Behavior of Cardiac Receptors with Nonmyelinated Vagal Afferents during Spontaneous Respiration in Cats

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SUMMARY Activity from left atrial and left ventricular receptors with nonmyelinated vagal afferents (mean conduction velocity, 1.2 m/sec) was recorded in 13 closed-chest spontaneously breathing cats anesthetized with α-chloralose. The anatomic position of each receptor was determined by probing the opened heart at the conclusion of the experiment. Three of eight left atrial receptors and four of five left ventricular receptors were silent under resting conditions. The mean discharge frequency under resting conditions for the six receptors displaying spontaneous activity was 1.0 ± 0.15 impulse/sec. Thus cardiac receptors with vagal nonmyelinated afferents have a low resting discharge in spontaneously breathing cats. The frequency and pattern of discharge of atrial but not of ventricular receptors was altered during spontaneous respiration. The atrial receptors discharged with cardiac rhythmicity during end inspiration and early expiration when transmural pressure was greatest and were silent for the remainder of the respiratory cycle. When respiration was augmented by CO₂ breathing or blood volume was increased, the rate of discharge was a linear function of atrial transmural pressure. Eleven ventricular receptors with nonmyelinated afferents (mean conduction velocity, 1.0 m/sec) were exposed to graded volume expansion and phenylephrine infusion in eight open-chest and three spontaneously breathing cats. Raising left ventricular end-diastolic pressure alone increased the frequency of discharge, and a concomitant increase in systolic pressure caused a further increase in firing.

PREVIOUS STUDIES on the activity of cardiac receptors with nonmyelinated vagal afferents (C fibers) have provided no data as to the frequency and pattern of receptor discharge in the closed-chest animal with normal cardiac volume. The importance of this point resides in the observation by several investigators that the spontaneous discharge of cardiac receptors with nonmyelinated afferents is sparse and irregular; some receptors apparently have no spontaneous activity and discharge only when an appropriate stimulus is applied.¹⁻⁶ Such observations make it difficult to envisage cardiac C fibers serving as a significant source of tonic inhibition of the vasomotor center under normal circumstances.

All of the foregoing studies were conducted with the chest open, a circumstance in which heart size is reduced by 25–30%.

An increase in blood volume and thus of cardiac volume has been shown to result in an increased discharge of both atrial and ventricular receptors and in the appearance of cardiac rhythmicity in a previously irregular pattern of activity.³⁻⁶ Therefore, in closed-chest animals in which cardiac volume is normal, the spontaneous discharge of these receptors might be significantly greater than recorded with the chest open, and could constitute a physiologically important source of information to the central nervous system. An objective of the present study was to test this hypothesis by determining the frequency and pattern of discharge of left atrial and left ventricular receptors with nonmyelinated vagal afferents in naturally breathing, lightly anesthetized cats.

In a study of cardiac receptors with myelinated afferents conducted in naturally breathing cats, Paintal¹ showed that inspiration increased the activity of atrial A and B receptors but caused little or no change in the discharge frequency of ventricular receptors. The present goal of determining the spontaneous activity of cardiac receptors with nonmyelinated afferents in closed-chest cats with normal cardiac volumes offered the opportunity to examine how this spontaneous activity was affected by respiration.

The third line of inquiry derives from the observations that during acute increases in outflow resistance, left ventricular receptors were activated during systole,¹⁻²⁻⁴ but the increase in receptor discharge was best correlated with the end-diastolic pressure and appeared unrelated to peak systolic pressure.²⁻⁴ The present studies examined this point both in closed and open-chest cats, but used infusions of phenylephrine instead of aortic occlusion to obtain graded increases in resistance to left ventricular outflow. It was found that left ventricular systolic pressure influenced the frequency with which the ventricular receptors discharged.

Methods

Experiments were carried out in cats weighing 2–5 kg. General anesthesia was induced with ketamine (30 mg/kg, intramuscularly) 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 by additional doses of chloralose. The trachea was exposed and cannulated. Rectal temperature was maintained at 37-39°C by external heating.

Two groups of experiments were carried out. In the first, the chest was closed and the cats breathed spontaneously. In the second, the chest was opened; this necessitated positive pressure ventilation with oxygen at tidal volumes of approximately 10 ml/kg. The cats ventilated artificially were treated with gallamine triethiodide (Flaxedil, 2 mg/kg, intravenously, as needed) to prevent muscle movement. Arterial Po2, PCO2, and pH were measured prior to nerve recording in both groups. The pH was maintained between 7.3 and 7.4 and the PCO2 between 30 and 40 mm Hg, by the intravenous infusion of NaHCO3 and, in the artificially ventilated group, by adjusting the tidal volume. The spontaneously breathing cats rarely required NaHCO3 administration.

SURGICAL PROCEDURES

The isolation of vagi, sympathetic trunk, and carotid arteries in the neck and identification and isolation of the right main cardiac nerve in the chest were carried out as previously described. For those studies in which the chest was opened and the cat artificially ventilated, a bilateral intercostal transsternal incision was used. The pericardium was opened and attached to the surrounding thoracotomy margins. Snares were placed around the pulmonary artery and aorta to increase pressures in the right and left sides of the heart, respectively. Left atrial pressure was raised by inflation of a balloon-tip catheter (Swan Ganz, 5Fr) positioned near the mitral valve via the left atrial appendage. The vagal trunk was sectioned caudal to the point of entry of the main right cardiac nerve to minimize afferent traffic from the lungs and abdomen.

For those studies in which the cats breathed spontaneously, a right thoracotomy was performed under pentobarbital anesthesia (50 mg/kg administered intraperitoneally) at least 5 days before study using sterile technique. The azygos vein was ligated and divided to reveal the right main cardiac nerve running beneath it. The vagal trunk was ligated and divided caudal to the point of entry of the main right cardiac nerve. A polyethylene cannula fitted with a stylet was positioned in the pulmonary vein draining the right middle lobe so that the tip of the cannula protruded into the left atrial chamber. The other end of the cannula was brought out through the intercostal incision so that it could be buried beneath the skin when the chest was closed. At the time of study, the stylet was removed and the catheter used to measure left atrial pressure was passed through the cannula. The right middle lobe was removed, the lungs reinflected, and the chest closed. Procaine penicillin G, 100,000 U, and benzathine penicillin G, 100,000 U, were administered intramuscularly just prior to surgery; no further antibiotic coverage was used. Of 40 cats prepared in this fashion, there were no deaths; 75% of the left atrial cannulas remained patent.

PRESSURE RECORDINGS

Pressures were measured with Statham P23Db transducers via catheters (PE 50, 90, or 160) inserted in the aorta, left ventricle, and left atrium, respectively, through the right femoral artery, the left common carotid artery, and through the pulmonary vein draining the right upper lobe (open chest) or through the cannula implanted in the right middle lobe pulmonary vein (closed chest). In the spontaneously breathing cats, an esophageal catheter (PE 240) attached to a Statham transducer (P23Db) was positioned at heart level to measure changes in intrathoracic pressure associated with respiration. The distal inferior vena cava was cannulated from the right femoral vein for drug injection, volume expansion, and bleeding.

The catheter manometer systems for the measurement of left atrial and left ventricular pressures were optimally damped so that their response was flat (+5%) up to at least 35 Hz. The 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 Wavetek model 180 sine wave generator.

The electrocardiogram was recorded from the right fore and hind legs by positioning the left arm electrode of standard lead 1 on the right leg. This resulted in excellent P wave and QRS morphology.

All pressures, including phasic and mean left atrial, phasic left ventricular high and low gain, phasic and mean aortic and intraesophageal pressures, along with the electrocardiogram, nerve recordings, and output of the spike counter, were recorded on a Honeywell Ultraviolet Visicorder (model 1508) writing at speeds ranging from 2.0 to 200 mm/sec.

RECORDING OF NERVE ACTIVITY

The right cervical vagus was placed on a black plastic dissecting stage and immersed in a pool of mineral oil (temperature, approximately 36°C). With a binocular operating microscope the nerve sheath was removed from a 2-cm segment of the right vagus, the perimysium was split with a sharp probe, and thin filaments were obtained and cut centrally for recording. The filaments were placed on Ag/AgCl electrodes connected to a Grass probe (HIP 511E) and the signal was amplified by a Grass bandpass amplifier (P511). The high frequency cutoff was set at 300-3000 Hz and the low frequency cutoff at 30 Hz. The output of the amplifier was displayed on a Tektronix oscilloscope and on the Visicorder. The output of the Grass amplifier was also led into a loudspeaker and into a two-window discriminator unit which counted spikes whose voltages exceeded the respective windows. The signals could be integrated over selected intervals of time or per beat, using the QRS complex of the electrocardiograph (ECG) to reset the counter. The output of the discriminator unit was also recorded on the Visicorder. In both open- and closed-chest groups, the experiments were carried out on single unit preparations, that is, there was
only one unit that exhibited activity spontaneously or in response to the experimental interventions employed. There were, however, other nerve fibers in the filament; these were activated only by electrical stimulation. The rate of discharge was determined by the rate meter function of the discriminator unit and was checked repeatedly by manually counting the actual traffic recorded.

The conduction velocity of the afferent fibers in the open-chest experiments was determined as previously described by electrically stimulating the exposed but intact right cardiac nerve and recording the evoked potential. The distance from the right cardiac nerve to the recording electrodes in the open-chest studies was approximately 10 cm. In a few cases, several previously silent C fibers were activated, in addition to the afferent of the receptor under study. The latter could be identified easily by the spike height and morphology. The conduction velocity was determined by dividing the nerve conduction time by the distance between the stimulating and recording electrodes. The accuracy of this method of determining conduction velocity has been discussed previously. The minimal current possible was used to activate the afferent by starting with a 1-V stimulus and increasing the voltage until the evoked potential of the afferent under study could be identified.

In the closed-chest experiments, determination of nerve conduction velocity required stimulation of the entire right cervical vagal trunk. This raised certain problems in clearly identifying the evoked spike potential of the receptor under study. Even though the smallest voltage capable of activating the afferent fiber was used, stimulation of the entire vagal trunk could be expected to activate most of the nerve fibers which lay on the recording electrode. It thus was necessary to reduce the number of fibers to the minimum by pairing the filament to the smallest possible size. The filament finally obtained was barely visible under the highest magnification of the microscope (40×). In addition, the entire right vagus nerve was isolated from its point of exit from the chest to the nodose ganglion to allow maximal separation (4–6 cm) of the stimulating and recording electrodes. This distance was great enough so that evoked potentials, carried in fibers with different conduction velocities, arrived at the recording electrodes at times sufficiently different to permit identification of spike heights and morphologies.

Attention to the above details permitted the evoked potential of the afferent fiber under study to be distinguished from action potentials of other fibers simultaneously activated by the stimulus. In addition, the nerve conduction velocity of 11 of 13 fibers again was determined at the conclusion of the experiment by stimulating the right cardiac nerve after the chest had been opened. Nerve conduction velocities, measured both by stimulation of the cervical vagus and the right cardiac nerve, differed by less than 10%.

To determine the period of the cardiac cycle during which the receptors were activated, the conduction time from the receptor site to the recording electrodes was determined in 13 experiments. Following mechanical localization of the receptor in the open heart, the stimulating electrodes were applied to the myocardium in that area. The minimal current needed to activate the receptor was used, beginning with a 1-V stimulus and slowly increasing the voltage until an evoked potential was elicited whose spike height and morphology were those of the receptor under study. The conduction time could then be read directly from the oscilloscope or the visicorder recording. Since the conduction time was known, the position in the recorded trace of the spontaneously occurring spike potential could be corrected, and thus the period of the cardiac cycle during which the receptor was activated could be determined. This is necessary for these slowly conducting C fibers, since these and previous experiments have shown that 300 msec or longer may be required for conduction of the action potential from the receptor to the recording electrodes.

SPONTANEOUSLY BREATHING CATS

In these experiments, a Fogarty embolectomy catheter (SF) was positioned in the aortic arch to allow partial aortic occlusion. Since it was the intent of this study to examine the behavior of left atrial and left ventricular receptors with nonmyelinated afferents, each small bundle of vagal fibers was screened for receptors that responded to partial aortic occlusion. When a receptor responded to this intervention with an increase in frequency of discharge and the determination of the nerve conduction velocity in the neck indicated that the afferent was a C fiber, the receptor's response to volume expansion, to phenylephrine infusion, and to aortic occlusion was studied. Once a study of a receptor was initiated, the entire experiment had to be carried out rapidly because the afferents began to deteriorate if the entire study extended much beyond 30 minutes. This deterioration was more evident in the experiments on spontaneously breathing cats than in the open-chest group. This probably reflects the fact that in the former group of experiments it was necessary to pare the filament down to a very small size.

At the conclusion of the study and with the afferent still on the recording electrode, the abdomen was opened and the inferior vena cava divided to induce hemorrhagic hypotension and reduce the extent of the bleeding when the chest was subsequently opened. The chest was opened carefully in a fashion similar to that used for the open-chest experiments. The lungs were immediately overinflated to ensure that the receptor was not a lung receptor which might respond both to lung inflation and to changes in pulmonary venous pressure. Then the pericardium was opened and the atria were stretched by hooking the ventricular apex and applying moderate tension. If the receptor increased its rate of discharge with this maneuver, the left atrium was opened to permit full visualization of the atrial endocardium and was probed with a rod 0.5 mm in diameter. The receptor's location was established when the probing of a small area of the left atrium resulted in a large increase in receptor discharge. If there was little or no response to pulling on the apex or if there was a response but the receptor could not be activated by probing the left atrium, then the left ventricle was opened widely from apex to base by dividing the ventricular septum, and that chamber was probed to localize the receptor as described above.
OPEN-CHEST CATS

Since this group of experiments was designed to study the behavior of left ventricular receptors with nonmyelinated afferents, each small bundle of vagal fibers was screened for activity resulting from brief periods of aortic and pulmonic occlusion. Receptors that responded to aortic occlusion were examined further during mitral occlusion. A receptor whose rate of discharge was increased by aortic occlusion and was uninfluenced or reduced by mitral occlusion was considered to be a left ventricular receptor. The behavior of each receptor so identified was examined during phenylephrine infusion and graded expansion of the blood volume. At the conclusion of the experiment, the left ventricle was opened and the receptor was localized to a specific part of the ventricle by probing with a rod 0.5 mm in diameter.

Results

The results reported are based on recordings from eight left atrial and five left ventricular receptors studied in spontaneously breathing cats, and from eight left ventricular receptors studied in open-chest artificially ventilated cats. The conduction velocities in the afferent nerves ranged from 0.9 to 2.0 m/sec [mean, 1.09 ± 0.02 (SE) m/sec] and permit their classification as C fibers that probably were nonmyelinated. 10-11 Seven of the eight left atrial receptors were located at the venoatrial junctions. One receptor was located in the posterior atrial wall. The left ventricular receptors were distributed throughout the cardiac chamber but nearly half were in the papillary muscles and the ventricular myocardium near the base of the papillary muscles. One receptor was judged to be epicardial and three to be endocardial in location since they responded vigorously to light pressure applied to a small area of the epicardium and endocardium, respectively. The remaining nine receptors appeared to be located more deeply in the myocardium as greater pressure with the probe was required to elicit receptor discharge.

SPONTANEOUS RECEPTOR DISCHARGE DURING NATURAL RESPIRATION

During quiet natural respiration and prior to any experimental interventions, three of the eight left atrial receptors and four of the five left ventricular receptors had no spontaneous activity. The findings for an individual cat were consistent. A receptor that was silent in the resting state remained so throughout the study and became active only in response to experimental interventions.

For receptors displaying spontaneous activity under resting conditions, the average resting discharge frequency was determined by averaging the number of spikes over periods of 30-120 seconds at the beginning of the study and following each intervention, when left atrial and left ventricular pressure and the depth of respiration were the same as the values recorded initially. Measurements of resting discharge frequency were made three to four times during the course of each study; the total sample was from 2.5 to 4 minutes of recording time and thus was representative of the resting activity of each receptor.

The mean and individual (in brackets) average number of impulses per second in resting states for the five spontaneously active left atrial receptors were, respectively, 1.09 (1.29, 1.67, 0.75, 0.65), 1.61 (1.48, 1.91, 1.43), 1.55 (1.69, 1.61, 1.34), 0.72 (0.90, 0.52, 0.74), and 0.49 (0.55, 0.50, 0.43). The ventricular receptor displaying spontaneous resting activity had average discharge frequencies of 0.31, 0.27 and 0.93 impulse/sec. Thus in closed chest, naturally breathing cats, seven of 13 receptors whose anatomical location in the heart had been determined were silent during quiet respiration. The average discharge frequency for the six cardiac receptors exhibiting spontaneous activity under these conditions was 1.0 ± 0.15 impulse/sec (mean ± SE).

Two of the eight left ventricular receptors studied in the open-chest artificially ventilated cats were silent under resting conditions. The average resting discharge frequency for the six receptors with spontaneous activity was 1.35 ± 0.18 impulses/sec.

INFLUENCE OF RESPIRATION ON LEFT ATRIAL RECEPTORS

The five left atrial receptors that discharged spontaneously under resting conditions exhibited respiration-induced changes in the pattern of afferent discharge. Figure 1 shows the typical discharge pattern of a left atrial receptor with nonmyelinated vagal afferent in the closed-chest spontaneously breathing cat. The asterisks indicate the time during the cardiac cycle during which the receptor is activated when the appropriate correction is made for conduction time from receptor to recording electrodes. Receptor's anatomical location was the venoatrial junction draining the left lower lobe. The left atrial pressure tracing is overdamped due to slight wedging of the catheter tip.
atrial receptor during quiet breathing. When the appropriate correction was made for conduction time from the receptor to the recording electrodes, it was found that the receptor fired during the end-inspiratory and early expiratory phases of respiration and usually was silent during the remainder of the ventilatory cycle. The receptor first began to fire at a time when left atrial pressure was lowest and when intrathoracic pressure was most negative. Also shown in Figure 1 is the pattern of discharge of the same left atrial receptor after expansion of the blood volume with 25 ml of Rheomacrodex. The discharge frequency was greater and the receptor was seen to fire with cardiac rhytmicity throughout the ventilatory cycle and to increase its rate of discharge with each inspiration. The increase in the rate of discharge occurred early in the inspiratory phase of respiration and extended well into the expiratory phase. The three left atrial receptors that were silent in the resting state also exhibited this respiratory modulation of receptor discharge after receptor activity had been evoked by expansion of the blood volume.

Augmentation of respiration by carbon dioxide inhalation in four experiments increased the average frequency of discharge of the receptors by 94 ± 9%. This is illustrated in Figure 2, which also shows that inhalation of a gas mixture containing 10% CO₂ and 90% O₂ increased the depth of respiration without obviously altering the phase relationship with receptor activity. Since the changes in mean left atrial pressure were quite modest, most of the increased discharge could be attributed to the large decreases in intrathoracic pressure that accompanied each breath. It is unlikely that the increase in receptor discharge was related to increase in arterial PCO₂, since the relationship between discharge frequency and atrial transmural pressure was the same for CO₂ inhalation and for volume expansion for four atrial receptors for which both interventions were studied. Also it is known that CO₂ decreases the activity of slowly adapting pulmonary stretch receptors, and Coleridge et al. and Sleight and Widdicombe have found that ventilation with CO₂ does not increase activity in ventricular receptors characterized by an irregular sparse discharge. The spontaneous activity of most avian cardiac receptors is negatively correlated with arterial PCO₂.

Changes both in intra-atrial and intrathoracic pressure

![Figure 2 Influence of hyperpnea induced by inhalation 10% CO₂-90% O₂ for 15 seconds on the discharge of the left atrial receptor with nonmyelinated afferent. Mean left atrial pressure (MLA) was minimally affected. Receptor localized to venoatrial junction draining right upper lobe.](image)

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![Figure 3 Relation between atrial transmural pressure (mm Hg) and rate of discharge (impulse/beat) for a left atrial receptor with nonmyelinated afferent (O) and for two left atrial type B receptors with myelinated afferents (A, A). These data were obtained in spontaneously breathing cats before and during graded expansion of the blood volume with Rheomacrodex and CO₂ inhalation.](image)

Contribution to changes in atrial transmural pressure, and because the latter is the principal determinant of atrial volume, the relationship between the rate of atrial C fiber discharge and atrial transmural pressure was examined in the closed-chest cat. A typical result is shown in Figure 3. Data were obtained during quiet respiration in the resting state, during inhalation of CO₂, and during expansion of blood volume, alone or combined with CO₂ breathing. Observations on two atrial type B receptors with myelinated afferents are included for comparison. The relationships between the rate of discharge of the receptors by 94 ± 9%. This is illustrated in Figure 2, which also shows that inhalation of a gas mixture containing 10% CO₂ and 90% O₂ increased the depth of respiration without obviously altering the phase relationship with receptor activity. Since the changes in mean left atrial pressure were quite modest, most of the increased discharge could be attributed to the large decreases in intrathoracic pressure that accompanied each breath. It is unlikely that the increase in receptor discharge was related to increase in arterial PCO₂, since the relationship between discharge frequency and atrial transmural pressure was the same for CO₂ inhalation and for volume expansion for four atrial receptors for which both interventions were studied. Also it is known that CO₂ decreases the activity of slowly adapting pulmonary stretch receptors, and Coleridge et al. and Sleight and Widdicombe have found that ventilation with CO₂ does not increase activity in ventricular receptors characterized by an irregular sparse discharge. The spontaneous activity of most avian cardiac receptors is negatively correlated with arterial PCO₂.

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EFFECT OF RESPIRATION ON CARDIAC VAGAL FIBERS/Thames et al.

Fig. 4 Influence of volume expansion on the rate and pattern of discharge of left ventricular receptor with nonmyelinated afferent. Note absence of respiration-induced changes in discharge. Receptor localized to posterior wall of left ventricle.

10% CO₂ during volume expansion; respiration still was without effect on the discharge frequency of the ventricular receptors.

AUGMENTATION OF VENTRICULAR RECEPTOR DISCHARGE BY INCREASE IN OUTFLOW RESISTANCE

The effect of graded increases in outflow resistance and in blood volume on the discharge frequency of the same ventricular receptor was examined in eight open-chest artificially ventilated cats and in three spontaneously breathing cats. Both groups of cats responded similarly to each intervention. Graded increases in outflow resistance were obtained by step increases in the rate of intravenous infusion (5-50 μg/min) of phenylephrine, a drug with potent peripheral vasoconstrictive but minimal inotropic effect. Graded increases in blood volume were obtained by step increases in the volume of intravenous infusion of Rheomacrodex (dextran 40, 10% w/v). Although neither intervention exclusively affected left ventricular systolic pressure (LVSP) or left ventricular end-diastolic pressure (LVEDP), Figure 5 shows that, in eight open-chest cats, phenylephrine induced its earliest and largest effect on LVSP with only modest changes in LVEDP; in five cats, LVSP increased by 20 to 100 mm Hg for a concomitant rise in LVEDP of 1 mm Hg. Also shown is that transfusion had its major effect on LVEDP; during volume expansion, LVSP was unchanged in two cats and decreased slightly in two cats. Heart rate was not changed by the interventions. Peak left ventricular dP/dt increased by less than 5% in the three experiments in which it was measured in the open-chest cat. In the three spontaneously breathing cats, peak left ventricular dP/dt increased by less than 10%.

In neither experimental situation did any left ventricular receptor increase its rate of discharge until there was an increase in LVEDP. This is illustrated in Figure 6 which shows the typical response to phenylephrine infusion of a receptor studied in an open-chest cat. This receptor was silent during the control period and failed to fire in spite of an increase in systolic pressure from 100 to 160 mm Hg. However, an increase in diastolic pressure of 1 mm Hg was accompanied by the first evidence of activity in the receptor. When the rate of discharge of each of the eight ventricular receptors studied in the open-chest cat is plotted against LVEDP for both phenylephrine infusion and for volume expansion, it can be seen that, over the range of values of LVEDP associated with an increase in receptor activity, the discharge frequency at a given receptor activity is greater than when LVEDP was achieved by volume expansion (Fig. 7). Left ventricular systolic pressures were significantly greater ($P < 0.01$) during phenylephrine infusion than during volume expansion over the entire range of diastolic pressures associated with an increase in receptor discharge.

Figure 8 shows results from three receptors studied in the same fashion in spontaneously breathing cats. As in the open-chest experiments, over the range of LVEDP associated with an increase in receptor activity, the discharge frequency and LVSP at a given LVEDP were greater during phenylephrine infusion than during volume expansion.

Fig. 5 Changes in left ventricular systolic and end-diastolic pressure which resulted from phenylephrine infusion (●) and from expansion of the blood volume (○) in eight cats studied with chest open. The curves for each of the eight experiments have been identified numerically.
Discussion

The present experiments provide the first data on the frequency and pattern of discharge of cardiac receptors with nonmyelinated vagal afferents in the closed-chest spontaneously breathing cat, as all previous studies have been carried out in open-chest artificially ventilated preparations. In their study of slowly conducting vagal fibers from afferent endings in the major veins and arteries and the atria of cats and dogs, Coleridge and colleagues examined several endings in spontaneously breathing animals. However, cardiac receptors were not among those so investigated.

The data from the present study showed that of 13 cardiac receptors examined during natural breathing, seven were silent in the resting state and only discharged in response to distention of the appropriate cardiac chamber. The pattern of resting discharge of the five atrial receptors and the one ventricular receptor exhibiting spontaneous activity was irregular. The mean resting discharge frequency of these six cardiac receptors was 1.0 impulse/sec. These findings therefore argue against the hypothesis that the irregular and low discharge frequencies previously reported for cardiac vagal C fibers were due to reduction in cardiac volume as a consequence of thoracotomy. It is not thought that the present findings were due to failure of the heart to reexpand to the preoperative volume. Rushmer et al. reported that the cardiac x-ray silhouette returned to the control value in 24 hours; no cat was studied earlier than 5 days postoperatively.

It has been shown that interruption of vagal afferents from the cardiopulmonary region results in reflex vasoconstriction in the kidney, hindlimb, and splanchnic vascular beds, thus indicating that under the circumstances in which the experiments were done, receptors in the cardiopulmonary area exerted a tonic inhibition on the vasomotor center. Most of these experiments were carried out in dogs with aortic nerves cut and carotid sinuses either denervated or isolated and perfused at pressures which were usually low (40-50 mm Hg). There are some data that suggest that these conditions can result in an increase in the rate of discharge of left heart receptors with nonmyelinated afferents. It may be that the often impressive responses to vagal interruption observed under these special conditions results from blocking traffic from receptors whose rate of discharge and, thus, whose vasomotor inhibitory influence, is increased by the circumstances of the experiment. Our data indicate that under conditions which are close to normal, many of these receptors are silent, whereas those with spontaneous activity discharge at approximately 1 impulse/sec. These findings would argue against cardiac receptors with nonmyelinated vagal afferents exerting a significant inhibition of the vasomotor center in normal circumstances. However, two factors may offset the implications of the low discharge frequency of individual cardiac receptors. It has been shown that 75% of the afferent fibers in the right cardiac nerve of the cat are C fibers. Also, electrical stimulation of cardiac vagal nonmyelinated afferents at low frequency (1 Hz) resulted in significant cardiovascular effects (30% increase in renal conductance and 50 mm Hg decrease in arterial pressure). Thus the total afferent input from vagally innervated cardiopulmonary receptors may be sufficient to exert some degree of tonic inhibition of the vasomotor center.

These studies also provide the first information that cardiac receptors with nonmyelinated vagal afferents are influenced by respiration. This appeared to apply only to atrial receptors. The difference between the response of atrial and ventricular receptors probably reflects the greater distensibility of the atrial chamber and can be of value in the initial localization of cardiac receptors while the chest is closed. The data indicate that in circumstances in which the rate and depth of respiration are augmented, left atrial receptor discharge is increased by 94%.

It had been shown previously that during aortic occlusion the increase in discharge frequency of left ventricular receptors with nonmyelinated vagal afferents correlated best with LVEDP. Though the receptors were activated during the systolic portion of the cardiac cycle, LVSP appeared to have little influence on the frequency of discharge. However, other experiments led Thoré to postulate that ventricular contraction must have a role in determining the frequency of discharge. The studies reported here provide data to support this contention.
Thorén increased afterload by slowly occluding the aorta with a snare. It is difficult, with this technique, to gradually increase the resistance to outflow and to avoid a near isovolumic contraction of the left ventricle. This was circumvented in the present study by using step increases in the rate of infusion of phenylephrine to increase peripheral resistance. The previous observation that receptor discharge correlated with LVEDP was confirmed. It was shown, in addition, that although elevation in diastolic pressure alone increased receptor discharge, a further increase was obtained with a concomitant rise in LVSP.

The present studies emphasize the difficulty in proposing a physiological role for a group of receptors when both the natural stimulus and the determinants of receptor activity are not completely understood. If, as has been suggested, the left ventricle is the principal receptor station for cardiac vagal C fibers, it probably is of functional importance that ventricular receptors are sensitive both to left ventricular end-diastolic and to peak systolic pressure.

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