Characteristics of Left Ventricular Receptors with Nonmedullated Vagal Afferents in Cats

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SUMMARY Activity from left ventricular receptors with nonmedullated afferents was recorded in the right cervical vagus in anesthetized, thoracotomized cats. Probing of the open heart demonstrated that the receptors were distributed throughout the free wall and the interventricular septum. Fibers from posterior receptors pass along the posterior descending coronary artery and the lateral surface of the right atrium to join the right main cardiac nerve; those from the anterolateral region pass behind the aorta and the pulmonary trunk. The control receptor discharge was 1.4 impulses/sec at a mean left ventricular end-diastolic pressure (LVEDP) of 4.5 (range, 2-10) mm Hg. It was observed that receptor discharge increased with progressive increase in LVEDP produced either by transfusion or by aortic occlusion. At a mean LVEDP of 8 mm Hg, the mean discharge rate was 3.2 impulses/sec, and at 16 mm Hg it was 7.0 impulses/sec. It was also found that propranolol reduced and isoproterenol increased the discharge frequency at any given LVEDP. Measurement of total conduction times indicated that during the increase in LVEDP the receptors were activated principally in the systolic portion of the cardiac cycle. Despite this there was no obvious relationship between the discharge frequency and left ventricular systolic pressure.

LEFT ventricular receptors signaling in nonmedullated vagal afferents have been described in cats1,2 and dogs.3-6 When activated, these receptors induce depressor reflexes, characterized by bradycardia, and also vasodilation,2-4 which is especially pronounced in the kidney.7 The receptors also activate the vomiting center15,16 and are probably the main receptor stations for the Bezold-Jarisch reflex.2,7 The receptors increase their activity during brief aortic occlusion,2,4,5 carotid occlusion,2,5 transfusion,2 and injection of epinephrine2,4,5 or isoproterenol.4

The relationship of the discharge of these receptors in the left ventricle to change in ventricular pressure and contractility has not been quantified. The major goal of the present study was to obtain such data. In addition, the distribution of the receptors within the left ventricle and their intracardiac pathways were studied, and an attempt was made to determine the time of the receptor activation in the cardiac cycle.

Methods

Cats were anesthetized with 30-40 mg/kg of pentobarbital, intraperitoneally. Additional doses of 10 mg/kg were given at intervals as required. A tracheotomy was performed, and positive-pressure ventilation was induced by giving the cats gallamine triethiodide (Flaxedil), 2 mg/kg; additional doses of 10 mg/kg were given at intervals as required. A tracheotomy was performed, and positive-pressure ventilation was induced by giving the cats gallamine triethiodide (Flaxedil), 2 mg/kg, in repeated intravenous injections. Rectal temperature was measured and maintained at 37°C to 38°C by means of external heating. The P02, Pco2, and pH were measured at intervals, and Pco2 and pH were maintained within the normal range (30-40 mm Hg and 7.35-7.45, respectively) by adjusting the tidal volume or by injecting small amounts of NaHCO3 (1 mEq/ml).

SURGICAL PROCEDURES

The vagus nerves, the sympathetic trunks, and the carotid arteries were dissected free in the neck. The thorax was opened by a bilateral, intercostal, transsternal incision. The pericardium was split and the edges were suspended by ligatures from the chest wall. Snares were placed around the ascending aorta and the pulmonary artery so that the pressure in the left and right sides of the heart could be elevated separately. A balloon catheter (Swan-Ganz 93-110, 5 F) was placed in the mitral valve through an incision in the tip of the atrial appendage. The right main cardiac nerve running from the heart to the vagal trunk in the chest was dissected free after division of the azygos vein.18 In those experiments in which it was possible to identify a separate branch from the cardiac nerve running to the lung root, this branch was cut. The right vagal trunk was likewise cut in the chest just below the entrance of the cardiac nerve. The right upper lung lobe was removed.

RECORDING OF PRESSURES AND ELECTROCARDIOGRAM

Pressures were measured by Statham transducers (P23De and SP32) connected to catheters (PE-90) inserted into the aorta, left ventricle, right atrium, and left atrium through a femoral artery, left carotid artery, femoral vein, and right upper lung vein, respectively. All pressures were referred to mid-right atrial level.

The left ventricular pressure catheter was connected to two transducers (P23De and SP32) to measure the systolic pressure and the end-diastolic pressure with different gain. The left ventricular catheter system was damped optimally by means of a small needle valve between the catheter and...
the transducer; the degree of damping was tested before each experiment by a Hewlett-Packard function generator (model 202A) connected to a piston phone. The response of the catheter system measuring left ventricular systolic and end-diastolic pressures was flat (±5%) up to 55-65 Hz and 30-35 Hz, respectively.

The rate of increase in left ventricular pressure was measured by an electronic device. The overall frequency response in the system measuring dp/dt was flat (±5%) to 55-65 Hz.

The aortic blood pressure, the left ventricular systolic and end-diastolic pressures, and the rate of increase in left ventricular pressure were recorded together with the electrocardiogram, the nerve traffic, and a signal on a Honeywell ultraviolet Visicorder (model 1508) writing intermittently with fast speed (5-20 cm/sec).

The aortic pressure, the left ventricular pressure, and the mean pressure in the left and right atria were recorded on a six-channel Brush recorder, writing continuously with slow speed (2.5-12.5 cm/min). One femoral artery and one femoral vein were also cannulated for bleeding and transfusion.

A bipolar electrocardiogram was recorded with one needle electrode in the left side of the chest wall and the other electrode in the esophagus behind the heart.

**RECORDING OF NERVE TRAFFIC**

The right vagus nerve was placed on a black plastic dissection plate. A pool was made by the surrounding muscles and skin and was filled with mineral oil (temperature, 35-36.5°C). The nerve sheath around the right vagus was removed by means of sharp forceps under a binocular dissection microscope. Thin filaments were obtained and cut centrally, the rest of the vagus nerve being left intact. The filaments were placed on a bipolar silver/silver chloride electrode and connected to a Grass probe (HIP 511E) and amplified by a Grass amplifier (P 511).

The high frequency cutoff normally was set at 300-1,000 Hz and the low frequency cutoff at 10-30 Hz. The output from the amplifier was displayed both on an oscilloscope (Tektronix 564) and on the Visicorder. The Grass amplifier was also connected to a loudspeaker and to a rate meter equipped with a discriminator, which could count either all spikes exceeding a preset value or only spikes with amplitudes between two predetermined levels. The output of the rate meter was recorded on both the Brush recorder and the Visicorder. The receptor activity was calculated from the spike-counter recordings. Numerous spot checks were made in each experiment by manual counting of the actual traffic.

The conduction time in the afferent fibers was determined by applying an electrical stimulus (Grass stimulator S4) to the right cardiac nerve and recording the evoked potential. A stimulus just above threshold was used to minimize spread of current. In several filaments some previously inactive fibers were excited by the electrical stimulation; however, it was possible to identify the active fiber by the spike morphology and amplitude. The distance between the stimulation and recording electrodes was measured, and since the conduction time was known, the conduction velocity could be calculated.

The major error in the measurement of conduction velocity is the estimation of the length of the nerve between the stimulating and recording electrodes. In five cats the in situ measurement was compared with the length measured after the nerve had been dissected free. The in situ length was shorter but the difference never exceeded 15%. Since the time from the onset of the electrical stimulus to the inscription of the action potential cannot be longer than the duration of the electrical stimulus (1-2 msec), and since the total conduction time in the vagal fibers was about 100 msec, this is not an important source of error.

The total conduction time from the receptor site was measured in a similar way by recording the potential evoked by electrical stimulation of the area in the non-beating heart that had been found by mechanical probing to contain the receptor. This measurement allowed correction of the position of the recorded spike in the tracing. The relation of receptor activation to events within the cardiac cycle could then be established.

For the purpose of mapping the cardiac pathway of the fibers subserving the receptors, the myocardium in the region of the receptor site was explored with the stimulating electrode, and points at which an evoked potential could be recorded were identified. In this manner the entire cardiac pathway from the mechanically identified receptor site to the main vagus nerve trunk was defined. The length of the intracardiac pathway could be estimated by placing a string along the pathway and then measuring the length of the cut string. The conduction velocity in the heart could be calculated from the length of the intracardiac pathway and the difference between the total conduction time and the conduction time in the vagus nerve.

**EXPERIMENTAL PROCEDURES**

As a screening procedure to find ventricular C fibers, which normally have a low, irregular discharge, the activity in all filaments dissected from the vagus was observed during a brief (3-6 seconds) occlusion of the ascending aorta. Every filament that responded with increased activity to this maneuver was dissected further until a filament with only one active fiber was obtained. The localization of the receptor to the left ventricle was further established by the failure of the receptor activity to increase during occlusion of the mitral valve and of the pulmonary artery. In most cases the final anatomical location of the receptor in the ventricle was obtained by exploring the heart with a fine probe after the cat had been killed.

Receptor activity, recorded in single- or few-fiber preparation, was observed during alterations in the pattern of cardiac contraction induced by (1) graded aortic occlusion (afterload), (2) step increases in blood volume by transfusion (preload) with dextran 40 (Rheomacrodex), and (3) intravenous infusion of isoproterenol hydrochloride (Isuprel) (increased contractility). Isoproterenol was given as a bolus (2-5 μg) or as a continuous injection (1.2-6.25 μg/min). The aortic occlusion was maintained for 15-25 seconds at each level, at which time pressure and discharge frequency were measured. Each step infusion was completed in 15 seconds; pressure and discharge frequency were measured 45 seconds later.
The receptor response to graded aortic occlusion was repeated after infusion of isoproterenol (1.25–2.5 μg/min) and after intravenous injection of propranolol (0.2–0.3 mg/kg). The receptor response to transfusion was also tested after intravenous injection of propranolol (0.2–0.3 mg/kg).

The receptor response to ventricular fibrillation was observed after electrical fibrillation of the ventricle (100 Hz, 2 msec, 6 V) and in some experiments after spontaneous defibrillation.

The significance of changes was determined by Student's t-test for paired observations.

**Results**

This study is based on recordings from 55 left ventricular receptors in 53 filaments in 37 cats. Forty-three of the recordings were made with only one active fiber and the others with two or three active fibers; the latter had clearly different spike heights, and so the activity in the individual fibers could be calculated separately.

The conduction velocity in the vagal nerve (55 receptor afferents) varied for the individual fibers from 0.6 to 2.4 m/sec (mean ± se, 0.90 ± 0.05 m/sec), and the total conduction time (16 fibers) varied from 77 to 330 msec (mean 216 ± 18 msec). Thus these fibers belong to the C fiber category.

The mean intracardiac conduction velocity of 12 receptor afferents was 0.54 ± 0.04 m/sec. The mean conduction velocity in the vagus nerve for the same 12 afferents was 0.78 ± 0.05 m/sec. This difference is statistically significant (P < 0.01).

The control discharge was averaged for periods of over 30 seconds in 55 fibers and was between 0 and 6 impulses/sec (mean 1.4 ± 0.2 impulses/sec) at a mean left ventricular end-diastolic pressure of 4.5 (range, 2–10) mm Hg. A peculiar pattern was observed in eight receptors; the low spontaneous discharge changed suddenly to an irregular or cardiac-modulated discharge of high frequency (6–12 impulses/sec) that lasted for several seconds to many minutes without any obvious changes in intraventricular pressure.

The receptor response to mechanical probing of the heart was recorded in 39 receptors. Firing rates varying from 8 to 55 impulses/sec (mean 20 ± 1.5 impulses/sec) were obtained. In most cases the receptor stopped firing with cessation of the mechanical stimulation. However, 12 receptors continued to fire for 3–60 seconds.

**RECEPTOR LOCATION AND INTRACARDIAC PATHWAY**

The location of 26 receptors was established in the nonbeating heart. The receptors were located throughout the ventricle, including the interventricular septum. The general location of the 29 other receptors in the left ventricle was established by the increased discharge during aortic occlusion and the unaltered or decreased discharge during mitral valve occlusion and pulmonary artery occlusion.

Six of the 26 receptors could be localized to the interventricular septum by probing the opened heart. The spontaneous discharge and response to aortic occlusion were not different from those of other left ventricular receptors. Five of these receptors had an immediate increase in discharge during pulmonary artery occlusion with maximal frequencies ranging from 2 to 6 impulses/sec.

The intracardiac pathways of 14 of the receptor afferents were mapped (Fig. 1). In general, fibers from receptors in the posterior region of the left ventricle ascended to the base of the heart along the posterior descending coronary artery and then swept across the lateral surface of the right atrium to join the right main cardiac nerve. Fibers from receptors in the anterolateral region passed along the superior aspect of the left and the right atrium behind the aorta and pulmonary trunk to join the right main cardiac nerve. One fiber ascended along the anterior descending coronary artery. Two fibers on the anterior surface of the heart made their exit in the pathway described for the posteriorly situated receptors.

**RESPONSE TO AORTIC OCCLUSION**

The receptor response to a 3- to 6-second aortic occlusion was tested in all receptors (55 fibers) and was found to be between 3.5 and 22 impulses/sec (mean 9.4 ± 0.7 impulses/sec). Seven receptors did not show a sustained increase in activity. When the occlusion was released, the activity returned to control values in parallel with the decrease in left ventricular systolic pressure (LVSP) and end-diastolic pressure (LVEDP). However, six receptors continued to fire for 3–8 seconds after the pressures had returned to control levels.

The discharge frequency during graded aortic occlusion was examined in 24 receptors. Recordings made from one receptor are shown in Figure 2. During the first grades of occlusion, when the systolic pressure was increased from 120 to 220 mm Hg there was no increase in LVEDP, mean left atrial pressure, or receptor discharge. However, with further occlusion, receptor discharge increased in parallel with the increase in LVEDP. LVSP was more or less constant around 240 mm Hg during this period of increased receptor discharge.

In five of the 24 receptors the discharge during graded aortic occlusion was irregular, and no relation between ventricular pressures and receptor discharge could be established; in the 19 other receptors the discharge pattern was similar to that shown in Figure 2. The relation be-
FIGURE 2 Effect of a graded aortic occlusion on aortic blood pressure, left ventricular pressure, left ventricular end-diastolic pressure (LVEDP), mean left atrial pressure, and spike frequency in a single left ventricular C fiber. Letters in spike frequency recording (fourth panel) correspond to neurograms below. During graded aortic occlusion this receptor does not respond to a change in left ventricular systolic pressure from 120 to 220 mm Hg. However, when aortic occlusion is further accentuated, receptor increases discharge in parallel with increase in LVEDP.

FIGURE 3 Activity in 11 left ventricular C fibers (10 cats) plotted against left ventricular systolic pressure (upper panel) and left ventricular end-diastolic pressure (lower panel) during graded aortic occlusion. Heavier line indicates receptor in Figure 2. For clarity, actual points are excluded and only lines, drawn by inspection, are shown.

FIGURE 4 Effect of a graded increase in blood volume (transfusion of dextran) on aortic blood pressure, left ventricular pressure, left ventricular end-diastolic pressure (LVEDP), mean left atrial pressure, and discharge frequency in a single left ventricular C fiber. Letters in spike frequency recording (fifth panel) correspond to neurograms below. During transfusion, receptor activity increases from about 1 to 10 impulses/sec in parallel with change in LVEDP and discharges with cardiac rhythmicity. Time of activation in the cardiac cycle is indicated by an asterisk (*).

Between the receptor discharge and the ventricular systolic and end-diastolic pressures is plotted in Figure 3 for 11 receptors. The eight other receptors had similar responses (which were not plotted, in order to make the figure more readable). As is evident from the figure, the receptor discharge is not obviously related to the systolic pressure, but it correlated well with end-diastolic pressure with a threshold of 2-13 mm Hg.

RESPONSE TO TRANSFUSION

The discharge frequency during transfusion was examined in 13 receptors that showed a sustained response of more than 5 impulses/sec to brief aortic occlusion. The observations in one receptor are shown in Figure 4. This receptor increased from a low frequency discharge of about 1 impulse/sec to a maximal discharge of 10 impulses/sec in parallel with the increase in end-diastolic pressure. The data for 11 receptors are shown in Figure 5.
The threshold ranged from 2.5 to 12 mm Hg, and at 15 mm Hg the mean discharge was 5.8 impulses/sec. Data from two receptors were omitted because there was no sustained response.

RESPONSE TO INTRAVENOUS INJECTION OF ISOPROTERENOL

The response to an intravenous injection of isoproterenol in bolus doses of 2 or 5 μg was tested in 18 receptors. Nine of the receptors increased their activity with maximal frequencies from 0.5 to 10 impulses/sec, and the firing was often episodic. The nine other receptors did not respond. The response to brief aortic occlusion was augmented in 10 of 14 receptors after the bolus injection of isoproterenol. The mean response before isoproterenol was 5.7 ± 0.8 impulses/sec and after isoproterenol it was 8.8 ± 1.0 impulses/sec. This difference is statistically significant \( P < 0.005 \).

RESPONSE TO AORTIC OCCLUSION DURING CONTINUOUS INFUSION OF ISOPROTERENOL

The response to graded aortic occlusion before and during a continuous intravenous infusion of isoproterenol (1.25-2.5 μg/min) was tested in five receptors (Fig. 6). During the infusion, the response curve relating LVEDP and receptor discharge was shifted to the left. The maximal discharge was higher with isoproterenol.

Left Ventricular Pressure: Systole End-Diastole

Receptor 49:2

F1gure 6 Activity in five left ventricular C fibers plotted against left ventricular systolic and end-diastolic pressures during graded aortic occlusion before and during infusion of isoproterenol (1.25-2.5 μg/min). Values for maximal rate of increase in left ventricular pressure \( \text{dpl/dt}_{\text{max}} \) reflect changes in ventricular inotropism.

RESPONSE TO AORTIC OCCLUSION AND TRANSFUSION AFTER PROPRANOLOL

Injection of propranolol (0.2-0.3 mg/kg) increased mean LVEDP from 5.3 ± 1.4 mm Hg to 10.9 ± 1.7 mm Hg and decreased the maximal rate of increase in left ventricular pressure. Values for maximal rate of increase in left ventricular pressure \( \text{dpl/dt}_{\text{max}} \) reflect changes in ventricular inotropism. (Receptors shown in upper two panels are the same as those shown in corresponding panels in Figure 6 during isoproterenol infusion.)

Figure 7 Activity in five left ventricular C fibers plotted against left ventricular systolic and end-diastolic pressures during graded aortic occlusion before and after administration of propranolol (0.2-0.3 mg/kg). Values for maximal rate of increase in left ventricular pressure \( \text{dpl/dt}_{\text{max}} \) reflect changes in ventricular inotropism. (Receptors shown in upper two panels are the same as those shown in corresponding panels in Figure 6 during isoproterenol infusion.)

Figure 8 Activity in four left ventricular C fibers is plotted against left ventricular end-diastolic pressure during graded transfusion (dextran) with normal and decreased inotropism (propranolol, 0.2-0.3 mg/kg). Values for left ventricular \( \text{dpl/dt}_{\text{max}} \) before transfusions are also shown. Note that receptor response to transfusion is depressed after propranolol.
One receptor discharged irregularly. Within a few seconds the firing often became continuous. Trifiri-Tors were activated during each systolic period (Fig. 9).

During control periods, seven receptors showed no or an irregular discharge, and nine discharged usually during cardiac cycle during which the receptor was activated.

**FIRING PATTERN IN THE CARDIAC CYCLE**

The total conduction time was measured for 16 receptors and their afferents to establish the period within the cardiac cycle during which the receptor was activated. During control periods, seven receptors showed no or an irregular discharge, and nine discharged usually during systole (Fig. 9).

Immediately after aortic occlusion, 15 of the 16 receptors were activated during each systolic period (Fig. 9). Within a few seconds the firing often became continuous. One receptor discharged irregularly.

**EFFECT OF FIBRILLATION ON LEFT VENTRICULAR C-FIBER DISCHARGE**

During transfusion the five receptors tested were activated in systole. Three of the receptors showed occasional or sustained firing during diastole.

**EFFECT OF VENTRICULAR FIBRILLATION ON RECEPTOR ACTIVITY**

The effect of ventricular fibrillation on activity was recorded in 14 receptors. Eight receptors showed a slight increase in activity, two were unaffected, and four showed decreased discharge after a few seconds of fibrillation. The mean activity was unchanged (2.1-2.0 impulses/sec) during the fibrillation, despite an increase in LVEDP from a mean control value of 6.1 to 14.5 mm Hg and visible distention of the ventricle. Figure 10 shows an example of decreased activity during fibrillation.

In four of five instances in which the heart defibrillated spontaneously, there was a transient increase in receptor activity for several seconds (Fig. 10). The frequency increased from a mean of 2.0 impulses/sec to 6.0 impulses/sec when the ventricle again began to contract from an increased end-diastolic pressure.

**Discussion**

The existence of a large number of receptors in the left ventricle with afferent vagal fibers has been confirmed in this study. Many of the filaments dissected from the right vagus contained C fibers originating in the left ventricle. In contrast, only two medullated fibers from the ventricle were identified. The receptors are distributed throughout the left ventricle, including the interventricular septum. In general, fibers from receptors in the posterior region of the ventricle ascend to the base of the heart along the posterior descending coronary artery, then sweep across the lateral surface of the right atrium to join the right main cardiac nerve. Fibers from receptors in the anterolateral region pass along the superior aspect of the left and right atria behind the aorta and pulmonary trunk to join the right main cardiac nerve. The mean estimated intracardiac nerve conduction velocity (0.5 m/sec) was less than in the vagal nerve (0.8 m/sec). Although the measurement of the length of the intracardiac pathway undoubtedly is subject to error, the difference of 30% between the mean values would suggest that intracardiac nerve conduction velocity is in fact slower.

**RECEPTOR CHARACTERISTICS**

In the control situation, the receptors discharged with a low frequency or were silent. This is in contrast to medullated fibers which normally discharge at high fre-
ventricular C fibers in dogs.24 Even if the discharge frequency is low and many receptors are not spontaneously active, the aggregated input from a large number of fibers might exert an influence on the vasomotor center.

The present studies were conducted in open-chest animals, and this markedly diminished the size of the heart.22 It is likely that the resting discharge will be higher in animals breathing spontaneously. Also, low frequency (1 Hz) electrical stimulation of cardiac vagal C fibers in the cat induced an increase of about 30% in renal conductance25 and a reduction of 50 mm Hg in arterial blood pressure.17

The discharge in all receptors increased with progressive increase in LVEDP produced either by transfusion or by graded aortic occlusion. At a mean LVEDP of 8 mm Hg, the mean discharge rate was 3.2 impulses/sec, and at 16 mm Hg it was 7.0 impulses/sec. Thus in situations involving increases in preload and afterload, one would expect that these C fibers would exert a significant influence on the vasomotor center.

WHAT IS THE MECHANISM BEHIND THE RECEPTOR DISCHARGE?

Measurement of total conduction time indicated that in the control state more than half of the receptors were activated during systole; when receptor discharge was increased, systolic activation was the rule. The observation that left ventricular receptors are activated mainly in systole supports earlier findings in the dog by Muers and Sleight4 and contradicts the statement by Öberg and Thorén17 that left ventricular C fibers are activated mainly during diastole. The latter conclusion was reached from an incorrect estimation of intracardiac nerve conduction time. However, in spite of systolic activation of the receptors, the frequency of receptor discharge did not appear to be related to the peak ventricular pressure during aortic occlusion. Also, an increase in cardiac inotropism by itself failed to increase discharge frequency in nine of the 18 receptors studied.

The finding that the discharge in most of these receptors correlated well with LVEDP might indicate that the receptors responded mainly to change in end-diastolic ventricular volume. However, during ventricular fibrillation, in spite of an increase in LVEDP from 6.1 to 14.5 mm Hg, there was no increase in discharge frequency until synchronous cardiac contractions were resumed spontaneously. Thus ventricular contraction must have a role in determining the frequency of receptor discharge. Further evidence for this conclusion is given by the fact that depression of ventricular contractility impaired the receptor response to pressure and volume loading, while increase in cardiac inotropism during graded aortic occlusion increased the receptor discharge at any given LVEDP.

We are thus left with the observations that left ventricular receptors are activated during systole and that the frequency of discharge appears related to diastolic volume. In certain circumstances ventricular contraction can modulate the frequency of discharge. Clearly, we are far from understanding the mechanisms that determine the rate of firing of left ventricular C fiber receptors.

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