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Response of Left Ventricular Mechanoreceptors to Changes in Pressure and Muscle Length (39703)[1]

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Previous studies have provided evidence for afferent sympathetic nerves from the heart which traverse the left upper thoracic white rami communicantes. Anatomically, these fibers have been studied by Mizeres (1), and sensory endings of sympathetic nerve fibers have been histologically located by King (2) and Khabarova (3). Cardiac sympathetic afferent nerve activity has been reported to be spontaneous and can be stimulated by various chemical and mechanical means (4–6). Tonic activity of sympathetic afferents related to normal cardiac events and entering the spinal cord at T-3 has also been noted (6, 7). Recent studies in our laboratory by Hess *et al.* (8) have specifically related cardiac afferent sympathetic nerve activity to isolated changes in peak-developed left ventricular pressure.

The purpose of these experiments was (i) to measure left ventricular mechanoreceptor response to changes in left ventricular volume and pressure, and (ii) to correlate sympathetic afferent nerve activity in left thoracic white rami communicantes with changes in left ventricular pressure and muscle length during the cardiac cycle. After cardiopulmonary bypass, cardiac afferent nerve discharge was studied during isovolumetrically developed changes in left ventricular pressure and during isobarically developed changes in myocardial muscle length.

Materials and Methods. Afferent nerve activity was studied in 14 small single and multifiber nerve preparations in 11 mongrel dogs (25–35 kg) anesthetized with sodium pentobarbital (Nembutal, Abbott Laboratories), 30 mg/kg intravenously. The animals were intubated and ventilated with 40% oxygen in air, using a Bird Mark VII respirator. The animals were placed on total cardiopulmonary bypass (Fig. 1). In the following, the procedures and methods, which have been previously described in detail (8), are outlined. A cannula in the right ventricle allowed drainage of coronary venous blood. The right and left lungs were tied at the hilum, and aortic perfusion pressure was maintained at approximately 90 mm Hg using a Sarns roller pump. During bypass, arterial blood gases and pH were maintained between 7.35–7.45 pH, 38–42 mm Hg PCO_2, and PO_2 greater than 200 mm Hg. Muscle relaxation was obtained with 20 mg of gallamine triethiodide (Flaxedil, Davis and Geck). This dose was repeated every 45 min along with supplementary doses of sodium heparin (3000 IU) and Nembutal as required.

The heart was supported with a pericardial cradle. Electrocardiographic electrodes were sewn directly into the myocardium using stainless steel monostrand suture.

Two balloons, one liquid filled for isovolumetric and one air filled for isobaric studies (designed to be used interchangeably), were pulled into the left ventricle through the ventricular apex and securely anchored to the apical endocardium. A drain for removal of Thebesian and bronchial venous blood was also inserted into the left ventricle. Balloon compliance was such that it did not significantly alter pressures within the expected range of measurements. Isobaric contractions of the left ventricle were studied using a closed system consisting of a balloon attached to wide-bore polyethylene tubing and connected to a source of air pressure and a 50-liter Nalgene bottle. A Fleisch

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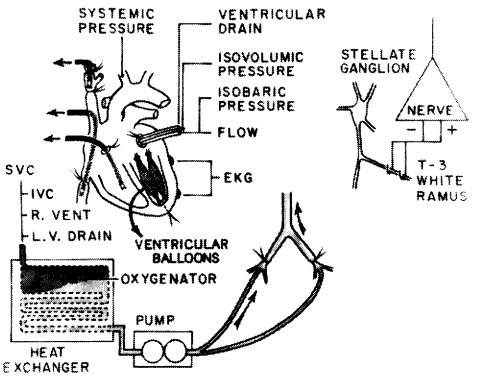

FIG. 1. Systemic perfusion system. SVC, superior vena cava; IVC, inferior vena cava; R. Vent., right ventricle; L.V. drain, left ventricular drain; EKG, electrocardiographic electrodes.

pneumotachometer, a Statham PM97 differential pressure transducer, and a Statham 23 DC pressure transducer were placed in the system for measurement of pressure and flow. The isobaric apparatus permitted changes in cardiac volume without associated changes in intraventricular pressure. Ventricular ejection into this closed system resulted in system pressure fluctuations of less than 1%.

Isobaric flow curves and isovolumetric and isobaric ventricular pressures were recorded along with systemic arterial pressure on the Grass polygraph. These parameters (excluding systemic pressure) were recorded on a Tandberg Series 100 FM tape recorder. Taped data could then be replayed for computer analysis and also visually examined on a Honeywell Model 1912 visicorder. Arterial blood gases and pH were analyzed on a Radiometer Type PHA927b blood gas machine.

Nerve recording. The sympathetic chain of the left upper thoracic region was exposed and a white rami communicantes, usually T-3, was isolated, stripped of connective tissue, and cut to eliminate efferent activity. The peripheral end of the nerve was divided into slips and placed on bipolar recording electrodes. Nerve activity was passed through a low noise AC preamplifier, an active electronic variable band-pass filter, and displayed on a Tektronix 564B oscilloscope. Nerve data was also stored on FM tape. Nerve amplifier output was used to drive a loudspeaker which facilitated recognition of cyclic nerve discharge.

Data acquisition. When nerve activity was found which cycled with cardiac rhythm: (i) Isobaric pressures were recorded with the isovolumetric balloon completely collapsed and pressures elevated in 25 mm Hg steps. Nerve activity was recorded and collected in steps for 32 nonarrhythmic heart beats up to the final recording pressure of 100 mm Hg. The isobaric balloon was then collapsed for isovolumetric studies using the same nerve fiber. (ii) Isovolumetric pressures were recorded in increments of 50 mm Hg peak systolic pressure. Nerve activity was recorded for 32 nonarrhythmic heart beats including a final recording at 150 mm Hg peak pressure.

Data analysis. The tape-recorded nerve activity was electronically filtered and fed into a window discriminator which selected action potentials on the basis of amplitude. The discriminator output was accumulated in an Ortec Model 4620 histogram computer. Poststimulus time histograms of nerve activity were obtained for 32 cardiac cycles. The upstroke of the R wave of the electrocardiogram was used to initiate the analysis of nerve activity, pressure, and flow data in 5-msec time increments. Frequency histograms, average isovolumetric pressure, and isobaric volume curves were traced out by a Honeywell 530 X–Y plotter.

Mechanical systole in the isovolumetrically contracting left ventricle was defined as the interval between the onset and termination of isovolumetrically developed ventricular pressure. In the isobarically contracting preparation, mechanical systole was taken as the interval between the onset and termination of the ejected volume signal. Nerve activity was averaged with respect to time during systole and diastole for each of the manipulated pressure levels. Data for each preparation were normalized by setting the maximum nerve activity recorded during systole and diastole as 100%. The data from all of the preparations were combined at each of the pressure steps utilizing these normalized values. Nerve activity at elevated pressures, both isovolumetric and isobaric, was compared to control values at 0 mm Hg. Significant differences in mean val-

ues from control were established using a Student's t distribution.

Results. Isobaric nerve activity was studied in eight nerve preparations in five mongrel dogs. Isovolumetric nerve activity was studied in six nerve preparations in six animals. Three of the fourteen small nerve fiber preparations were from animals in which isobaric and isovolumetric conditions were imposed alternately. The origin of the receptors which were stimulated by changes in left ventricular pressure or volume was confirmed by probing the epicardial surface of the left ventricle with a blunt insulated probe. Receptors were present throughout the left ventricle, and activation of a receptor by means of probing resulted in sustained nerve activity.

Representative nerve activity recorded from the third thoracic white ramus during isovolumetric contraction at 100 mm Hg peak systolic isovolumetric pressure is shown in Fig. 2A. Grouped systolic nerve activity was evident beginning with the onset of ventricular systole and through the period of ventricular pressure development. Minimal nerve activity was observed during ventricular diastole when pressures were at minimal levels.

Representative responses of afferent nerve activity during isobaric contraction are shown in Fig. 2B. Minimum values of ejected volume represent periods when ventricular diameter was maximum. Ejection of air by the contracting ventricle into the large reservoir of relatively high compliance and inertance produced the oscillations seen in the flow signal. In each case, ventricular contraction with concomitant reduction in ventricular diameter decreased the nerve activity from that seen in diastole. Delays due to conduction velocity (8–15 m/sec; 20-cm distance) and delays due to the transducer system are in the same direction and tend to partially cancel each other. Delays of the nerve activity relative to the transducer system are expected to be only 5–10 msec.

Poststimulus time histograms of afferent nerve activity recorded from R wave to R wave of the ECG for 32 cardiac cycles are shown in Fig. 3. Isovolumetric contraction produced increases in mean spike frequency occurring beneath the systolic pressure

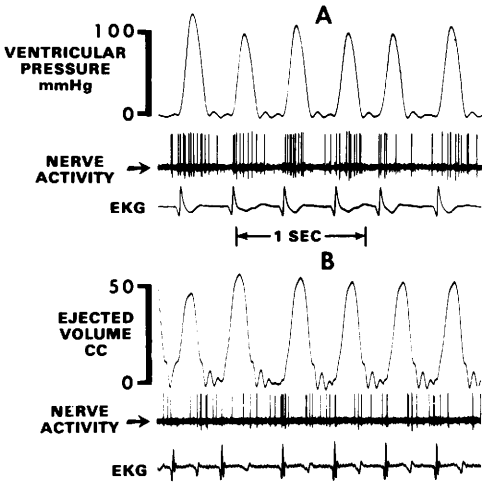

FIG. 2. (A) Effect of isovolumetric contraction on sympathetic afferent nerve activity. Peak systolic isovolumetric pressure at approximately 100 mm Hg. (B) Effect of isobaric contraction on sympathetic afferent nerve activity. Peak ejected volume at approximately 50 cm^3.

curve. Isobaric contractions produced increases in mean spike frequency occurring outside of isobaric systole.

Isobaric contraction resulted in no change in nerve activity during isobaric systole; however, return of the ventricle to diastolic dimensions resulted in increases in spike frequency. During isobaric studies, the most evident alterations in mean spike frequency occurred in late ventricular systole, early ventricular diastole, and during the early part of the ventricular systole associated with tension development in the myocardium.

Maximum discharge frequencies during isovolumetric contraction ranged from 87–169 impulses/beat during diastole. Maximum discharge frequencies during isobaric contraction ranged from 75–181 impulses/beat during systole and from 71–212 impulses/beat during diastole. Average nerve activities were plotted as percentages of maximum nerve activity accumulated for 32 cardiac cycles (Fig. 4). Mean discharge frequency and total nerve activity during isovolumetric systole responded to elevations in isovolumetric pressure. Nerve activity at peak systolic isovolumetric pressures of 100 and 150 mm Hg was significantly different ($P < 0.05$) from that of control taken as 0

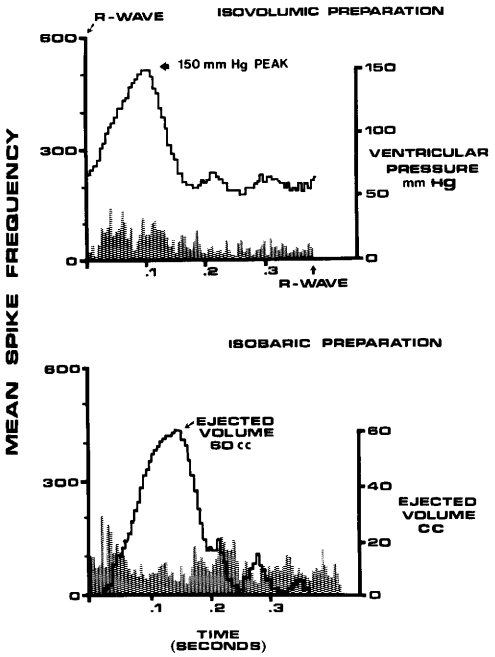

FIG. 3. Poststimulus time histograms of spike frequency recorded for 32 cardiac cycles. Activity was recorded during the R-R interval of the ECG. The dark lines represent average pressure (above) and flow (below) tracings.

mm Hg. Diastolic nerve activity at a diastolic pressure of 50 mm Hg was significantly different from control.

Isobaric left ventricular systole resulted in no significant changes in nerve activity at any isobaric pressure. Diastolic isobaric nerve activity was significantly increased ($P < 0.05$) by increases in isobaric pressure and ventricular diameter. The average ejected volumes at isobaric pressures of 0, 25, 50, 75, and 100 mm Hg were 0, 40, 60, 80, and 75 ml, respectively. Systolic nerve activity was independent of ejected volume in the range of 0–80 ml. Diastolic nerve activity was significantly increased when ejected volume increased from 0–80 ml.

Discussion. Sympathetic afferent nerve activity of left ventricular origin responded to incremental increases in peak systolic isovolumetric pressure with significant increases in average nerve activity. These data confirm earlier evidence by Hess *et al.* (8) of pressure-sensitive left ventricular mechanoreceptors with fibers traversing the left upper thoracic white rami communicantes. In the present study, during isovolumetric conditions, nerve activity was influenced to a greater extent by the development of systolic pressure than by diastolic pressure.

Elevation of isobaric pressure during isobaric systole resulted in no significant alterations in the percentage of maximum systolic nerve activity. Since intraventricular pressure remained constant during isobaric systolic contraction, ventricular contraction alone, in the absence of pressure changes, was not capable of altering afferent nerve activity.

Significant changes in maximum nerve activity under isobaric conditions were evident during the period of ventricular diastole at elevated isobaric pressures. Large alterations in diastolic ventricular dimensions appeared to produce the most significant response in these cardiac afferent fibers. Cardiac sympathetic afferent receptors may be similar to ventricular receptors with vagal

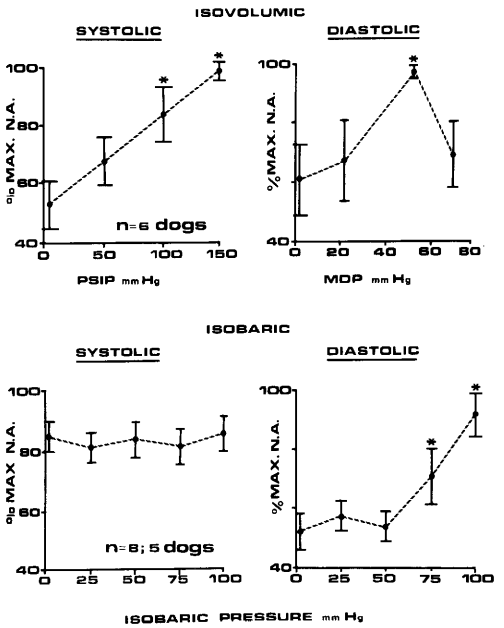

FIG. 4. Comparison of isovolumetric and isobaric average nerve activity plotted as percentage of maximum nerve activity during systole and diastole. Isovolumetric systolic nerve activity is plotted against peak systolic isovolumetric pressure (PSIP) in mm Hg. Isovolumetric diastolic nerve activity is plotted against mean diastolic pressure (MDP) in mm Hg. Systolic and diastolic isobaric nerve activity are plotted against isobaric pressure in mm Hg. Vertical bars represent ± standard error.

afferents which respond to changes in ventricular pressure and/or volume, as described by Coleridge *et al.* (14).

An isobaric method has been described previously by Monroe *et al.* (9). A modification of this method was used in the present study. The unique experimental apparatus employed in the present study related cardiac afferent nerve activity to changes in left ventricular mechanics in a manner not previously described. Previous studies of the isovolumetrically contracting ventricle (8) may have selected solely for sympathetic afferent nerves responding to changes in developed pressure and did not demonstrate the full capabilities of the afferent response.

The afferent nerve activity described here may initiate reflexes, as suggested by Schwartz *et al.* (10). Activation of this reflex produced an increase in sympathetic afferent activity resulting in a rise in arterial pressure (11), an increase in myocardial contractility (12), and an acceleration of heart rate (13), accompanied by a decrease in cardiac vagal activity (10).

Summary. We conclude that the increase in isovolumetrically developed intraventricular pressure is associated with an enhanced activity of cardiac sympathetic afferents traversing the left upper thoracic white rami communicantes, as reported by Hess *et al.* (8). Moreover, the sympathetic afferent nerve fibers respond to alteration in myocardial muscle length occurring in isobaric diastole and thus respond to a displacement stimulus as well as to a pressure stimulus.

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