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Somato-Autonomic Reflexes in Conscious and Anesthetized Dogs

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SOMATO-AUTONOMIC REFLEXES IN CONSCIOUS AND ANESTHETIZED DOGS

by

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Dedicated with love to my parents - Mom and Dad

and to my wife Cathy

BIOGRAPHY

James W. Kozelka, son of Stephen and Dorothy Kozelka, was born on June 8, 1952, in Chicago, Illinois. He attended elementary school in Chicago and Notre Dame High School in Niles. He graduated from Northern Illinois University in 1974 with a Bachelor of Science in Biology.

In the summer of 1976 the auther began graduate studies at Loyola University in the Department of Physiology. He worked under the direction of Dr. Robert D. Wurster from July of 1976 through September of 1980. In April of 1979 he was inducted into the National Jesuit Honor Society. Later that year he was awarded an Aurthur J. Schmitt Dissertation Fellowship. On August 9, 1980, James married Catherine M. Collins, also from Chicago. In September of 1980 he enrolled in Medical School at the University of Illinois in Chicago.

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CHAPTER I

INTRODUCTION

Ascending spinal pathways mediating somato-sympathetic reflexes have been the subject of extensive investigation. Chung and Wurster [28] working in anesthetized cats, localized the afferent limb of somato-sympathetic reflexes mediating both pressor and depressor responses in the dorsolateral sulcus area (DLS) and dorsolateral funiculus (DLF) of the spinal cord, respectively. Quest and Gebber [142] showed that in anesthetized and decerebrate cats somatic afferent systems are also involved in vagal parasympathetic regulation of heart rate. Baroreceptor mediated bradycardia induced in these animals was attenuated by high intensity stimulation of the sciatic nerves. In anesthetized cats Geis and Wurster [63] effectively eliminated this somatic afferent-parasympathetic interaction by placing bilateral spinal cord lesions in the DLS. These authors suggested that a relatively discrete bundle of axons ascending in this region interact with neurons 1) in the dorsal motor nucleus of the vagus influencing myocardial contractility and 2) in the nucleus ambiguus which mediate chronotropic activity [64].

The afferent systems involved in the somato-autonomic reflexes outlined above are presumed to participate in cardiovascular responses to nociception and/or exercise. Paterson [136] proposed that the blood pressure elevation which accompanied exercise in man was brought about by activation of afferent fibers originating in contracting muscles. This hypothesis found significant support in other studies on human subjects by Alam and Smirk [2,3,4,5], Asmussen and Nielsen [11], and Lind et al. [108,109]. More recently, Coote et al. [36] and McCloskey and Mitchell [118] confirmed the participation of muscle afferents in pressor reflexes evoked in anesthetized and decerebrate cats. Coote et al. [36] induced tetanic contraction of hind limb muscles by ventral root stimulation (L6-S1) which was accompanied by significant elevations in blood pressure. The reflex nature of this response was confirmed by stepwise section of the dorsal roots (L6-S1) which progressively eliminated the pressor response to ventral root activation. Since sectioning the articular nerves in the working limb did not alter the blood pressure elevation, they surmised that muscle afferents were most likely involved. Furthermore, the stimulus appears to be chemical in nature in that simultaneous muscle contraction and hind limb arterial occlusion potentiates the pressor response. McCloskey and Mitchell [118] obtained similar results, but also suggested the partial involvement of mechanoreceptors in

the cardiovascular response to such exercise.

The present investigation examines the localization and activity of the ascending limb of somato-autonomic reflexes in anesthetized and unanesthetized dogs. In acute preparations, these reflexes were evoked by 1) direct electrical activation of somatic afferent nerves or 2) stimulation of multiple ventral roots which elicited sustained hind limb muscular contraction. As in the anesthetized and decerebrate cat preparations described by Coote et al. [36] and McCloskey and Mitchell [118], occlusion of the blood supply to working muscles in this study (chloralose or pentobarbital anesthetized dogs) resulted in an accentuation of the pressor response to induced exercise. Furthermore, the location of the ascending spinal systems which mediate this cardiovascular reflex were found to be similar to the pathways activated by direct stimulation of somatic afferent nerves.

In conscious dogs, blood pressure and heart rate were elevated in response to treadmill running. Restricted hind leg blood flow during such exercise significantly potentiated this pressor response. Finally, the effects of sectioning the ascending spinal pathways which mediate somato-autonomic reflexes in dogs (acute study) upon the cardiovascular response to exercise with or without hind limb ischemia were noted.

CHAPTER II

LITERATURE REVIEW

A. Background: Studies Employing Direct Stimulation of Somatic Afferent Nerves

1. Somato-sympathetic Reflexes

It has long been known that electrical activation of somatic afferent nerves results in alterations in blood pressure and heart rate in anesthetized animals. Hunt [85], in 1895 noted that weak stimuli bring about a depressor response while strong stimulation of the same sensory nerve elicits a pressor reflex. More specifically, the cardiovascular response to somatic afferent activation depends upon the intensity [116,141] and frequency [73,170] of the stimulus. Hunt explained this phenomenon as the differential activation of pressor and depressor fibers in peripheral afferents with altered strength of stimuli.

Ranson et al. [143-146] proposed that altered stimulus parameters brought about activation of different pathways in the central nervous system. In a preliminary investigation, Ranson [146] demonstrated that similar cardiovascular responses could be elicited with identical

stimulation of brachial and sciatic nerves. In later studies [143,144,145] various lesions were placed in the lower thoracic and upper lumbar spinal cord under aseptic conditions. Following recovery from this initial surgical procedure (3 hours to 30 days later) the cardiovascular responses to strong and weak stimulation of brachial and sciatic nerves were examined. These authors found that bilateral lesion of the dorsolateral sulcus area (DLS) resulted in a marked reduction in the pressor response to high intensity sciatic nerve stimulation. This spinal section did not effect the blood pressure increment following similar activation of the brachial nerve. The depressor response to low intensity sciatic nerve stimulation was lost following bilateral lesion of the lateral funiculi. Again, these lesions did not alter the response to brachial nerve stimulation. These findings led Ranson and co-workers to suggest that afferent pressor and depressor pathways ascend bilaterally in the DLS and lateral funiculi, respectively. They concluded that high or low intensity stimulation of the same peripheral nerve activates different central systems. This theory challenged the existence of separate pressor and depressor fibers in peripheral sensory nerves proposed by Hunt.

In 1943 Gordon [69] carried out experiments which supported the theories of both Hunt and Ranson. Gordon found that direct application of cocaine to the sciatic

nerve selectively blocked the pressor reflex, while asphyxia blocked depressor responses. This investigator suggested that small, unmyelinated fibers are more profoundly influenced by cocaine application and are the "pressor fibers" described by Hunt. Conversely larger, myelinated fibers are more susceptible to asphyxia and may be responsible for activation of depressor reflexes. Gordon also found that a depressor response could be converted to a pressor response by increasing stimulus frequency while holding intensity constant. This implied that stimulation of the same afferent fibers may activate pressor or depressor systems depending upon the stimulus parameters employed (as proposed by Ranson). This hypothesis is also supported by the work of Chung et al. [28].

As outlined above, the early interest in somato-sympathetic reflexes was focused upon the cardiovascular response to somatic afferent stimulation. However as nerve activity recording techniques improved, studies aimed at elucidating the central pathways for somato-sympathetic reflexes expanded [19,34,98,154,155]. Sato et al. [156] recorded changes in gross nerve activity in the lumbar sympathetic trunk in response to sciatic nerve stimulation. These authors noted spinal and supraspinal components of such somato-sympathetic reflexes. The spinal component was preserved following C8 or T1 spinal

transection and is presumed to be a local (encompassing 2-3 spinal segments) activation of sympathetic preganglionic neurons. The supraspinal component is lost following this spinal section and is thought to ascend to the medulla where activation of higher centers brings about a generalized activation of the sympathetic nervous system via activation of descending systems.

The spinal pathways for the descending limb of somato-sympathetic systems have been localized on the surface of the dorsolateral funiculus (DLF) 1.5-2mm ventrolateral to the DLS [50]. The ascending limb, as initially described by Ranson has also undergone extensive investigation. Johannson [87] was unable to verify the spinal pathways for pressor and depressor systems described by Ranson. Johannson could not abolish the pressor response to peroneal nerve stimulation with a gross lesion of the entire dorsal half of the spinal cord at C3. This investigator suggested that the ascending pressor pathways are a diffuse system at this level. Conversely, Coote and Downman [34], using electrophysiological techniques suggested that the ascending spinal pathways for somato-sympathetic reflexes are in the dorsal horns and the dorsal portion of the lateral funiculus. Recently, Chung and Wurster [28] have described a discrete pressor pathway ascending bilaterally in the DLS and a depressor system which ascends

bilaterally in the DLF. Further, Chung et al. [27] have shown that A afferent fibers activate the depressor system while C fibers activate the pressor system.

2. Somato-parasympathetic Reflexes

Stimulation of somatic afferent nerves may also bring about alterations in parasympathetic activity. The first description of somatic afferent-parasympathetic interaction was reported by Johansson in 1962. This investigator noted a vagally-mediated heart rate reduction in response to low intensity stimulation of the hamstring nerve in anesthetized cats [87]. Irichijima and Kumada [86] in 1963 recorded spontaneous activity in cardiac branches of the vagus nerve in anesthetized dogs. These authors noted that high intensity (10V, 100Hz) stimulation of the saphenous or brachial nerves resulted in a marked reduction of this tonic vagal activity. Irichijima and Kumada suggested that stimulation of peripheral sensory nerves may activate a center in the medulla which simultaneously enhances sympathetic output and reduces parasympathetic output from the central nervous system.

While the central pathways for somato-sympathetic reflexes were extensively studied through the 1960's (see previous section) the first investigation into the central mechanism of somato-parasympathetic reflexes was not forthcoming until 1972 (Quest and Gebber [142]). In this study vagally-mediated bradycardia was induced by 1)

intravenous phenylephrine, 2) carotid sinus nerve (CSN) stimulation, 3) electrical stimulation of the nucleus tractus solitarius (NTS) and nucleus ambiguus (NA), and 4) peripheral vagus nerve stimulation. The bradycardia induced by phenylephrine administration was abolished by section of carotid sinus and aortic depressor nerves and is thought to be a baroreceptor mediated phenomenon [167]. It is also known that the NTS is a medullary terminus for baroreceptor fibers [38,39,131] activated by CSN stimulation and that the NA contains the cells of origin of cardiac vagal afferents [62,74,93] (see Geis and Wurster below). The heart rate reductions brought about by intravenous phenylephrine, NTS and CSN stimulation were attenuated by high intensity bilateral stimulation of the sciatic nerves. Conversely, low intensity and low frequency stimulation of these somatic afferent nerves enhanced the heart rate reductions in response to these manipulations. The heart rate responses to electrical activation of the NA and the peripheral vagus nerves were unaltered by sciatic nerve stimulations. In conclusion, Quest and Gebber proposed that somatic afferent systems interact centrally with the cardiovagal component of baroreceptor reflexes.

Geis and Wurster confirmed and extended these findings in their study of the spinal and medullary pathways for somato-parasympathetic reflexes [62]. These

authors described three distinct medullary regions which contain cardiac vagal preganglionic somata: the dorsal motor nucleus of the vagus (DMN), the NA and an intermediate zone between these two regions. In a functional study Geis and Wurster [63] monitored heart rate and ventricular contractility (strain gauge output and dP/dt) in response to medullary stimulations. They found that activation of cell bodies in the DMN elicited a reduction in ventricular contractility but did not influence heart rate. Conversely, NA stimulation produced only negative chronotropic effects. Recently, [64] these investigators monitored chronotropic and inotropic alterations in response to CSN stimulation. These vagally mediated cardiac responses were influenced by peroneal nerve stimulation, confirming the central interactions of somatic afferent systems and baroreceptor reflexes. This interaction was eliminated following bilateral DLS lesion placement in the lumbar spinal cord of these animals (anesthetized cats). Geis and Wurster suggested that a relatively discrete bundle of axons ascending in this region interact with neurons 1) in the DMN, influencing myocardial contractility and 2) in the NA which mediate chronotropic activity.

Recently, Kozelka et al. [99,100] reported that the cardiovascular responses to sciatic nerve stimulation in pentobarbital or chloralose anesthetized dogs were

completely eliminated by DLS section in the lumbar spinal cord. The spinal site for the ascending portion of this somato-autonomic interaction is comparable to the location of fibers mediating somato-sympathetic [28] and somato-parasympathetic [64] reflexes in anesthetized cats. However, the antagonism of baroreceptor induced, vagally mediated bradycardia (induced by phenylephrine administration) by somatic afferent stimulation was still present following this lesion. In these animals, interruption of somatic afferent-parasympathetic interactions was not achieved until spinal lesions were extended to include both the DLS and the DLF. Therefore, the ascending pathways of the somato-autonomic reflexes bringing about heart rate responses appear somewhat more diffuse in the anesthetized dog than might have been expected with extrapolation of data from cats [28,64].

B. Somatic Afferent Stimulation: Physiological Implications

It is well known that normal behavioral adaptation to environmental stimuli include alterations in autonomic activity which bring about changes in blood pressure and heart rate. For example, injections of endogenous algesic agents such as bradykinin, 5-hydroxytryptamine, histamine and potassium which result in pseudo-affective responses in animals [75] and pain in man [92,112] also bring about an increase in blood pressure and heart rate in

experimental animals [23,132]. These substances may partake in the physiological responses to tissue damage (ie. nociception). In this vein, Lim et al. [107] noted a powerful pressor response to intra-arterial injection of bradykinin, and suggested that this substance may be involved in the generation of muscle pain. Dopart [43] proposed that the pain that occurs in response to exercise may result from stimulation of sensory nerve endings by potassium, which is known to accumulate in working muscles [46,78].

The behavioral and autonomic alterations brought about by intra-arterial injection of algesic substances are thought to be due to the activation of group III [48,53,124,125] and IV [77,124,125] afferent fibers in skeletal muscle (as well as small myelinated and unmyelinated fibers of cutaneous origin). These fibers are also thought to act as thermal receptors and chemoreceptors in muscle [115] which mediate cardiovascular responses to non-painful exercise [37] (also see sect C2).

Unfortunately, the central mechanisms mediating the cardiovascular responses to such stimuli have not been well studied. However, as outlined in the preceding section the central pathways for somato-autonomic reflexes evoked by electrical activation of peripheral afferent nerves have been well characterized. Additionally, by

altering stimulus parameters specific groups of afferent fibers can be activated, thereby simulating more physiological responses to pain or exercise. For example, altering stimulus parameters to activate A beta, A delta and C fibers of skin or group II, III and IV fibers of muscle nerves results in enhanced sympathetic output. Conversely, activation of group II and III or A beta fibers reduces sympathetic activity (for review see Coote [32] and Wurster [171]).

In the following sections the literature describing the physiological activation of somatic afferent fibers (ie. activation by muscular work or chemical irritation) are reviewed. However, it must be kept in mind that many of the concepts regarding the central mechanisms of such physiological somato-autonomic interactions are based upon the studies outlined in sections A1 and A2.

C. Physiological Activation of Muscle Afferents

1. Response to Exercise in Man

Cardiovascular responses to physical exertion were first noted in the 1890's. In 1904 Bowen [22] noted a biphasic increase in heart rate in humans during dynamic leg exercise (bicycling). This investigator reported a rapid primary rise in pulse rate at the onset of work followed by a more gradual secondary cardiac acceleration. The initial, rapid rise in heart rate was attributed to stimulation of the circulatory centers by the motor cortex

and sensory nerve endings of the contracting muscles. The slower, secondary response was proposed to be due to altered nervous input into cardiovascular centers due to heat and metabolic waste products developed in the heart and working muscles. Bowen also observed a gradual rise in blood pressure which leveled off after several minutes of mild to moderate exertion. This pressor response to bicycle exercise was attributed to the increased pulse rate, contraction of abdominal muscles and increased venous return from the legs in response to alternate contraction and relaxation of large muscle groups.

Krogh and Lindhard [101] observed the respiratory and cardiovascular responses to the sudden onset of strenuous exercise on a bicycle ergometer. In one of their subjects (anticipating heavy work) they noted a marked increase in ventilation at the onset of mild exertion (minimum brakeload). These authors suggested that the initial cardiovascular and respiratory responses to exercise were due to an irradiation of impulses from the motor cortex and were not reflex in nature. Similarly, Gillespie [65] suggested that the blood pressure and heart rate elevation in response to muscular work was similar to the cardiovascular alterations induced by mental work. However, physiological evidence supporting the direct activation of circulatory and respiratory centers by the motor cortex was slow to arrive.

Paterson [136] carried out experiments similar to those of Krogh and Lindhard. However, in his experiments the subjects began bicycling against a small resistance. As exercise continued, the work load was progressively increased resulting in steady increments in blood pressure and heart rate. This methodology reduced the emotional influence upon blood pressure and heart rate brought about by the anticipation of "the considerable initial effort required to overcome the inertia of the flywheel". In contrast to the findings of Krogh and Lindhard, Paterson noted only a slight elevation in these cardiovascular variables at the onset of work. This investigator suggested that the progressive elevation of blood pressure and heart rate with increasing work loads was reflex in nature. Specifically, he proposed that increased metabolic activity stimulated afferent fibers in the working muscles which ultimately elicited a pressor response.

In 1936 Nielsen [133] noted an increased excitability of respiratory centers during muscular work. Assmussen et al. [12] demonstrated that this altered central excitability was not induced by blood borne substances originating in exercising muscles and must be cortical (Krogh and Lindhard) or reflex (Paterson) in nature. These findings led Asmussen et al. [11] to investigate the nature of the respiratory alterations observed during

muscular activity. These authors found identical ventilatory responses to both voluntary and stimulation induced muscular exercise, and concluded that these respiratory alterations were reflexly induced.

The reflex nature of the cardiovascular responses to exercise was also supported by the observations of Alam and Smirk. In 1937 these authors noted that the pressor response to rhythmic exercise was markedly elevated by interruption of the circulation leading to the working muscles [3]. Specifically, rhythmic contraction of forearm muscles with no occlusion produced an increase in systolic blood pressure on the order of 10 mm Hg over a period of 3 minutes. This same exercise resulted in a 45 mm Hg pressor response over a similar time course when blood flow was interrupted at the upper arm. After the cessation of muscular activity, blood pressure did not return to pre-exercise levels until the circulatory occlusion was released. These authors also noted the maximum blood pressure elevation during vascular occlusion before and after the onset of pain in working muscles. They reported that significant pressor responses could be induced in the absence of pain [2,3]; however, the blood pressure elevations were markedly greater with the onset of severe discomfort in these experiments. In a subsequent paper, Alam and Smirk [5] noted that simultaneous exercise-occlusion also results in an

elevation in heart rate. These authors suggested that the cardiovascular responses to exercise were reflexly induced by chemical stimulation of nerve endings in voluntary muscles.

To test the above hypothesis, cardiovascular responses to rhythmic exercise with simultaneous occlusion were tested by Alam and Smirk [4] in a person with a unilateral spinal cord lesion. This spinal pathology resulted in a complete sensory deficit in the right leg up to 4 inches above the knee. In this patient the pressor response to exercise-occlusion in the affected (lower right) leg and the same muscle group in the unaffected leg was identical. As described above, systemic arterial pressure remained elevated following left leg exercise as long as the circulation in this limb was obstructed. However, with cessation of exertion in the right leg, blood pressure returned to pre-exercise levels despite the maintenance of vascular occlusion. These observations led Alam and Smirk [4] to conclude that the pressor response to exercise was due to both cortical and reflex activation of the brain stem centers which control blood pressure. Specifically, the pressor response evoked during exercise was thought to be influenced by cortical input to these centers. Conversely, post-exertion occlusion was proposed to result exclusively from chemical stimulation of muscle afferent fibers which were interrupted on the affected

side.

Rythmic exercise leads to a significant increase in cardiac output [13,108]. However, total systemic vascular resistance falls in proportion to the intensity of muscular activity [72]. Consequently systolic pressure rises but diastolic pressure does not [25,166], accounting for the relatively small rise in mean blood pressure observed during dynamic exercise [82,167]. As pointed out above, these pressor responses are greatly elevated by occlusion of the blood vessels leading to the working muscles. Conversely, static or isometric exercise results in marked elevations in blood pressure and heart rate because ischemia is greater during static work due to mechanical obstruction of blood flow by the working muscles [6,7,8,9,15,16,20,49,69,70]. The chronotropic response to static exercise is mediated by vagal withdrawal [55], while vasoconstriction in non-active vascular beds (mediated by the sympathetic nervous system [56]) is responsible for the large rise in arterial pressure [42,84,111,138].

Lind et al. [109] took advantage of the large pressor responses which occur during isometric contractions in an effort to determine whether these responses were reflex, humoral, or central in nature. These investigators noted the cardiovascular alterations to sustained hand grip contractions in a patient with unilateral syringomyelia.

In these experiments Lind et al. found that the blood pressure response to sustained forearm work on the unaffected side was similar to that observed in healthy subjects. Conversely, isometric contraction of forearm muscles on the affected side resulted in a significantly smaller pressor response. These observations were taken as evidence for the reflex nature of the blood pressure response to static exercise.

There is a large body of evidence supporting the reflex nature of the pressor responses to exercise both in man (outlined above) and in animals (next section). However, the cortical irradiation hypothesis proposed by Krogh and Lindhard has also found support. In 1965 Asmussen et al. [10] monitored cardiovascular and respiratory alterations induced by static exercise in human subjects before and after partial curarization. This drug reduces muscle strength such that greater central command is required to achieve a given level of muscular activity [68]. These authors found that the blood pressure, heart rate, and ventilatory responses to identical levels of dynamic work were greater in partially curarized subjects. Asmussen suggested that these findings may be due to increased activity in muscle spindle afferents or an "increased activation of the gamma loop". However, animal experiments indicate that activation of limb muscle spindle afferents by vibration

produces no appreciable cardiovascular or respiratory alterations [80,117,118]. It has also been demonstrated that anodal blockade of Golgi tendon and muscle spindle afferents does not alter the cardiovascular and respiratory responses mediated by muscle afferents during contraction (see next section). Therefore, the findings of Asmussen et al. may be interpreted as evidence for the partial involvement of central motor command in initiating the cardiovascular responses to exercise [68,138].

Freyschuss [54] carried out experiments in which the subjects were instructed to perform hand grip (isometric) exercise after succinylcholine block of motor nerves in the arm. This investigator reported significant increases in blood pressure and heart rate in these individuals despite the absence of muscle work, and suggested this response was of central origin. However, Goodwin et al. [67] pointed out that acutely paralyzed individuals are psychologically stressed, and this emotional state may significantly contribute to the autonomic alteration induced by the attempted exercise [44]. This criticism also complicates the interpretation of data on partially curarized subjects (Asmussen et al. 1965).

In an effort to minimize the emotional factors described above Goodwin et al. [68] designed experiments in which central command could be altered reflexly. Specifically, the central effort necessary to perform a

given level of biceps exercise could be reduced by vibrational stimulation of primary muscle spindle afferents in that muscle. Conversely, when such afferents were stimulated in the triceps (antagonist) muscle, greater central command was required to achieve similar biceps work. These authors reported that the blood pressure, heart rate and pulmonary ventilation responses to a constant level of isometric exercise were increased when central command was greater, and decreased when central effort was reduced.

Recently, Mitchell et al. [130] have further demonstrated that the cardiovascular response to static exercise in man appears to be dependent upon both central and peripheral control mechanisms. However, conclusions drawn from such experimentation must be substantiated by direct physiological observations which can only be performed in laboratory animals. Toward this end the nature of the pressor response to muscular exertion (both static and dynamic) has been extensively investigated in animal preparations. These experiments are reviewed in the next section.

2. Muscular Work Induced in Anesthetized and Decerebrate Animal Preparations

As described in the previous section, the observations of Alam and Smirk and others strongly suggest that the cardiovascular and respiratory responses to

exertion involve the participation of a chemosensitive reflex. However, because several factors may be acting simultaneously in conscious exercising man, experiments were designed in which muscular work could be induced in anesthetized animals. In 1942 Comroe and Schmidt [31] evoked muscular activity in anesthetized dogs and cats by stimulation of lumbar and sacral ventral roots. This "exercise" resulted in marked increases in minute respiratory volume in both species. In dogs the respiratory alterations evoked during hind limb work were eliminated by spinal cord transection, thus establishing the reflex nature of this response. Conversely, changes in ventilation brought about by ventral root stimulation in cats were unaltered by spinal section, indicating that species differences may exist.

In 1947 Euler and Liljestrond [45] induced cardiovascular alterations by direct stimulation of skeletal muscle in rabbits, cats and dogs. These authors could not evoke the pressor response to muscular work which had been previously described in human experimentation. In fact, they observed significant reductions in blood pressure and heart rate following direct muscle stimulation confirming the observations of McDowall [120]. This depressor response was enhanced by carotid sinus and depressor nerve section, and was still present after L1-L2 spinal cord transection. Finally,

they noted that upon cessation of work the blood pressure occasionally rose above resting levels. This post-exercise pressor response was augmented by administration of gas mixtures "rich in carbon dioxide and poor in oxygen". These observations led Euler et al. to conclude that blood pressure was maintained by baroreceptor reflexes during muscular work. They further suggested that central carbon dioxide accumulation and/or oxygen deficit may also influence the blood pressure during exercise.

The apparent discrepancy between the findings of Euler and Liljestrand and the blood pressure responses observed in exercising man were not resolved for several years. It is now well known that both pressor and depressor responses can be evoked by direct activation of skeletal muscle depending upon the stimulus parameters employed. Clement et al. [30] noted that blood pressure reductions following 5 Hz muscle stimulation were converted to pressor responses by increasing stimulus frequency to 20 Hz. These authors further noted that blood pressure increments following high frequency muscle stimulation were eliminated or converted to depressor responses following muscle-blocking doses of gallamine. Conversely, blood pressure reductions following low frequency stimulation were unaltered by drug induced paralysis. Clement et al. [29,30] proposed that depressor

responses of this nature may result from direct activation of muscle afferents known to bring about blood pressure reductions in cats [159] and dogs [127]. However the observation that the depressor responses evoked by skeletal muscle stimulation are still present after spinal transection (Euler et al. above) suggests that humoral factors are released from the activated muscles.

The involvement of blood borne substances in the cardiovascular responses to exercise were examined by Kao and Ray [89,90]. These authors demonstrated an increase in ventilation and cardiac output in dogs in response to direct stimulation of hind limb muscles. They further employed cross circulation techniques to determine whether these responses were initiated by neural or humoral stimuli. "Neural" dogs (exclusively neural communication between exercising muscles and the rest of the animal) demonstrated increases in pulmonary ventilation and cardiac output significantly larger than those observed in intact animals responding to such exercise. In "humoral" animals (receiving blood from the exercising extremities of another animal) the increase in cardiac output during exertion was less than noted in the intact (neural and humoral) preparation. "Humoral" dogs also displayed large increases in A-V oxygen difference implying that humoral factors alone are not sufficient to regulate cardiac activity during exercise. Kao and Ray concluded that

humoral factors released during direct stimulation may lead to "peripheral circulatory failure" (a depressor response).

These observations, together with those of Euler and Liljestrond and more recently Clement et al. suggest that both neural and humoral mechanisms may partially account for blood pressure reductions following direct stimulation of skeletal muscle. However, the physiological significance of such responses are not clear because 1) blocking muscular work did not alter the responses and 2) direct muscular stimulation activates afferent fibers in an unpredictable sequence and may give misleading results.

In 1971 Coote et al. [36] suggested that direct muscle stimulation may lead to indiscriminant activation of large numbers of afferent fibers which could distort appropriate sensory input arising from the contracting muscles. These authors sought to avoid such artifacts by a more natural means of induced exercise. More specifically, they induced tetanic contraction of hind limb muscles by (L6-S1) ventral root stimulation (a la Comroe and Schmidt). This sustained (one minute) work was accompanied by a significant elevation in arterial pressure [35,36]. The reflex nature of this response was confirmed by stepwise section of the (L6-S1) dorsal roots, which progressively eliminated the pressor response to ventral root activation. Since sectioning the articular

nerves in the working limb did not alter the blood pressure elevation, they surmised that muscle afferents were most likely involved. Furthermore, the stimulus appeared to be chemical in nature in that simultaneous muscle contraction and hind limb arterial occlusion potentiated the pressor response.

The observations of Coote et al. were confirmed and extended by McCloskey and Mitchell [118,129]. These authors noted a rise in arterial blood pressure, heart rate and pulmonary ventilation during static contraction with simultaneous occlusion. However, the tachycardia in these experiments (anesthetized cats) was much smaller than the heart rate increments observed in man during isometric exercise.

This observation may be due to baroreceptor buffering of heart rate during the pressor responses induced by ventral root stimulation. Conversely, in conscious exercising man [21,24,122] the baroreflex is thought to be less sensitive to pressure increases [148] which would allow greater heart rate elevations.

McCloskey et al. also noted the effect of differential nerve block upon the pressor response to these isometric contractions. These authors applied direct current anodal block to the L7-S1 dorsal roots. This procedure is thought to preferentially inhibit conduction of larger (group I and group II) myelinated

fibers [123]. Anodal nerve block did not alter the cardiovascular response to isometric excercise in these animals, therefore implicating the involvement of group III and/or group IV muscle afferents. This observation has subsequently been confirmed in anesthetized dogs [166]. Finally, McCloskey and Mitchell monitored blood pressure at the cessation of exercise while maintaining circulatory occlusion. They noted a partial return to pre-exercise levels in these experiments and suggested that mechonoreceptors, as well as chemoreceptors, may be involved. This conclusion is supported by the findings of Barron and Coote [18] in decerebrate cats. These authors noted modest increases in blood pressure and heart rate induced by passive hind limb movement which was abolished by anesthesia or denervation of Type III or IV fibers.

The difference in heart rate responses to exertion in anesthetized and conscious subjects may be due to altered baroreceptor sensitivity as described above (see McCloskey and Mitchell [118]). However, the partial involvement of higher centers in the pressor response to exercise (Krogh and Lindhard [101]) may also explain this difference. In this vein, Rushmer et al. [151,152] presented evidence supporting the concept that central drives may influence cardiovascular centers during exertion. These investigators implanted indwelling electrodes in hypothalamic and subthalamic structures of dogs for later

use in the unanesthetized preparation. They reported that electrical activation of these structures in awake animals induced cardiovascular alterations similar to those observed in the same dogs during treadmill exercise. It has further been demonstrated elsewhere [160,169] that the cardiovascular responses evoked by hypothalamic stimulation are very similar to those observed during muscular exertion.

More recently, Gebber and Snyder [59] suggested that the central drives described by Rushmer et al. may in fact influence baroreceptor function during exercise. They noted that the bradycardia elicited by carotid sinus nerve stimulation was blocked by hypothalamic stimulation in spinal cats. These authors concluded that hypothalamic activation inhibits the efferent cardiac vagal component of baroreceptor reflexes. This observation (confirmed by others [41,83]) suggests that central inputs may modify the cardiovascular reflexes originating in working muscles.

Conversely, Coote and Dodds [33] noted that the inhibition of baroreceptor reflexes by hypothalamic stimulation may simulate the defense reaction, and not the cardiovascular response to exercise. These authors confirmed the findings of Quest and Gebber which indicate a central interaction between baroreflexes and somatic afferent stimulation (section A-2). However, they were

unable to demonstrate a similar interaction when somatic afferents were activated by muscular contraction (ventral root stimulation). They suggested that electrical activation of peripheral afferents may simulate nociception rather than physiological exercise and that central mechanisms mediating the responses to stimulation and contraction appears to be different. In this model of induced exercise, however, input to the hypothalamus from higher centers was not studied. Such input may account for the differences in the cardiovascular responses to exercise in conscious and anesthetized subjects.

3. Chemical Stimulation

It is well known that the pressor response and tachycardia which occur during exercise are greatly enhanced by circulatory occlusion (see sections IIA and IIB and refs 11,162). This cardiovascular response is thought to result from the activation of a chemosensitive reflex which originates in muscle afferents in response to an accumulation of metabolites. This theory has gained support from studies employing local injections of 2,4 dinitrophenol which uncouples oxidative phosphorylation and may simulate exercise hypermetabolism [115]. This substance has been found to cause reflex increases in heart rate and blood pressure when injected into the hind limb of animals [105,165]. Among the metabolic alterations known to occur during muscular ischemia are 1)

decreased oxygen, 2) increased carbon dioxide, 3) decreased nutrients eg. glucose, lipids, ketone bodies, etc., 4) increased hydrogen ion and potassium ion concentrations and 5) increased tissue osmolarity [70,71].

In 1960 Lassar [104] noted that intra-arterial infusions of hypertonic, but not hypotonic solutions of saline, urea and dextrose resulted in increases in blood pressure and heart rate. Paintal [134] reported that such hypertonicity stimulates sensory nerve endings in skeletal muscle and may be involved in pain perception. In more precisely controlled experiments Windenthal et al. [168] studied the effects of close-arterial injections of potassium chloride (0.3-1.0 molar) in the vascularly isolated hind limb of dogs. Vagotomy or atropinization did not alter the cardiovascular response to these infusions while beta adrenergic blockade with propranolol reduced only the tachycardia following intra-arterial potassium. Finally, the blood pressure and heart rate responses to KCl infusion were eliminated by section of the femoral and sciatic nerves in these animals. These observations have been confirmed in other studies on dogs [113] and cats [1].

Hnik et al. [79] recorded sensory nerve activity in the peripheral stump of muscle afferents during close arterial infusions of potassium ions. These authors noted that nearly all fibers, both proprioceptive and non-

proprioceptive, responded to KCl infusions by either "increasing their rate of discharge or by the appearance of activity in previously silent endings." Importantly, the venous blood potassium ion concentration was raised from 4-5 to 7.5-12.5 mEq per liter during the infusions which is in the physiological range for venous blood after muscular activity [95].

In light of these observations, it seems reasonable to conclude that metabolic by-products such as potassium ions may be involved in the cardiovascular reflexes originating in working muscles. As noted in the previous section (and elsewhere [139]), exercise reflexes appear to be mediated by slowly conducting (group III and group IV) afferent fibers. It has also been demonstrated [17,161] that such fibers originate as free nerve endings surrounding arterioles and capillaries in muscle. This location would be ideal for detection of the physicochemical alterations known to occur during exercise.

Chapter III

Methods and Materials

A. Acute Study

Twenty-six adult mongrel dogs, ranging in weight from 12.5 to 29.5 Kg. were anesthetized with sodium pentobarbital (30 mg/Kg, i.v.; N=5) or alpha chloralose (100 mg/Kg, i.v.; N=21). These anesthetized preparations were catagorized into four subgroups based upon experimental protocol. The aorta was cannulated via the femoral (Group I-III) or omocervical (Group IV) artery, and blood pressure was monitored with a pressure transducer (Statham P23 Db) and oscillograph (Grass, Model 7). Heart rate was determined by a cardiotachometer triggered by the pulse wave in all animals. All drugs were administered via a cannula inserted into the femoral (Group I-III) or internal jugular (Group IV) veins. Rectal temperature was monitored and maintained at 37+/-1 C by a warm water heating pad.

In groups I-III a L1-L2 laminectomy was performed, the dura mater resected and a mineral oil bath was made around the exposed spinal cord. The sciatic nerves were isolated, sectioned and likewise immersed in a mineral oil

bath. The central portions of these nerves were placed upon bipolar electrodes, and pressor responses were elicited by bilateral stimulation (15-20 V, 1 msec duration, 100 Hz for 25 seconds). The dogs were paralyzed with decamethonium (.3-.5 mg/Kg, i.v.) to eliminate reflex muscle movements in response to somatic afferent activation, and placed on a positive pressure respirator. Additional bolus injections of decamethonium were administered as needed during the course of the experiment.

In group IV animals pneumatic occluders (4 mm and 10 mm inner diameter) were fitted around both external iliac arteries and the inferior vena cava, respectively. In these animals a L3-S1 laminectomy was performed and the dura mater was resected. A mineral oil bath was then fashioned around the exposed spinal cord and maintained at 37+/-1 C. The L6, L7 and S1 ventral roots on both sides were dissected and sectioned close to the spinal cord. The peripheral portions of these nerves were placed upon bipolar electrodes. Prior to stimulation, these dogs were fixed in position with clamps anchoring the lumbar vertebra (L1), the ilium, the femur and the distal tibia. Contraction of hind limb muscles was brought about by ventral root stimulation (1-2 V, .1 msec duration, 30-50 Hz, for 45-150 seconds).

Baroreceptor mediated bradycardia was brought about

by a single pressor dose of phenylephrine (8-10 mg/kg, bolus injection, i.v.). The interaction between somatic afferent activation and phenylephrine-induced bradycardia was noted in group II, III and IV animals.

Group I (Dogs: A-E) In this group of alpha chloralose anesthetized animals the cardiovascular responses to sciatic nerve stimulation were monitored before and after bilateral cervical vagotomy. Blood pressure and heart rate were also recorded prior to and following bilateral lesion placement in the lumbar (L1-L2) spinal cord in these dogs (site of lesion placement outlined in figure 21; see results).

Group II (Dogs: F-O) In this subgroup three animals were anesthetized with pentobarbital and seven with alpha chloralose. The cardiovascular responses to sciatic nerve stimulation, as well as somatic afferent-parasympathetic interactions (ie. peripheral nerve stimulation during phenylephrine-induced bradycardia) were monitored before and after lumbar spinal cord lesion placement. DLS lesions preceded DLF sectioning in these dogs.

Group III (Dogs: P-T) Two of these dogs were anesthetized with pentobarbital and three with chloralose. The protocal followed in this group was identical to that outlined above for group II except that DLF preceded DLS section in these animals. Figure one illustrates the order and location of lesion placement in groups I, II and

III. The actual site of lesion placement is outlined in results section figures 21 and 22.

Group IV (Dogs: U-Z) The blood pressure and heart rate responses to isometric contraction of the hind limbs were monitored with and without simultaneous vascular occlusion (external iliacs and inferior vena cava) in these alpha chloralose anesthetized animals. To test the relative contribution of parasympathetic withdrawal in these cardiovascular responses the cervical vagus nerves were cold blocked. This cooling was brought about by placing the nerves in notches fashioned in silver plated brass rods which made contact with a cold plate. The temperature at the nerve rod interface was monitored with a thermister and maintained at 1-4 C during blocking procedures. Vagal responsiveness was tested before, during and after cold block with pressor doses of phenylephrine. In all experiments reported, the nerve block was reversed by slow rewarming to 37 C. The heart rate response to muscle contraction was also monitored during phenylephrine-induced bradycardia (vagus temperature, 37 C). All of the blood pressure and heart rate responses to ventral root stimulation outlined in this paragraph were monitored before and after L2-L3 lesion placement (see figures 21 and 22). In dogs U, V and W, DLS lesions preceded DLF sectionings. Conversely in dogs X, Y and Z the order of spinal cord sectionings was

FIGURE 1

SCHEMATIC REPRESENTATION OF LESION PLACEMENT IN GROUPS I-III

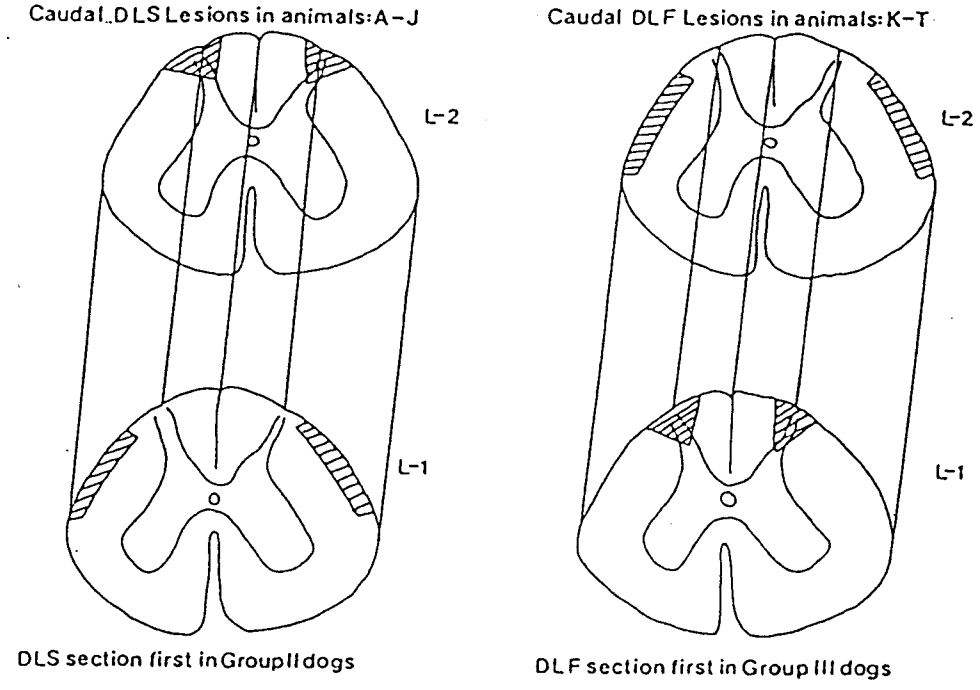

FIGURE 1

LEGEND

Diagramatic representation of the order and location of spinal cord lesion placement in the lumbar spinal cord of anesthetized dogs. The respective sections were separated by approximately one spinal segment to facilitate the histological verification of DLS and DLF lesions separately.

FIGURE 2

SCHEMATIC REPRESENTATION OF

ACUTE EXPERIMENTS

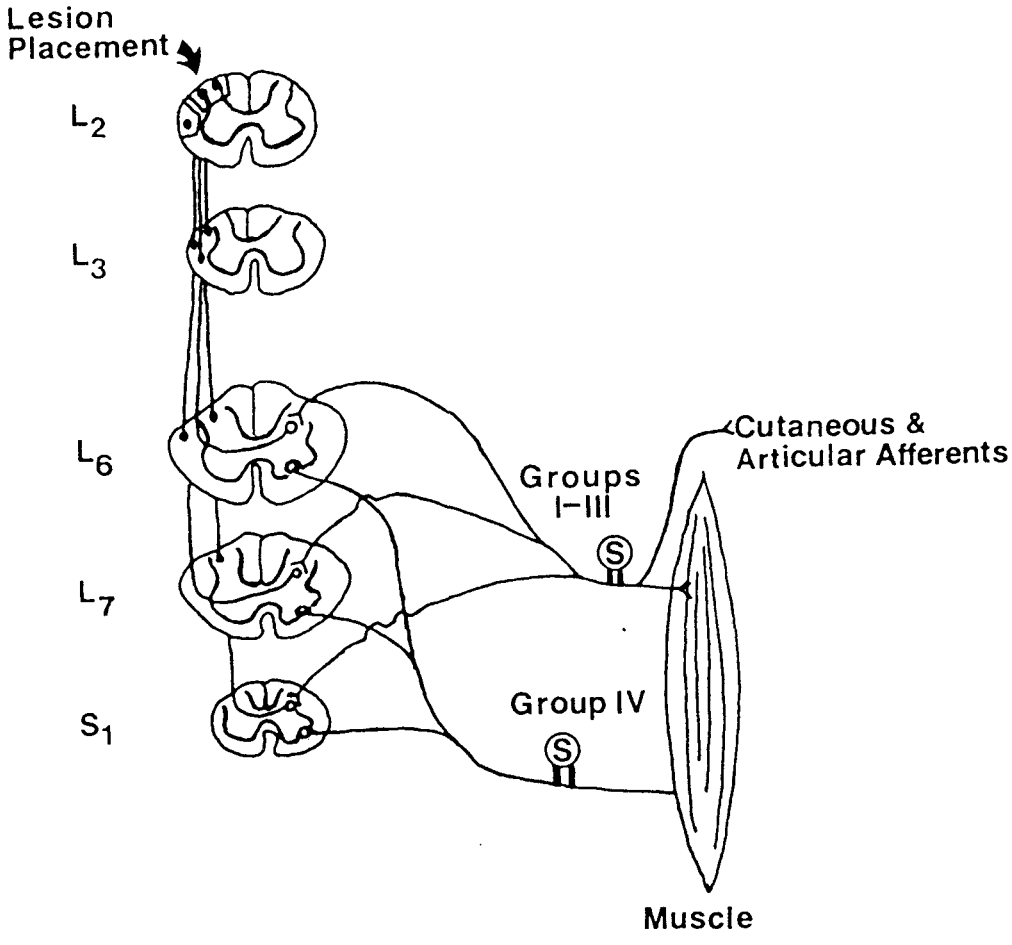

FIGURE 2

LEGEND

Schematic representation of acute experiments in which the central pathways for somato-autonomic reflexes in anesthetized dogs were determined. In groups I-III somatic afferent activation was brought about by electrical stimulation of the sciatic nerves (bilaterally) which include muscular, cutaneous and articular afferent fibers. In group IV, bilateral stimulation of L6, L7 and S1 ventral roots at 30-50 Hz elicits tetanic contraction of the hind limbs. This "exercise" brings about increased activity in primarily muscle afferents. The reflex cardiovascular alterations to somatic afferent stimulation were tested before and after spinal cord lesion placement in the DLF and/or DLS at L2 (groups I-III) or L3 (group IV). These lesions are above the level of entry of hind limb afferents and do not interfere with descending autonomic output.

reversed.

The cardiovascular responses to sciatic nerve stimulation (Groups I-III) and muscle contraction (Group IV) before and after spinal cord lesions were monitored and compared using the students unpaired T-test. P values of less than .05 were taken to indicate statistically significant differences. The responses to sciatic nerve stimulation with varied anesthetic agents, or in vagotomized vs. non-vagotomized animals were also compared and tested for statistical significance with the students unpaired T-test. Again P values of less than .05 were taken to indicate significant differences.

In figure 2 the general experimental design for acute experiments (animals A to Z) is outlined. The ascending pathways pictured in this figure appear unilateral in the interest of clarity; however, these systems ascend bilaterally in the spinal cord. Additionally, all stimulations (eg. sciatic nerves or ventral roots) and spinal cord lesions were bilateral.

B. Chronic Study:

Cardiovascular parameters were monitored in dogs in the conscious state before and after placing lesions in the spinal cord. These spinal sections (placed at L2; see results, figure 23) were aimed at interrupting the ascending limb of the somato-autonomic reflexs localized in acute experiments (Section III A). Blood pressure and

heart rate were monitored in these animals at rest, in response to bilateral carotid artery occlusion (BCO), and at various levels of exercise with and without transient hind limb ischemia. In each animal the average 48 hour heart rate (taken from EKG tracings monitored every thirty minutes for 30 second intervals with a Holter counter) was recorded three times, 1) prior to initial instrumentation, 2) at least one week after instrumentation and 3) 7-14 days after spinal cord lesion placement.

Twenty mongrel dogs ranging in weight from 13.5-28 Kg were used in this study. These animals were trained daily to run on a treadmill on all four legs and on hind legs only (front legs supported by a shelf). After this training period (approximately 4 weeks), the animals were anesthetized (sodium pentobarbital, 30 mg/kg, i.v.) and instrumented using sterile surgical techniques. This instrumentation consisted of cannulation of the axillary or internal jugular vein and the arch of the aorta via the omocervical artery with indwelling catheters. The common carotid arteries were isolated and fitted with pneumatic occluders which were used to elicit BCO's. In 10 animals the left external iliac artery was isolated and fitted with a pneumatic occluder. The catheters and tubing leading to the occluders were advanced subcutaneously to the back of the neck and externalized to facilitate their use in the unanesthetized animal. All wounds were closed,

and the dogs were maintained on procain penicillin (900,000 units/day, i.m.) for a minimum of two weeks.

During the first week (post instrumentation) blood pressure and heart rate at rest, in response to BCO and external iliac artery occlusion (in 10 animals) were monitored daily. Eight to ten days after instrumentation these cardiovascular parameters were recorded at rest (in response to BCO and iliac artery occlusion) and during hind limb running at 2, 4, and 6 Km/hr. (5 min. at each speed, 0% grade) and running on all fours at 2, 4, 6, and 8 Km/hr. (5 min. at each speed both 0% and 10% grades). In animals fitted with left external iliac occluders, the cardiovascular responses to exercise were monitored at all levels with and without transient (80-150 seconds) interruption of blood flow through this artery. Pre-exercise resting heart rates were recorded while the animals stood on the treadmill. Exercise was not initiated until this heart rate was within 15% of the 48 hour control rate recorded in that dog. Each animal was run nine times prior to lesion placement, three times on hind legs only, three times on all fours at 0% and three times on all fours at a 10% grade. These dogs were not run more than once a day, and the three run average for each animal was taken as the control (N=1) cardiovascular response to exercise and/or exercise-ischemia.

Following this control period, the animals were again

anesthetized (sodium pentobarbital, 30 mg/Kg, i.v.) for making spinal lesions under sterile conditions. In this procedure a partial laminectomy was performed at the L2 level. The right or left sciatic nerve was then isolated unilaterally and stimulated (15 V, 100 HZ, 1 msec duration, for 25 seconds). The blood pressure and heart rate responses to this activation, as well as the interaction between somatic afferent stimulation and phenylephrine-induced bradycardia were noted. Bilateral lesions were then placed in the DLF and DLS area. These spinal sections were considered complete when the blood pressure and heart rate responses to unilateral sciatic nerve stimulation were reduced by 70% or more. After a 2-3 week recovery period, cardiovascular parameters were again monitored at rest, in response to BCO, and at various levels of exercise with and without simultaneous hind limb ischemia. As in the control period, nine runs were taken as the post lesion (N=3) cardiovascular response to exercise and/or exercise iliac occlusion. Blood pressures and heart rates at rest and during exercise (without occlusion) were subjected to statistical annalysis (annalysis of variance, ie. ANOVA). If this test indicated a significant difference ($p<.05$) between these cardiovascular variables at various levels of exertion the students paired T-test was performed (comparing the blood pressure and heart rate responses to

succesive levels of exercise with and without simultaneous iliac occlusion and comparing pre-lesion to post-lesion responses). Once again, p values of less than .05 were taken to indicate statistically significant differences [157].

To insure that the initial lesions had interrupted the ascending limb of the somato-autonomic reflexes, animals were re-anesthetized 4-6 weeks after lesion placement. At this time the cardiovascular responses to bilateral sciatic nerve stimulation as well as somatic afferent-baroreceptor interactions (see Section III A) were monitored. Following this procedure the external iliac and/or common carotid arteries were checked for constriction by the occluders. The animals were then sacrificed and the spinal cord (L1-L3) was removed and placed in 10% buffered formalin solution. The extent of each lesion was histologically verified and plotted using a Leitz orthoplan drawing attachment in both chronic and acute studies (see results figures 21, 22 and 23).

CHAPTER IV

RESULTS

A. Acute Study

These experiments were carried out to localize the ascending spinal pathways which mediate somato-autonomic reflexes in dogs. Information gained from this preparation will then be used in the investigation into the functional significance of such reflexes in conscious animals.

In chronic preparations (next section) all surgical procedures are performed during sodium pentobarbital anesthesia. While this agent depresses autonomic activity acutely [137], it is preferred to other anesthetics (eg. alpha chloralose) in that functional neurological recovery is more or less complete after 2-4 days. Importantly, the completeness of lesion placement in chronic preparations will be confirmed (next section) by comparing the cardiovascular response to sciatic nerve stimulation before and after spinal section. For this reason the blood pressure and heart rate responses to such somatic afferent activation were noted with different anesthetics.

Figure three depicts blood pressure and heart rate at

rest and in response to bilateral sciatic nerve stimulation in dogs anesthetized with alpha chloralose or pentobarbital. The effect of vagotomy upon these variables is also displayed. It should be noted that the resting blood pressures and heart rates were significantly greater ($p<.05$) in pentobarbital anesthetized or vagotomized dogs than in chloralose anesthetized animals. Vagotomy also resulted in a significant ($p<.05$) increase in the tachycardia following somatic afferent activation. There was also a significant reduction in the blood pressure response to sciatic nerve stimulation when animals were subjected to pentobarbital anesthesia ($p< .05$). However, since these differences were quantitative and not qualitative the cardiovascular responses to somatic afferent activation were pooled in these experiments.

In figure four, the blood pressure and heart rate responses to bilateral sciatic nerve stimulation (Stim) and bilateral carotid artery occlusion (BCO) are displayed before and after DLS lesion placement at L2. The cardiovascular responses to BCO were unaltered by this spinal section (pressor response 40%, tachycardia 22%, pre-lesion; 37% and 20% post lesion, respectively). Conversely, DLS sectioning eliminated the response to sciatic nerve stimulation (pressor response 25%, heart rate increment 14%, pre-lesion; 2% and 0% post lesion

FIGURE 3

EFFECTS OF ALTERED ANESTHETICS AND VAGOTOMY UPON CARDIOVASCULAR RESPONSIVENESS

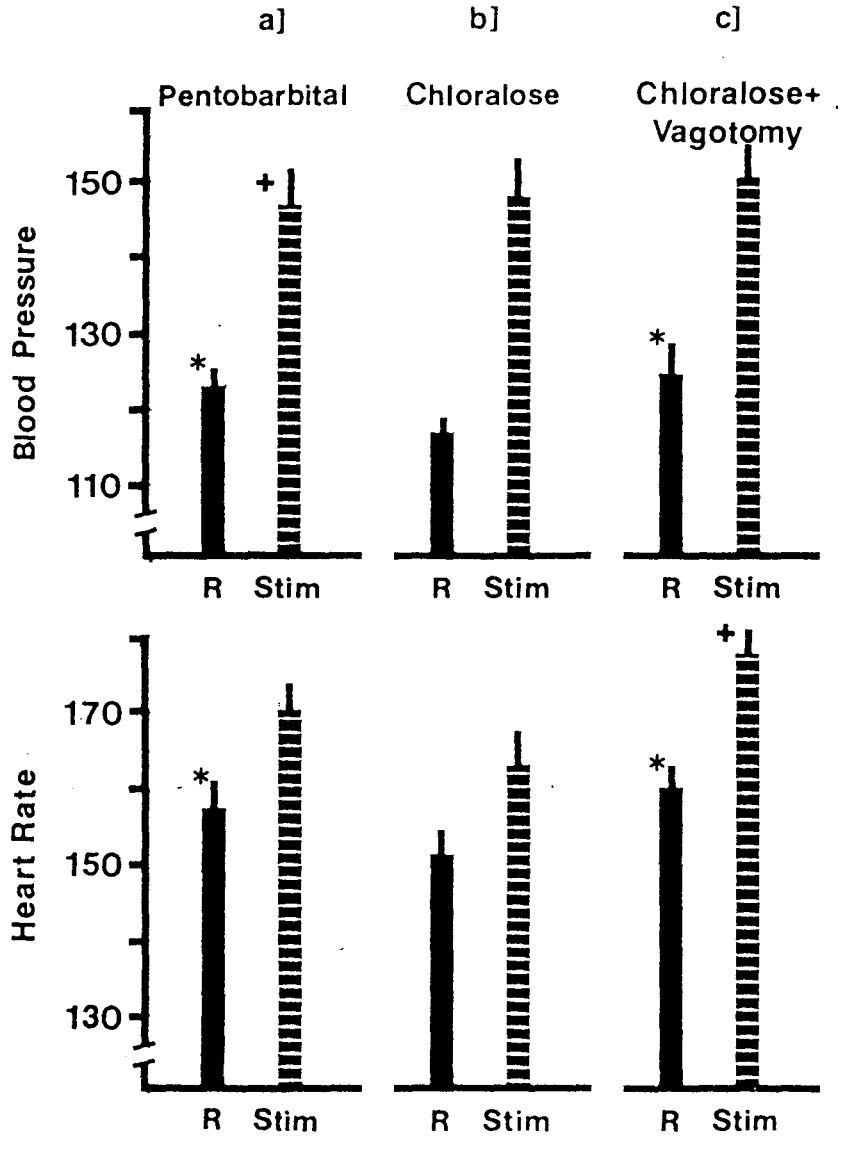

FIGURE 3

LEGEND

Mean blood pressure in mm Hg and heart rate in beats per minute at rest (R) and during bilateral sciatic nerve stimulation (Stim). In panel a] these parameters are displayed for pentobarbital anesthetized dogs (N=5). Data from chloralose anesthetized animals with intact (b], N=15) and sectioned (c], N=5) vagus nerves are presented. Bars indicate standard error of the mean. Resting values for blood pressure and heart rate in panels a] and c] were compared with (R) values from panel b] ($p < .05$, *).Alterations in these cardiovascular parameters during stimulation in panels a] and c] were also compared to (Stim) responses in panel b] ($p < .05$, +).

FIGURE 4

CARDIOVASCULAR RESPONSIVENESS BEFORE AND AFTER DLS LESIONS

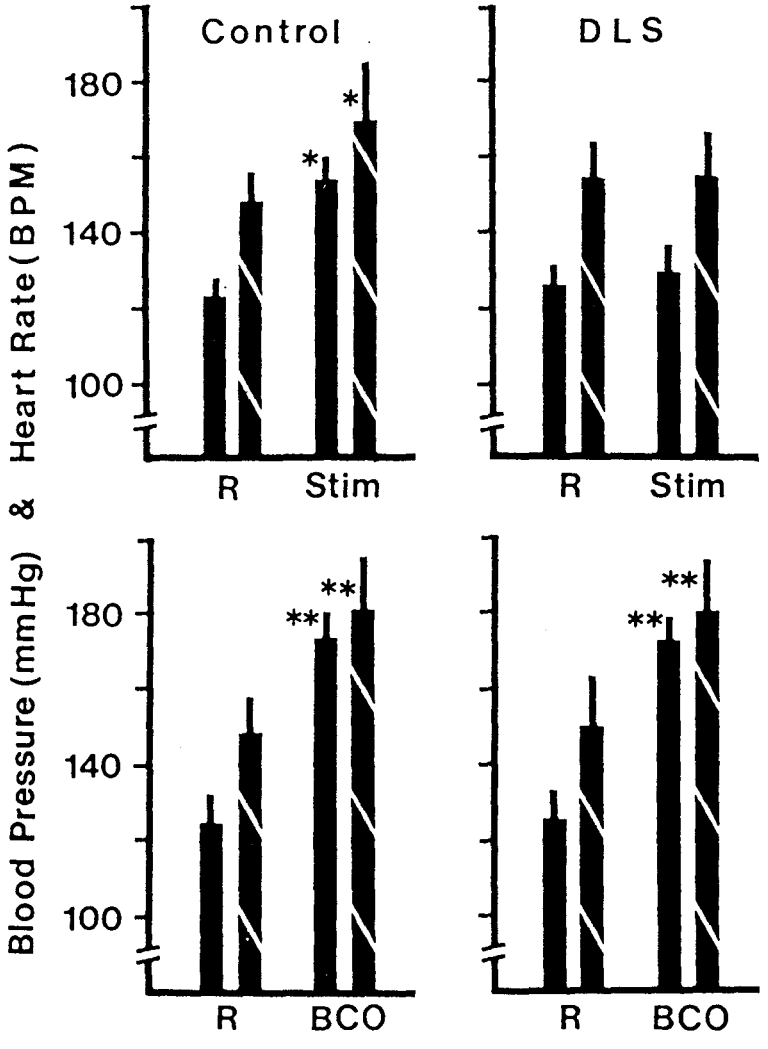

FIGURE 4

LEGEND

Cardiovascular parameters monitored in group II dogs at rest, in response to bilateral sciatic nerve stimulation (Stim) and during bilateral carotid occlusion (BCO). Solid bars indicate blood pressure and striped bars represent heart rates. Lines indicate standard errors. Blood pressure and heart rate at rest (R) were compared with (Stim) and (BCO) values before (Control) and after (DLS) spinal cord lesion placement ($p < .05$, * ; $p < .05$, **).

respectively).

Resting heart rates in these anesthetized preparations (148 +/-7.9 beats per minute; N=20) were markedly greater than resting heart rates in conscious animals (48 hr. average 93 +/- 9.4 bpm; N=20). This observation may be explained by the vasolytic actions of the anesthetics used in this study. It should also be pointed out that the cardiovascular responses to sciatic nerve stimulation in vagotomized animals (Fig. 3) are also eliminated following bilateral DLS lesions. In order to investigate the interaction between somatic afferent activation and the parasympathetic nervous system in this preparation, vagally mediated heart rate reductions were induced. Phenylephrine (8-10 mg/kg, i.v.) caused a 57.1 +/- 7.8 mm Hg increase in mean arterial blood pressure and a 53.7 +/- 6.2 beats per minute (BPM) decrease in heart rate (N=20). This bradycardia is baroreceptor mediated and is not present in vagotomized dogs (Group I). In other experiments reported herein, (Group IV), it has been demonstrated that phenylephrine-induced heart rate reductions are reversibly blocked by vagal cooling.

In figure five the interaction between phenylephrine-induced bradycardia (PHE) and supramaximal sciatic nerve stimulation (Stim) are depicted before and after spinal cord lesion placement. Somatic afferent activation was induced at the nadir of this bradycardia (10-20 seconds

after a bolus injection of phenylephrine, i.v.) and resulted in a 92+/-4.9% return to resting heart rate after ten seconds of stimulation. Upon termination of the stimulation the bradycardia returned (Post is not significantly different from Pre). Sectioning of the DLS in these animals had no effect upon the interaction between somatic afferent stimulation and baroreceptor-induced bradycardia (Fig. 5-DLS). However, when the spinal lesions were extended laterally to the dentate ligament (sectioning the DLF) this interaction was virtually eliminated (Fig. 5-DLS and DLF).

These observations may be interpreted as evidence for separate ascending spinal pathways mediating somato-sympathetic and somato-parasympathetic reflexes in the dog. To test this hypothesis a second group of animals were subjected to similar experimental procedures with DLF sectioning preceding DLS lesion placement (see methods, Group III). Blood pressure and heart rate responses to phenylephrine administration in these dogs were similar to those described in Group II (Fig. 5). Additionally, simultaneous sciatic nerve stimulation resulted in an 87% +-6.3% return to pre-drug heart rate (see Fig 6). Bilateral lesion of the dorsolateral funiculus did not significantly ($p > .05$) alter the interaction between this baroreceptor-mediated bradycardia and somatic afferent stimulation. In fact, only combined lesion of both the

FIGURE 5

SOMATIC AFFERENT-BARORECEPTOR INTERACTIONS : THE EFFECT OF DLS OR COMBINED DLS-DLF LESION PLACEMENT

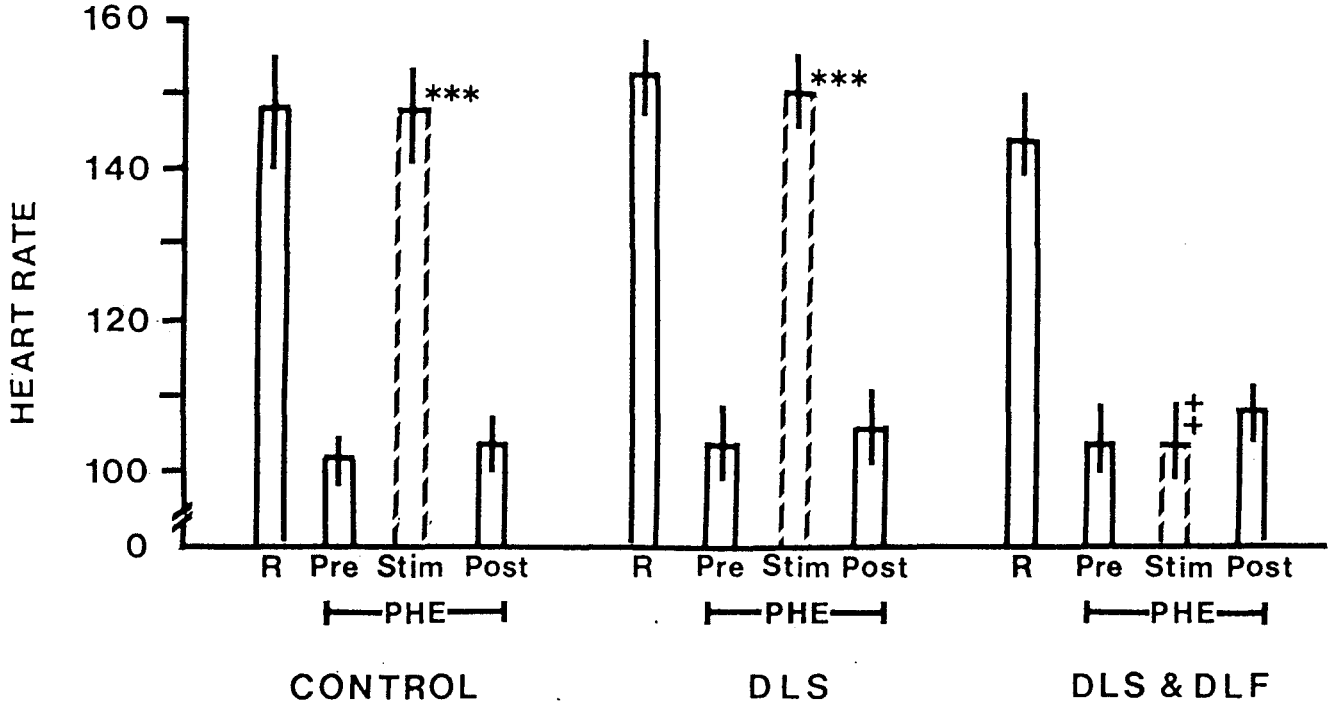

FIGURE 5

LEGEND

Heart rates are presented as means +/- SE at rest and during phenylephrine-induced bradycardia (PHE). In the intact animal (CONTROL) supramaximal sciatic nerve stimulation (Stim) interrupts this baroreceptor-mediated heart rate reduction. Heart rates immediately preceding "Pre" and following "Post" sciatic nerve stimulation during phenylephrine-induced bradycardia are not significantly different. The effect of spinal lesions placed in the DLS or in both the DLS and DLF, upon baroreceptor-somatic afferent interaction are also shown. Data taken from group II dogs (N=10). The students unpaired T-test was used to compare (Pre) vs. (Stim) ($p < .001$ ***) and (R) vs. (Stim) ($p < .01$ ++).

FIGURE 6

SOMATIC AFFERENT-BARORECEPTOR INTERACTIONS : THE EFFECT OF DLF OR COMBINED DLF-DLS LESION PLACEMENT

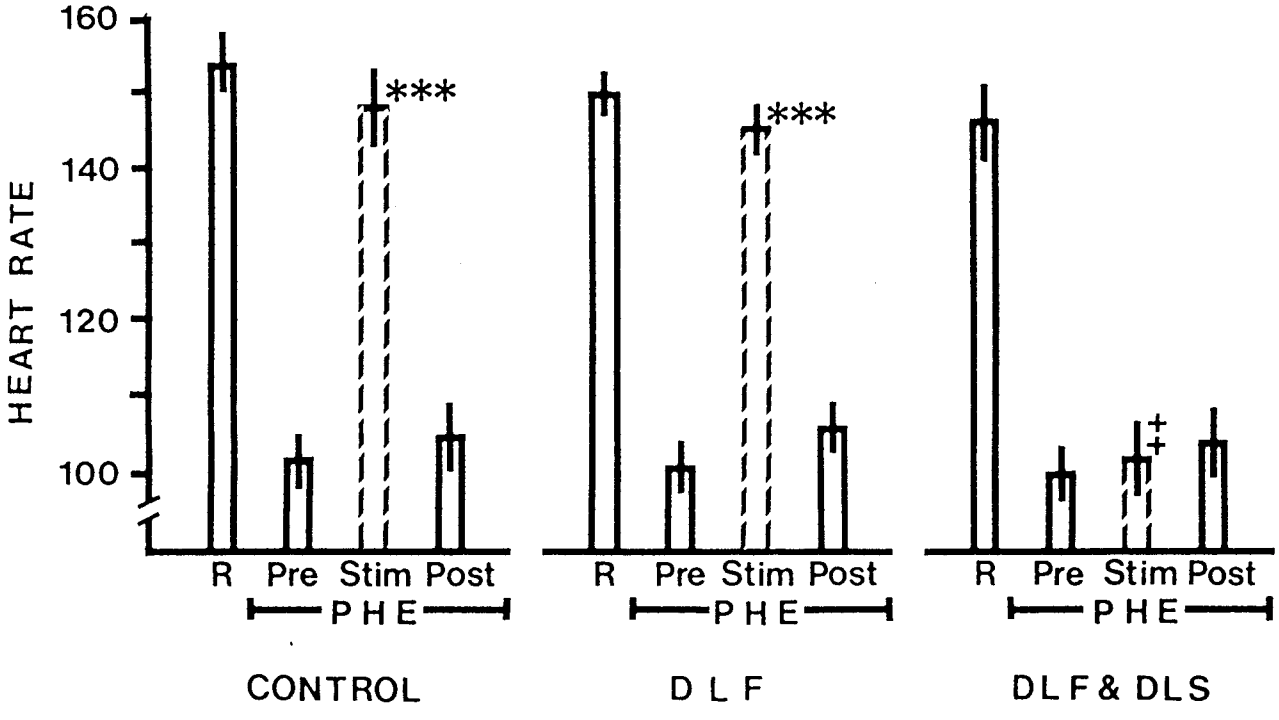

FIGURE 6

LEGEND

Interaction between sciatic nerve stimulation and phenylephrine-induced bradycardia (Abbreviations same as Figure 5). The data presented in this graph was taken from Group III animals (N=5). "Pre" and "Post" heart rates are not significantly different in control or lesioned dogs. The interaction between baroreceptor-mediated bradycardia and high intensity somatic afferent stimulation is unchanged by DLF lesion ($p > .05$) and eliminated by combined DLS and DLF sectionins. Statistical comparisions (unpaired T-tests) were made between (Pre) and (Stim) ($p < .001$ ***) and between (R) and (Stim) ($p < .01$ ++).

FIGURE 7

CARDIOVASCULAR RESPONSIVENESS BEFORE AND AFTER DLF OR COMBINED DLS-DLF LESIONS

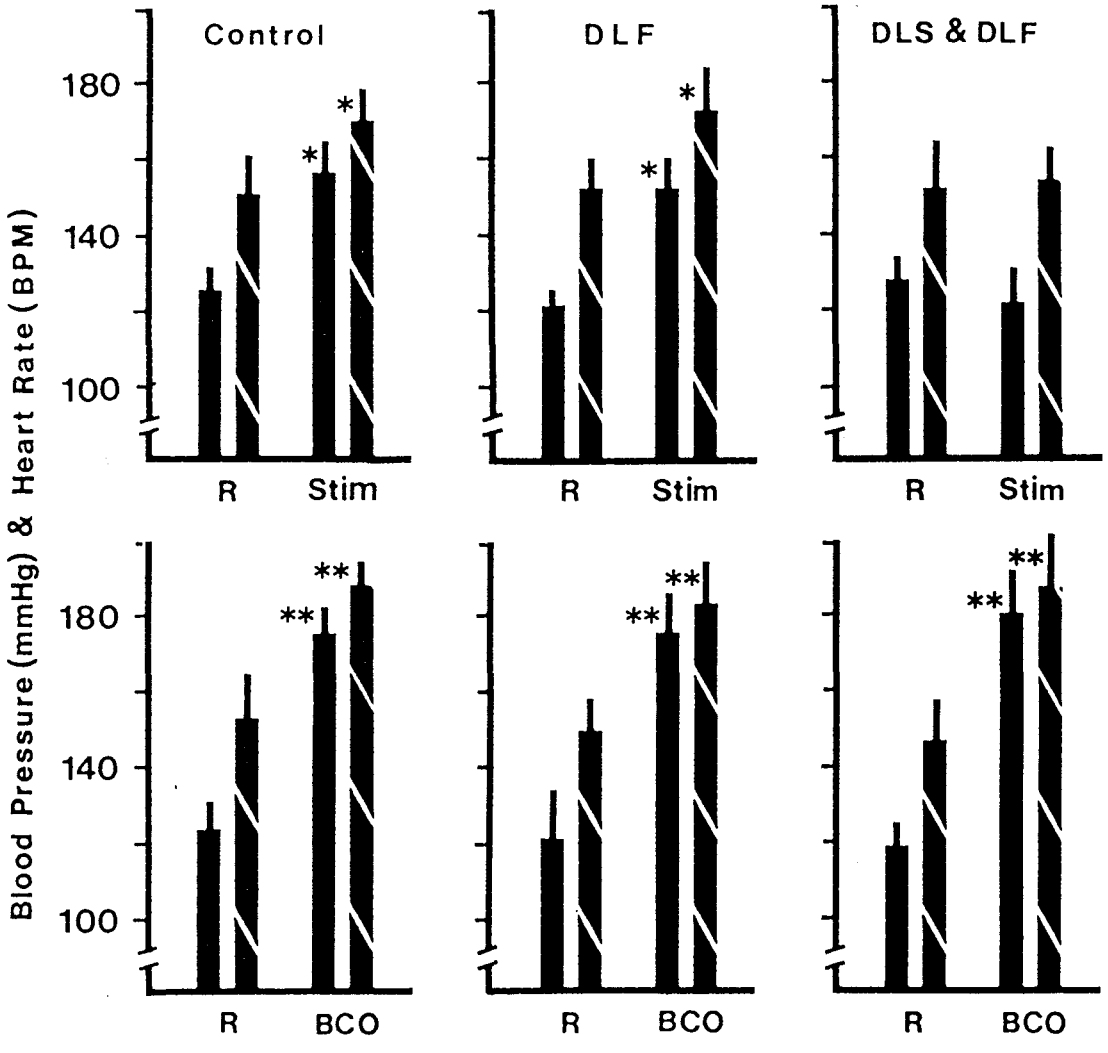

FIGURE 7

LEGEND

Mean blood pressure (solid bars) and heart rate (striped bars) +/- SE at rest (R) , in response to bilateral carotid occlusion (BCO) and sciatic nerve stimulation (Stim). The students unpaired T test was used to compaire (R) vs.(BCO), and (R) vs. (Stim) in these experiments ($p < .05$ * ; $p < .01$ **). Bilateral lesions of the dorsolateral funiculus (DLF) preceded dorsolateral sulcus area (DLS) sectioning in these doss (see methods group III).

DLS and DLF were effective in interrupting this interplay. It must be concluded that the ascending spinal systems which mediate this somato-parasympathetic reflex are more diffuse than the pathway described in the cat spinal cord.

In figure seven, the blood pressure and heart rate responses to bilateral sciatic nerve stimulation and BCO are shown before and after DLF and combined DLF and DLS spinal lesions. Section of the DLF (bilaterally) was not effective in altering the blood pressure or heart rate responses to BCO or sciatic nerve activation. However, when the lesions are extended to include both the dorsolateral sulcus area and the dorsolateral funiculus, the cardiovascular responses to electrical activation of somatic afferents are eliminated. These lesions do not effect the pressor response or tachycardia which result from bilateral carotid occlusion, indicating that descending autonomic systems are intact. The failure of DLF sectioning to significantly alter the cardiovascular response to sciatic nerve stimulation in this preparation indicates that ascending axons destined to interact with the sympathetic nervous system are 1) not present in the DLF or 2) not present in great enough numbers to overcome the depression brought about by anesthesia and/or decamethonium.

While electrical activation of peripheral afferent nerves is a useful tool in establishing the central

pathways of somato-autonomic reflexes, this means of stimulation is far from physiological. Since it will be contended that such reflexes play a role in the cardiovascular responses to exercise in conscious animals (next section), experiments were designed in which muscular work could be evoked in anesthetized dogs. In these animals (methods, Group IV) cardiovascular parameters were monitored during ventral root stimulation for 45-150 seconds. In figure eight, resting (R) as well as peak blood pressure and heart rate during muscular contraction (C) are displayed. This "exercise" evoked a significant pressor response (19.8+/-2.6 mm Hg, range 13 to 28 mm Hg; $p<.01$, N=6) which was not accompanied by a significant tachycardia (4.2+-1.9 BPM, range -1 to 9 BPM; $p>.05$, N=6). This cardiovascular response to sustained hind leg contraction was not altered by reversible vagal blockade (17.1+/-2.8 mm Hg, range 9 to 25 mm Hg; $p<.01$, N=6: 8.3+/-4 BPM range -4 to 16; $p>.05$, N=6). However, bilateral lesion placement in the dorsolateral sulcus area completely eliminated the pressor response which accompanies ventral root stimulation (-3.7+/-1.4 mm Hg, range -1 to -7 mm Hg).

Vagal responsiveness was tested in these experiments by monitoring heart rate responses to pressor doses of phenylepherine (8-10 mg/Kg, i.v.). Prior to cooling this drug caused an increase in blood pressure which was

similar to that noted previously in Group II and III animals (59+/-8.2 mm Hg) and a significant bradycardia (55+/-4.9 BPM). During vagal cooling the pressor response to this drug was significantly greater (83+/-6.1 mm Hg; 41% greater than the pre-cooling response) while the reflex bradycardia was reduced to 14% of control (8.4+/-3.1 BPM). After slow (45 minutes) rewarming of the vagus nerves to 37 C the response to phenylephrine administration was again tested and returned to pre-cooling levels (blood pressure increase, 61+/-9.0 mm Hg; heart rate reduction, 52+/-4.7 BPM).

The interaction between induced muscular contraction (C) and vagally mediated bradycardia was tested in six animals. This relationship is displayed in figure 9 along with the interaction of somatic afferent stimulation (S) and phenylephrine-induced bradycardia (Phe) before and after vagotomy or lumbar spinal cord lesion placement. In this figure the percentages indicate heart rates relative to resting (before drug administration) values. For example, phenylephrine alone causes a 33% reduction in heart rate (151+/-7.3 to 102+/-4.7 BPM; $p<.001$; N=26). This is recorded as 67% of the resting heart rate in figure 9. When the sciatic nerves are stimulated (S) shortly after administration of this drug the heart rate returns to 92% of the resting values (see figures 5 and

FIGURE 8

CARDIOVASCULAR RESPONSE TO INDUCED HIND LIMB CONTRACTION

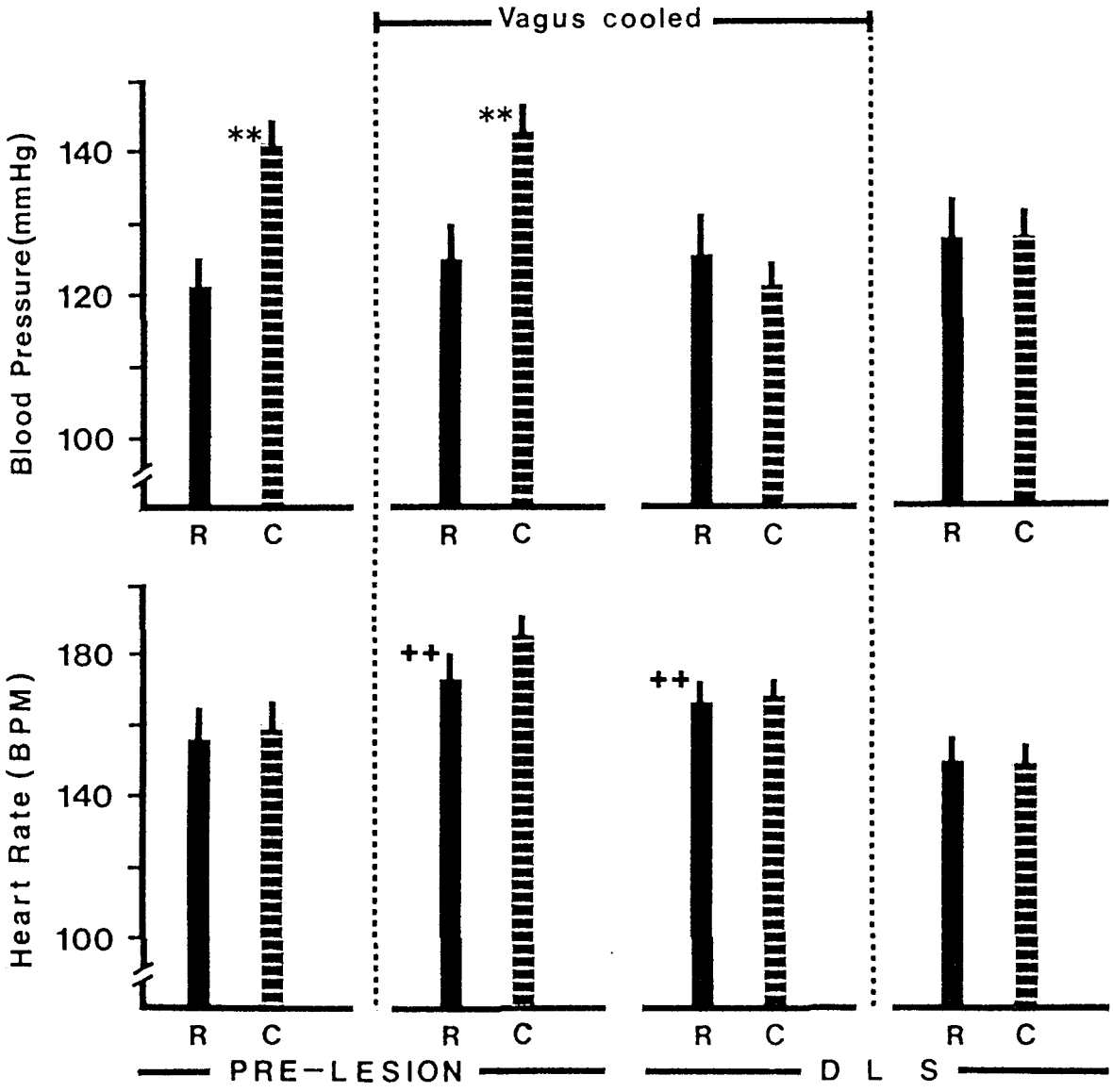

FIGURE 8

LEGEND

Blood pressure and heart rate at rest (R) and during induced hind limb contraction (C) are expressed as means +/- SE (Group IV, N=6). Significant differences between blood pressure or heart rate at rest and during contraction are indicated as follows:($p < .01$ **). Resting values were also compared before and after vagal cooling and/or spinal sections ($p < .01$ ++). DLS indicates the placement of bilateral lesions in the dorsolateral sulcus area.

FIGURE 9

SOMATO-PARASYMPATHETIC INTERACTIONS WITH ALTERED VAGAL RESPONSIVENESS, SPINAL LESIONS AND MEANS OF SOMATIC AFFERENT ACTIVATION

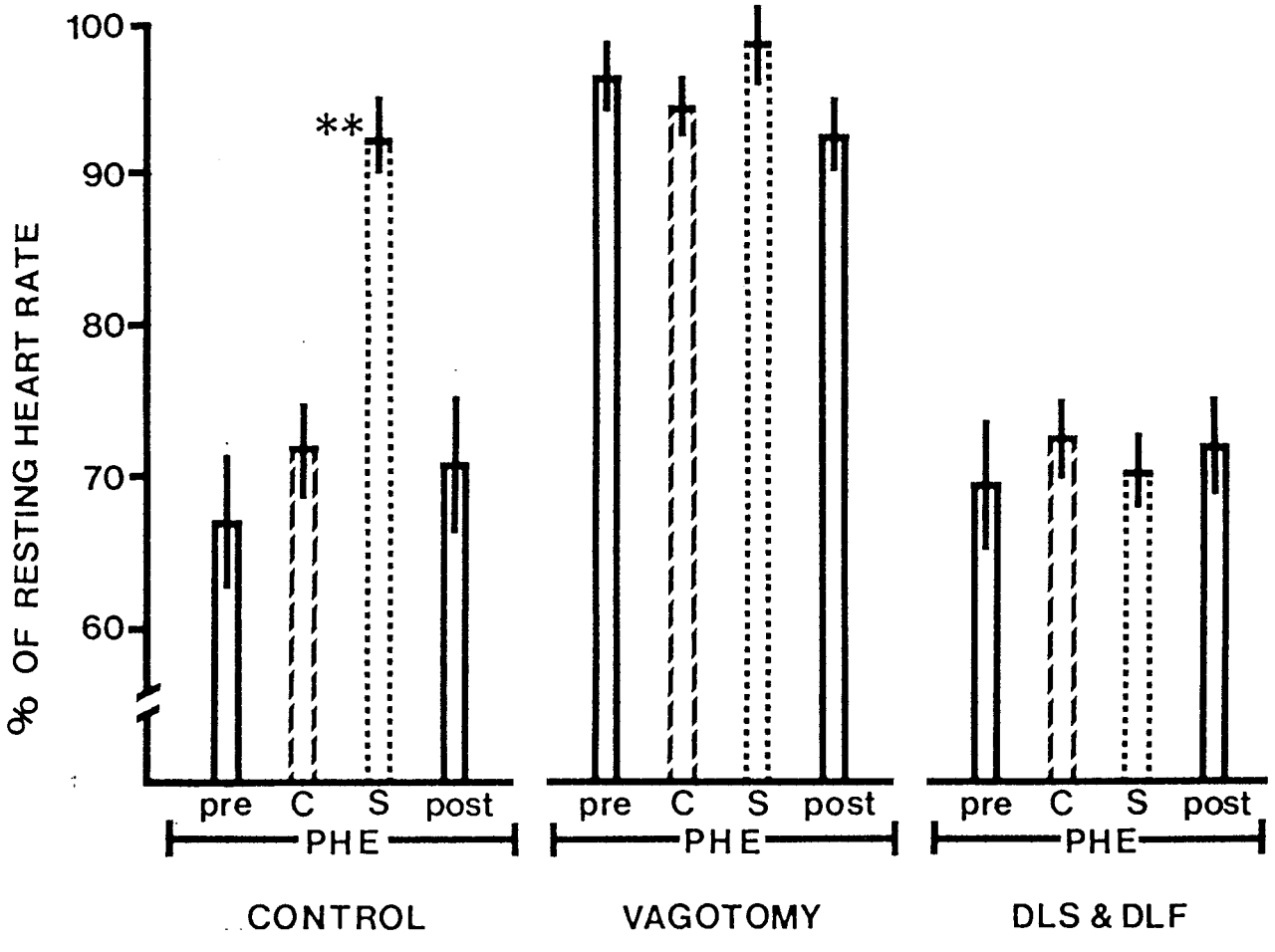

FIGURE 9

LEGEND

Percentages of resting (pre-phenylephrine) heart rates in group I-IV dogs. These animals were intact "CONTROL", vagotomized via bilateral vagus nerve section (Group I) or vagal cooling (Group IV), "VAGOTOMY", or had vagus nerves intact with spinal lesions placed in both the dorsolateral funiculus and the dorsolateral sulcus area "DLS & DLF". Percentages are expressed as means +/- SE. Statistical comparisons (unpaired T-test) between pre and C revealed no significant differences in intact, vagotomized or lesioned animals. The students unpaired T-test was also used to compare pre and S heart rates in each group ($p < .01$, **). The number of animals for each manipulation was as follows. "CONTROL" : pre = Groups I-IV, N=26; C = Group IV, N=6; S = Groups I-III, N=20; post = Groups I-IV, N=26. "VAGOTOMY" : pre = Groups I & IV, N=11; C = Group IV, N=6; S = Group I, N=5; post = Groups I & IV, N=11. "DLS & DLF" : pre = Groups II-IV, N=21; C = Group IV, N=6; S = Group II & III, N=15; post = Groups II-IV, N=21.

FIGURE 10

BLOOD PRESSURE DURING INDUCED CONTRACTIONS WITH AND WITHOUT SIMULTANEOUS VASCULAR OCCLUSION: EFFECT OF DLS OR COMBINED DLS-DLF LESION PLACEMENT

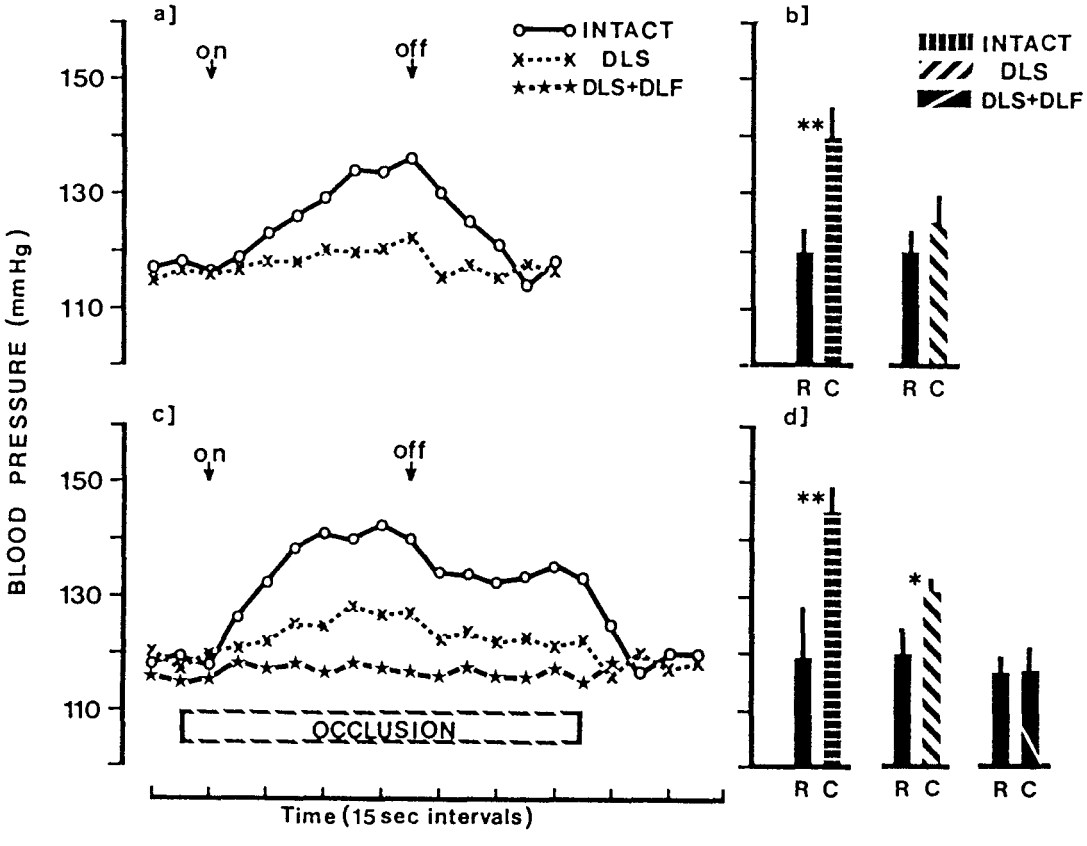

FIGURE 10

LEGEND

Mean blood pressure in intact (N=6), DLS sectioned (N=3) and combined DLS and DLF (N=6) lesioned dogs in response to induced hind limb contraction (Group IV). In panels a] and c] arrows indicate the initiation (on) and termination (off) of ventral root stimulation. In panel c] bilateral external iliac artery and inferior vena cava occlusion preceded induced contraction by 8 seconds and was maintained for 105 seconds. In panels b] and d] blood pressures are expressed as means +/- SE at rest (R) and at the peak response to contraction (C), which occured after 45 to 150 seconds of ventral root stimulation. Values for (R) and (C) were compared in these panels and the differences are indicated as follows: ($p < .05$, * ; $p < .01$, ** ; $p < .001$, ***).

FIGURE 11

BLOOD PRESSURE DURING INDUCED CONTRACTIONS WITH AND WITHOUT SIMULTANEOUS VASCULAR OCCLUSION: EFFECT OF DLF OR COMBINED DLF-DLS LESION PLACEMENT

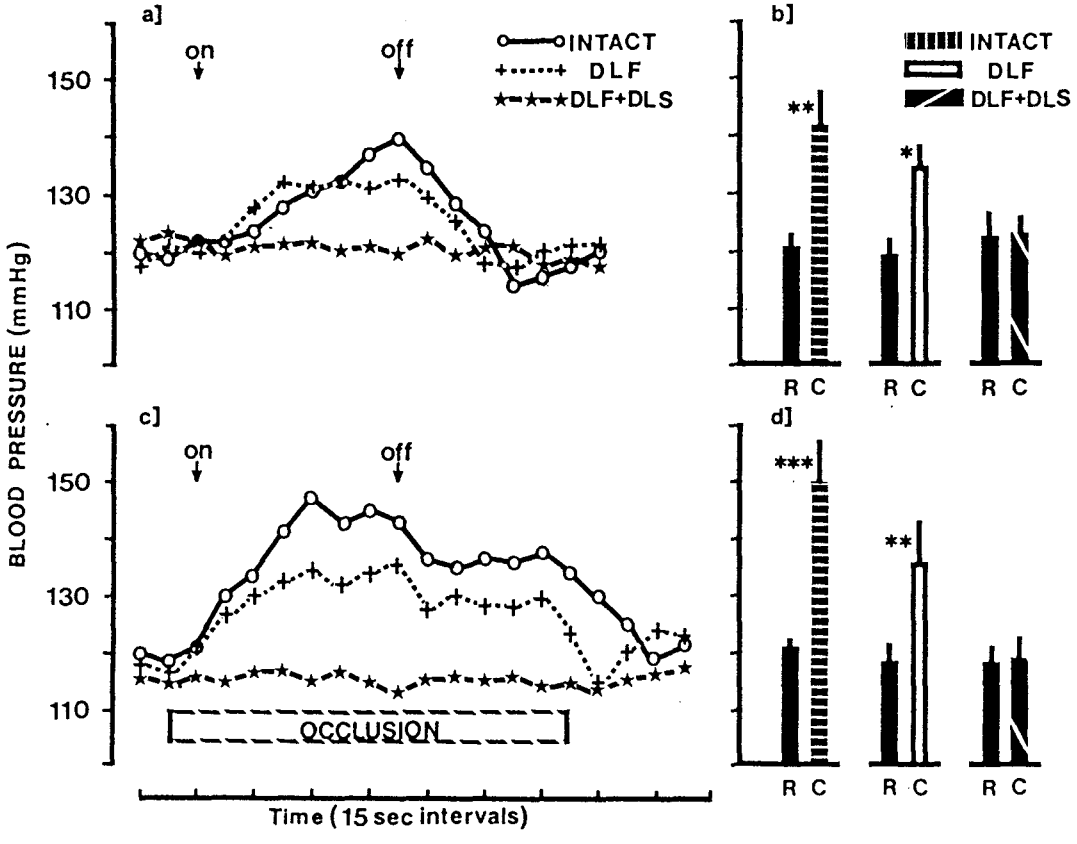

FIGURE 11

LEGEND

Mean blood pressure in intact (N=6), DLF sectioned (N=3) and combined DLF and DLS (N=6) lesioned dogs in response to induced hind limb contraction (Group IV). Statistical comparisons and abbreviations as in Figure 10.

6). Conversely, when muscular contraction (C) was induced during baroreceptor mediated bradycardia, there was no significant change in heart rate (96+/-5.2 to 103+/-4.8 BPM; Fig. 9 (Pre) 67%, (C)=72%; p>.05). Vagal cooling as described above, or vagotomy (methods group I) eliminated the reflex bradycardia brought about by phenylephrine. Finally, the effect of combined DLS and DLF lesions upon these somatic afferent-baroreceptor interactions were noted (Figure 9, far right).

In figures 10 and 11 the blood pressure alterations which accompany sustained hind leg contraction are displayed with and without simultaneous vascular occlusion. In panels a] and c] the time course of this pressor response was followed. In these experiments ventral root stimulation was maintained for 52 seconds and terminated (off), whether or not the blood pressure had stablized. In panels b] and d] mean blood pressures during induced contraction (C) represent the maximal responses to "exercise" (stimulus maintained for 45-150 seconds) in these animals.

Returning to figure 10 panels a] and c], each point represents the mean blood pressure for all animals before, during (between arrows) and after ventral root stimulation. In panel c] blood flow through the external iliac arteries and the inferior vena cava (occlusion) preceded contraction by 8 seconds, and was maintained for

45 seconds after the termination of "exercise". Standard error brackets were not included in panels a] and c] in the interest of clarity. Blood pressure was monitored during ventral root stimulation with and without vascular occlusion in unlesioned animals (INTACT, N=6), following DLS section at L3 (DLS, N=3) and after combined lesions (DLS and DLF, N=6). DLS sectionins in these doss completely eliminated the pressor response to sustained contraction in the absence of vascular occlusion (panel b], R vs. C; p>.05). While this lesion did not completely eliminate the pressor response to exercise-occlusion (panel c], DLS vs. DLF and DLS; p<.05; panel d], DLS-R vs. C; p<.05), DLS sectionins significantly reduced this blood pressure elevation (panel c], intact vs. DLS; p<.05). Interestinsly, only combined lesions of the dorsolateral funiculus and dorsolateral sulcus area completely eliminated the pressor response to exercise-occlusion (panel d], DLS and DLF-R vs. C; p>.05).

One final point which is apparent upon close observation of panel c] in fisure 10 is the sisnificant reduction in blood pressure with the termination of contraction despite maintained occlusion. Specifically, blood pressure drops from 140+/-3.1 mm Hs just prior to the release of stimulation to 133+/-2.7 mm Hs after stimulus termination (p<.05). However, arterial pressure remains sisnificantly above restins levels (panel c],

points to the right of (on)) until occlusion is released. In three animals the order of lesion placement was reversed (ie. DLF preceded DLS sectioning, see figure 11). In these dogs section of the dorsolateral funiculus resulted in a small but significant reduction in the pressor response to hind limb contraction with and without simultaneous occlusion (intact vs. DLF; $p<.05$).

Comparison of the blood pressure responses to ventral root stimulation in animals with DLS lesion only (Figure 10, N=3) and DLF lesion only (figure 11, N=3) should also be carried out. Such comparison reveals that the pressor response to "exercise" in DLS sectioned animals (contraction only, 5.2+/-5.5 mmHg; $p>.05$: contraction occlusion, 11.8+/-3.9 mm Hg; $p<.05$) is significantly less than that observed in dogs with lesion of the DLF exclusively (contraction only, 15.1+/-4.1 mm Hg; $p<.05$: contraction-occlusion, 17.8+/-3.4; $p<.01$). This may indicate that the ascending systems which mediate the cardiovascular responses to exercise are more concentrated in the dorsolateral sulcus area, but they do extend laterally into the dorsolateral funiculus.

B. Chronic Study

Resting heart rates in conscious dogs were sampled every 30 minutes for 48 hours, three times in each animal (see methods). These control pulse rates were: 1) 91+/-6.5 BPM; range 38+/-7.4 to 144+/-8.5 BPM (N=12), prior to

instrumentation, 2) 88+/-5.7 BPM; range 39+/-6.8 to 147+/-9.1 BPM one week post-instrumentation (N=12) and 3) 84+/-6.1 BPM; range 42+/-5.8 to 141+/-8.1 BPM, 7 to 14 days after spinal cord lesion placement (N=12). The large variability in these 48 hour heart rates (note the mean ranges above) was most likely dependent upon altered internal (eg. sleep vs. alertness) and external (presence or absence of other animals or people in the vicinity) cues.

Eight to ten days after instrumentation, both heart rate and blood pressure were monitored continuously for 1-2 hour periods with the animal on the treadmill. The initial resting heart rate in these animals was 123+/-6.8 BPM, or 40% above the 48 hour value. After 30 to 120 minutes, the resting pulse rate returned to within 15% of this control reading (ie. 88+/-13 BPM). Over the same time course blood pressure declined from 115+/-4.2 to 107+/-3.1 mm Hg. Bilateral carotid arterial occlusion in these dogs resulted in an increase in arterial pressure (from 107+/-3.1 to 155+/-5.3 mmHg) and heart rate (from 99+/-4.7 to 127+/-6.1 bpm, N=12). Occlusion of the left external iliac artery for two minutes did not significantly alter these cardiovascular parameters at rest (107+/-3.5 to 109+/-3.8 mm Hg, and 98+/-6.4 to 101+/-5.8 bpm; $p>.05$, N=6).

Blood pressure and heart rate was monitored at rest,

in response to BCO and iliac arterial occlusion (as outlined above) every day for 9 to 15 days prior to and during treadmill exercise. After recording these variables in the intact preparation, animals were anesthetized and lesions were placed at L1-L2. The effectiveness of these spinal sections was confirmed by testing: 1) the pressor response and tachycardia accompanying right or left sciatic nerve stimulation and 2) the interaction between sciatic nerve stimulation and phenylepherine-induced bradycardia. This pre-lesion, unilateral stimulation (25 second trains, 15 v, 1 msec duration) resulted in increments of blood pressure (from 127+/-6.3 to 151+/-7.1 mm Hg, $p<.001$) and heart rate (from 162+/-4.8 to 173+/-5.9 bpm; $p<.05$, N=12). This stimulation also caused a 51% reduction in the reflex bradycardia brought about by phenylephrine administration. Bilateral lesions (Fig. 23) resulted in a significant reduction in the pressor response (from 124+/-6.1 to 131+/-5.2 mm Hg, a 71% reduction in the blood pressure increment) and the tachycardia (from 158+/-7.1 to 161+/-2.3, a 73% reduction in the heart rate increment) following sciatic nerve stimulation. These lesions also interrupted the interaction between phenylephrine-induced heart rate reduction and sciatic nerve activation (stimulation cause a 15% return to pre-drug pulse rate after lesion placement). At the time immediately

preceding sacrifice, these animals were again anesthetized and the functional effectiveness of the lesions were verified. Blood pressure and heart rate responses to bilateral sciatic nerve stimulation at this time were 89% and 86% below pre-lesion responses to unilateral stimulation, respectively. In three animals, unilateral stimulation of the sciatic nerve during lesion placement resulted in temporary peripheral nerve damage, as indicated by unilateral drop foot which lasted for 3-5 weeks. These animals were not run until this symptom disappeared.

In eight animals (Fig. 23, dogs 13-20) the spinal damage was extensive and resulted in permanent hind limb paralysis. These dogs were sacrificed after two to three weeks of recording the cardiovascular responses to BCO (N=8) and common iliac artery occlusion (N=4). These responses were not significantly different from those obtained in the same animals prior to spinal sectionins. In fact, the blood pressure and heart rate at rest and in response to BCO and iliac occulsion (without exercise) were unaltered by spinal lesions in all animals tested (Fig. 23, dogs 1-20).

In figures 12-18 the cardiovascular parameters monitored during treadmill runnins are displayed. Transient iliac artery occlusion at various levels of exercise are indicated by the treadmill speed (in

FIGURE 12

BLOOD PRESSURE DURING TREADMILL RUNNING

(ALL FOURS 10% GRADE)

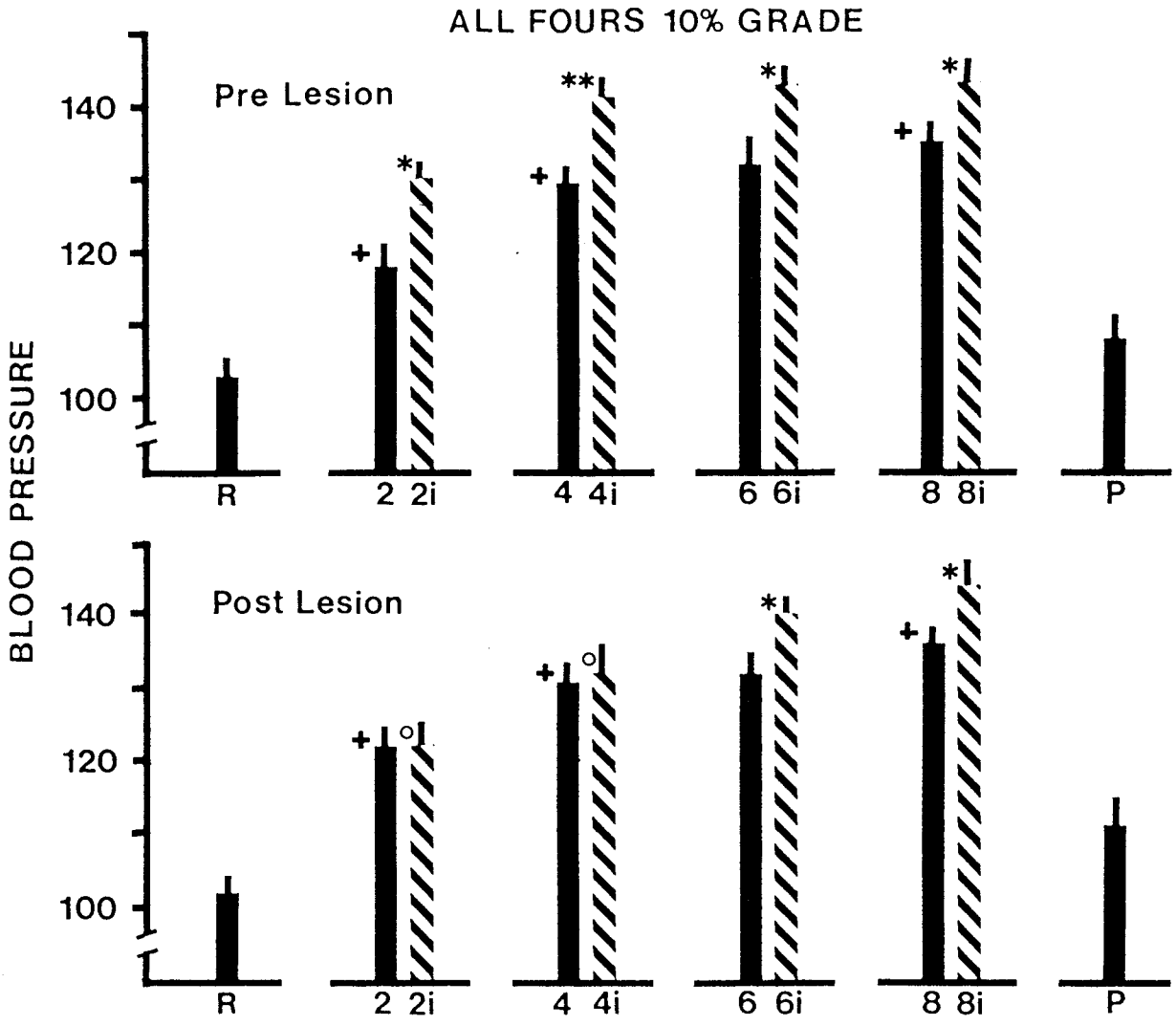

FIGURE 12

LEGEND

Mean blood pressure +/- SE in conscious dogs at rest (R), during various levels of exercise (10% grade), and 10 minutes post exercise (P) before and after spinal cord lesion placement. Numbers on the abscissa indicate the treadmill speed in kilometers per hour. Pre and post lesion runs without arterial occlusion are indicated by solid bars (N=12). Striped bars represent the blood pressure in these animals during exercise with simultaneous iliac artery occlusion ("i", N=6). Blood pressures at R, 2, 4, 6, and 8 (without occlusion) were subjected to statistical analysis (ANOVA) and found to be significantly altered by exercise ($p<.05$). The paired T-test was then used to compare the cardiovascular responses to succesive levels of exercise (ie R vs. 2, 2 vs. 4,etc.: $p< .05$,+) and such responses with and without simultaneous occlusion (ie. 2 vs. 2i, 4 vs. 4i, ect.: $p< .05$, *; $p< .01$, **; $p< .001$, ***). Blood pressure at each level was further compared before and after spinal sectioning (ie. (R) pre vs. (R) post, 2 pre vs. 2 post, 2i pre vs. 2i post, etc.: $p< .05$, o; $p< .01$, oo; $p<.001$, ooo).

FIGURE 13

HEART RATE DURING TREADMILL RUNNING

(ALL FOURS 10% GRADE)

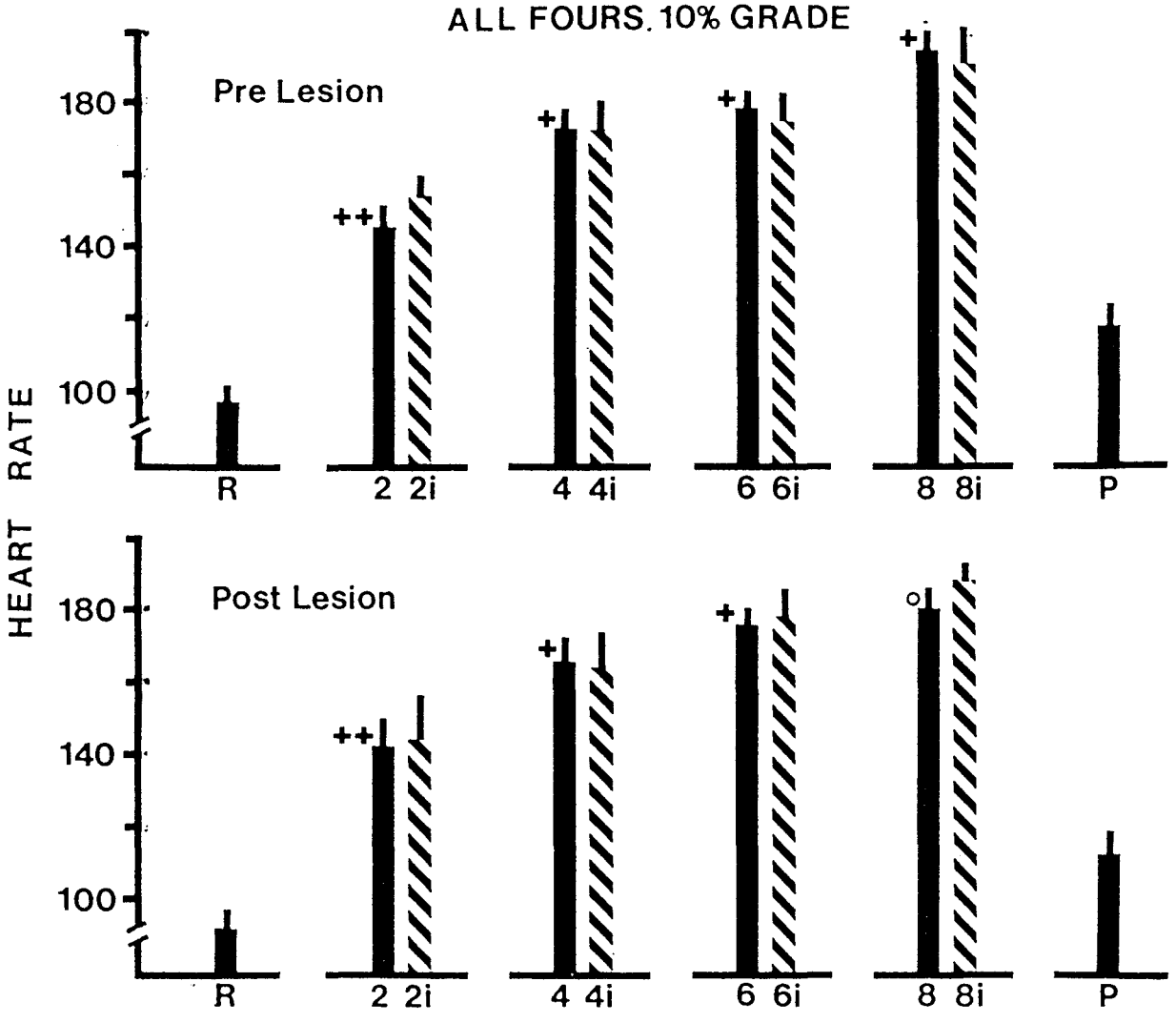

FIGURE 13

LEGEND

Mean heart rates +/- SE which accompany the blood pressure responses to treadmill exercise outlined in the previous figure. Statistical comparisons and abbreviations as in figure 12.

FIGURE 14

BLOOD PRESSURE DURING TREADMILL RUNNING

(ALL FOURS 0% GRADE)

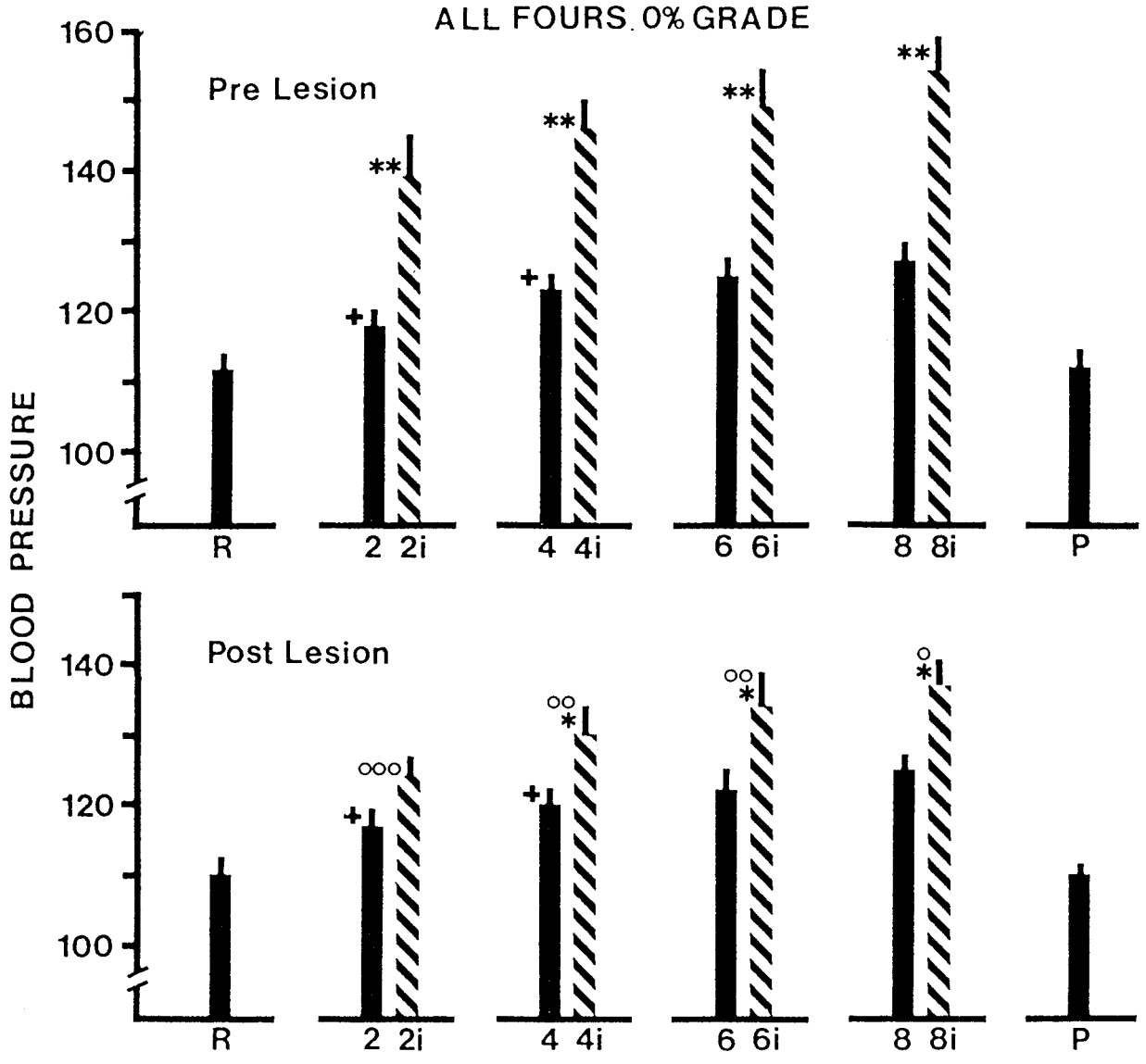

FIGURE 14

LEGEND

Mean blood pressure +/- SE in conscious dogs at rest (R) and during treadmill running (0% grade) at various speeds before and after spinal cord lesion placement. Statistical comparisons and abbreviations as in figure 12.

FIGURE 15

HEART RATE DURING TREADMILL RUNNING

(ALL FOURS 0% GRADE)

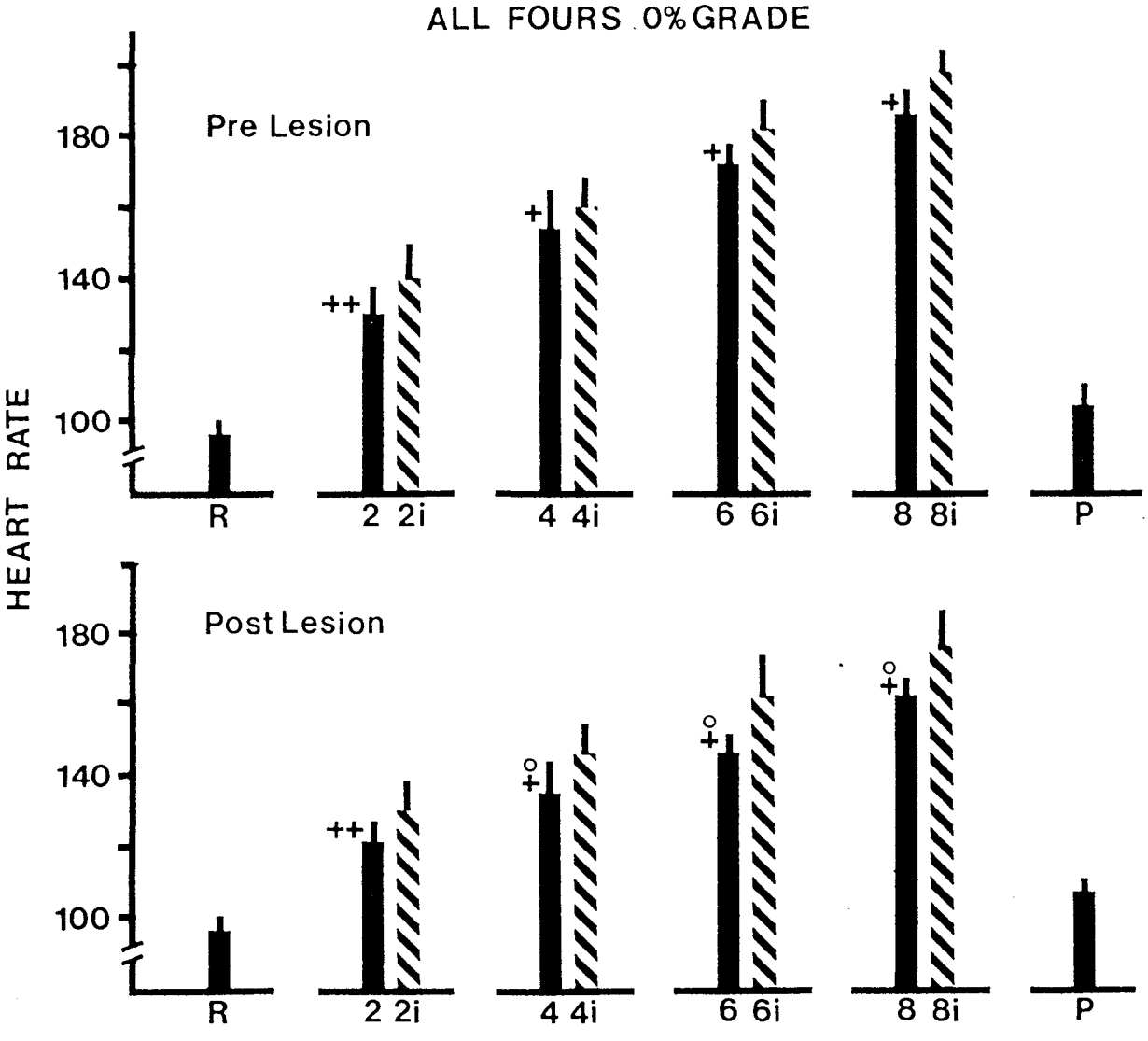

FIGURE 15

LEGEND

Mean heart rates +/- SE which accompany the blood pressure responses to treadmill running on all fours at a 0% grade (see figure 14). Statistical comparisons and abbreviations as in figure 12.

FIGURE 16

BLOOD PRESSURE DURING TREADMILL RUNNING

(HIND LIMBS ONLY 0% GRADE)

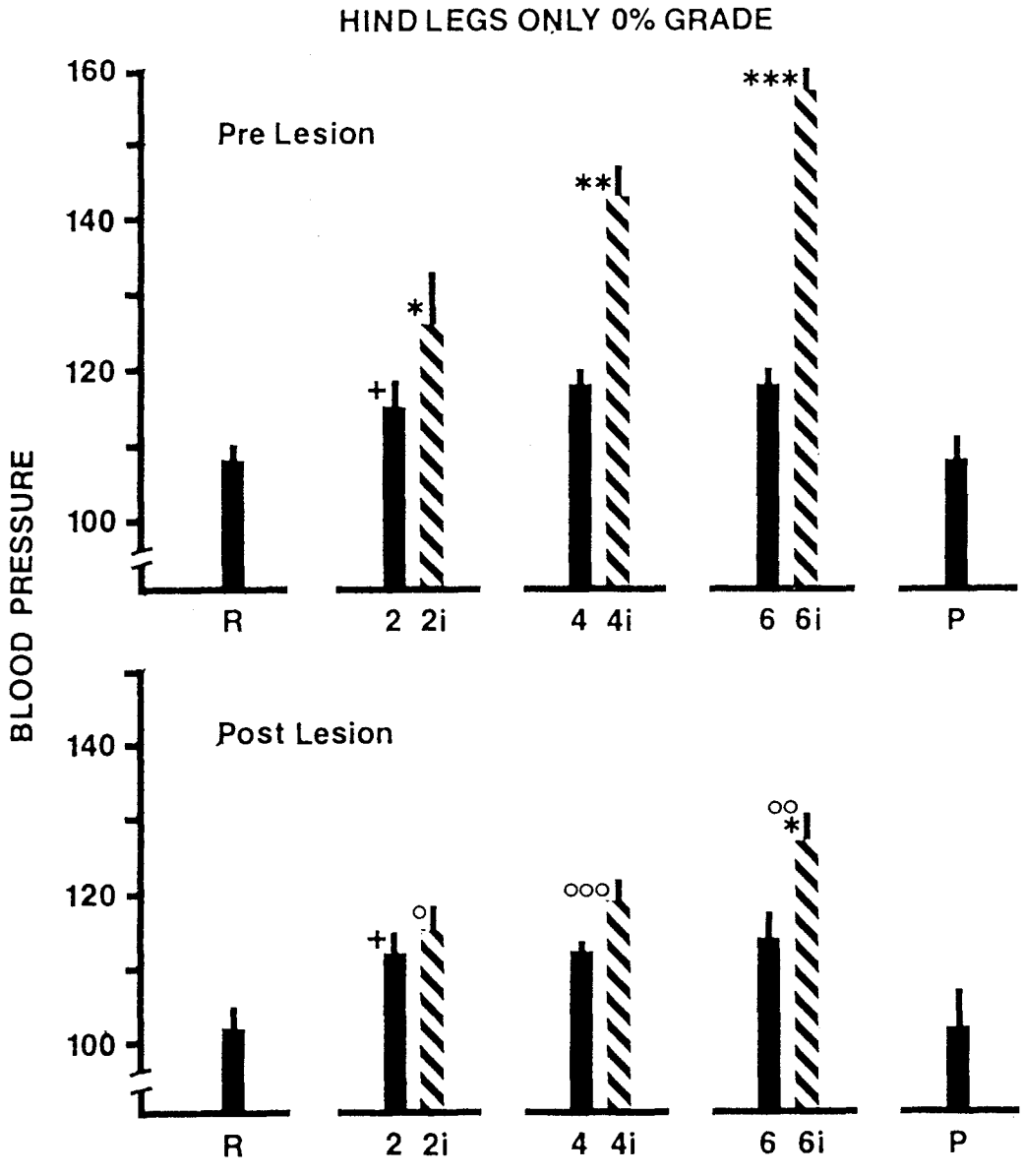

FIGURE 16

LEGEND

Mean blood pressure +/- SE in conscious dogs at rest (R) and during treadmill running (hind legs only; 0% grade) at various speeds before and after spinal cord lesion placement. Statistical comparisons and abbreviations as in figure 12.

FIGURE 17

HEART RATE DURING TREADMILL RUNNING

(HIND LEGS ONLY 0% GRADE)

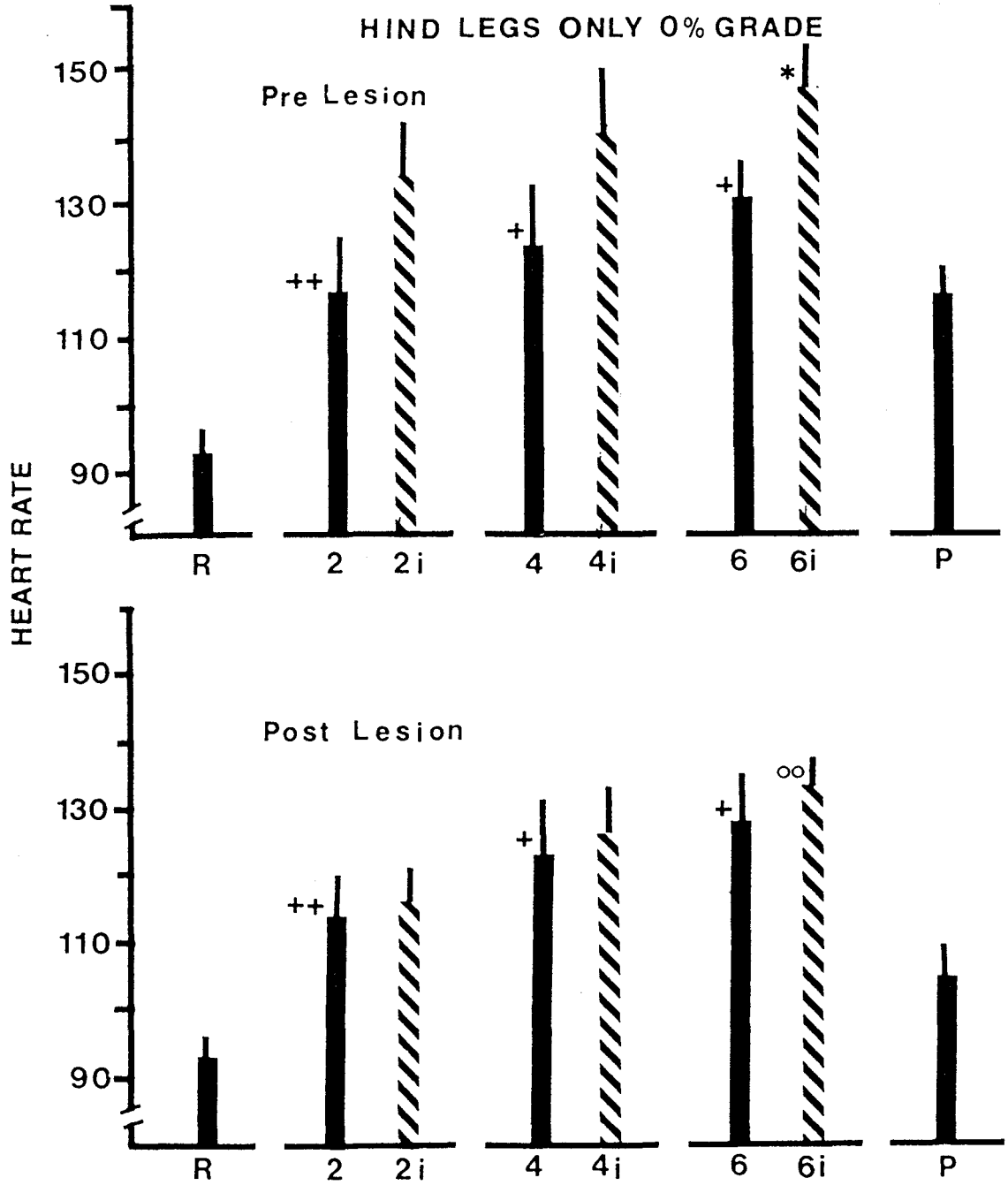

FIGURE 17

LEGEND

Mean heart rates +/- SE which accompany the blood pressure responses to treadmill running on a 0% grade with hind legs only (see figure 16). Statistical comparisions and abbreviations as in figure 12.

FIGURE 18

BLOOD PRESSURE DURING EXERCISE

(ORIGINAL POLYGRAPH TRACINGS)

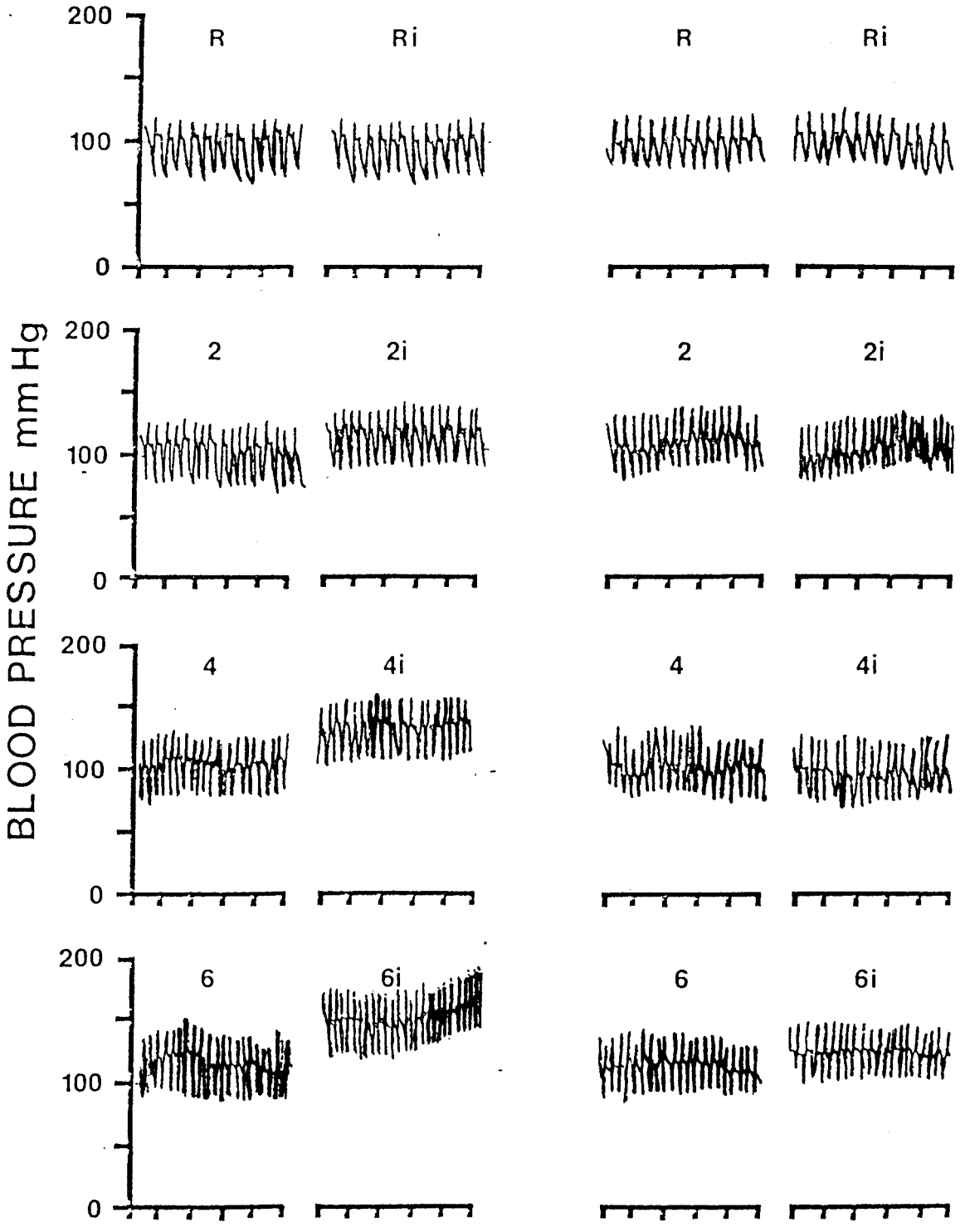

FIGURE 18

LEGEND

Ten second intervals of polygraph tracings taken during one continuous run in dog number 10 (see methods and figure 23). The maximum blood pressure attained at each level of exercise with and without simultaneous iliac arterial occlusion in this dog is displayed. Vertical calibrations indicate time (2 second intervals).

kilometers per hour) followed by the letter i. Treadmill speed alone implies running without simultaneous occlusion in these figures.

In figure 12 the blood pressure responses to treadmill running with and without simultaneous hind limb ischemia are presented for the same animals before and after DLF and DLS lesion placement. The pressor response which accompanies this moderate (10% grade, 2-8 km/hour) exercise was unaltered by such spinal sections. However, the additional blood pressure increment that occurs during external iliac artery occlusion was reduced by these lesions. Specifically, iliac occlusion resulted in significant pressor responses at all treadmill speeds prior to (pre-lesion: 2 vs. 2i, 4vs. 4i, 6 vs. 6i and 8 vs. 8i; $p<.05$) but not after interruption of the DLS and DLF at L2 (post lesion: 2 vs. 2i and 4 vs. 4i; $p>.05$). At 6 and 8 kilometers per hour (10% grade) the pressor response following iliac occlusion was unaltered by spinal cord lesion placement. Finally, in four animals blood pressure was monitored during iliac artery occlusion 10 minutes after cessation of exercise. This procedure did not elicit a significant pressor response (105+/-4.3 mmHg to 108+/-5.2 mmHg; $p>.05$).

Heart rate was monitored continuously during treadmill running at a 10% grade and data from these experiments is presented in figure 13. This level of

exercise resulted in a substantial tachycardia, which was not altered by combined section of the DLS and DLF at 2, 4 and 6 Km./hr. It is also apparent from careful observation of this figure that hind limb ischemia during running at this grade does not significantly alter the pulse rate. It seems possible that sensory information capable of eliciting heart rate increments during dynamic, whole body exercise may overshadow the afferent input from one ischemic limb at this work load. To test this hypothesis, the effect of exercise-occlusion was tested at lower levels of whole body exercise (all fours 0% grade). Finally, the relative contribution of afferent information from the ischemic limb was maximized by observation of the cardiovascular responses to primarily hind limb work. The blood pressure response to treadmill running at a 0% grade (mild to moderate work load) is presented in figure 14. The pressor response evoked by this exercise was significantly smaller than that elicited by higher work loads (fig. 12), and was not altered by lumbar spinal cord lesions. Conversely, the blood pressure increments brought about by simultaneous exercise-occlusion were significantly greater than observed at a 10% grade ($p<.01$) for each level of exercise. These responses were markedly reduced, though not eliminated, by section of the DLS and DLF at L2. Interestingly, the pressor response evoked by hind limb occlusion during exercise at a 0% grade was

maximal at 2 kilometers per hour (ie. 2-2i=21+/-5.1 mm Hg, 8-8i=27+/-6.3 mm Hg; p>.05).

In figure 15 heart rate increments which accompany the pressor response to treadmill running at a 0% grade are presented. While the tachycardia that occurs during such exercise is significantly less than observed during 10% running, there is no significant response to exercise occlusion. However, spinal cord lesions did cause a marked reduction in the heart rate response to non-ischemic exercise at 4, 6 and 8 kilometers per hour. The failure of iliac artery occlusion in eliciting a change in heart rate, as well as the observation that the blood pressure response to exercise-occlusion does not appear to be related to the level of exercise, may still be explained by the significant sensory input from non-ischemic areas. Such input is presumably reduced when animals run on their hind legs only (front legs supported by a shelf).

Blood pressure was monitored continuously during hind limb running in 12 dogs before and after lumbar spinal cord lesion placement. The data from these experiments are presented in figure 16. This exercise resulted in modest elevation in blood pressure; however, there was no significant increase in this variable after 2 kilometers per hour (ie. 2 vs. 6; p>.05), and spinal cord lesions did not alter the response. Conversely, the arterial pressure

increment which occurred during hind limb running with simultaneous iliac artery occlusion was directly related to the level of exercise in these experiments. Further, lesion placement in the DLS and DLF markedly reduced, but did not eliminate this response. In figure 17 the heart rate response to hind limb running with and without simultaneous iliac artery occlusion is presented. This exercise results in modest tachycardia which is not altered by spinal cord lesion placement in the DLS and DLF. Additionally, simultaneous hind leg running and iliac artery occlusion results in significant elevation in heart rate which is not related to the level of exercise. Lesion placement in the lumbar spinal cord of these animals (fig. 23, animals 1-12) caused a small but significant reduction in this response to exercise-ischemia.

In figure 18 an example of the raw data which was used to construct figures 12-17 is displayed. These polygraph tracings were taken during one continuous run (hind limbs only, 0% grade) in dog number 10 (see methods and figure 23).

As mentioned briefly above, the blood pressure response to simultaneous exercise-occlusion is reduced, but not completely eliminated by lesion placement in the DLF and DLS at L2. In figures 19 and 20 the time course of the maximal pressor response to iliac artery occlusion

FIGURE 19

TIME COURSE OF THE MAXIMAL PRESSOR RESPONSE

TO ISCHEMIA DURING LIGHT EXERCISE

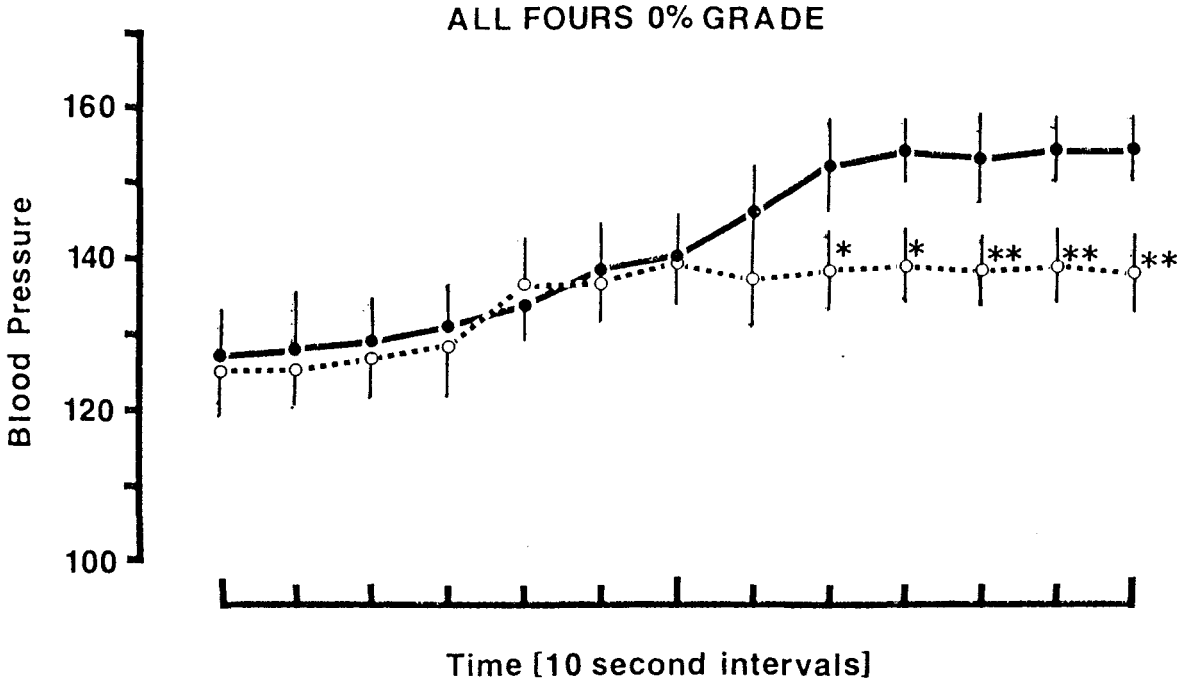

FIGURE 19

LEGEND

Blood pressure (in mmHg +/- SE) was monitored continuously over two minutes during treadmill exercise (all fours, 0% grade, 6 Kph) with simultaneous occlusion of the left external iliac artery. The solid line represents the change in this cardiovascular parameter in intact dogs (N=6) while the dotted line indicates blood pressure alterations in the same dogs after lumbar spinal cord lesion placement. Comparisons between intact and post lesion responses were performed using the students paired T-test ($p<.05$, *; $p< .01$, **).

FIGURE 20

TIME COURSE OF THE MAXIMAL PRESSOR RESPONSE

TO ISCHEMIA DURING HIND LIMB EXERCISE

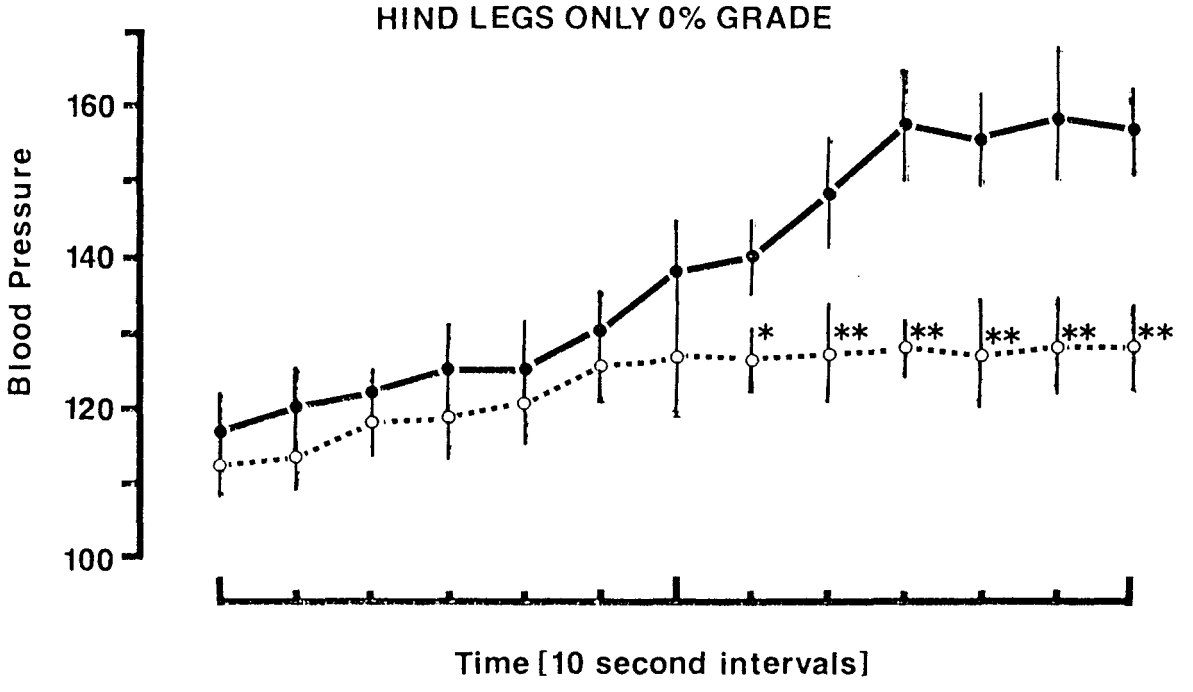

FIGURE 20

LEGEND

Blood pressure (in mmHg +/- SE) was monitored continuously over two minutes during treadmill exercise (hind legs only, 0% grade, 6 Kph) with simultaneous occlusion of the left external iliac artery. This cardiovascular parameter was monitored in conscious dogs before (solid line) and after (dotted line) lesion placement in the DLS and DLF at L-2. Comparisons between intact and post lesion responses were performed using the students paired T-test ($p<.05$, *; $p< .01$, **).

during treadmill running on all fours (at a 0% grade) and hind limbs only, respectively, are presented. Careful observation of figure 19 reveals that the pressor response to exercise-ischemia before lesion placement is triphasic. Specifically, there is an initial, slow increase in arterial pressure during the first minute of occlusion, followed by a rapid increase over the next thirty seconds and finally, a leveling off between 90 and 120 seconds. With more prolonged ischemia there may be a further increase in arterial pressure; however, occlusion was only maintained for two minutes in most animals. After lesion placement, the increase in blood pressure normally observed over the first minute of exersice-ischemia was unaltered. However, no further increase in blood pressure was noted over the next 60 seconds of maintained occlusion.

The multiphasic nature of the blood pressure response to exercise-ischemia, as a function of time was also noted during hind limb only running, prior to lesion placement (Fig. 20). However, the pressor response to exercise-occlusion was greater with this form of exercise. Once again the interruption of ascending systems thought to mediate somato-autonomic reflexes, preferentially altered the response to prolonged exercise-ischemia and left the early portion of this response unchanged.

FIGURE 21

DLS SPINAL CORD LESIONS-ACUTE EXPERIMENTS

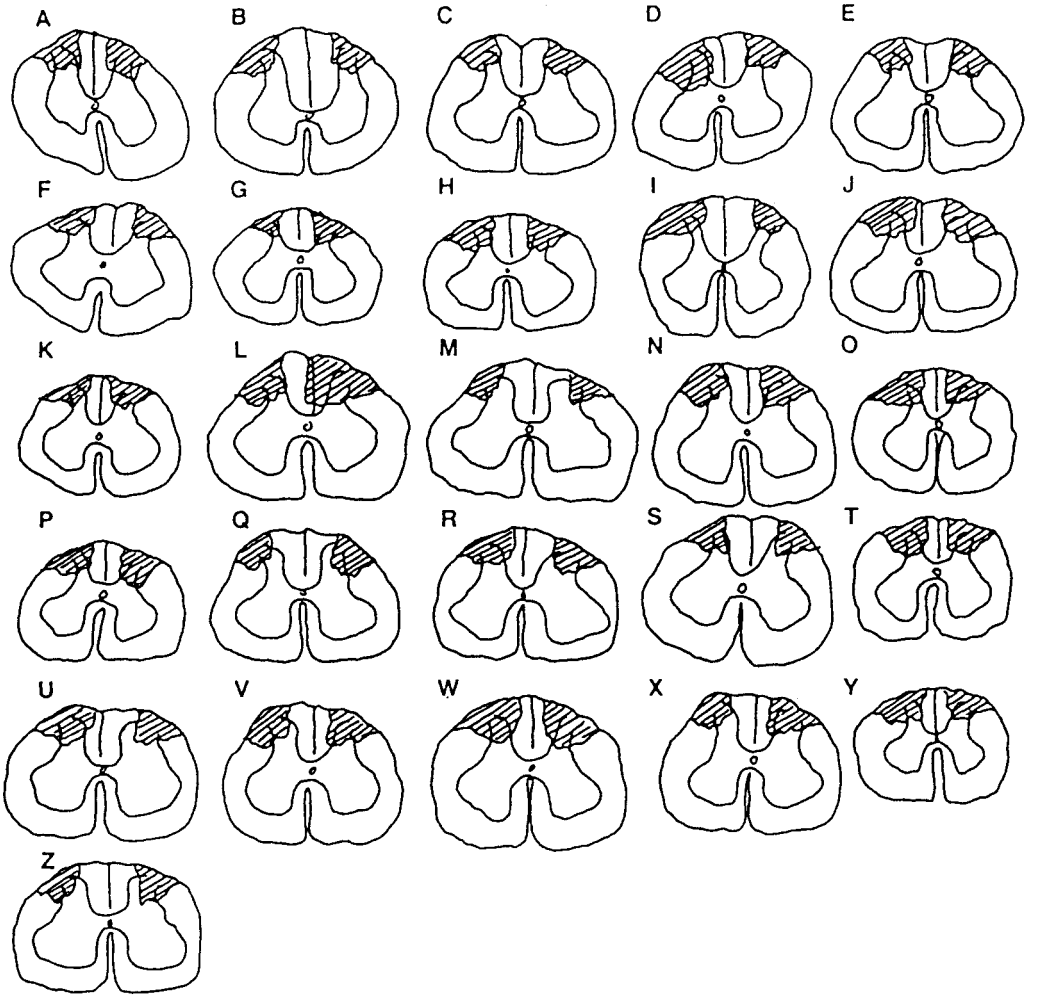

FIGURE 21

LEGEND

Cross sections of lumbar spinal cords from acute experiments in which the actual site of lesions aimed at interrupting ascending systems in the DLS are outlined (diagonal lines). Sections reproduced using a Leitz Orthoplan drawing attachment.

FIGURE 22

DLF SPINAL CORD LESIONS-ACUTE EXPERIMENTS

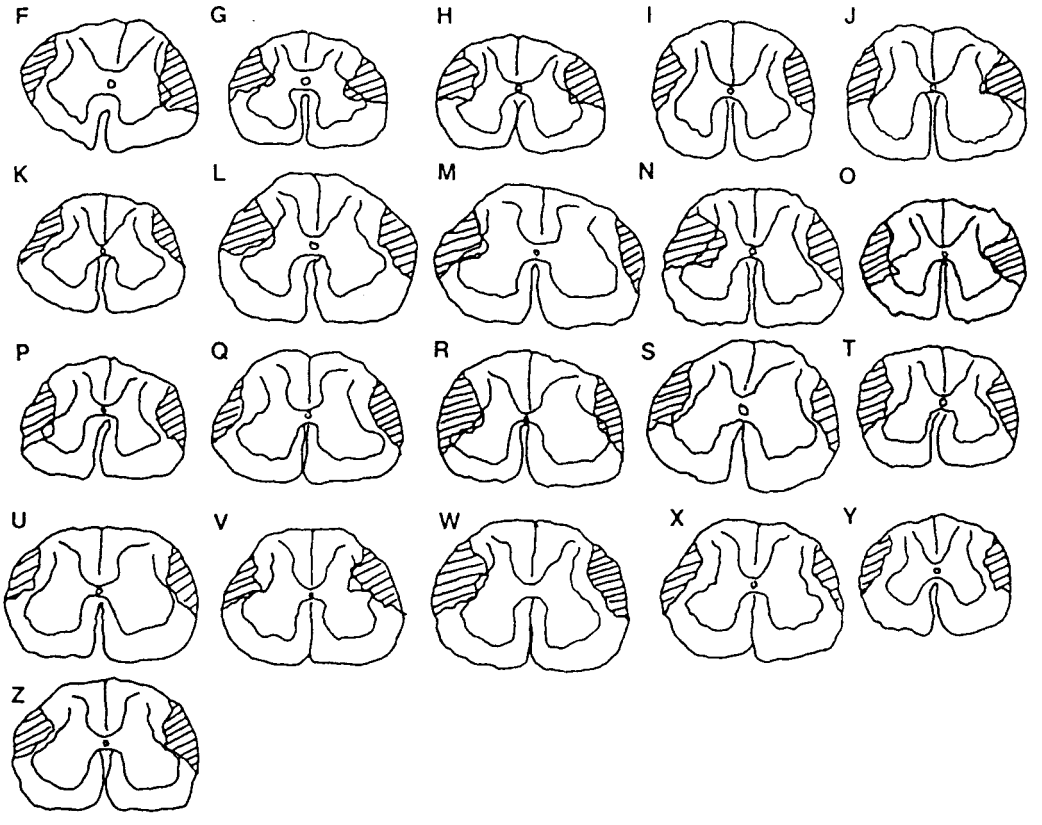

FIGURE 22

LEGEND

Cross sections of lumbar spinal cords from acute experiments in which the actual site of lesions aimed at interrupting ascending systems in the DLF are outlined (diagonal lines). Sections reproduced as in fig 18.

FIGURE 23

SPINAL CORD LESIONS-CHRONIC EXPERIMENTS

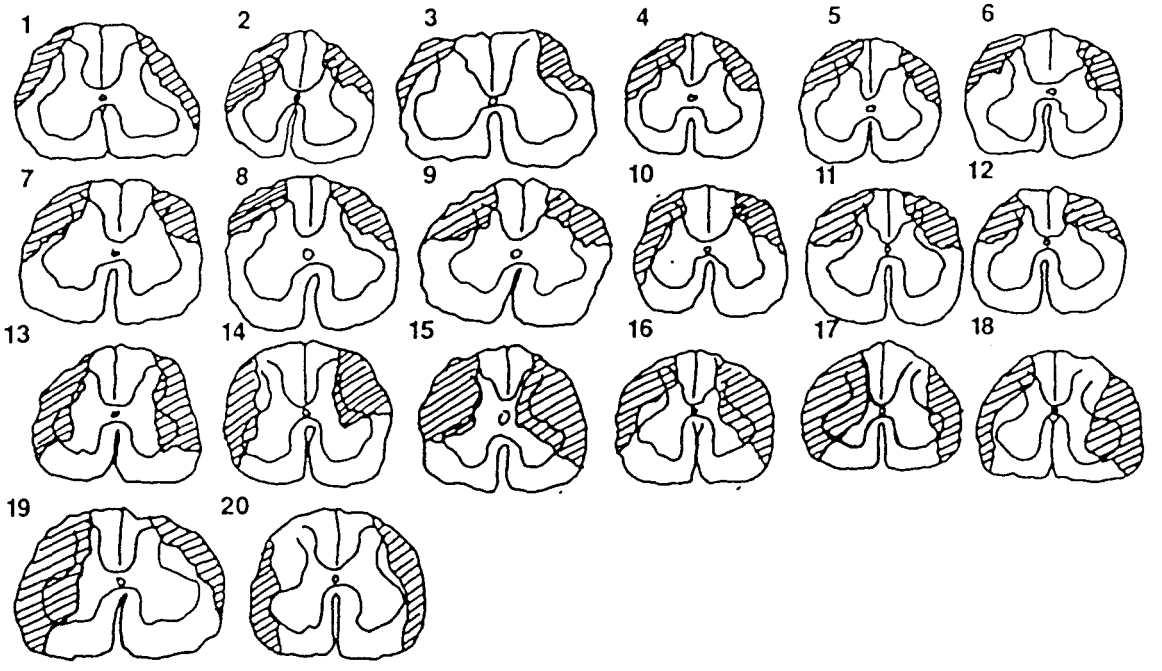

FIGURE 23

LEGEND

Cross sections of lumbar spinal cords from chronic experiments in which the actual site of lesions aimed at interrupting ascending systems in both the DLS and DLF are outlined (diagonal stripes). Sections reproduced as in figure 18.

CHAPTER V

DISCUSSION

Acute experiments were performed upon anesthetized dogs (chloralose or pentobarbital) in an effort to localize the ascending pathways which mediate somato-autonomic reflexes. In this study somatic afferent activation was elicited : 1) by electrical stimulation of the sciatic nerves (bilaterally) or 2) by a reflex originating in the hind limbs in response to induced tetanic contractions (ventral root stimulation). Ascending systems were interrupted by placing discrete lesions in the lumbar spinal cord above the level of entry of hind limb afferents [81]. The cardiovascular responses to bilateral carotid artery occlusion were unaltered by these spinal sections, indicating that descending systems which influence autonomic output [50,51,60,94] were left intact.

Bilateral stimulation of the sciatic nerves in these dogs resulted in significant increases in blood pressure (29.7 +/- 5.1 mmHg) and heart rate (26.1 +/- 7.4 bpm) prior to spinal cord lesion placement. These data compare well with those reported by Tibes [166], who carried out

experiments upon hexobarbital anesthetized dogs. This investigator monitored alterations in cardiovascular and respiratory parameters in response to bilateral sciatic nerve activation during cold blockade of various portions of these nerves. With low intensity, high frequency stimulation, Tibes noted significant elevations in heart rate and minute ventilation in the absence of nerve block. Conversely, cold block distal (inhibiting muscular contraction) or proximal (interrupting afferent fiber conduction) to the stimulating electrodes, eliminated these responses to low intensity stimulation. This author concluded that such stimulation brought about a reflex activation of muscle afferent fibers, mimicing the physiological response to exercise. When the sciatic nerves (proximal to the stimulation site) were cooled to 4-8 C, blocking conduction in primarily myelinated fibers [52], this reflex was not altered. However, when the proximal nerve temperature reached 1 C, blocking group III and IV afferents [52], the cardiovascular and respiratory responses to stimulation were lost despite maintained muscular contraction. Finally, when muscular contraction was blocked with succinylcholine or curare, only high intensity stimulation capable of activating small, unmyelinated fibers [87,88] elicited a pressor response and tachycardia.

In the experiments reported herein, muscle block was

achieved with decamethonium administration and the sciatic nerves were stimulated at several times threshold for group III and IV fiber activation [98]. The blood pressure and heart rate responses to such stimulation were completely eliminated by DLS section in the lumbar spinal cord of these animals. The spinal site for the ascending portion of this somato-autonomic interaction is comparable to the location of fibers mediating somato-sympathetic [28] and somato-parasympathetic [61,64] reflexes in anesthetized cats.

The absolute degree of central sympathetic and parasympathetic depression in these anesthetized preparations is not clear. However, resting (pre-stimulation) heart rates indicate that vagal tone may be markedly reduced in these dogs. This observation is in agreement with the findings of Lieb and Mulinas [106] and Shafer et al. [158] who reported smaller heart rate reductions in response to vagal stimulation during barbituate anesthesia. Peiss and Manning [137] and others [121] also noted significant reductions in the cardiovascular responses to sciatic nerve stimulation following intravenous sodium pentobarbital. This finding is confirmed in the present study (figure 3) in which the pressor response following bilateral sciatic nerve stimulation is significantly smaller in pentobarbital (30 mg/kg) than chloralose (100 mg/kg) anesthetized dogs.

Further, the observation that bilateral cervical vagotomy does not attenuate this somato-autonomic reflex indicates that parasympathetic centers are more profoundly depressed than central sympathetic activity. Therefore, simple observation of the blood pressure and heart rate alteration following sciatic nerve stimulation in these animals may provide insight into somato-sympathetic and not somato-parasympathetic reflexes.

In 1972 Quest and Gebber [142] noted an interaction between baroreceptor induced, vagally mediated bradycardia and somatic afferent stimulation. Since this time Geis et al. [61,64] have presented substantial evidence supporting the existance of somato-parasympathetic reflexes. These authors found that this interaction was mediated by spinal pathways ascending bilaterally in the DLS in anesthetized cats. In the present experiments performed upon anesthetized dogs, the antagonism of phenylephrine-induced bradycardia by sciatic nerve stimulation was still present following DLS lesion placement. When these bilateral spinal sections were extended laterally to include the DLF, somatic afferent-parasympathetic interactions were no longer observed. This finding may indicate that ascending pathways which mediate somato-parasympathetic reflexes in the dog are 1) separate from the systems destined to interact with sympathetic centers 2) more diffuse than ascending sympathetic pathways or 3)

interacting with selectively activated (by drug-induced blood pressure increment) parasympathetic centers.

To test the possibility that the ascending pathways for somato-sympathetic and somato-parasympathetic reflexes are separate in the canine spinal cord, further lesion studies were designed. Since somatic afferent-baroreceptor interactions were eliminated only after spinal sections were extended to include the DLF, it was hypothesized that fibers ascending in this area may be destined for parasympathetic centers, exclusively. However, bilateral lesion placement in this area did not alter the blood pressure or heart rate response to sciatic nerve stimulation. This implies that in this preparation, afferent fibers ascending toward parasympathetic centers occupy a larger portion of the spinal cord than those systems mediating sympathetic reflexes.

The lesion studies outlined above do not prove that the ascending axons mediating somato-sympathetic and somato-parasympathetic reflexes follow different spinal pathways. In fact, it seems likely that the same fibers conveying sensory information from the hind limbs may be capable of interacting with centers which modify output from both branches of the autonomic nervous system. In this regard, the observation that larger spinal sections are necessary to interrupt the interaction between phenylephrine-induced bradycardia and somatic afferent

activation may simply imply that the parasympathetic centers are specifically activated by such baroreflexes. At the same time sympathetic reactivity would be expected to decline during these drug-induced pressor responses. Finally, the effectiveness of DLS sections in eliminating somato-sympathetic reflexes may reflect depression of sympathetic centers [103] by the anesthetics employed. Therefore, it can not be stated that the location of the ascending limb of somato-sympathetic reflexes in anesthetized dogs is identical to the well characterized pathway mediating such reflexes in cats. In fact, these studies imply that the ascending systems which mediate some somato-autonomic reflexes are more diffuse in dogs than in cats.

While electrical activation of peripheral nerves elicits significant alterations in autonomic output, the physiological significance of such reflexes is unclear. It is largely believed that somatic afferent stimulation mimics the sensory input to the central nervous system that occurs during nociception and/or exercise. The nociceptive function of small myelinated and unmyelinated afferent fibers have been well documented [48,96,97,102,126]. In these studies altered nerve activity in group III and IV muscle afferents were noted following close arterial injections of algesic substances. Most of the early evidence supporting the involvement of

these sensory fibers in the cardiovascular adjustments to exercise were obtained from human experimentation (Chapter II, section C-1). Due to the non-invasive nature of these experiments, only indirect data were obtained. However, recent electrophysiological experiments (Chapter II, section C-2) have substantiated the involvement of group III and IV afferent fibers in cardiovascular reflexes brought about by muscular activity.

The most reproducible means of inducing muscular work and the blood pressure increments associated with it in acute animal preparations was first described by Coote et al. [36] in 1971. These authors stimulated L6-S1 ventral roots unilaterally in decerebrate or chloralose anesthetized cats and noted markedly greater pressor responses to induced contraction in the absence of anesthetic agents. The experiments reported in the present paper were performed upon chloralose anesthetized dogs. In an effort to maximize the pressor response to sustained contraction in these animals, L6-S1 ventral roots were stimulated bilaterally. In this regard, Mitchell and others [119,128,130,147,153] have demonstrated that the cardiovascular response to isometric exercise is related to the muscle mass involved.

Observation of figures 10 and 11 reveals a steady increase in blood pressure during ventral root stimulation (117 mmHg to 136 mmHg; 16%) which usually leveled off

after contraction was maintained for approximately 40 seconds. This pressor response was significantly accentuated (118 mmHg-143 mmHg; 21%) when the external iliac arteries and the inferior vena cava were occluded prior to and during the exercise period. The blood pressure increment following induced contraction without occlusion, is qualitatively similar to the responses reported by Fisher and Nutter [47]. These authors observed an 11% increase in mean arterial pressure following bilateral stimulation of the L6-L7 ventral roots in chloralose anesthetized dogs. The slightly higher pressor response noted in our experiments may reflect the greater muscle mass involved during L6-S1 ventral root stimulation. Fisher and Nutter also noted that occlusion of the femoral artery, or femoral vein and artery during ventral root stimulation did not augment this blood pressure increment. Conversely, in the present experiments the maximum increase in blood pressure, as well as the time course of this pressor response to sustained contraction, were altered (figures 10 and 11). This difference may be due to the reduced risk of contralateral circulation during external iliac and vena cava occlusion.

The reflex nature of the cardiovascular response to induced exercise (as described above) has been well established. Coote et al. [36] progressively eliminated

the pressor response to ventral root (L6-S1) stimulation by stepwise section of corresponding (L6-S1) dorsal roots. Since sectioning the articular nerves in the working limb did not alter the blood pressure elevation during such exercise, they surmised that muscle afferents were most likely involved. McCloskey and Mitchell [118] confirmed and extended these findings, demonstrating that the sensory fibers involved in such reflexes were group III and IV muscle afferents.

In the present experiments, the central pathway of afferent fibers activated by induced muscular contraction were studied. The pressor response to ventral root stimulation without simultaneous vascular occlusion was virtually eliminated by section of the DLS at L3 in these animals. Sectioning the DLF alone caused only a modest reduction in the maximal blood pressure increase during such induced contraction. Interestingly, when the blood flow through the external iliac arteries and the inferior vena cava was restricted during muscular work, neither DLS nor DLF section alone completely eliminated the exercise reflex. In fact, only combined DLF and DLS lesions obliterated the cardiovascular response to simultaneous exercise-occlusion.

These lesion studies seem to imply that the ascending spinal pathways mediating exercise reflexes are similar to the systems involved in somato-autonomic interactions,

localized with electrical activation of peripheral afferents. Further, the fact that both the DLF and the DLS must be sectioned to eliminate the cardiovascular response to exercise-occlusion may suggest the involvement of somato-parasympathetic interplay in this reflex. However, we observed no change in phenylephrine-induced bradycardia with simultaneous ventral root stimulation. Similarly, Coote and Dodds [33] were unable to demonstrate an interaction between baroreceptor activity and induced contraction in decerebrate cats. It must be concluded that the ascending systems involved were interacting with sympathetic centers exclusively. These spinal pathways appear more diffuse than those observed in experiments employing electrical activation of the sciatic nerves which may reflect the ganglionic blocking activity of decamethonium in these animals.

In conscious man [149,150] dogs [58] or cats [66], the pressor response to voluntary exercise is accompanied by a marked tachycardia. Bristow et al. [24] and others [40,76,140] have suggested that baroreceptor sensitivity is reduced during such exertion, permitting large elevations in heart rate despite increasing arterial pressure. This debuffering may involve the activation of higher centers such as the hypothalamus, which are known to inhibit baroreceptor-induced vagal activation [41,83]. However, when muscular activity is induced in anesthetized

or decerebrate animals heart rate does not rise significantly (figure 8 and references [36,118,163]). McCloskey and Mitchell [118] have suggested that this discrepancy between voluntary and induced exercise may be due to: 1) altered baroreceptor sensitivity in these two preparations or 2) the origin of the heart rate response to exercise in conscious man and/or animals is central as opposed to reflex in nature.

If indeed arterial baroreceptors are active in the anesthetized preparation, one would expect any heart rate responses to induced contraction in these animals to be largely obscured. In the present experiments heart rate was monitored during ventral root stimulation before, during and after vagus nerve cooling. It was presumed that baroreceptor buffering of heart rate during induced contraction would be eliminated during such vagal blockade. In these experiments (N=6) there was no significant tachycardia during ventral root stimulation regardless of the degree of vagal patency. This finding suggests that the heart rate responses which are observed during voluntary exercise may not originate reflexly in the exercising muscles. However, once again the degree of anesthetic-induced depression in these dogs is not clear. Toward this end, it should be noted that the resting heart rate in these chloralose anesthetized dogs was on the order of 160 beats per minute. While vagal cooling

FIGURE 24

ASCENDING AXONS INVOLVED IN SOMATO-AUTONOMIC REFLEXES

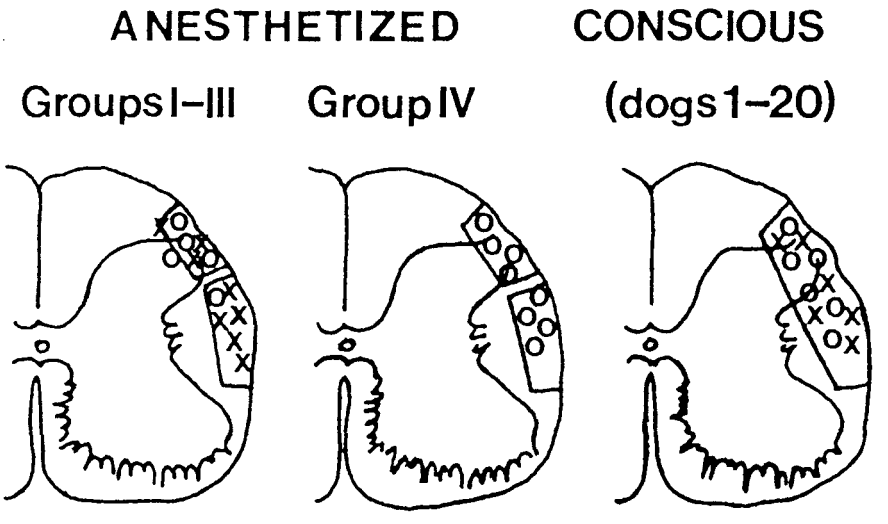

FIGURE 24

LEGEND

Schematic representation of the spinal organization of ascending axons destined to interact with vagal (X) and sympathetic (O) systems. Lesion placement was bilateral in both chronic (conscious) and acute (anesthetized) preparations.

significantly increased the control rates in all six animals (Figure 8) we did note a marked tachycardia in three of these dogs during induced contraction (during vagus nerve blockade). Therefore, these observations taken alone only point out the need for further investigation into the mechanisms of exercise induced tachycardia in conscious man or animals. Importantly, the tachycardia which accompanies static exercise in man is mediated by vagal withdrawal [55], which is not possible in the anesthetized animals studied herein.

Blood pressure was monitored in the conscious, dynamically exercising dog before and after lumbar spinal cord lesion placement. These spinal sections were aimed at interrupting the ascending pathways which mediate somato-sympathetic and somato-parasympathetic reflexes (discussed above in anesthetized preparations). In figure 24 the possible distribution of these ascending systems is depicted. In this figure the location of fibers destined to interact with sympathetic centers are represented as circles. Experiments employing direct electrical activation of the sciatic nerves suggest that these fibers are most concentrated in the dorsolateral sulcus area. However, when somatic afferent nerves were activated reflexly (by stimulation of ventral roots) the axons ascending upon sympathetic centers appeared to be more diffuse occupying both the DLS and the DLF. The ascending

systems which mediate somato-parasympathetic reflexes were localized in this same area (fibers represented by the letter X in figure 24). It is not clear from the studies carried out upon anesthetized dogs whether these fibers play a role in the cardiovascular response to exercise. However, it should be noted that the spinal lesions placed in the chronic animal preparation interrupted ascending systems which mediate both somato-sympathetic and somato-parasympathetic reflexes. These lesions significantly altered the cardiovascular responses to exercise with and without simultaneous vascular occlusion in conscious dogs (outlined below).

The actual site of all spinal lesions were verified histologically (see Results; Figures 21, 22 and 23). In eight chronic animals trained for treadmill running (Figure 23, animals 13-20) these spinal sections were extensive, including the ventral horn and/or adjacent white matter. All of these dogs were paraplegic after such lesion placement as the descending systems which mediate voluntary motor activity were interrupted [26,81].

In the chronic animal preparation, increments in blood pressure and heart rate were evoked by treadmill exercise. These cardiovascular responses were followed during whole body (all fours) and hind limb only (front less supported by a shelf) running at various work loads. During non-ischemic exercise, blood pressure and heart rate increased

in these animals in a stepwise fashion as the work load (treadmill grade and/or speed) increased. Additionally, the pressor response to exercise at any level was potentiated by transient occlusion of the left external iliac artery. Careful observation of figures 12 and 14 however, reveals that blood pressure elevation evoked by simultaneous exercise-occlusion was not related to the level of exertion during whole body running. In fact, decreasing the work load from a 10% grade to a 0% grade actually increased the cardiovascular response to iliac artery occlusion during running on all fours. This observation may be explained by the relatively greater sensory input from non-ischemic areas at higher work loads. In an effort to maximize the percentage of the total sensory input arising from the ischemic leg, the cardiovascular response to running on hind limbs only was monitored. When this protocal was followed, the pressor response to simultaneous exercise-occlusion was found to be directly related to the work load. Finally, interruption of blood flow through the external iliac artery at rest did not significantly change the blood pressure or heart rate in these dogs. This indicates that muscular activity is necessary for the elicitation of the cardiovascular reflexes reported herein.

The observations outlined above support the findings of Lind et al. [110] who noted that the pressor response

to static exercise in man was potentiated by vascular occlusion. In later experiments Lind and co-workers [111] demonstrated that the pressor response to unilateral forearm exercise was not seen in a patient with a sensory deficit (pain and temperature) in that limb due to syringomyelia. These authors suggested the involvement of a chemical mediator released by exercising muscles in a cardiovascular (somato-autonomic) reflex (see Longhurst [114] for a review of the potential chemical mediators involved).

In the present experiments, the pressor responses brought about by ischemic and non-ischemic exercise were monitored before and after lesion placement in the lumbar spinal cord. The blood pressure elevation which occurred during treadmill running was not altered by these lesions. However, the marked pressor response evoked by simultaneous exercise-occlusion in control runs (pre lesion) was significantly reduced by section of the DLF and the DLS at L2. This finding provides strong support for the involvement of somato-autonomic reflexes in the cardiovascular adjustments which occur during ischemic exercise.

While this reflex appears to involve the release of chemical substances within the working muscles, it is not certain whether chemoreceptors, nociceptors or both are involved. Since pain is one of the characteristics of

severe (especially ischemic) exercise [14,135], one can not overlook the possible involvement of nociception in these responses. Conversely, Lind et al. [110] suggested that pressor responses evoked during static exercise were not a manifestation of pain. These authors argued that discomfort did not arise during sustained hand grip contractions until half way through a contraction held to fatigue, while the blood pressure response to such exercise followed a shorter latency of onset. Similarily Dorpat [43] noted that the onset of pain occurred after 20-30 seconds of sustained (static) exercise.

As depicted in figures 19 and 20, the time course of the pressor response to simultaneous exercise occlusion was followed over a two minute period. Upon careful observation of these figures, it is apparent that the blood pressure elevation which occurs during ischemic exercise is multiphasic. Specifically, there is a slow rise in mean arterial pressure over the first 40-60 seconds of simultaneous exercise-occlusion which is not influenced by lesion placement in the lumbar spinal cord. This is followed by a relatively rapid increase in blood pressure over the next 40 to 60 seconds of maintained occlusion during treadmill running. This secondary (40-60 second latency of onset) pressor response was profoundly influenced by section of the DLS and the DLF at L2. Interestingly, the latency of this response is very

similar to that of the onset of pain perception in human subjects performing ischemic exercise [3,43]. It is therefore tempting to speculate that this portion of the exercise reflex may actually be a response to nociceptive information. In this regard it should be noted that these dogs began to show some degree of discomfort and gait change during the later stages of occlusion (especially at higher work loads).

The changes in heart rate which accompany treadmill running were also monitored in conscious dogs. During such exercise the pulse rate was directly proportioned to the level of work performed. At high work loads (all fours, 10% grade) this exercise induced tachycardia was minimaly influenced by spinal cord lesion placement (figure 13) presumably due to the extensive sensory input from the working front limbs. However, when the treadmill grade was lowered to 0%, the heart rate response to running on all fours was reduced by such lesions (fig 15). Interestingly, the tachycardia which accompanied running on hind legs only was not altered by section of the DLS and DLF at L2.

The observations outlined above indicate that the tachycardia which occurs during non-ischemic exercise may involve more than one mechanism. The participation of an excercise-reflex originating in working skeletal muscles is strongly suggested by the effectiveness of L2 spinal

sections in altering the heart rate response to running on all fours. During running on hind limbs only, the afferent fibers which originate in actively working muscles should be more effectively interrupted by spinal lesions at this level. However, section of the DLS and DLF did not influence the modest tachycardia observed during such exertion. This finding suggests the involvement of central elements capable of increasing heart rate during exercise which are independant of peripheral reflexes. The nature of these central elements presents a further problem from the standpoint of interpretation. For example, the involvement of emotional factors in the cardiovascular response to unnatural (hind limbs only) running can not be eliminated even though such influences were minimized by: 1) extensive training and 2) keeping the level of exercise quite low. It is also possible that the front less (supported by a shelf above the treadmill surface) were performing a limited amount of static work during such running. Therefore, the involvement of a reflex originating in the ischemic hind limb in this exercise induced tachycardia may have been masked by emotional factors and significant forelimb ischemic reflexes. However, when these animals ran on hind limbs only, unilateral iliac artery occlusion evoked a significant tachycardia (presumably due to enhanced accumulation of metabolites in the hind limbs sufficent to

overcome similar forelimb reflexes). The time course of this response could not be determined because of the extreme variability noted in these animals. It should be noted however, that the heart rate elevation evoked by hind limb running during simultaneous occlusion was eliminated by lumbar spinal cord lesion placement. This finding further supports the involvement of a reflex originating in the working muscles which brings about alterations in both blood pressure and heart rate.

CHAPTER VI

CONCLUSIONS

Experiments were designed to determine the site and functional significance of ascending spinal pathways in anesthetized and conscious dogs. The following observations and conclusions can be drawn from the data obtained in this study:

1. The afferent systems which mediate somato-autonomic reflexes in dogs ascend bilaterally in both the dorsolateral sulcus area and the dorsolateral funiculus. The location of these fibers is similar, but not identical to the site of such ascending pathways in the cat.

2. Bilateral stimulation of L6-S1 ventral roots results in a significant elevation in blood pressure. This pressor response to induced hind limb contraction is eliminated by bilateral section of the dorsolateral sulcus area at L3 in anesthetized dogs.

3. Induced muscular contraction in these animals does not result in a significant tachycardia. The lack of cardiac acceleration is probably not due to baroreceptor

buffering via the vagus nerves in that vagal cooling does not unmask a heart rate response to ventral root stimulation.

4. Somato-parasympathetic interactions can be demonstrated by observation of the interplay between phenylephrine induced (vagally mediated) bradycardia and sciatic nerve stimulation. However, when somatic afferents are activated by induced muscular contraction such somato-autonomic reflexes are not demonstrable. This finding sheds some doubt upon the involvement of somato-parasympathetic interactions in the heart rate responses to physiological exercise.

5. The pressor response to induced hind limb contraction is virtually eliminated by bilateral lesion placement in the dorsolateral sulcus area. However, when the working hind limbs are made ischemic by vascular occlusion the blood pressure increment is larger and not completely lost after such spinal sectionings. Only combined lesions of the dorsolateral sulcus area and the dorsolateral funiculus are effective in interrupting the cardiovascular response to this induced ischemic exercise.

6. The increase in blood pressure which occurs during non-ischemic exercise in conscious dogs is not influenced by spinal sections aimed at interrupting the ascending limb of somato-autonomic reflexes. This indicates that the pressor response to such exercise: a) does not

originate reflexly b) may arise reflexly (at least in part) in the muscles but does not ascend in the DLS or DLF or c) may arise reflexly but the sensory information from exercising muscles in the front limbs masks the influence of spinal lesions.

7. Transient arterial occlusion during treadmill running results in a marked potentiation in the blood pressure response to such exercise. Bilateral lesion placement in the dorsolateral sulcus area and the dorsolateral funiculus at L2 significantly reduces this response to ischemic work. This suggests the involvement of somato-autonomic reflexes in the cardiovascular adjustments which occur during ischemic exercise and/or pain in the conscious dog.

8. The pressor response to exercise with simultaneous vascular occlusion is triphasic when followed over a period of two minutes. The initial, slow rise in blood pressure is not changed by lumbar spinal cord lesions. The rapid, secondary increase in mean arterial pressure is profoundly influenced by section of the dorsolateral sulcus area and the dorsolateral funiculus at L2. This long latency pressor response occurs after approximately one minute of vascular occlusion which coincides with the time course for the onset of pain during ischemic exercise in man.

9. The cardiac acceleration which accompanies non-

ischemic exercise in conscious dogs was significantly reduced by section of the DLS and DLF at L2.

10. Transient iliac arterial occlusion significantly potentiates the tachycardia which occurs during treadmill running on hind limbs only. This chronotropic response is significantly reduced by spinal lesions aimed at interrupting the ascending limb of somato-automonic reflexes.

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The dissertation is therefore accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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