Behavior of Left Ventricular Mechanoreceptors with Myelinated and Nonmyelinated Afferent Vagal Fibers in Cats

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SUMMARY. The purpose of this study was to determine the behavior of left ventricular mechanoreceptors with myelinated vagal afferents and to compare them with endings with nonmyelinated vagal afferents. Single unit activity was recorded from 13 endings with nonmyelinated vagal afferents (conduction velocity 2.1 ± 0.3 m/sec) and from 16 endings with myelinated vagal afferents (conduction velocity 7.3 ± 1.3 m/sec). Resting discharge frequencies of nonmyelinated vagal afferents and of myelinated vagal afferents were 1.7 ± 0.3 and 2.7 ± 0.5 imp/sec (P < 0.1), respectively (at left ventricular end diastolic pressure of 6 mm Hg for both groups). Ten of 16 myelinated vagal afferents had pulse synchronous discharge under basal condition, whereas only 3 of 13 nonmyelinated vagal afferents had such activity. During aortic occlusion, the discharge of myelinated vagal afferents increased 1.7 ± 0.3 imp/sec per mm Hg, whereas nonmyelinated vagal afferents increased significantly (P < 0.05) less (0.5 ± 0.1 imp/sec per mm Hg). Discharge for both groups was linearly related to left ventricular end-diastolic pressure but not to left ventricular systolic pressure. Increases in left ventricular systolic pressure alone did not increase firing for either group. During aortic occlusion, the maximum discharge rates of myelinated vagal afferents (43 ± 7 imp/sec) were significantly higher than those of nonmyelinated vagal afferents (14 ± 3 imp/sec) at left ventricular end-diastolic pressure of 30 ± 2 and 24 ± 2 mm Hg, respectively. Both groups increased their discharge during volume expansion with myelinated vagal afferents showing greater sensitivity than nonmyelinated vagal afferents. All endings studied were in the inferoposterior wall of the left ventricle. All nonmyelinated vagal afferents were in or near the epicardium. In contrast, myelinated vagal afferents were equally distributed between the endocardium and the epicardium. Myelinated vagal afferents had discrete receptive fields (1-2 mm²) whereas those of nonmyelinated vagal afferents were much larger (1 cm²). In conclusion, the discharge of left ventricular endings with nonmyelinated vagal afferents and myelinated vagal afferents both appear to be determined mainly by changes in left ventricular end-diastolic pressure. They may be located at different depths in the left ventricular wall. Myelinated vagal afferents have greater sensitivity and maximum firing frequencies than nonmyelinated vagal afferents. (Circ Res 52: 291–301, 1983)

ACTIVITY has been recorded from myelinated and nonmyelinated afferent fibers coursing in the vagus which subserves sensory endings in all the chambers of the heart and in the great vessels (Paintal, 1973a, 1973b; Thoren, 1979). There has been great interest in determining the behavior of these endings because of the many powerful reflex responses which can result when they are stimulated. In recent years, the characteristics of endings with nonmyelinated afferent fibers have been studied extensively, particularly those in the left ventricle (Coleridge et al., 1964; Baker et al., 1979; Muers and Sleight, 1972; Thames et al., 1977; Thoren, 1977). These endings and their afferent fibers are thought to form the afferent limb of powerful vasodpressor and cardioinhibitory reflexes (Thoren, 1979). Under basal conditions, these ventricular endings have sparse, random, irregular discharge, are frequently silent, or have one spike per cardiac cycle which may occur in any phase of the cardiac cycle. When their discharge is augmented by a variety of interventions which distend the left ventricle, they discharge mainly during systole. It seems paradoxical that, even though their firing occurs mainly in systole, their discharge frequency correlates linearly with ventricular diastolic but not with systolic pressure (Thames et al., 1977; Thames, 1980; Thoren, 1977). Moreover, even though diastolic pressure is the principal determinant of the discharge of these nonmyelinated ventricular fibers, experiments with phenylephrine, isoproterenol, and propranolol indicate that the discharge of these endings also is affected by ventricular systolic pressure and by ventricular contractility (Thames et al., 1977; Thoren, 1977).

Only two studies have been made of endings in the left ventricle which were thought to be subserved by myelinated vagal afferents (Coleridge et al., 1964; Paintal, 1955). Paintal (1955) studied the responses to veratrum alkaloids of four such receptors which were considered to be in the left ventricle. Coleridge et al. (1964) studied eight left ventricular endings with vagal...
afferents (probably myelinated) which had pulse synchronous discharge under basal conditions and increased their firing during left ventricular distention. Neither Paintal’s study (1955) nor that of Coleridge et al. (1964) provided a systematic assessment of the mechanoreceptor behavior of the ventricular myelinated fibers which they investigated.

The major goal of this study was to characterize left ventricular mechanoreceptors with myelinated afferent vagal fibers and to contrast their behavior with that of the more extensively studied left ventricular endings with nonmyelinated vagal afferents. The results indicate that there are important differences and similarities between these groups of ventricular mechanoreceptors.

Methods

Experiments were carried out in cats weighing 1.2-4.7 kg. General anesthesia was induced with an intramuscular injection of 5 mg of acepromazine (Ayerst Laboratory) and 15 mg/kg of ketamine hydrochloride followed by an initial dose of α-chloralose, 30 mg/kg, administered intravenously in normal saline. Supplemental doses of chloralose, 10 mg/kg, were given until the desired plane of light anesthesia was obtained. This was maintained throughout the experiment with additional doses of chloralose. The trachea was exposed and cannulated and the animals were ventilated with a mixture of oxygen and room air. The tidal volume was kept at 10 ml/kg with the rate set at 15-20 cycles/min. Arterial Po2, PcO2, and pH were measured periodically during the experiments, and their values were maintained within the normal range by adjusting either the tidal volume or the pump rate. The Po2 was maintained above 100 mm Hg, PcO2 between 30 and 40 mm Hg, and pH between 7.35 and 7.45. Before beginning the protocol, we treated the animals with gallamine triethiodide, 2 mg/kg, intravenously as needed to prevent muscle movement.

Surgical Procedures

The isolation of the vagi, sympathetic trunk, and carotid arteries in the neck and identification and isolation of the cardiac branches of the right vagal nerve in the chest were carried out as previously described (Thames et al., 1977, Thoren, 1977). The chest was opened through a bilateral intercostal transsternal thoracotomy at the level of the 4th or 5th intercostal space. Snares were placed around the right upper lobe. The right vagal trunk was sectioned caudal to the right cervical vagus as described previously (Thames et al., 1977; Thames 1980). In brief, thin filaments were obtained from the right cervical vagus and cut centrally for recording. The filaments were placed on silver-silver chloride electrodes connected to a Grass probe (HIP 511 E), and the signal was amplified by a Grass amplifier (P' 511 J). The high frequency cutoff was set at 1000-3000 Hz and the low frequency cutoff at 30 Hz. The output of the amplifier was displayed on a Tektronix oscilloscope and on the Gould recorder. The output of the Grass amplifier was also led into an audioamplifier and into a spike counter which has been described previously in detail (Felder and Thames, 1981). The counter is digital in design and can count linearly to instantaneous firing rates of 10 kHz. The functioning of the spike counter was frequently checked by counting the spikes manually.

Action potentials were recorded from single unit preparations; that is, the experiments were performed with only one unit active under resting conditions or with interventions. There were, however, other nerve fibers in the filament; these were activated only by electrical stimulation of the caudal vagal nerve or vagal trunk.

The conduction velocity of each afferent fiber was assessed by determining the time for the evoked potential to be conducted from the stimulated cardiac nerve to the recording electrodes and by measuring the distance between the stimulating and recording electrodes. By dividing the length of the conduction pathway by the conduction time, conduction velocity was obtained. The filament was small enough to permit identification of the evoked potential of the afferent under study by its amplitude and morphology, even when several silent fibers also were activated by electrical stimulation. The minimal current necessary was used to activate the afferent by starting with one volt stimulus and increasing the voltage until the evoked potential of the afferent under study could be identified. The accuracy of this method of determining conduction velocity has been discussed previously (Thames et al., 1977). The timing of the activation of the receptor in relation to cardiac events was determined by measuring the conduction time for the evoked potential to travel from the site of the receptor ending in the open, non-beating heart to the recording electrodes. The receptor ending was stimulated with current just sufficient to activate it when stimulating electrodes were applied directly to the area of the left ventricle most sensitive to mechanical probing. By knowing this conduction time, we were able to determine the timing of the spike potential in relationship to mechanical events of the heart. Endings were considered to fire during systole if they could be shown to discharge following the onset of the rising phase of left ventricular pressure and before the end of the falling phase of the left ventricular pressure trace. Endings which fired at other times were considered to fire during diastole.

Pressure Recordings

Pressures were measured with Century Technology Pressure transducers (CP-01) via catheter (PE 50, 90, or 160) inserted into the aorta (via a femoral artery), left ventricle (via the left carotid artery), and left atrium (via the right middle lobe pulmonary vein), respectively. All strain gauges were positioned at heart level. The distal inferior vena cava was cannulated from the right femoral vein for drug injection, volume expansion, and bleeding. The catheter manometer system for the measurement of left ventricular pressure was optimally damped in most experiments so that its response was flat (±5% up to at least 30 Hz). Damping was accomplished with a needle valve placed between the catheter and the transducer. The frequency response was tested with a piston phone which was driven by a Wavetech model 18 sine wave generator. All pressures, including left atrial, left ventricular, and systemic arterial pressure, were recorded along with the electroneurogram and output of the spike counter on a Gould ES1000 electrostatic recorder writing at speeds ranging from 5 to 50 mm/sec.

Recording of Nerve Activity

Nerve activity was recorded from afferent fibers traversing the right cervical vagus as described previously (Thames et al., 1977; Thames 1980). In brief, thin filaments were obtained from the right cervical vagus and cut centrally for recording. The filaments were placed on silver-silver chloride electrodes connected to a Grass probe (HIP 511 E), and the signal was amplified by a Grass amplifier (P' 511 J). The high frequency cutoff was set at 1000-3000 Hz and the low frequency cutoff at 30 Hz. The output of the amplifier was displayed on a Tektronix oscilloscope and on the Gould recorder. The output of the Grass amplifier was also led into an audioamplifier and into a spike counter which has been described previously in detail (Felder and Thames, 1981). The counter is digital in design and can count linearly to instantaneous firing rates of 10 kHz. The functioning of the spike counter was frequently checked by counting the spikes manually.
Protocol

Recordings were obtained from left ventricular receptors with nonmyelinated and myelinated afferent vagal fibers. Since the goal of our study was to investigate the behavior of left ventricular endings, initial aortic and pulmonic occlusions were performed to localize the ending to the left or right side of the heart. If the ending responded to aortic but not pulmonic occlusion, then it was considered to be on the left side of the heart and the response to mitral occlusion then was assessed. Receptors which failed to increase their discharge during increases in left atrial pressure but which increased their firing frequency during aortic occlusion were considered to be in the left ventricle and were studied. After determining the conduction velocity of the afferent fiber, we investigated the responses of the mechanoreceptive ending to aortic occlusion, to volume changes, to the administration of phenerenpine and of isoproterenol or propranolol, the latter two with or without volume expansion. At the end of the experiment, the exact anatomical location of the mechanoreceptor under study was determined by opening the heart and probing the left ventricle while recording the activity so provoked. In addition to determining the topographic location of the receptor within the left ventricle, its location within the wall of the left ventricle (epicardial, myocardial, or endocardial) was ascertained by paring away the heart in layers beginning with the endocardium until the mechanoreceptor could no longer be activated by probing.

Data Analysis

Differences in conduction velocity, basal discharge frequency, and maximum firing frequency for myelinated and nonmyelinated fibers were determined and the significance of the difference was tested by unpaired t-test. The stimulus-response relationship for the receptors was determined using linear regression analysis and the slopes obtained were compared with a paired t-test (within group) or by an unpaired t-test (between groups). Differences within or between groups were considered significant for P < 0.05.

Results

Single unit recordings were obtained from 29 afferent vagal fibers whose endings were located in the left ventricle. Sixteen of these afferent vagal fibers had conduction velocities ranging from 4.6 to 15 m/sec (mean ± se of 7.23 ± 1.25 m/sec) and are included in the myelinated group. The conduction velocities of the nonmyelinated (n = 13) afferent vagal fibers ranged from 1.1 to 3.8 m/sec (mean ± se of 2.05 ± 0.25 m/sec). Only three of these nonmyelinated fibers had conduction velocities in excess of 2.5 m/sec which generally has been considered the maximum conduction velocity of nonmyelinated fibers (Iggo, 1958). Since the minimum conduction velocity of finely myelinated fibers is taken to be 4.5 m/sec (Iggo, 1958), we have included these three fibers with the nonmyelinated group. Paintal (1967) made a similar assumption in his study of aortic afferents by classifying several fibers with conduction velocities between 2.5 and 3 m/sec as nonmyelinated.

Resting Discharge under Basal Conditions

The basal discharge rates which we report were observed during a 30- to 60-second period just prior to starting the protocol. The mean resting discharge rate of the ventricular endings with myelinated afferent vagal fibers was 2.7 ± 0.5 imp/sec, range 0-5.6 imp/sec. Ten of these endings exhibited cardiac rhythmic regular discharge of 1-2 imp/cardiac cycle. Three of these endings had irregular discharge which alternated between periods of silence and periods in which an occasional spike would occur during different phases of the cardiac cycle. Only three of the endings were silent under resting conditions. The mean left ventricular end-diastolic pressure at which the resting discharges were obtained was 6 ± 2 mm Hg with a range of 2-12 mm Hg.

The mean discharge rate of endings with nonmyelinated afferent fibers was 1.7 ± 0.4 imp/sec (range 0-3.6 imp/sec). Three endings were silent under basal conditions. Seven of the endings exhibited sparse irregular discharge which had no cardiac rhythmicity. This irregular discharge consisted of occasional spikes occurring in some cardiac cycles separated by several cycles in which there was no activity. Three endings exhibited regular pulse synchronous discharge of 1-2 spikes per cardiac cycle. The diastolic pressure at which these resting discharges were obtained was 6 ± 1 mm Hg (range 3-8 mm Hg). Although there was a tendency for the resting discharge of the nonmyelinated vagal afferent fibers to be less than that of the myelinated vagal fibers, the difference was not significant (P < 0.1). There was a significantly larger number of myelinated fibers with pulse synchronous discharge under basal conditions.

Responses to Aortic Occlusion

Figure 1 shows a representative record illustrating the responses of a ventricular myelinated fiber during aortic occlusion. This figure shows the responses of a fiber with resting discharge under basal conditions. For 14 myelinated fibers, aortic occlusion resulted in a rise of left ventricular end-diastolic pressure from 6 to 30 mm Hg and of left ventricular systolic pressure from 91 to 224 mm Hg. As the pressure rose, the activity of the endings increased, at first exhibiting pulse synchronous discharge but ultimately with discharge frequently becoming continuous. Increases in the discharge of these left ventricular myelinated fibers were linearly correlated with left ventricular end-diastolic pressure but not with left ventricular systolic pressure. Increases in left ventricular systolic pressure in the absence of increases in diastolic pressure did not increase the firing of these fibers (Fig. 2 and below). During aortic occlusion, the discharge of myelinated vagal afferent fibers increased 1.7 ± 3 imp/sec per mm Hg increase in end-diastolic pressure (correlation coefficient, r = 0.91). The average maximum discharge rate of these myelinated vagal afferent fibers was 43 ± 7 imp/sec (at an end-diastolic pressure of 30 ± 4 mm Hg).

In contrast to the myelinated vagal afferent fibers, nonmyelinated vagal afferent fibers (n = 12) increased their discharge 0.5 ± 0.1 imp/sec per mm Hg (r = 0.89) increase in left ventricular end-diastolic pressure. As previously reported (Thames et al., 1977; Thoren, 1977) and as indicated below, increases in
FIGURE 1. A representative record illustrating response to aortic occlusion of a left ventricular mechanoreceptor with myelinated afferent vagal fiber. Traces show (from top to bottom) integrated nerve activity of the recorded spikes, left atrial pressure, left ventricular and systemic arterial pressure and electroneurogram. Note that shortly after the initiation of aortic occlusion there was a rapid increase in left ventricular pressure with minimal change in firing frequency. As left ventricular end-diastolic pressure (and thus left atrial pressure) rose, there was a marked increase in the firing of this receptor.

left ventricular systolic pressure alone were without effect on the discharge of these nonmyelinated vagal afferents, and discharge of these fibers correlated linearly with left ventricular end-diastolic pressure but not with systolic pressure. The maximum discharge rate of these nonmyelinated fibers also was significantly less than that of the myelinated fibers and was 14 ± 3 imp/sec at a left ventricular end-diastolic pressure of 24 ± 2 mm Hg. Figure 3 shows the contrasting responses to aortic occlusion of the myelinated (medullated) and nonmyelinated (nonmedullated) vagal afferents in this study. Linear regression analysis of the relationship between left ventricular end-diastolic pressure and discharge frequency indicates that there is a significantly higher sensitivity of the myelinated vagal fibers than of the nonmyelinated vagal fibers during increases in left ventricular pressure induced by aortic occlusion. The threshold pressures (intercepts with the x axis) of the two groups were not significantly different.

Responses to Volume Changes

The responses of 12 ventricular endings with myelinated vagal fibers and of eight endings with nonmyelinated vagal fibers to intravascular volume changes were studied during infusion of 6% dextran in normal saline (156 mEq/liter) and during withdrawal of the infused volume. Representative responses of a ventricular myelinated fiber are illustrated in Figure 4. Again, discharge frequency correlated linearly with left ventricular end-diastolic pressure, and increases in discharge frequency often occurred with little or no changes in left ventricular systolic pressure as left ventricular end-diastolic pressure rose. In six experiments, volume expansion increased end-diastolic pressure 17 ± 4 mm Hg and discharge frequency by 12 ± 3 imp/sec. Left ventricular systolic pressure decreased in two of these experiments (—5 and —15 mm Hg) and increased modestly in four (by 5, 5, 5, and 15 mm Hg). In the other experiments on myelinated fibers, systolic and diastolic pressure increased together during volume changes. Left ventricular fibers with myelinated afferents increased their firing 0.9 ± 0.1 imp/sec per mm Hg rise in left ventricular end-diastolic pressure (r = 0.94), whereas nonmyelinated fibers increased 0.4 ± 0.1 imp/sec per mm Hg (r = 0.85) (Fig. 3). These were significantly different, and the responses of the myelinated fibers were also significantly less than were observed during aortic occlusion. A similar tendency was observed for the nonmyelinated afferents, although the difference was not statistically significant (P < 0.1).

Responses to Phentylephrine

Responses of 14 myelinated and three nonmyelinated afferents were determined during phentylephrine-induced increases in left ventricular pressure. The strategy of these experiments was to determine whether large increases in left ventricular systolic pressure in the absence of increases in end-diastolic pressure would increase the firing of these endings. In 12 of the 14 myelinated fibers studied, phentylephrine increased left ventricular systolic pressure by 50–100 mm Hg without changing left ventricular end-
diastolic pressure. These large increases in left ventricular systolic pressure were not accompanied by changes in nerve activity. However, in the other two myelinated afferents, the discharge increased during phenylephrine infusion due to a concomitant rise in end-diastolic and systolic pressure. Figure 2 shows a representative response of a myelinated afferent to phenylephrine infusion. For this fiber, increases in left ventricular systolic pressure alone did not influence the discharge of the fiber (Fig. 2A). However, raising end-diastolic pressure by an infusion of volume increased the discharge of this ending at a systolic pressure that was well below that observed during phenylephrine (Fig. 2B).

The three nonmyelinated afferents studied responded in a fashion similar to that of the 12 myelinated fibers and failed to increase their discharge during increases in left ventricular systolic pressure of 75–105 mm Hg which were unaccompanied by increases in diastolic pressure.
Effects of Isoproterenol and Propranolol
The responses of six myelinated and four nonmyelinated ventricular afferents to aortic occlusion or volume expansion were determined (Figs. 5 and 6) before and after β-adrenoceptor stimulation with isoproterenol (5–10 g bolus) and following β-adrenoceptor blockade with propranolol (2–5 mg intravenously). During aortic occlusion (Fig. 5), the slope of the line relating discharge frequency and left ventricular end-diastolic pressure for the myelinated afferents was $2.5 \pm 0.6$ imp/sec per mm Hg ($r = 0.92$) before and $3.84 \pm 1.04$ imp/sec per mm Hg ($r = 0.97$) after isoproterenol. These slopes were significantly different. After propranolol, aortic occlusion resulted in $2.6 \pm 0.63$ imp/sec per mm Hg ($r = 0.99$) increase in left ventricular end-diastolic pressure. This slope was not significantly different from control. In the same six myelinated afferents, the slopes obtained during volume expansion (Fig. 6) before and after isoproterenol were $0.97 \pm 0.19$ ($r = 0.97$) and $1.5 \pm 0.3$ imp/sec per mm Hg ($r = 0.98$), respectively. These responses were significantly different. After propranolol, volume expansion increased firing by $0.75 \pm 0.13$ imp/sec per mm Hg ($r = 0.96$) increase in diastolic pressure, which was not significantly different from control.

Since we studied the responses of only four nonmyelinated afferents, no attempt was made to analyze these data statistically. However, as reported previously, there was a tendency for isoproterenol to increase the slope and for propranolol to decrease the slope of the relationship between firing frequency and end-diastolic pressure (Thames, 1980; Thoren, 1977).

Timing of Activation of the Endings
In order to determine the phase of the cardiac cycle during which the afferents discharged, conduction time from the ending to the recording electrodes was determined. This was necessary because of the slow conduction times of both nonmyelinated and some myelinated fibers. As noted above, under basal conditions, 10 of the 13 nonmyelinated fibers were silent or generally had a sparse irregular discharge which had no cardiac rhythmity. Only three fibers had a pulse synchronous discharge of 1–2 spikes per cardiac cycle. This discharge occurred during diastole for all three fibers. On occluding the aorta or infusion of volume, all afferents at first discharged with pulse synchronous activity which later became continuous as ventricular pressures continued to rise. When the burst duration lengthened, it was classified as occurring in systole if the first spike coincided with systole even though spikes occurring late in the burst occurred during diastole. The same criterion was used in classifying burst activity as systolic. The burst activity of 5 afferents occurred during diastole, whereas it occurred during systole for the other 8 endings. The 3 endings with pulse synchronous discharge in diastole under basal conditions fired mainly during systole when the pressures were raised.

Ten of the 16 myelinated fibers had pulse synchronous discharge with 1–2 spikes per cardiac cycle under basal conditions. The discharge occurred in seven during diastole and three during systole. Like nonmyelinated afferents, myelinated fibers also had pulse synchronous bursting discharge on raising ventricular pressures. On further raising the pressures,
FIGURE 4. Representative records illustrating the response of a left ventricular mechanoreceptor with myelinated vagal afferent fiber to graded expansion of the blood volume. Shown in the figures are (top to bottom) integrated nerve activity, left atrial pressure, left ventricular and systemic arterial pressure, and electroneurogram. Panel A illustrates activity observed under basal conditions before volume expansion. Panels B and C illustrate responses to progressive expansion of the plasma volume. The relationship between left ventricular end-diastolic pressure and discharge frequency for both myelinated and nonmyelinated fibers during volume expansion is shown in Figure 3.
endings are small. In the paragraphs that follow, we will discuss each of these points. The discussion of similarities and differences in the behavior of myelinated and nonmyelinated ventricular fibers should help to highlight the functional characteristics of the myelinated fibers. We will close with a few comments on the potential functional implications of our findings.

There appears to be a substantial number of left ventricular mechanoreceptors with myelinated vagal afferents in the cat. Our experiments were conducted in consecutive cats, and we generally recorded from...
whichever type of ending we found in the course of our experiment. The fact that the myelinated fibers were found as frequently as nonmyelinated fibers is due in part to the fact that they are more likely to be detected because of their pulse synchronous discharge under basal conditions. Thus, the techniques employed tend to favor the detection of myelinated instead of nonmyelinated ventricular afferents. Despite this, little is known about the behavior of these endings. Paintal (1955) studied the veratrum sensitivity of four left and seven right ventricular endings with vagal afferents in cats. No conduction velocities were determined in the study. However, Paintal assumed that the fibers he studied had conduction velocities in excess of 10 m/sec based on their spike heights. In our experience, and that of Iggo (1958), such an assumption is unwarranted. The exact anatomical location of these endings only was determined by probing the nonbeating heart for one left and three right ventricular fibers. The mechanoreceptor behav-

| TABLE 1 | Summary of Major Characteristics of Left Ventricular Mechanoreceptors with Medullated and Nonmedullated Vagal Afferents |
|-------------------|-------------------|-------------------|-------------------|
|                   | Myelinated         | Nonmyelated       |                  |
| **n**             | 16                | 13                |                  |
| **Conduction velocity** | 7.3 ± 1.3 m/sec  | 2.1 ± 0.3 m/sec  |                  |
| **Basal discharge (at left ventricular end-diastolic pressure)** | 2.7 ± 0.5 m/sec (6.0 ± 2.0 mm Hg) | 1.7 ± 0.3 m/sec (6.0 ± 1.0 mm Hg) |                  |
| **Sensitivity* (aortic occlusion)** | 1.7 ± 0.3 imp/sec per mm Hg (increase in end-diastolic pressure) | 0.5 ± 0.1 imp/sec per mm Hg (increase in end-diastolic pressure) |                  |
| **Sensitivity* (volume changes)** | 0.9 ± 0.1 imp/sec per mm Hg (increase in end-diastolic pressure) | 0.4 ± 0.1 imp/sec per mm Hg (increase in end-diastolic pressure) |                  |
| **Maximum discharge frequency** | 43 ± 7 imp/sec (30 ± 4 mm Hg) | 14 ± 3 imp/sec (24 ± 2 mm Hg) |                  |
| **Receptive fields** | 1-2 mm²           | 1 cm²             |                  |
| **Topographic locations** | Posterior Wall     | Posterior Wall     |                  |
| Epicardial         | 7                 | 12                |                  |
| Myocardial         | 0                 | 1                 |                  |
| Endocardial        | 9                 | 0                 |                  |

* P < 0.05 myelinated vs. nonmyelinated.
ior of these endings was not characterized systematically, although it was found that their discharge increased when the aorta was occluded. Coleridge and colleagues (1964) studied the behavior of 8 endings with vagal afferents in the left ventricle and 11 such endings in the right ventricle of dogs. They had pulse synchronous discharge under basal conditions, increased their discharge with ventricular distention, and behaved generally like the myelinated fibers from which we recorded, although no measurements of conduction velocity were obtained. Finally, some of the left ventricular endings from which Armour (1973) recorded activity may have been subserved by myelinated fibers, although little information is provided regarding the behavior of these endings, and no conduction velocities were determined. Most of his recordings were obtained from close cardiac nerves, making it virtually impossible to determine whether the endings he studied were subserved by vagal or sympathetic afferent fibers.

Left ventricular mechanoreceptors with myelinated vagal afferents generally exhibit tonic, pulse synchronous discharge under resting or basal conditions. This was true for 10 of the 16 endings we studied, and for most of the endings studied by Paintal (1955) and by Coleridge et al. (1964). This stands in contrast to the behavior of left ventricular nonmyelinated fibers which generally have sparse and irregular discharge under basal conditions (present study and those of Coleridge et al., 1964; Muers and Sleight, 1972; Sleight and Widdicombe, 1965; Thames et al., 1977; Thoren, 1977). We found that the basal pulse synchronous activity may occur in systole or in diastole as previously observed by Coleridge et al. (1964). The fact that the timing of the discharge changed from systole to diastole (and vice versa) when ventricular pressures were raised has not been reported previously. This type of behavior was also observed for three nonmyelinated fibers in the present study. We speculate that the conversion of discharge from one part of the cardiac cycle to the other may relate to the way in which these endings are tethered into the myocardium.

The discharge of left ventricular myelinated fibers seems to be most dependent on cardiac filling pressure and, thus, on ventricular volume or distention. In fact, increasing systolic pressure 50-100 mm Hg without changing the diastolic pressure (phenylephrine infusion) was without effect on these endings. Increases in diastolic pressure augmented the firing of these endings, even when systolic pressure didn’t increase or increased modestly (volume expansion). This characteristic is similar to that of left ventricular nonmyelinated fibers included in the present study and of those previously studied (Thames et al., 1977; Thoren, 1977). However, systolic pressure appears to have some effect on the discharge of these myelinated endings, since the increases in firing observed during aortic occlusion were significantly larger than those during volume expansion. Although both interventions cause large increases in filling pressure, only aortic occlusion was consistently accompanied by large increases in systolic pressure. A similar tendency was observed for nonmyelinated fibers in this study and even more striking differences have been reported for ventricular nonmyelinated fibers during phenylephrine infusion in contrast to volume expansion (Thames et al., 1977).

A major difference between the left ventricular myelinated and nonmyelinated fibers is the greater sensitivity of the endings with myelinated fibers to cardiac distension. The myelinated endings were three times more sensitive than non-myelinated fibers during aortic occlusion and at least twice as sensitive to volume changes. This difference in sensitivities is similar to that previously reported for atrial myelinated and nonmyelinated fibers (Thames et al., 1977; Thoren, 1976).

Neither β-adrenoceptor stimulation nor blockade alone had a significant effect on the discharge of the ventricular myelinated fibers. However, in four of six experiments, isoproterenol administration resulted in decreases both in end-diastolic pressure (−2 ± 1 mm Hg) and in discharge frequency (−1 ± 0.5 imp/sec). In the other two experiments, there was no basal discharge, and these fibers were not activated after isoproterenol administration. After propranolol, end-diastolic pressure rose in all six experiments. The two previously quiescent fibers began to fire as filling pressure rose. The responses of basal discharge of the other four fibers to propranolol were small and variable. These findings are consistent with the view that the firing frequency of these myelinated endings is determined mainly by ventricular filling pressure and volume.

β-Adrenoceptor stimulation with isoproterenol significantly increased the discharge of myelinated endings when left ventricular filling pressure was increased by aortic occlusion (Fig. 5) or by volume expansion (Fig. 6). β-Adrenoceptor blockade with propranolol generally tended to decrease the sensitivity of the myelinated fibers (Figs. 5 and 6) although the effects of propranolol were less striking than those of isoproterenol. Similar effects of β-adrenoceptor stimulation and blockade on ventricular nonmyelinated fibers were observed in the present and in previous studies (Thames, 1980; Thoren, 1977). The discharge of myelinated fibers which were activated during systole or diastole both were influenced by β agonism or antagonism. We suggest that this is the result of the influence of these interventions on diastolic as well as systolic function of the left ventricle.

All of the endings from which we recorded were in the posterior wall. The fact that activity was not recorded from endings in other regions of the left ventricle suggests that there is a preferential distribution of these receptors (both myelinated and non-myelinated) to the posterior wall. Evidence from reflex studies supports the existence of such a preferential distribution (Thames et al., 1978). It has been the finding of several investigators that ventricular endings with nonmyelinated fibers are located mainly in the epicardium or “epimyocardium” (Coleridge et al., 1964; Muers and Sleight,
1972). This view has been based largely on the vigor of the probing needed to activate these endings when probing from the epicardial or endocardial surfaces of the left ventricular wall. The present study provides additional support to this view, but relies on the technique of paring away the left ventricular wall in slices (beginning from the endocardium) until the activity of the ending is obliterated. Although nearly half of the myelinated endings also were epicardial, the remainder were in or near the endocardium. Many of the ventricular fibers studied by Coleridge and colleagues (1964) also seemed to be in or near the endocardium based on responses to probing. Some of the fibers from which Armour (1973) recorded also were most easily stimulated by stroking the endocardium.

We found a striking difference between the size of the receptive fields subserved by myelinated (1–2 mm²) and by nonmyelinated (approximately 1 cm²) endings. Such a difference was also suggested by the prior study of Coleridge et al. (1964), although they did not report an estimate of the size of the receptive fields in their study. We estimated the size of these receptive fields by using light probing in the region of the receptor to determine the approximate area that was most sensitive to this probing.

It has recently been suggested that the inhibitory influence of vagal cardiopulmonary baroreceptors on sympathetic outflow to the periphery is mediated mainly by nonmyelinated vagal fibers (Thoren, 1979). Studies in the cat and rabbit using selective cold block of the vagi, anodal block of myelinated vagal fibers, and electrical stimulation of cardiac vagal afferents support this view (Thoren, 1979). About a third of cardiac vagal afferents are myelinated (Agostoni et al., 1957). Of these, the majority pass to the atria (Thoren, 1979). Recent experiments in dogs using selective vagal cold block suggest that at least atrial myelinated fibers may exert an inhibitory influence on sympathetic outflow to the kidney (Linden et al., 1980). In view of the presence of ventricular myelinated fibers with spontaneous discharge and in view of their greater sensitivity to increases in cardiac filling pressure, it is possible that these ventricular myelinated fibers also contribute to inhibitory influences on the vasomotor centers controlling sympathetic outflow to the periphery.

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