muscles. Similar studies during static exercise have been reported by Hultman and Sjöholm[9] and their findings are shown in Figure 2. Subjects performed static quadriceps contractions voluntarily or the contractions were stimulated electrically. As shown in Figure 2, the heart rate (HR) and BP responses were exactly the same whether the static contractions were electrically elicited (no central command) or voluntarily produced. They concluded from this study that the response must be due to a reflex neural mechanism arising in the muscle and that central command was not necessary for the response.

Other studies,[10-13] however, have strongly suggested that a central neural mechanism can also be responsible for the cardiovascular changes that occur during exercise. Freund et al[14] have shown that the normal relation of cardiac output to oxygen consumption during dynamic exercise is not altered when the sensory input from working muscle has been blocked by spinal anesthesia. In addition, they showed that during static exercise the relation of the increase in arterial BP to the tension developed by the active muscle was not changed when the reflex neural mechanism was blocked.[14] The results of this study are shown in Figure 3. While the sensory input from working muscle remained blocked and motor strength progressively recovered after spinal

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anesthesia, there was an increase in mean arterial BP appropriate to the amount of force developed by the contracting muscle. This study demonstrated that an appropriate cardiovascular response to both dynamic and static exercise occurs when the reflex neural mechanism is blocked and only the central neural mechanism is operative.

In this article, the reflex neural mechanism and the central neural mechanism, either of which can be shown to elicit the cardiovascular response during exercise, will be examined.

Reflex Neural Mechanism

The most direct method to study the reflex neural mechanism that is activated during exercise (exercise pressor reflex) is to use an animal preparation in which the cut peripheral ends of the ventral roots are electrically stimulated to cause muscular contractions.[15,16] This preparation is shown in Figure 4. The ventral roots of L_7 and S_1 are placed over a pair of electrodes. Electrical stimulation of the spinal ventral roots is used to elicit contraction in the muscles of a hind limb. The corresponding dorsal roots, which carry the majority of the sensory input from the contracting muscle to the spinal cord, are left intact. Measurements are made of arterial BP, HR, left ventricular (LV) pressure and the rate of LV pressure development.[16]

The response to simulated static exercise in the study by Mitchell et al[16] is shown in Figure 5. Stimulation of the ventral roots to induce muscle contraction was given between the bars. During induced exercise there was an increase in arterial BP, HR, LV pressure and the maximal rate of LV pressure development. When stimulation of the ventral roots was stopped, all the factors returned to control values. Also, it was demonstrated that these responses were abolished when the corresponding dorsal roots (Fig. 4) were transected.[16] Thus, sensory endings in skeletal muscle whose fibers travel in the dorsal root serve as the afferent limb of this reflex.

Four groups of afferent nerve fibers from skeletal muscle have been identified. They enter the central

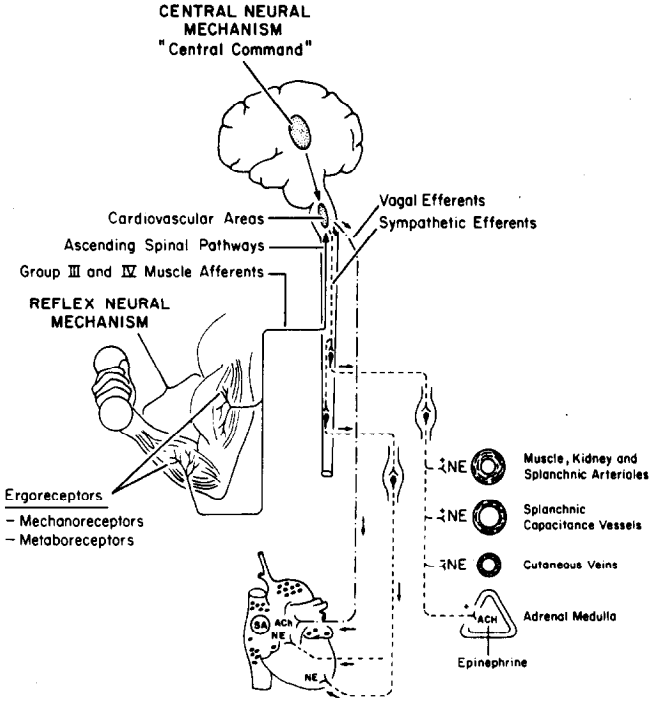

FIGURE 1. Cardiovascular control during exercise: central and reflex neural mechanisms. With onset of exercise, neural inputs are received by the cardiovascular areas from a neural mechanism that is related to central activity for recruitment of motor units ("central command") and from receptors in activated skeletal muscle. Receptors activated by exercise have been termed ergoreceptors. These receptors respond to metabolic and mechanical alterations and their afferent impulses are conducted by groups III and IV fibers to the spinal cord where they ascend to the cardiovascular areas. As a result of these 2 inputs to the cardiovascular areas, the parasympathetic activity to the heart decreases and the sympathetic activity to the heart, blood vessels and adrenal medulla increases. ACH = acetylcholine; NE = norepinephrine; SA = sinoatrial node. Adapted from Shepherd et al, reprinted with permission from Circ Res.[2]

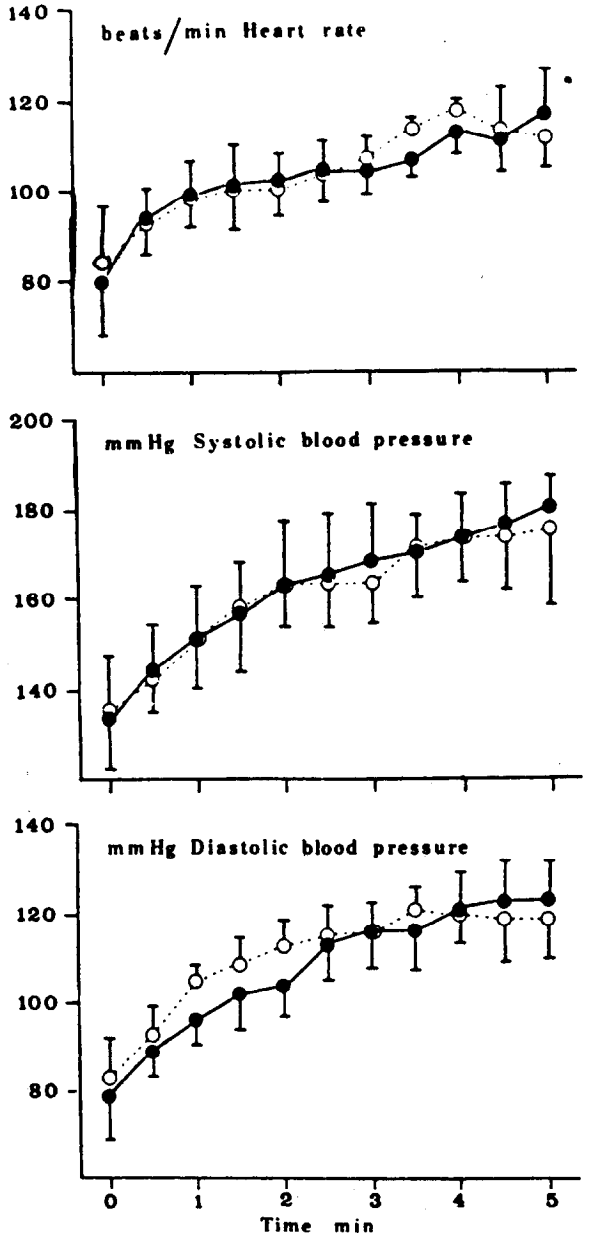

FIGURE 2. Heart rate and blood pressure response to static exercise. Voluntary contraction (●——●) and electrical-induced contractions (O·····O). Values are mean ± standard deviation (N = 6). Reprinted with permission from Acta Physiol Scanda.[9]

TABLE I Classification of Sensory (Afferent) Fibers from Skeletal Muscles

Type	Diameter (μm)	Velocity (meter/s)	Receptor
Ia	12–20, myelinated	71–120	Muscle spindle, primary ending
Ib	12–20, myelinated	71–120	Golgi tendon organ
II	4–12, myelinated	31–70	Muscle spindle, secondary ending Pacinian corpuscle
III	<4, myelinated	2.6–30	Paciniform corpuscle, free ending
IV	Unmyelinated	≤2.5	Free ending

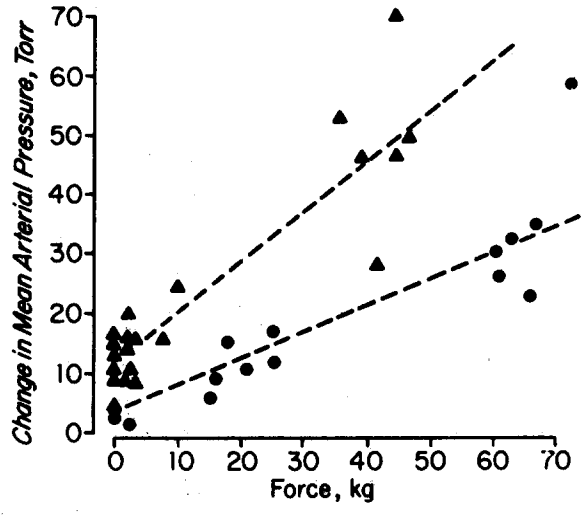

FIGURE 3. Effect of maximal static contractions of leg extensor muscles on changes in blood pressure during recovery of motor strength after peridural anesthesia in 2 subjects (▲ and ●). Reprinted with permission from Am J Physiol.[14]

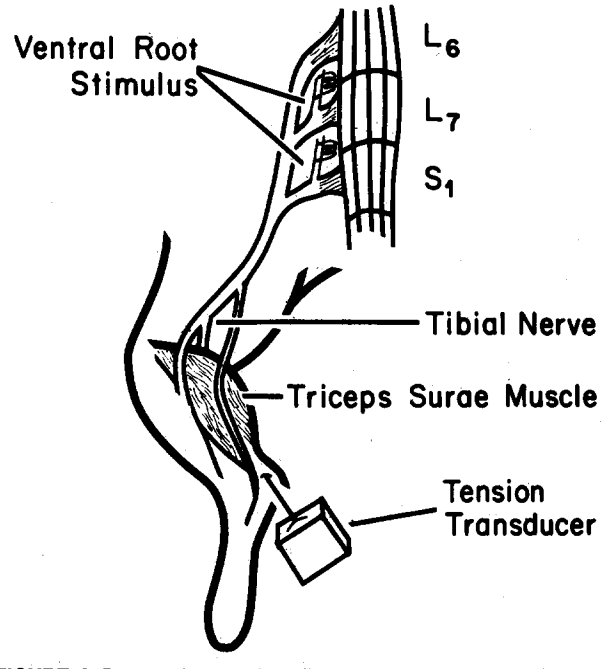

FIGURE 4. Preparation for providing static muscular contractions in a hind limb by ventral root stimulation. Cut peripheral ends of L_7 and S_1 were placed on electrodes. Corresponding dorsal roots were isolated for later sectioning. Force of contraction of the triceps surae muscle was measured with a tension transducer.

nervous system principally by the dorsal roots.[15,17] These afferent fibers have been classified by either their diameter or their conduction velocity, and this classification is shown in Table I. The anatomy and function of the receptors of groups I and II muscle afferent fibers have been extensively studied. The receptors of groups III and IV afferent fibers are Paciniform corpuscles and free nerve endings. The function of these receptors is not clearly understood. These receptors have been generally classified into 2 groups, ergoreceptors and nociceptors.[15,17] Ergoreceptors are defined as those activated by muscle contraction, and nociceptors as those activated by noxious stimuli and responsible for muscle pain.

Experimental studies have demonstrated that electrical or chemical activation of groups I and II fibers causes little or no cardiovascular response,[18–20] whereas electrical or chemical activation of groups III and IV fibers can cause a marked cardiovascular response.[18,19,21] It has been shown by differential blockade of the afferent fibers from skeletal muscle in the dorsal root that groups III and IV afferents are responsible for the cardiovascular effects seen during the exercise pressor reflex.[22] Thus, it seems clear that the fine muscle afferent fibers (groups III and IV) are responsible for the reflex neural mechanism activated during muscular contraction (exercise pressor reflex).

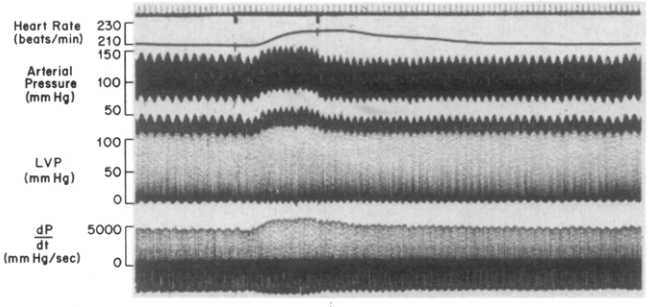

FIGURE 5. Response to static exercise induced by ventral root stimulation. LVP = left ventricular pressure; dP/dt = rate of left ventricular pressure development. Time marks = 1 second. Induced exercise is between bars. Adapted from Mitchell et al, reprinted with permission from Am J Physiol.[16]

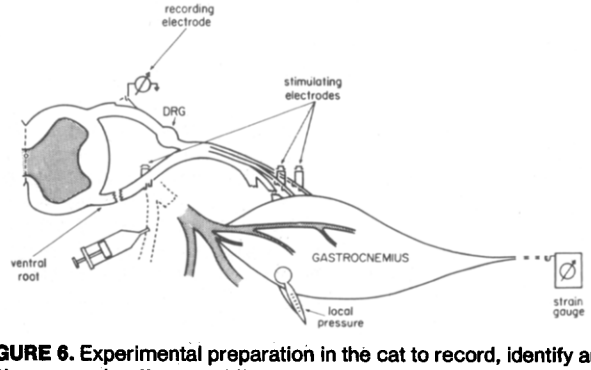

FIGURE 6. Experimental preparation in the cat to record, identify and activate muscle afferents. Afferent impulses recorded in dorsal roots. Gastrocnemius muscle contraction induced by electrically stimulating cut peripheral ends of ventral roots. DRG = dorsal root ganglia. Reprinted with permission from J Appl Physiol.[24]

The discharge properties of groups III and IV muscle afferent fibers, which are activated during muscular contraction (ergoreceptors), have been recorded from fine filaments dissected from the dorsal roots, while muscle contractions are induced by stimulation of the peripheral cut end of the ventral roots[23,24] (Fig. 6). In the study by Kaufman et al,[24] each fine muscle afferent was shown to have its receptive field in the gastrocnemius muscle, and its conduction velocity was determined. The latter was accomplished by electrically stimulating the lateral and medial gastrocnemius nerves and calculating the conduction velocity by dividing the conduction distance between the stimulating electrode and the recording electrode by the conduction time.

The effects of static contractions on the activity of fine afferents from muscle are shown in Figure 7.[24] In Figure 7,A, a group III fiber discharged vigorously at the onset of static contraction and then its discharge decreased. In Figure 7,B, another group III fiber also discharged vigorously at the beginning of contraction, adapted and then again increased its firing. In Figure 7,C, a group IV fiber began to fire after the onset of contraction and then gradually increased its firing rate throughout the contraction. Another group IV fiber in Figure 7,D also began to fire after the onset of contraction but then fired more irregularly. In this study by Kaufman et al[24] the discharge patterns of the majority of the group III fibers suggested that they were stimulated by the mechanical effects of the muscular contraction. Conversely, the discharge patterns of most of the group IV fibers suggested that they were stimulated by metabolic changes caused by the muscular contraction.

The cardiovascular response to static muscular contraction is greater when the arterial supply is occluded than under normal conditions of blood flow.[22] This would suggest that the activity of fine muscle afferents is increased during ischemic contractions compared with nonischemic contractions. Mense and Stahnke[23] and Kaufman et al[25] have studied the activity patterns of fine muscle afferents during an ischemic contraction compared with a normal contractions with the same developed tension. Kaufman et al[25] found a population of groups III and IV muscle afferents that were stimulated more by static contractions with ischemia than by normal contractions when the tension developed by both contractions was the same. This activity pattern was found predominantly in group IV fibers, an example of which is shown in Figure 8. During a normal contraction of about 45 seconds the afferent fired 43 impulses (Fig. 8,A) and during a contraction with ischemia of the same duration it fired 68 impulses, an increase of 58% (Fig. 8,B). In both of these studies[23,25] the tension developed by the contracting muscles was the same. Thus, there is a population of fine muscle afferents that are activated more by a static contraction during ischemia than during a control contraction and these afferent fibers may be responsible for the enhanced cardiovascular response.[25]

A recent study[26] was performed to determine the central pathways involved in the reflex neural mechanism that can elicit the cardiovascular response to exercise. Ciriello and Calaresu[27] showed that lesions in the lateral reticular nucleus (LRN) abolished the pressor response evoked by electrical stimulation of high threshold afferents in the sciatic nerve. It was, therefore, of interest to determine whether bilateral lesions in the LRN modified the cardiovascular response caused by static contractions of the muscles of the hind limb.

The effect of bilateral LRN lesions on the BP response in the study by Iwamoto et al[26] is shown in Figure 9. The muscle contraction caused by ventral root stimulation produced an increase in BP and HR shown in Figure 9,A; however, after bilateral LRN lesions the cardiovascular response to induced muscular contraction was abolished (Fig. 9,B). The extent of the lesions responsible for these findings is shown in Figure 9,C.

This study of the effects of bilateral LRN lesions on the reflex neural mechanism does not precisely describe its involvement in the response. Lesioning experiments do not provide conclusive evidence of the participation

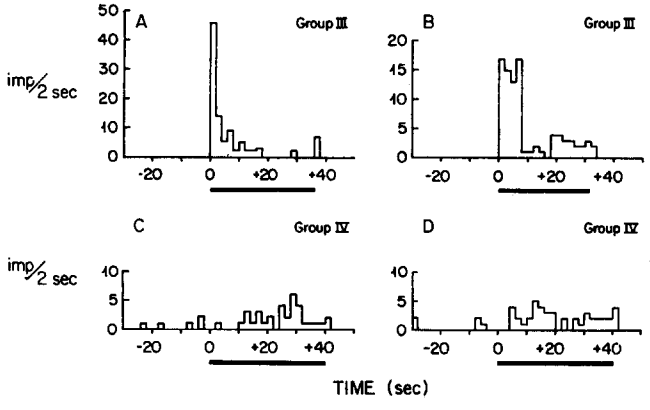

FIGURE 7. Discharge patterns in imp/2 seconds of thin fiber muscle afferents that respond to induced static contraction (**black bar**). **A** and **B** are group III fibers that behave more like mechanoreceptors; **C** and **D** are group IV fibers that behave more like metaboreceptors. (See text.) Reprinted with permission from J Appl Physiol.[24]

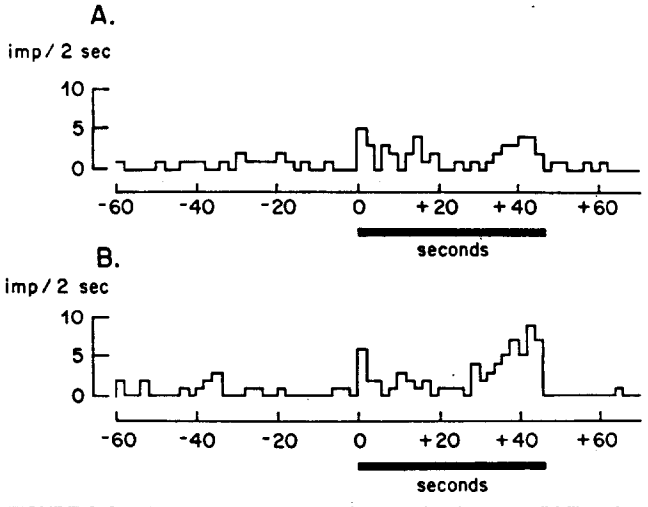

FIGURE 8. Discharge patterns in imp/2 seconds of a group IV fiber that was activated by induced static contraction (**black bar**) of the triceps surae muscle. **A,** response of the afferent to normal contraction. **B,** response of the afferent to ischemic contraction. Reprinted with permission from J Appl Physiol.[25]

of cell bodies in a reflex because fibers en passage may be involved. For this reason the autoradiographic tracing techniques of labeling metabolically active cells and terminals with 2-[carbon-14] deoxyglucose (2-DG) have been used to identify the caudal brainstem groups participating in the reflex neural control mechanism.[28] A schematic of this experiment is shown in Figure 10. In anesthetized cats static hind limb exercise was maintained by alternatively stimulating the appropriate ventral roots on each side for 45 minutes. At the start of the stimulation 100 μCi/kg of 2-DG was injected intravenously. Two other animals that were prepared identically but whose ventral roots were not stimulated served as controls. At the end of the experiments the brainstem was fixed and removed. Coronal sections were cut with a cryostat maintained at −20°C. Sections cut at 40 μM were collected on slides and stained with cresyl violet to reveal cell groups. Adjacent sections cut at 20 μM were collected on cover glass and placed against x-ray film for about 2 months.

The data from 1 control animal and 1 animal with induced static exercise in the study by Iwamoto et al[28] are shown in Figure 11. Enhanced uptake of 2-DG is seen in the inferior olive (medial accessory olive) and in the LRN of the animal in which static exercise was induced. These findings support the observation that bilateral LRN lesioning abolished the reflex neural mechanism that caused the cardiovascular response during induced static exercise. They suggest that activity in the cells of this nucleus, not simply fibers en passage, is the important factor eliminated by the LRN lesions. These findings are consistent with the hypothesis that the LRN is a key relay station in the reflex neural mechanism that is activated during induced static exercise.

Central Neural Mechanism

The central neural mechanism ("central command") has been studied both in man and more recently in conscious animals. When partial curarization was administered to human subjects to reduce the strength of their exercising muscle, the HR and BP responses during dynamic exercise were greater than during dynamic exercise without curarization, even though the workloads were the same for both conditions.[29,30] Thus, the cardiovascular response appeared to be related to the greater motor command needed to achieve a given level of dynamic work. Goodwin et al[11] studied the cardiovascular response to static exercise in man by activating primary muscle afferents either in the contracting muscle or in its antagonist to vary the central command required to achieve a given tension. When the same muscle tension was achieved with less central command during static exercise, the increase in BP and HR was less, and when the same tension was achieved with more central command, the cardiovascular response was greater. They concluded that cardiovascular control areas are activated by descending central command during voluntary static exercise in man.

Hobbs[31] has reported a larger increase in HR and BP during partial neuromuscular blockade than during control when the same absolute force was developed during voluntary static exercise in baboons. Recently, the effects of partial neuromuscular blockade on the BP and HR responses to static exercise in man have been studied.[32] Experiments were performed on healthy young men. Heart rate (electrocardiogram) and arterial BP (brachial arterial catheter) were measured while the subjects performed static muscle contractions with the knee extensor muscles as shown in Figure 12.[32] In ad-

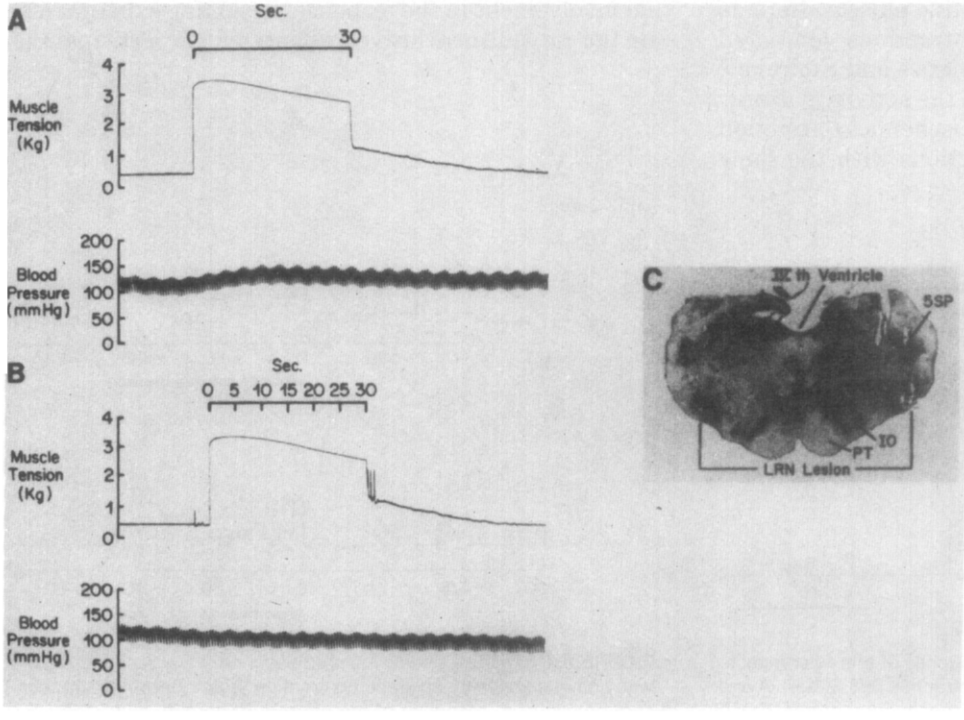

FIGURE 9. Effect of bilateral lesions of the lateral reticular nucleus (LRN) on blood pressure response to induced static muscular contraction in the cat. **A,** control study: static exercise induced by stimulation of the L_7 and S_1 ventral roots caused an increase in arterial blood pressure. **B,** after bilateral LRN lesioning. Induced static exercise caused no change in arterial blood pressure. **C,** stippled area reveals extension of the lesion that abolished blood pressure response to induced static exercise. 5SP = spinal tract of trigeminal; IO = inferior olive; PT = pyramidal tract. Reprinted with permission from Circ Res.[26]

dition, measurements were made of the rectified smooth electromyogram from surface electrodes placed over the vastus lateralis muscle and of the force generated by lower leg extension. Maximal voluntary contraction (MVC) of the knee extensors was obtained and then static contractions were performed at the same *absolute* force (10% of the original MVC) or with the same *relative* force (30% of the MVC performed immediately before exercise). The subjects were studied before and after neuromuscular blockade with either decamethonium or tubocurarine both of which were titrated to reduce MVC to 50% of the control value. The metabolic component of the reflex neural mechanism was evaluated by application of an arterial occlusive cuff for 30 seconds before end of exercise and for the following 3 min of recovery.

The effect of partial neuromuscular blockade with decamethonium on the response of mean arterial BP to a static contraction developing the same *absolute* force (10% of the control MVC) is shown in Figure 13.[32] During exercise the mean arterial BP response was larger during neuromuscular blockade with decame-

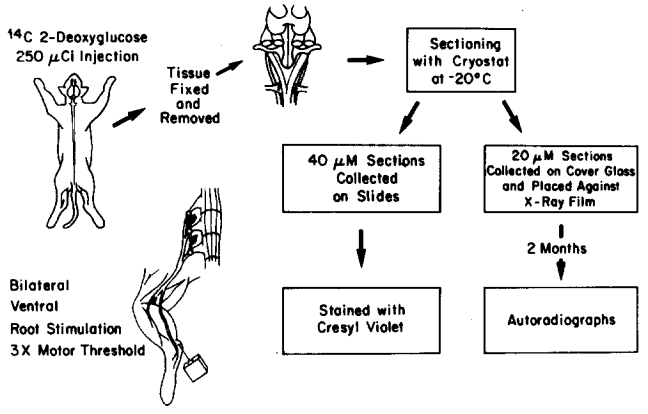

FIGURE 10. Experimental protocol for using autoradiographic tracing technique of labeling metabolically active cells and terminals with 2-[carbon-14] deoxyglucose to study the caudal brainstem cell groups participating in the reflex neural mechanism of induced static contraction in the cat. (See text.)

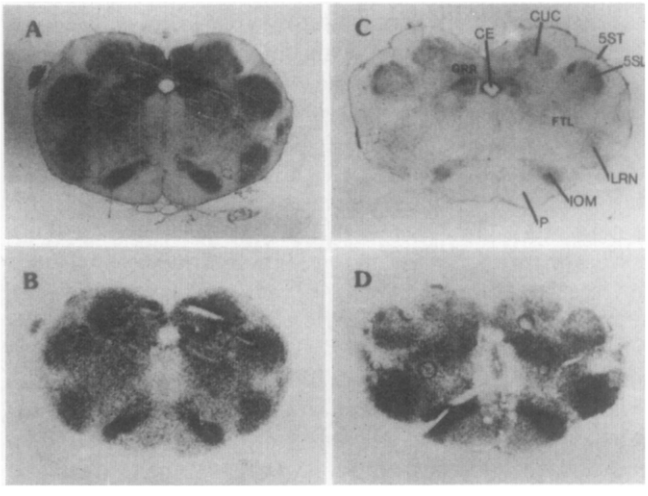

FIGURE 11. Labeling of the caudal brainstem with 2-[carbon-14] deoxyglucose during induced static exercise. **A** and **C**, normal histology (stained with cresyl violet); **B** and **D**, autoradiographic data. A and B are from a control animal and C and D are from an animal in which ventral roots were stimulated to produce static contractions. Enhanced uptake is observed in the lateral reticular nucleus (LRN) with its adjacent lateral trigeminal field (FTL) and in the inferior olive (medial accessory inferior olive, IOM). CE = central canal; CUC = cuneate nucleus; 5ST = spinal tract of the trigeminal; 5SL = laminar spinal trigeminal nucleus; GRR = gracilis nucleus; P = pyramidal tract. Reprinted with permission from Brain Res.[28]

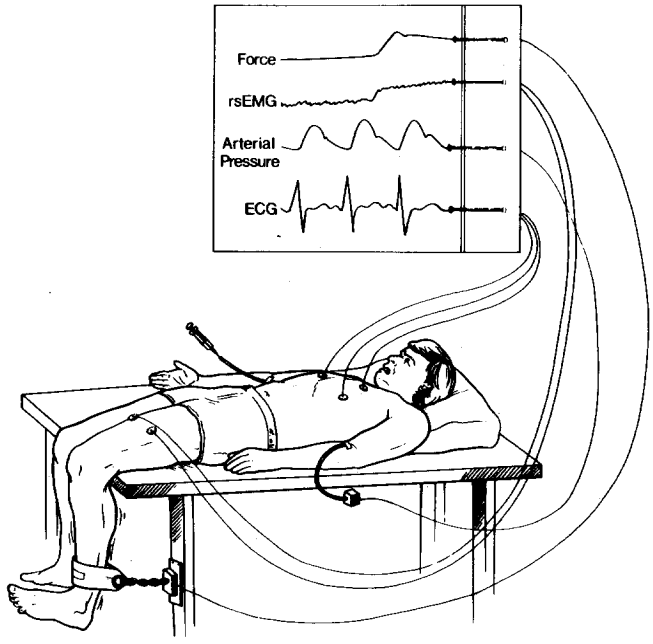

FIGURE 12. Experimental preparation for studying the cardiovascular responses to static contraction of the knee extensor muscles. (See text.) ECG = electrocardiogram; rsEMG = rectified smooth electromyogram. Reprinted with permission from J Physiol (Lond).[32]

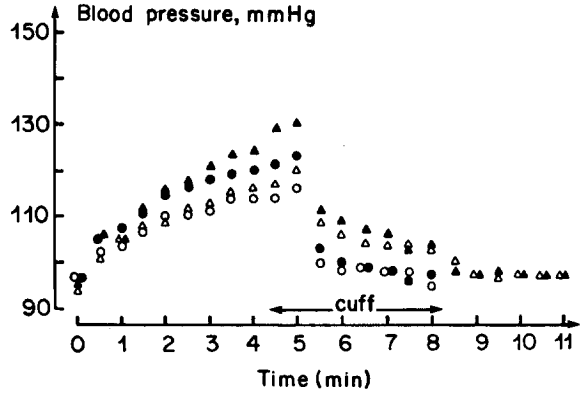

FIGURE 13. Arterial blood pressure response during control contractions and contractions performed with partial neuromuscular blockade using decamethonium (C_{10}). Same absolute force = 10% maximal voluntary contraction. Values shown for experiment with and without an arterial cuff applied during last 30 seconds of contraction and for next 3 min of rest. ○ = control contraction; △ = control contraction + cuff; ● = contraction + C_{10}; ▲ = contraction + cuff + C_{10}. Adapted from Leonard et al, reprinted with permission from J Physiol (Lond).[32]

thonium than during the control contraction. After the contraction was over, mean BP decreased immediately. It should be noted, however, that the inflation of the arterial occlusive cuff did not affect BP during the final 30 seconds of the contraction but that during recovery the value was higher until the cuff was released. Similar experimental results were obtained after neuromuscular blockade with tubocurarine.

The effect of partial neuromuscular blockade with decamethonium on the response of mean arterial BP to a static contraction developing the same *relative* force (30% of MVC performed immediately before exercise) is shown in Figure 14.[32] During exercise, the BP was slightly higher during control than during the contraction after neuromuscular blockade with decamethonium. The response during the contraction was not affected by application of the cuff but after contraction BP remained elevated in those studies in which the cuff was applied. After blockade with tubocurarine BP response to the same relative force was no different from that during the control contraction.[28]

The finding that HR and BP are greater during static contractions at the same absolute force during neuromuscular blockade suggests that central command is important in determining the cardiovascular response.[32] This conclusion is further supported by the finding that static contractions at the same relative force after neuromuscular blockade elicit the same cardiovascular response when the force is only one-half of that during control static contractions. Normally, either central ("central command") or reflex (exercise pressor reflex) neural mechanisms can elicit the observed cardiovascular responses, and the 2 neural mechanisms work in concert. Thus, the appropriate cardiovascular response may be elicited by either of the mechanisms, because they appear to influence the same neural circuits in the central nervous system. However, when there is a disproportionate signal from the central neural mechanism as compared to the reflex neural mechanism, the larger of the two seems to dictate the HR and BP response.[32]

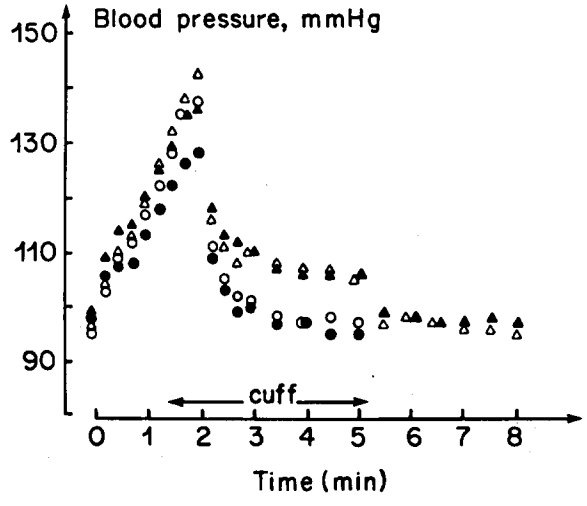

FIGURE 14. Arterial blood pressure response during control contraction and contractions performed with partial neuromuscular blockade using decamethonium (C_{10}). Same relative force = 30% of present maximal voluntary contraction. Values shown for experiment with and without an arterial cuff applied during last 30 seconds of contraction and for next 3 min of rest. O = control contraction; Δ = control contraction + cuff; ● = contraction + C_{10}; ▲ = contraction + cuff + C_{10}. Adapted from Leonard et al, reprinted with permission from J Physiol (Lond).[32]

Conclusions

In summary, experimental studies[2,17] strongly suggest that both central and reflex neural mechanisms can be responsible for the cardiovascular changes that occur during dynamic and static exercise. Also, an appropriate cardiovascular response occurs in the absence of either a central[7–9] or a reflex neural mechanism,[14] supporting the concept that either neural control mechanism can elicit the cardiovascular response to exercise. It seems clear that central and reflex neural mechanisms are not simply added to produce the combined cardiovascular response to exercise. These 2 systems appear to be redundant and simple neural occlusion may be operative.[11,17,32]

To argue the relative importance of central and reflex neural mechanisms in determining the overall cardiovascular response to exercise seems of little value.[17] It is likely that a central neural control mechanism, which is related to the central activity for the recruitment of motor units (central command), and a reflex neural control mechanism, which involves the activation of mechanoreceptors predominantly connected to group III skeletal muscle afferents, initiate the cardiovascular responses and determine the beginning level of the efferent activity of the autonomic nervous system to the heart and blood vessels. Both of these mechanisms should provide information concerning the mass of skeletal muscle involved in the exercise being performed. A reflex neural control mechanism also exists that serves as a feedback system from the exercising skeletal muscle by monitoring the effectiveness of the blood flow to meet the increased metabolic needs.[33,34] The activation of receptors predominantly connected to group IV skeletal muscle afferents probably relays this information. Thus, during light-intensity dynamic exercise the metabolic reflex neural mechanism may not be activated. However, during dynamic exercise at a moderate intensity or during static exercise at a level that restricts blood flow, the metabolic reflex neural mechanism may signal a flow error that is important in eliciting the level of efferent autonomic activity to the heart and blood vessels.[34] Thus, redundant neural control mechanisms appear to exist that can elicit an appropriate cardiovascular response to the intensity of the exercise.[11,17]

Acknowledgment: The helpful advice and criticism of Gary A. Iwamoto, PhD, Marc P. Kaufman, PhD, George A. Ordway, PhD, and Tony G. Waldrop, PhD, are noted with gratitude. Also, the assistance of Ms. Janet Wright in the preparation of the manuscript is greatly appreciated.

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