Effect on Left Ventricular Performance of Stimulation of an Afferent Nerve from Muscle

By Jere H. Mitchell, M.D., Donald S. Mierzwiak, M.D., Kern Wildenthal, M.D., William D. Willis, Jr., M.D., Ph.D., and Alvin M. Smith, B.A.

ABSTRACT

The effect on left ventricular performance of electrical stimulation of the cut central end of the quadriceps nerve was studied in open-chest dogs. Stimulation of the nerve at 2 to 4 times threshold for the flexion reflex, which presumably activated intermediate-sized afferent fibers, caused a decrease in heart rate and arterial pressure. Stimulation at 5 to 25 times threshold, which presumably activated small-sized, high-threshold afferent fibers, increased heart rate, arterial pressure, and cardiac output. When heart rate, arterial pressure, and cardiac output were controlled, activation of high-threshold afferent fibers caused a significant increase in the maximal rate of pressure rise, stroke power, and mean rate of ejection of the left ventricle without an increase in the end-diastolic pressure. These same fibers may in some way be activated during muscular exercise and be partially responsible for the increase in left ventricular contractility that occurs during that time.

ADDITIONAL KEY WORDS

contractility of left ventricle
reflex inotropic changes of ventricle
left ventricular function
exercise
cardiovascular reflexes from limbs
dogs

It has been proposed that reflexes involving muscle afferent fibers play a role in the responses of the cardiovascular system to muscular exercise in cats (1), dogs (2, 3), and man (4-7); however, the physiological stimuli and the receptors concerned remain undefined. It seemed important, therefore, to determine whether stimulation of afferent nerve fibers from muscle can produce cardiovascular responses similar to those seen during muscular exercise.

Stimulation of the central end of a mixed nerve from the limbs has long been known to produce alterations in blood pressure and heart rate (8). More recently workers in several laboratories have shown that electrical stimulation of nerves from muscle from the limbs produces either pressor or depressor cardiovascular responses according to the types of nerve fibers activated (1, 9, 10).

The afferent fibers of nerves from muscle of the cat have been classified according to their size (11, 12). The myelinated fibers include groups I, II, and III. The unmyelinated fibers are called either group IV or C fibers. Group I afferent fibers have diameters of 12 to 20 µ and arise from primary endings of muscle spindles and from Golgi tendon organs (13). Group II fibers range in size from 4 to 12 µ and many originate at secondary endings of muscle spindles. Group III afferents are
myelinated fibers smaller than 4 μ. They innervate several kinds of receptors within and about muscle, including pressure-pain endings (14, 15). The C fibers are presumed to arise from pain receptors. The afferent fibers which have been shown to have cardiovascular effects include groups II and III and the C fibers.

In the present study cardiovascular responses elicited by stimulation of the afferent fibers of the quadriceps nerve were investigated in an open-chest dog preparation. This approach also allowed the determination of the reflex action of muscle afferent fibers upon ventricular function when heart rate, cardiac output, and blood pressure were held constant. Previous studies have emphasized the effects of such stimulation upon the peripheral vascular bed (1, 10).

Methods

Mongrel dogs were anesthetized with alphachloralose (50-100 mg/kg) in polyethylene glycol. Respiration was maintained by a Harvard pump, and end-expiratory PaCO₂ was monitored.

The experimental preparation is diagrammed in Figure 1, and the basic details have been described in a previous publication (16). In essence, the left ventricle ejected blood through a Starling resistance into a reservoir from which the blood was returned by a rotor pump into the...
thoracic aorta and common carotid arteries. The upper five pairs of intercostal arteries, brachiocephalic artery, and subclavian artery were all ligated, thus directing the cardiac output (except the coronary flow) into the extracorporeal circuit. A pacing electrode connected to a Grass stimulator (model S4) was sutured to the right atrium.

In some of the studies heart rate, aortic pressure, and aortic flow were not controlled. This was accomplished by disconnecting the Grass stimulator and excluding the Starling resistance, blood reservoir, and rotor pump from the extracorporeal circuit. In the controlled studies the heart was paced at a rate well above the spontaneous rate, while the aortic pressure and aortic flow were maintained constant by setting the Starling resistance and rotor pump, respectively.

Aortic pressure was measured by a Statham pressure transducer connected to a metal cannula, which was inserted through the right common carotid artery into the arch of the aorta. Left ventricular pressure was measured by a Statham pressure transducer connected to a metal cannula inserted directly into the left ventricle. The first derivative, dp/dt, has an almost uniform response to frequencies as high as 200 cycles/sec (17), was also inserted into the left ventricle. The first derivative, dp/dt, of this pressure recording was continuously computed by an R-C differentiating circuit that had a linear response to 70 cycles/sec. Aortic flow was measured by a Statham electromagnetic flowmeter (M-4001) utilizing an extracorporeal circuit. In the controlled studies the heart was paced at a rate well above the spontaneous rate, while the aortic pressure and aortic flow were maintained constant by setting the Starling resistance and rotor pump, respectively.

Aortic pressure was measured by a Statham pressure transducer connected to a metal cannula, which was inserted through the right common carotid artery into the arch of the aorta. Left ventricular pressure was measured by a Statham pressure transducer connected to a metal cannula inserted directly into the left ventricle at or near the apex. To determine the maximal rate of left ventricular pressure rise, a Daltons-Telco intracardiac micromanometer, which has an almost uniform response to frequencies as high as 200 cycles/sec (17), was also inserted into the left ventricle. The first derivative, dp/dt, of this pressure recording was continuously computed by an R-C differentiating circuit that had a linear response to 70 cycles/sec. Aortic flow was measured by a Statham electromagnetic flowmeter (M-4001) utilizing an extracorporeal transducer (A-2012) placed in the circuit proximal to the Starling resistance. Zero flow could be determined at any time during the experiment by directing aortic flow through a parallel shunt. The system was calibrated after the experiment was completed by pumping measured flows through the transducer. Heart rate was measured by a cardiograph. All values were continuously recorded on a Sanborn direct-writing recorder; intermittent high speed recordings during brief periods of imposed apnea were made on an Electronics for Medicine photographic recorder.

Since the dogs were supine for convenient access to the thoracic cavity, the most appropriate nerve for stimulation was the one to the quadriceps muscle. In each experiment, the quadriceps nerve was dissected free for several centimeters from its cut peripheral end and mounted on a pair of platinum electrodes in a pool of mineral oil held between skin flaps. Sometimes both quadriceps nerves were prepared in this fashion. A Grass S4 stimulator with an isolation unit provided rectangular pulses for stimulation. The stimulus duration was either 0.1 msec or 1.0 msec. The strength of stimulation was judged in terms of multiples of the minimal level (at a given stimulus duration) required to elicit a visible flexion reflex contraction (18). It was not feasible to relate the strength to the threshold for the most excitable afferent fibers because of the position of the dog.

We employed different stimulus strengths to activate afferent fibers of two size ranges. Intermediate-sized afferent fibers were presumably excited by stimuli two to four times the threshold for the flexion reflex. These fibers produced a depressor effect that was greatest when low frequencies of stimulation were used (about 1/sec). When stimulated in isolation, lower threshold afferents seemed to have no cardiovascular effect. Impulses in small-sized, high-threshold afferent fibers were presumably also activated by stimuli 5 to 25 times the threshold for the flexion reflex. The pressor response produced by these fibers was largest when the frequency of stimulation was high (generally 100/sec).

After the threshold strength for the flexion reflex was determined, it was often convenient to inject gallamine triethiodide (2 mg/kg, intravenously) to abolish reflex movements and spontaneous respiratory efforts. The subsequent paralysis did not appear to influence the experimental results and served to prevent secondary activation of afferent fibers from receptors in other parts of the limb.

Following stabilization, control recordings were taken. Stimulation of the nerve was begun, and then further recordings were obtained. In four of the dogs studied, propranolol (0.2-1.0 mg/kg) was administered intravenously, new control recordings were taken, and stimulation of the nerve was repeated. In two other dogs the studies were performed after bilateral adrenalectomy.

Measurements were made of aortic pressure, aortic flow, left ventricular pressure, left ventricular end-diastolic pressure, and the maximal rate of rise of the left ventricular pressure (max dp/dt). Stroke work, stroke power, and mean rate of ejection were calculated (19). The performance of the left ventricle was evaluated by a method which has been described previously (16).

The data were analyzed statistically by Student's t-test for paired observations (20).

Results

Cardiovascular Responses to Afferent Stimulation of the Quadriceps Nerve

In six dogs, either a depressor or a pressor cardiovascular response could be elicited by
afferent stimulation of the quadriceps nerve, depending upon the strength of the stimulus used. Examples of these responses are shown in Figure 2. A depressor response is shown in the left panel. Heart rate was held constant by a pacing electrode. The quadriceps nerve was stimulated at a frequency of 1/sec by pulses having a strength two times threshold for the flexion reflex. The period of stimulation is indicated by the black bar in the lower part of the tracing. During stimulation, aortic pressure, left ventricular pressure, and maximal rate of rise of left ventricular pressure all decreased, and left ventricular diastolic pressure remained unchanged. Such a response was almost invariably obtained when the quadriceps nerve was stimulated at two to four times threshold for the flexion reflex. A pressor response is shown in the right panel. The quadriceps nerve was stimulated at a frequency of 100/sec by pulses having a strength 20 times threshold for the flexion reflex. A small initial depressor response occurred; it may be attributed to activation of the intermediate-sized muscle afferent fibers which would have a more rapid conduction velocity than the fibers responsible for the pressor response. After the initial, brief depression, aortic pressure, left ventricular pressure, and maximal rate of rise of left ventricular pressure all increased, and left ventricular diastolic pressure remained relatively constant. Cardiac output also consistently increased at these stimulation levels. Both the depressor and pressor cardiovascular responses were still present after bilateral vagotomy.

Since the purpose of this study was to de-
termine whether stimulation of afferent nerve fibers from muscle can produce cardiovascular responses similar to those seen during muscular exercise, further observations were concerned only with the pressor response. An example of this response when heart rate was not controlled is shown in Figure 3. The small initial depressor response was again seen. Then there was an increase in aortic pressure, left ventricular pressure, maximal rate of left ventricular pressure rise, and heart rate. These changes were accompanied by a fall in left ventricular diastolic pressure. Heart rate increased by 50 beats/min. Cardiac output, not shown in this figure, also increased. In this study, a response was not seen until 15 seconds after the onset of nerve stimulation. The delay from onset of stimulation to response varied from 2 to 15 seconds in the series of experiments, a period of latency compatible with recruitment of neurons from repetitive stimulation. The depressor response that followed the pressor response in this study was abolished by bilateral transection of both carotid sinus and vagus nerves. Despite these procedures, however, arterial pressure and heart rate tended to return toward control values during continued stimulation.

**Effect of Afferent Stimulation of the Quadriceps Nerve on Left Ventricular Performance**

The effect of stimulation of the central end of the quadriceps nerve on left ventricular performance was studied in 32 experiments on eight dogs; an example is shown in Figure 4. In this experiment, with aortic pressure, aortic flow, and heart rate held constant, the quadriceps nerve was stimulated at a frequency of 100/sec by pulses having a strength 25 times threshold for the flexion reflex. During stimulation left ventricular end-diastolic pressure remained constant, and the maximal rate of left ventricular pressure rise increased by 1670 mm Hg/sec (41%) above the control level. Stroke power increased by 8.2 g-m/sec (12%), and mean rate of ejection increased by 6.0 ml/sec (9%).

A summary of the effects of afferent stimulation of the quadriceps nerve is given in Table 1. The quadriceps nerve was stimulated at a frequency of 100/sec and at intensities of 5 to 25 times threshold for the flexion reflex. The latency before a response was seen was similar to that observed with the aortic
FIGURE 4

Effect of afferent stimulation of the quadriceps nerve on left ventricular performance. AF = aortic flow; other abbreviations as in previous figures. A and B in upper slow-speed tracing (0.5 mm/sec) indicate times at which high-speed tracings (100 mm/sec) were obtained. Stimulation of the quadriceps nerve at 25 times threshold for the flexion reflex is indicated by the black bar in the upper tracing.

Circulation Research, Vol. XXII, April 1968
pressure and heart rate changes. In each experiment the left ventricular end-diastolic pressure remained constant or decreased slightly. The mean value for maximal rate of pressure rise increased by 408 mm Hg/sec (12%), stroke power increased by 4.3 g-m/sec (5%), mean rate of ejection increased by 2.7 ml/sec (4%), and stroke work increased by only 0.2 g-m (2%). The increase in maximal rate of pressure rise, stroke power, and mean rate of ejection without an increase in left ventricular end-diastolic pressure demonstrates an increase in contractility or a positive inotropic effect of the left ventricle. Although these mean changes are small, some individual experiments showed greater changes, as demonstrated in Figure 4.

To investigate the role of the cardiac beta-adrenergic receptors in the increase in left ventricular contractility, afferent stimulation of the quadriceps nerve was performed before and after the administration of propranolol in four dogs. In the control studies stimulation of the afferent fibers of the quadriceps nerve caused an increase in the maximal rate of pressure rise, stroke power, and mean rate of ejection with either no change or a decrease in left ventricular end-diastolic pressure. After administration of 0.8 mg/kg propranolol, these effects of stimulation of the quadriceps nerve were abolished. When the stimulation was again repeated 30 minutes later, the responses had returned toward those found during the control studies.

The increase in contractility of the left ventricle during afferent stimulation of the quadriceps nerve was not affected by bilateral vagotomy. Also, in two additional dogs the increase in contractility was present after bilateral adrenalectomy.

Discussion

The results of this study in dogs are in general agreement with previous studies on cats (1, 9, 10). Electrical stimulation of muscle afferent fibers may produce depressor or pressor responses, depending on the types of fibers excited and the frequency of stimulation. Antidromic firing of motor fibers can be ruled
out as a cause of cardiovascular responses, since ventral root stimulation produces no such effect (9). The present experiments have demonstrated that stimulation of muscle afferent fibers not only causes alterations in aortic pressure and heart rate, but also an increase in left ventricular contractility when aortic pressure, aortic flow, and heart rate are held constant during stimulation at intensities and frequencies which otherwise would have caused an increase in aortic pressure, aortic flow, and heart rate.

It is not possible at present to relate with certainty the stimulus strengths which produced cardiovascular responses in the present study to the specific types of muscle afferent fibers excited. This is due not only to the conditions of the experiments but also to the lack of data on the fiber composition of peripheral nerves and responses of the various fiber groups to electrical stimulation in the dog. However, there do seem to be parallels between the responses observed in this investigation and those seen in the cat. First, no cardiovascular effects were seen in dogs until the stimulus strength exceeded twice threshold for the flexion reflex. In the cat, group I fibers produce no detectable cardiovascular responses (1, 9, 10). Second, stimulation of what we presume to be intermediate-sized afferent fibers by low frequencies produces a depressor response in the dog (Fig. 2) as has been demonstrated in the cat (1, 9, 10). Third, high-frequency stimulation of what we believe are small-sized, high-threshold afferent fibers produces a pressor response in the dog (Figs. 2 and 3) as has also been demonstrated in the cat (1, 9).

The depressor response in cats is carried in group III fibers (1, 9, 10). In the present study in dogs, it is probable that the same group of fibers is involved; however, it is possible that a contribution was made by group II fibers. Both group II and group III fibers are participants in the flexion reflex mechanism and are known to activate ascending tracts which project onto reticular formation neurons (21, 22). The failure of bilateral midcervical vagotomy to abolish the decrease in arterial pressure and heart rate implies that cardiac sympathetic withdrawal is a factor in the efferent pathway of the depressor response in dogs. This is in agreement with Johansson's findings in cats (1).

A pressor response in cats has been reported with high frequency stimulation of group II fibers when the animals were decerebrate (9). However, with chloralose anesthesia, activation either of group III fibers at high frequencies (2) or of C fibers (1, 9) is required. The effects of activation of small-sized muscle afferents on cardiovascular function are probably mediated at least in part through the brain stem (1), although propriospinal connections to sympathetic preganglionic neurons may also be important, particularly for the pressor response (1). Furthermore, Sato and Schmidt (23) recorded reflex discharges from the cervical sympathetic trunk primarily in response to stimulation of group III fibers in muscle nerves of the hind limb of the cat. The activation of the sympathetic efferent system manifested by an increase in heart rate and arterial pressure in the uncontrolled preparation was demonstrated in the controlled experiments by significant increases in mean maximal dp/dt, mean stroke power, and mean rate of ejection without an increase in left ventricular end-diastolic pressure (Table 1). Thus, activation of these fibers caused an increased contractility of the left ventricle.

The fact that activation of the cardiac beta-adrenergic receptors was responsible for the increase in left ventricular contractility was demonstrated by the abolition of the response after the administration of propranolol. This response could be due to increased cardiac sympathetic efferent nerve activity, to catecholamine release from the adrenal medulla, or to both of these mechanisms. The persistence of the increase in contractility after bilateral adrenalectomy suggests that the cardiac sympathetic efferent fibers play a role in the response but does not rule out the participation of the adrenal medulla in the response as it is usually seen. This confirms the observation of Johansson (1) that a
pressor response can occur in the absence of adrenal medullary function. It should also be noted that bilateral vagotomy did not affect the response.

The possibility that small-sized, high-threshold muscle afferent fibers play a role in the responses of the cardiovascular system to muscular exercise is of interest. The changes produced in the present study are small compared with those seen in normal dogs during exercise; however, these responses were elicited by continuous stimulation of a nerve from a single muscle in an anesthetized animal. In an awake, exercising animal, more muscles would be involved and, since muscle contracts rhythmically, a continuous volley of impulses would not be present. Further, the physiological stimuli and the receptors concerned remain undefined. Group III afferents in the cat arise from various receptors located within and around muscle (14, 15). Although some of the receptors require high-intensity stimulation which might be considered painful, others are known to be activated by muscular contraction (14). It would be of considerable interest to know which types of receptors giving rise to group III fibers are involved in the production of pressor responses and which in production of depressor responses. Further studies are required to investigate the mode of activation of the C fibers found in muscle. Also, the proposal of Alam and Smirk (6, 7) that afferent fibers mediating the increase in cardiac activity may arise from receptors responsive to high local concentrations of metabolites of muscular exercise deserves consideration. The present study makes no attempt to identify the receptors or the central nervous system interconnections required for the reflexes that have been demonstrated. However, the study does suggest that small-sized, high-threshold muscle afferent fibers, when stimulated appropriately, may play some role in eliciting the increase in left ventricular contractility that occurs during muscular exercise.

Acknowledgment
The authors gratefully acknowledge the valuable technical assistance of Mr. Eugene Berry and Mr. James Jones, and the valuable assistance of Mrs. Joan Reisch in the statistical analyses.

References


Effect on Left Ventricular Performance of Stimulation of an Afferent Nerve from Muscle
JERE H. MITCHELL, DONALD S. MIERZWIAK, KERN WILDENTHAL, WILLIAM D. WILLIS, Jr. and ALVIN M. SMITH

Circ Res. 1968;22:507-516
doi: 10.1161/01.RES.22.4.507

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1968 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/22/4/507

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/