Atrial Receptors with Nonmedullated Vagal Afferents in the Cat

Discharge Frequency and Pattern in Relation to Atrial Pressure

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SUMMARY The response of 14 atrial receptors with nonmedullated vagal afferents to changes in atrial pressure was determined in anesthetized thoracotomized cats. Recordings were made from single fibers and three two-fiber filaments. Mean conduction velocity was 0.9 m/sec (range, 0.35 to 2.2 m/sec). During the control period, either no activity was detected or there was a sparse discharge (mean, 1.4 impulses/sec), which occasionally was related to the a or v waves. As atrial pressure was increased by transfusion or by occlusion of the aortic, pulmonary arterial, mitral, and tricuspid orifices, an increased rate of firing occurred, often related to the atrial v wave. The threshold for individual receptors was between 2 and 3 mm Hg (mean pressure) in the right atrium, and 5 and 12 mm Hg in the left atrium. The maximal firing rate was 5–11 impulses/sec for right atrial and 10–20 impulses/sec for left atrial receptors. The receptors were localized by probing the opened heart, and were identified in both atria, in the interatrial septum, and in the atrial-venous junctions. Thus receptors connected to vagal C fibers are present throughout both atria and are activated by moderate changes in pressure.

COMPLEX, unencapsulated sensory nerve endings served by medullated vagal afferents are present around the junctions of the pulmonary veins with the left atrium and of the caval veins with the right atrium. These endings discharge rhythmically in response to changes in atrial pressure, and the activity coincides with either atrial filling (v wave) or atrial contractions (a wave).

Recently, impulses have been recorded in slowly conducting nonmedullated vagal fibers (conduction velocity less than 2.5 m/sec) with endings located in the atria, atrial-venous junctions, and atrial appendages of anesthetized dogs and cats. These fibers normally are silent or have a sparse irregular discharge in the open-chest animal. Although variable changes in impulse frequency attended atrial distention, atrial pressure was not recorded and there was no systematic study of the relations between discharge frequency and pressure in the right or left atrium.

If atrial receptors with nonmedullated vagal afferents have a physiological role, their discharge would be augmented as atrial pressure is increased within the normal range. The purpose of the present study was to identify atrial receptors with nonmedullated vagal afferents in cats, to examine their discharge frequency and pattern as the pressure in the atria was increased, and to determine their anatomical location.

Methods

Cats were anesthetized with pentobarbital (30–40 mg/kg, intraperitoneally); additional doses (10 mg/kg) were given at intervals as required. A tracheotomy was performed and positive-pressure ventilation (Harvard respirator, model 670) was maintained with oxygen at a tidal volume of 8–12 ml/kg. To prevent muscle movements, the cats were given gallamine triethiodide (Flaxedil) (2 mg/kg, in repeated injections). The rectal temperature was measured and maintained at 37–38°C by means of external heating. Arterial Po2, Pco2, and pH were measured at intervals (Instrumentation Laboratories, blood gas analyzer, model 113), 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 the injection of small amounts of NaHCO3 (1 mEq/ml).

SURGICAL PROCEDURES

The vagus nerves, sympathetic trunk, and carotid arteries were dissected free in the neck. The thorax was opened by bilateral, intercostal, transternal 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 right and left sides of the heart could be increased separately. Balloon catheters (Swan-Ganz, 93–110, 5 Fr.) were placed in the mitral and tricuspid valves through incisions in the tips of the respective atrial appendages. The right main cardiac nerve running from the heart to the vagal trunk in the thorax was dissected free after division of the azygos vein. In those experiments in which it was possible to identify a separate branch from this cardiac nerve running to the lung root, this branch was cut. The vagal trunk was likewise cut in the thorax just below the entrance of the cardiac nerve. The upper lobe of the right lung was removed.

PRESSURE RECORDINGS

Pressures were measured by Statham transducers (P23De) via catheters (PE 90) inserted into the aorta, left ventricle, and right and left atria through a femoral artery, left carotid artery, femoral vein, and right upper lung vein.
respectively. All pressures were referred to mid right atrial level. One femoral artery and one femoral vein also were cannulated for bleeding and transfusion. The catheter systems were damped optimally by means of small needle valves placed between the catheters and the transducers; the degree of damping was tested before each experiment (Hewlett-Packard function generator, model 202A, connected to a piston phone). The response of the catheter systems was flat (±5%) up to 30–35 cycles/sec.

Phasic blood pressures from the atria, the aorta, and the left ventricle were recorded, together with the electrocardiogram and the spike activity, on a Honeywell ultraviolet Visicorder (model 1508) writing intermittently at fast speeds (2.5–20 cm/sec).

The aortic pressure, left ventricular pressure, and mean pressures in the left and right atria were recorded on a six-channel Brush recorder writing continuously at a slow speed (2.5 cm/min).

The electrocardiogram was recorded from one electrode in the esophagus at the atrial level and a second electrode in the chest wall.

RECORDING OF NERVE ACTIVITY

The right vagus was placed on a black plastic dissection plate. A pool was made from the surrounding muscles and skin and filled with mineral oil (temperature, 35–36.5°C). The nerve sheath around the right vagus was removed by forceps under a binocular dissecting microscope. Thin filaments were obtained and cut centrally; the rest of the vagus was left intact. The filaments were placed on a bipolar chlorided silver electrode connected to a Grass probe (HIP 511E), and the signal was amplified by a Grass amplifier (P 511). The high frequency cutoff was set at 300 or 1,000 Hz and the low frequency cutoff at 10 or 30 Hz. The output from the amplifier was displayed on an oscilloscope (Tektronix 564) and on the Visicorder. The Grass amplifier also was connected to a loudspeaker and to a rate meter equipped with a discriminator so that it could count either all spikes exceeding a preset value or only spikes with amplitudes between two preset values. The output of the rate meter was recorded on the Brush recorder.

The conduction velocity in the afferent fibers was determined by applying an electrical stimulus (Grass stimulator S4) to the exposed but otherwise intact right cardiac nerve and recording the evoked potential with the recording electrode. In several filaments the electrical stimulation of the cardiac nerve also activated a few silent C fibers. However, it was possible to identify the spontaneously active fiber by the spike morphology and amplitude. The conduction velocity was calculated by dividing the distance between the stimulating and the recording electrodes by the time elapsed between the stimulus and the evoked potential.

The major error in the conduction velocity measurement is the estimation of the length of the nerve between the stimulating and recording electrodes. In five cats the measurement in situ was compared with the length measured after the nerve was dissected free. The length in situ was shorter but the difference never exceeded 15%. Since the "setting-up time" at the stimulating electrode cannot be longer than the duration of the electrical stimulus (1–2 msec), and since the total conduction time in the vagal nerve was around 100 msec, this was not an important source of error.

The total conduction time from the receptor site to the recording electrode was measured in a similar way in nine cats by placing the stimulating electrode over the area of the heart that had been found to contain the receptor. This time, which varied from 44 to 380 msec, was used to identify the period in the cardiac cycle during which the receptor was activated.

EXPERIMENTAL PROCEDURES

As a screening procedure to identify these atrial non-medullated fibers which normally have no or only a low spontaneous activity; the activity in all filaments dissected from the vagus nerve was observed during a separate, brief (3–6 seconds) occlusion of the ascending aorta and the pulmonary artery. Every filament that responded to these maneuvers was dissected further until a filament with only one or two active fibers was obtained. The localization of the receptors in the atria was initially established by the response to mitral and tricuspid valve occlusion. At the end of the experiment the heart was opened and the atria were probed with a rod 0.5 mm in diameter to determine the precise location of the receptors.

The experiments consisted of recording the discharge from single-fiber or two-fiber preparations where the appropriate atrial pressure was increased and decreased in a systematic manner, either by graded obstruction of the circulation distal to the atria or during a graded transfusion. During the obstruction, the pressure was maintained at each level for 15–30 seconds and during the transfusions for 50 seconds to 2 minutes. The receptor activity was calculated from the spike counter recording. Numerous spot checks were made in each experiment by manual counting of the actual discharge traffic.

Results

This study is based on recordings from 14 atrial receptors with vagal afferents. The conduction velocities in the vagus nerve were measured for all receptor afferents and ranged from 0.35 to 2.2 m/sec (mean ± se, 0.94 ± 0.13 m/sec) for the individual fibers; this identified them as C fibers. Eleven of the recordings were made with only one active fiber, and three with two active fibers; the latter group had clearly different spike heights, therefore the activity in the individual fibers could be calculated separately. The other fibers in the two-fiber preparation did not come from the atria.

Receptors were localized in 11 cats by probing and were found to be distributed throughout the atria, the atrial appendages, the interatrial septum, and the junctions of the atria with the veins. The receptor field subserved by a single fiber was 2 × 2 to 4 × 4 mm.

SPONTANEOUS DISCHARGE

The mean spontaneous discharge for the 14 receptors was 1.4 impulses/sec (SE, ±0.3 impulse/sec), at mean control pressures of 2.7 mm Hg in the right atrium and 6.5 mm Hg in the left. The highest spontaneous discharge noted was 3.7 impulses/sec.
Normally there were no marked fluctuations in the spontaneous discharge, but three receptors showed a sudden marked increase from a low spontaneous discharge to an irregular or cardiac-modulated discharge that lasted for several seconds up to 2 minutes without any changes in atrial pressures.

Two receptors were silent and two discharged irregularly. Three receptors were usually activated during the a wave, and two usually during the v wave. For the five other receptors, the total conduction time was not determined, therefore the relation of the receptor activation to the cardiac cycle could not be determined.

RECEPTOR ACTIVITY DURING CHANGES IN ATRIAL PRESSURE (OUTFLOW TRACT OCCLUSION)

Recordings from a single left atrial C fiber are shown in Figure 1. The location of the receptor on the left side of the heart is evidenced by the sharp increase in discharge frequency during a brief occlusion of the aorta (neurogram A) and the reduction in firing during pulmonary artery occlusion (neurogram B). At the end of the experiment the heart was opened and probed. The receptor was located at the base of the left atrial appendage. Neurograms C through F show the progressive increases in receptor discharge and mean left atrial pressure recorded during graded occlusion of the ascending aorta.

![Figure 1](http://circres.ahajournals.org/)

**Figure 1** Effects of aortic occlusion, pulmonary artery occlusion, and progressive obstruction of the ascending aorta on aortic blood pressure, mean left atrial pressure, and spike frequency in a single left atrial C fiber (see left atrial receptor 5 of Fig. 2) localized at the base of the left atrial appendage. The letters in the spike frequency recording correspond to the neurograms below. During graded aortic occlusion, receptor activity increased in parallel with left atrial pressure. Increased activity showed a cardiac rhythmicity (E) or fired continuously (F).

The relationship of the firing pattern to the phasic changes in atrial pressure was examined in nine receptors. During aortic and pulmonary artery occlusion the receptors were activated mainly during the v wave and occasionally during the a wave. Periods of irregular activation throughout the cycle also occurred. During balloon occlusion of the mitral and tricuspid valves, ectopic beats were frequent and receptor activity usually was irregular. For this reason, the receptor discharge during outflow tract occlusion was plotted against mean atrial pressure.

The activity in five left atrial C fibers is plotted against mean left atrial pressure in Figure 2. In four of the five receptors examined the discharge frequency increased in a near-linear manner as the atrial pressure rose. The threshold value was 5-12 mm Hg mean left atrial pressure. At mean left atrial pressure ≥ 20 mm Hg; discharge frequencies ranged from 9 to 15 impulses/sec. Receptor 3 showed no correlation between discharge frequency and mean left atrial pressure when atrial pressures ranged from 7 to 17 mm Hg. Increase of atrial pressure above the latter value resulted in a sudden increase in receptor activity, discharge frequencies of 18 and 19 impulses/sec being recorded.

Figure 3 shows the relationship between mean atrial pressure and discharge frequency for four right atrial receptors. The threshold for activation was 2-3 mm Hg mean right atrial pressure. At 7-17 mm Hg, the highest atrial pressures obtained in the series, the discharge frequency ranged from 5 to 11 impulses/sec. The slope of the line relating receptor discharge to mean atrial pressure was less steep in the two experiments in which the pulmonary artery was occluded than in the two experiments in which the tricuspid valve was occluded. Generally, the activity returned to the control value when the atrial pressure returned to normal. In two receptors, the increased discharge continued for 8-20 seconds after release of the obstruction, although atrial pressure was normal (see also Fig. 6).

RECEPTOR ACTIVITY DURING CHANGES IN BLOOD VOLUME

An example of the progressive increase in discharge frequency of a right atrial C fiber during stepwise infusions of dextran 40 (Rheomacrodex, Pharmacia) is shown in Figure 4. The progressive increase in atrial volume is reflected in the increase in the height of the v wave. In the
control period (peak v wave pressure of 2 mm Hg), there was no spontaneous activity. From a discharge frequency of 1 impulse/sec at a threshold of 3.5 mm Hg (peak v wave) the activity increased to 7.3 impulses/sec at a v wave pressure of 15 mm Hg. The discharge of this receptor was related predominantly to the v wave (Fig. 4B, C, and D), although occasionally discharge coincided with the a wave (Fig. 4D).

Figure 5 shows the relationship between peak v wave pressure and discharge frequency for three right atrial and two left atrial C fibers. Peak v wave pressures were used in this series as the reference point because it was felt this best reflected the increase in atrial volume. The relationship between discharge frequency and atrial pressure was not significantly different when mean atrial pressure was used instead. The threshold pressure for the right atrium was about 2-3 mm Hg and for the left atrium, 6 and 8 mm Hg.

The frequency increased as the atrial pressure rose, with a maximal discharge of 5-8 impulses/sec in the right atrium at 10-13 mm Hg, and 12-20 impulses/sec in the left atrium at 21-22 mm Hg. In one receptor the pressure response curve during withdrawal was the same as during transfusion. In one the withdrawal curve was shifted to the right, and in one, to the left.

The firing pattern in relation to the cardiac cycle was examined in five receptors and all were activated mainly during the v wave; however, one receptor also was activated during the a wave, although at a higher threshold.
ATRIAL C FIBERS IN CATS

Figure 6 Effect of tricuspid valve occlusion, mitral valve occlusion, and fibrillation of the ventricles on left and right atrial pressures, ECG, and activity in a single interatrial septum receptor localized just above the foramen ovale. Tricuspid valve occlusion increased the receptor activity. With addition of mitral valve occlusion, receptor activity decreased; receptor fired with cardiac rhythmicity and was activated during ventricular fibrillation. (Asterisks indicate corrected position in cardiac cycle.) In contrast, mitral valve occlusion alone markedly increased receptor activity. During electrical fibrillation of ventricles, both atrial pressures increased and there was a modest increase in receptor activity (for details see text).

INTERATRIAL SEPTUM RECEPTORS

The three receptors that were localized in the interatrial septum by probing the opened heart responded to separate increases in pressure in each atrial chamber. The activity of one of these atrial septal receptors is shown in Figure 6. At the control mean atrial pressures of 3.5 mm Hg in the left atrium and 3 mm Hg in the right, there was little or no discharge from the receptor. When the mean right atrial pressure was raised to 5.5 mm Hg by tricuspid valve occlusion, the discharge frequency was 15 impulses/sec. With the additional occlusion of the mitral valve some 8 seconds later, the discharge frequency decreased to 7 impulses/sec, despite a rise in mean left atrial pressure to 8 mm Hg and no decrease in mean right atrial pressure. Mitral valve occlusion alone, which did not affect right atrial pressure, raised mean left atrial pressure from 4 to 16 mm Hg and increased receptor discharge from 0 to 40 impulses/sec. During ventricular fibrillation induced by electrical stimulation, both atria continued to beat. Mean right atrial pressure increased from 3.5 to 9 mm Hg and mean left atrial pressure from 4.5 to 11 mm Hg. Discharge frequency increased from 0.1 to 5.5 impulses/sec. These observations suggest that the discharge frequency of atrial septal receptors is more affected by the difference in pressure between the atria than by the absolute level of pressure in each chamber.

Discussion

In every experiment it was common to find one or several multifiber filaments containing C fibers whose atrial origin was evident from the augmented activity during increase in atrial pressure or mechanical probing of the atria. Although many of these multifiber preparations were destroyed during attempts to obtain single-fiber preparations, it was possible to obtain recordings from 11 single C fibers and from three two-fiber filaments from the atria. Nine of these receptors could be localized precisely and were in the atria, interatrial septum, and atrial appendages. This widespread distribution of receptors within the atria, and the common finding of C fiber activity in multifiber preparations, suggest that in the cat there exists a substantial population of atrial C fibers. It should be noted that the C fibers studied were selected by their response to pressure changes in the atria. It is possible that there are atrial C fibers that do not respond to pressure changes of the magnitude caused by the occlusions and so would not be detected in the present experiments.

The morphology of the atrial C fibers is unknown. It may be that these fibers, together with left ventricular vagal C fibers, are part of the widespread system of fine nerve endings termed the end-net. The spontaneous discharge rate in these receptors (when it is present) is low and either is irregular or exhibits cardiac rhythmicity. All receptors responded to an increase in pressure in the atria by an increase in firing rate, and in most experiments there was a near-linear relationship between the frequency of discharge and the atrial pressure, whether the pressure was increased by occlusion of the outflow tract or by transfusion. When the atrial pressure was increased, a cardiac-modulated discharge became evident. In these circumstances, and particularly during volume loading, the...
receptor discharge was related mainly to the v wave. This suggests that the receptors were activated principally by distention of the atria.

The present studies demonstrate that atrial C fibers can be activated by changes in atrial pressure within values recorded in normal conditions. However, the experiments required thoracotomy, which has been shown to cause a decrease in cardiac volume and also in the activity of atrial receptors subserved by medullated vagal afferents. If the same was true for atrial C fibers, these would have a higher spontaneous activity when the thorax is intact and respiration spontaneous.

Certain evidence suggests that nonmedullated cardiac vagal afferents are involved in cardiovascular control. Selective electrical stimulation of these fibers in cats causes bradycardia and systemic vasodilatation, especially in the renal vascular bed; in contrast, selective activation of the medullated cardiac afferents causes tachycardia and systemic vasoconstriction. It also has been shown recently that atrial receptors with vagal afferents exert a tonic vasomotor inhibition in the dog. It thus is possible that atrial C fibers are involved in cardiovascular control. The further observation that changes in blood volume within a physiological range in atrial pressure cause an increase in activity of these atrial C fibers might indicate a role in the control of blood volume.

Electrogenesis of Increased Norepinephrine Sensitivity of Arterial Vascular Muscle in Hypertension

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SUMMARY The possibility that the vascular muscle cell might contribute to the development of essential hypertension by being more responsive to norepinephrine because of an inherently lower membrane potential (E_m) was investigated. Experiments were designed to test the hypothesis that E_m of arterial vascular muscle cells from spontaneously hypertensive rats (SHR) are less negative than those from matched Kyoto normotensive rats (KNR). The caudal artery, a muscular, densely innervated regulating artery 300-400 μm in outside diameter, which is activated by graded (nonspiking) depolarization to produce a maintained contraction, was studied. Vascular muscle cells from SHR always had less negative E_m than those from KNR at 16°C, but not at 36°C, over a range of K^+ concentrations. However, depolarization by norepinephrine was greater over the middle of the dose-response curve, and this greater hyperpolarization that exceeds the calculated E_m (potassium equilibrium potential) when K^+ is replaced. The magnitude of the hyperpolarization on returning to 30 mM or 50 mM K^+ always was greater for vascular muscle of SHR than KNR. The apparently lower [K^+]_i, and more active (compensating) electrogenic ion transport in the SHR vascular muscle cells thus result in an unaltered E_m at body temperature in the physiological range of K^+ concentrations. However, depolarization by norepinephrine was greater over the middle of the dose-response curve, and this greater depolarization caused the contractions of SHR arteries to be greater. The altered electrogenesis of the SHR vascular muscle cells is postulated to provide a mechanism for the increased reactivity of arteries to norepinephrine in hypertension.

OF THE POSSIBLE causes for the increased peripheral resistance that is a primary characteristic of essential hypertension, for KNR. The caudal artery undergoes a large depolarization when K^+ is removed from the superfusing solution and a transient hyperpolarization that exceeds the calculated E_m (potassium equilibrium potential) when K^+ is replaced. The magnitude of the hyperpolarization on returning to 30 mM or 50 mM K^+ always was greater for vascular muscle of SHR than KNR. The apparently lower [K^+]_i, and more active (compensating) electrogenic ion transport in the SHR vascular muscle cells thus result in an unaltered E_m at body temperature in the physiological range of K^+ concentrations. However, depolarization by norepinephrine was greater over the middle of the dose-response curve, and this greater depolarization caused the contractions of SHR arteries to be greater. The altered electrogenesis of the SHR vascular muscle cells is postulated to provide a mechanism for the increased reactivity of arteries to norepinephrine in hypertension.

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