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Acute Coronary Artery Occlusion and Cardiac Sympathetic Afferent Nerve Activity[1] (40507)

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Cardiac sympathetic afferent nerves have been implicated in anginal pain during myocardial ischemia in man (1). Experimental animal studies have indicated that receptors in coronary arteries (2, 3) or within the myocardium (4–12) may be a source of increased cardiac afferent nerve activity during experimental coronary artery occlusion or intracoronary infusion of a number of pharmacologic agents. Some of the agents studied have been thought to play a role in producing local changes during coronary occlusion. Other studies have suggested that reflexly mediated changes in cardiac rhythm during acute experimental coronary artery occlusion may involve the sympathetic nervous system (13).

The purpose of the present study was twofold: (a) To study the changes in cardiac sympathetic afferent nerve activity arising from receptors located within the left ventricle during acute left coronary artery occlusion. Receptors located within the ischemic as well as nonischemic myocardium were studied. (b) To study the changes in left ventricular pressure and myocardial segment length during left coronary artery occlusion and to attempt to correlate changes in cardiac afferent nerve activity with the changes in ventricular pressure and segment length.

Materials and methods. Twelve mongrel dogs of either sex weighing 25–30 kg were anesthetized with sodium thiopental, 15–25 mg/kg, and halothane in oxygen, 0.5–1.0% inspired concentration. During the experiments, arterial blood gases and pH were maintained between 7.35 and 7.45 pH, 35–45 mmHg PCO_2, and PO_2 greater than 150 mmHg. Respiration was controlled via an endotracheal tube and Air Shields Company ventilator. The upper six or seven ribs from the left side were removed from the costovertebral joint to the costochondral junction. The sympathetic chain on the left side was dissected from the surrounding connective tissue, and the second or third thoracic white ramus communicans was isolated and sectioned to eliminate efferent activity. All afferent nerve activity was recorded from the distal end of the sectioned nerve. In all studies, the sympathetic trunk was cut below T_3 to eliminate afferents traveling up the sympathetic chain. The heart was exposed by pericardiotomy. Left ventricular pressure was recorded using a pressure transducer (Statham Instruments, P23D) and short polyethylene cannula inserted into the left ventricle through the apex. Aortic pressure was recorded using a pressure transducer (Statham Instruments, P23D) and catheter advanced through the anterior thoracic artery to the arch of the aorta (Fig. 1). A polyethylene cannula was introduced through an anterior thoracic vein for intravenous infusion.

To evaluate regional myocardial function, one-inch long Parks Electronics mercury-in-silastic length gauges were sutured to the epicardium in the areas of the ventricle supplied by the left anterior descending (LAD) and left circumflex (LC) coronary arteries. One Walton-Brodie strain gauge of 120 ohm resistance with adjustable feet was fixed with sutures in one area of the left ventricle, LAD or LC. Snares were placed at the origins of the LAD and LC coronary arteries. Regional length changes were expressed as per cent changes from the control values. Local electrocardiograms from the ischemic and nonischemic zones were recorded from silver pin electrodes inserted into the epicardial surface of the heart. All parameters were recorded with a Grass Model 7 polygraph, and any four of these parameters with voice were

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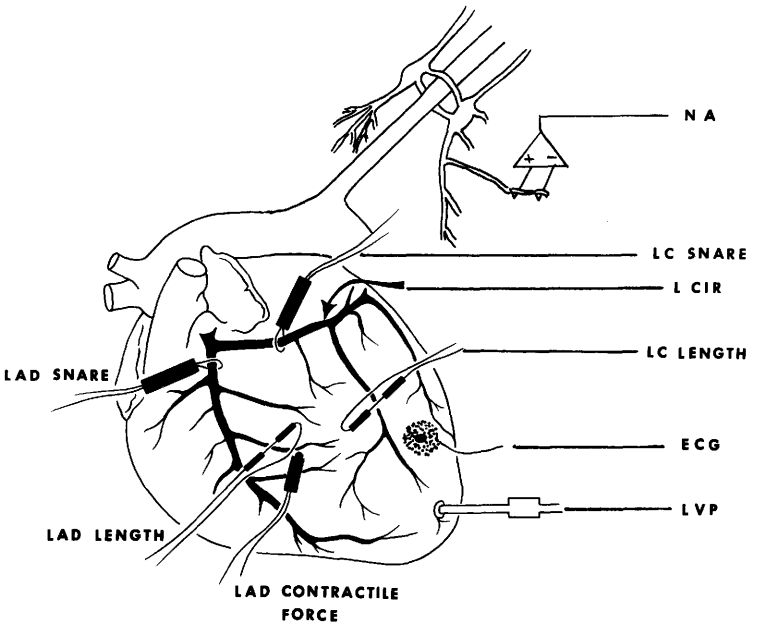

FIG. 1. Schematic representation of the experimental preparation of the left ventricle. LAD, left anterior descending; LC, left circumflex; LVP, left ventricular blood pressure; NA, nerve activity.

recorded on a Tandberg series 100 FM tape recorder for later analysis.

Nerve recording. The second or third white ramus communicans was divided into fine filaments under a Zeiss dissecting microscope at 200–800 magnification and laid across bipolar metal electrodes under oil prewarmed to 37°. The electrodes were connected to a high-input impedance preamplifier and amplifier equipped with high- and low-pass filters (1600–100 Hz). The signal was displayed on a Tektronix type 564B storage oscilloscope and monitored with a loudspeaker. A total of 12 nerve fiber preparations of left ventricular origin in the ischemic area were studied. Six of these nerve preparations were single fiber preparations, and six were small multifiber preparations. In addition, three small fiber preparations in the nonischemic area of the ventricle were also studied.

Conduction velocities were measured by stimulating one of the close cardiac nerves or the ventral ansa subclavia with a strength sufficient to evoke an action potential from the fiber which was studied during spontaneous activity. Stimulation characteristics of the generator were a square wave monophasic pulse, 0.1 msec pulse duration, and a constant current of 1–2 mAmps. The conduction velocity was calculated from the time of the stimulation artifact to the beginning of each evoked action potential and the distance from the stimulating to the recording electrodes. In some instances, conduction velocity was measured by placing the stimulating electrode over the receptive field of the left ventricular receptor. Usually much higher stimulus strengths were required to evoke the nerve fiber action potential using the latter technique.

The nerve activity, left ventricular pressure, and myocardial length changes were compared by playing the tapes on an Ortec averaging computer using the R wave of the ECG as a trigger. Nerve activity during 32 consecutive heart beats was accumulated at 5 msec time increments in the computer and printed out with the left ventricular pressure and length changes for the same heart beats using an X–Y plotter and digital printer. Only afferent nerve activity recorded from the left ventricular receptors was selected for this study. During the experiment, approximate location of the receptors was confirmed by mechanical probing of the epicardial surfaces of the left ventricle with a blunt insulated

probe having a tip diameter of 1 mm. An insulated probe was used in the study in order to reduce the noise artifact in the recording of nerve activity. Figure 2 is an example of afferent nerve activity recorded when a left ventricular receptor was located by the probe. Using this technique, the receptive fields could be localized within 2 to 3 mm for a single fiber preparation and varied up to 1 or 2 cm^2 for the small multifiber preparations studied in these experiments. Animals were killed by bleeding after every experiment; the nerve activity disappeared in the arrested heart and was not activated by coronary occlusion. However, nerve activity in the same fiber could be produced by mechanical probing of the receptor in the arrested heart, and more accurate location of the receptor field was obtained. The end diastolic length is shown as an inflection on the rising portion of the length trace. The epicardial segment length is maximal in the early part of the ejection period, as has been reported by Vokonas *et al.* (14) and Wyatt *et al.* (15) using similar methods for measuring changes in epicardial segment length. Average nerve activity was obtained from a precision half-wave rectifier and low-pass filter with a half amplitude point at 1 Hz.

Results. The response of left ventricular sympathetic afferent nerves to alterations in segmental length is shown as average nerve activity in Fig. 3. Acute left circumflex coronary artery occlusion produced an increase in

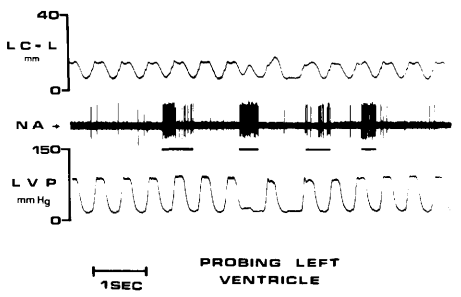

FIG. 2. Sympathetic afferent nerve activity of the left ventricular origin recorded from the third thoracic white ramus during probing of the left ventricle. LC-L, left circumflex length changes; NA, nerve activity; LVP, left ventricular pressure. Application of the probe is indicated by the bars which appear directly beneath the nerve activity.

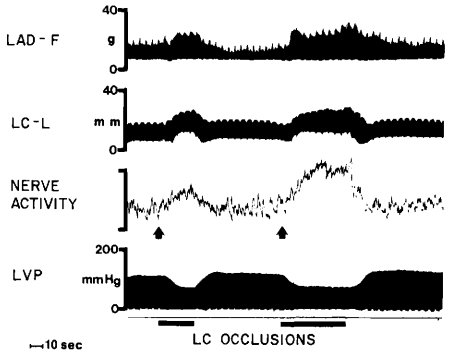

FIG. 3. Alterations in average nerve activity located in the LC area during 2 left circumflex occlusions. LAD-F, distant left anterior descending coronary artery contractile force; LC-L, left circumflex myocardial length; average nerve activity; LVP, left ventricular pressure.

segmental length in the area of the myocardium supplied by the occluded artery. The receptor responsible for the observed nerve activity was located within the distribution of the left circumflex and within 1 cm of the length gauge. The average increase in ventricular afferent nerve activity from the same segment coincided with changes in segmental myocardial length. In our study, the ventricular afferent nerve activity from the ischemic segment coincided with changes in segment myocardial length during coronary occlusion. In the study by Malliani *et al.* (4), only one left ventricular fiber was studied during perfusion of the left coronary artery, and latency for the excitation of the fiber during interruptions of left coronary flow was about 79 sec. The authors pointed out that in other studies by Brown and Malliani (2) the afferent cardiac sympathetic fibers increased their discharge during myocardial ischemia after a shorter latency (10–20 sec). They conclude that those fibers probably represented a different functional population.

Spontaneous sympathetic afferent discharge from small multifiber preparations was frequently observed, as shown in Fig. 4, without coronary occlusion. An increase in segmental length produced by occluding the circumflex coronary artery was associated with an immediate increase in afferent nerve activity. In the study depicted in Fig. 4, nerve activity and length increased while left ventricular pressure decreased. During the con-

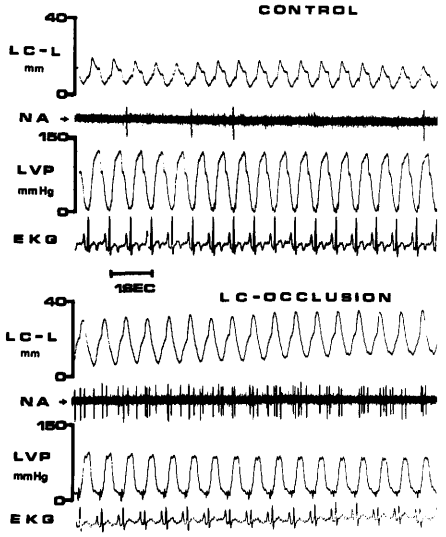

FIG. 4. Spontaneous sympathetic afferent discharge from the small multifiber preparation located in the LC region during control (top four tracings) and during left circumflex (LC) occlusion (bottom 4 tracings). LC-L, left circumflex length; NA, nerve activity; LVP, left ventricular pressure; EKG, electrocardiogram.

trol period, the segment length is maximum in the early part of the ejection period and shortens substantially during the systolic ejection period. During the occlusion, there is a significant increase in the epicardial end diastolic segment length of the ischemic segment shown as an inflection on the length curve and a sharp increase in the systolic segment length. The peak left ventricular pressure either decreased or remained unchanged during LAD occlusion when segment length and nerve activity both increased (Fig. 5). The maximum length of the epicardial segment appears to occur during systolic ejection and seems to be out of phase with the general changes in ventricular volume and pressure probably due to the position of the epicardial length gauge. During ischemia, both the systolic and diastolic lengths of the epicardial segment were increased. The conduction velocities in eight nerve preparations studied ranged from 7 to 13 m/sec. All of these nerve preparations were located in the left ventricle and responded to coronary artery occlusion with an increase in nerve activity. The afferent receptors located within the nonischemic myocardium did not show an increase in nerve activity during acute coronary occlusion.

In the neurohistogram (Fig. 6), nerve activity, left ventricular pressure, and LC length changes were compared during 32 consecutive heart beats. As shown, sympathetic afferent nerve activity was closely related to the segmental length changes and not to the left ventricular systolic pressure changes. In some instances, as segmental ventricular length increased and nerve activity increased, left ventricular pressure was observed to decrease during coronary artery occlusion (Figs. 3 and 6). The nerve activity on the histogram has been moved to the left portion of the figure for a time distance equal to the conduction velocity of the same fiber. Frequently, two systolic bulges were observed, as shown in Fig. 6, since length gauges covered a 1 in. area of the heart. Nerve activity before and after LC occlusion is random and has no relationship to LC-L. The LC length during control might not be sufficient to stimulate these fibers; and other factors, such as active shortening, might be responsible for random firing. Both vagi were intact in all experiments, but no significant changes in heart rate were observed during these short-term

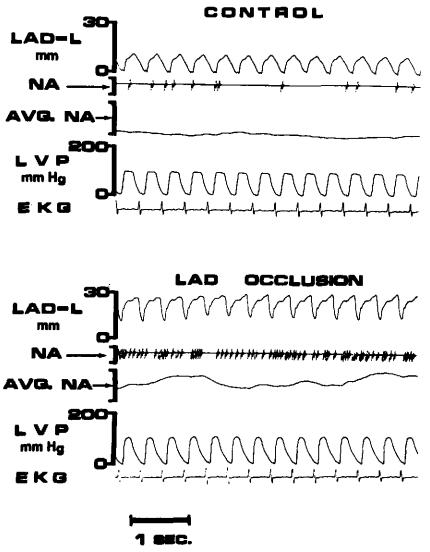

FIG. 5. Nerve activity changes during left anterior descending (LAD) occlusion in bottom four tracings. LAD-L, left anterior descending length; NA, nerve activity through discriminator; AVG. NA, average nerve activity; LVP, left ventricular pressure; EKG, electrocardiogram.

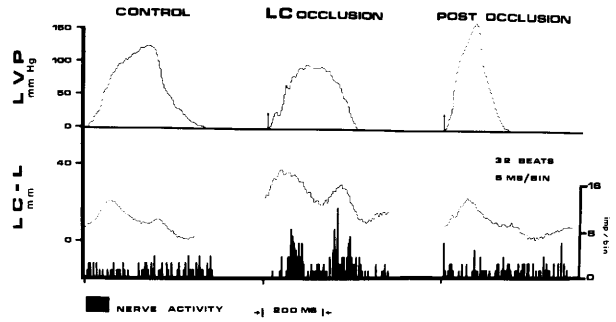

FIG. 6. Neurohistogram of left ventricular pressure (LVP), left circumflex length (LC), and nerve activity during 32 consecutive heart beats before, during, and after LC occlusion. Nerve activity was accumulated for 5 msec intervals (5 msec/BIN).

coronary artery occlusions.

The total range of the nerve activity in the impulses per heart beat is dependent upon the number of active fibers in the nerve preparation and the absolute changes in the segmental length. Using the data accumulated by the computer, it was possible to calculate the averaged increase in segmental length and averaged increase in nerve activity and express these values as a percent change from the control values, as shown in Fig. 7. The average increase in segmental length was 80% above the control length, and the average increase in afferent nerve activity was 115% above the control nerve activity for the 30 sec coronary artery occlusions.

Discussion. Cardiac nerves have been studied in detail by anatomists, and their content of sensory fibers has been unequivocally verified by physiologic testing in dogs and by observations after various types of cardiac denervation in man (1, 16). Miller and Kasahara (17) examined the sensory nerve endings in the heart and concluded that two types of endings are present in the ventricular wall, the socalled "nerve net" and the complex, unencapsulated endings. The nerve net endings are found throughout the entire endocardium, and a wide variety of both diffuse and compact types of unencapsulated endings are found in the epicardium. It can be concluded that all four chambers of the heart are innervated by myelinated and unmyelinated afferent sympathetic nerve fibers (1, 12). Sympathetic cardiac afferent nerves (Aδ and C fibers) were studied by Brown (18) and Uchida *et al.* (5, 6, 8–12), and anatomical identification of myelinated and unmyelinated afferent sympathetic nerve fibers was made in this laboratory (19).

Little is known about the function of cardiac sympathetic afferent nerves. During experimental coronary occlusion, cardiac sympathetic afferent nerve fibers have been studied by Brown and Malliani (2), Uchida *et al.* (10) and others. Malliani *et al.* (20) have studied changes in sympathetic efferent nerve activity during experimental coronary occlusion in the cat. Coronary occlusion induced an increased discharge of sympathetic efferent nerve fibers and authors proposed a sympathetic cardiocardiac reflex.

The myelinated fibers from sympathetic afferent nerves fire synchronously with passive extension and/or shortening of the ischemic myocardium in which the nerve endings are embedded; whereas, the unmyelinated fibers fire irregularly and independently, as shown by Uchida and Murao (5). It has

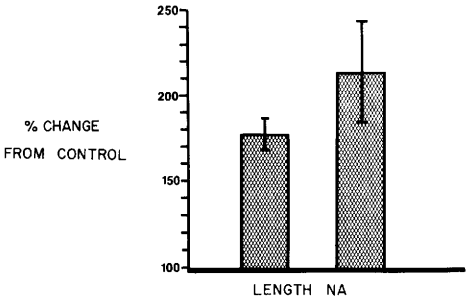

FIG. 7. Nerve activity (NA) and averaged length changes expressed as % change from the control values. Mean values with 1 SEM are presented from 12 cardiac receptors and 12 experimental animals. The % change from control values is significant ($P < 0.01$) for both length and nerve activity.

been suggested that mechanical factors were responsible for excitation of the myelinated fibers and chemical factors for the unmyelinated fibers (10, 12). In the present study, nerve discharge was frequently observed in myelinated fibers before coronary occlusion. During occlusion, these fibers fired regularly with a close relation to each cardiac cycle.

Conduction velocities for Aδ group afferent fibers ranged from 3–25 m/sec in studies by Uchida *et al.* (5, 10). In the present study, conduction velocities for fibers which responded to increased myocardial length ranged from 7 to 13 m/sec and, therefore, also belong to the Aδ group.

Ventricular receptors exhibiting a periodic discharge are few in number, and their pattern of discharge seems to follow the ventricular pressure curve as reported by Paintal (21) for cardiac vagal afferents and Hess *et al.* (22) for cardiac sympathetic afferents. Distension of the ventricular myocardium could also provide an adequate stimulus for afferent nerve activity (22). Unphysiological motion and systolic bulge of the left ventricular wall during ischemia may contribute to excitation of afferent myelinated fibers as suggested by Uchida and Murao (5).

In the present study, an increase in sympathetic nerve activity in the group of afferent nerves studied was closely related to the left ventricular segmental length changes during ischemia. In other studies, systemic administration of nitroglycerin reduced systolic bulge during experimental coronary occlusion and suppressed excitation of afferent nerve fibers (6). However, the authors presented no measurements of length changes. Propranolol has been reported to suppress excitation of the afferent cardiac sympathetic nerve fibers through reduction in heart rate (9). Intrajugular injection of acetylcholine caused excitation of afferent fibers through abnormal distension of the nerve endings (12). Other agents which may excite ventricular receptors are veratrine (23), bradykinin (7), potassium ions (8), and lactic acid (11). Acidosis is thought to play a role in excitation of the unmyelinated fibers induced by myocardial ischemia, but not in excitation of the myelinated fibers (11).

Distension of ventricular wall receptors may be involved in the reflex fall in blood pressure and bradycardia which may accompany acute experimental myocardial infarction (20). The depressor reflex may be associated with activation of ventricular mechanoreceptors with slow conducting vagal afferents as reported by Thorén (24). On the other hand, reflex tachycardia and changes in myocardial contractility mediated by the cardiac sympathetic nerve fibers may be components of reflexes initiated by stimulation of afferent cardiac sympathetic nerve fibers and may be involved in pressor responses to acute myocardial infarction (20, 23, 25). It has been demonstrated in a previous study by Purtock *et al.* (26) that left ventricular mechanoreceptors with sympathetic afferents may respond to ventricular pressure changes during systole or to changes in ventricular volume during diastole. Stimulation of afferent cardiac sympathetic nerve fibers might also reflexly modify the sympathetic control of the mechanical properties of the thoracic aorta, sensitivity of aortic mechanoreceptors, and characteristics of those reflexes initiated by them (27, 28). Thus, it appears that receptive mechanisms exist within the ventricular wall for initiation of both pressor and depressor reflexes. The conditions under which a particular type of reflex produces a dominant effect were not investigated in the present study and remain to be elucidated.

Summary. Myelinated sympathetic afferent fibers with conduction velocities in the Aδ range arising from receptors located within the left ventricle responded to acute coronary artery occlusion with an increase in activity. The increase in activity was over 100% above control levels of activity. The increase in afferent nerve activity was directly related to an increase in left ventricular segmental length produced by acute coronary artery occlusion.

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