Impaired Atrial Receptor Responses in Dogs with Heart Failure Due to Tricuspid Insufficiency and Pulmonary Artery Stenosis

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ABSTRACT

In a study of the effects of heart failure on the responses of cardiac receptors, ten dogs were subjected to tricuspid avulsion and pulmonary artery stenosis. One case of spontaneous heart failure was included in the series, and the electrical spike responses of atrial receptors to progressive changes in atrial stretch induced by infusion and hemorrhage were contrasted with those in normal control dogs. In the control dogs, the number of spikes per cycle increased very sharply with moderate, i.e., 5–10 cm H₂O, venous pressure increments before reaching a maximum at 20 cm H₂O. In the experimental dogs, the firing rate failed to increase to the same extent despite large increases in pressure. The resulting sets of curves exhibited a sharp dichotomy. This evidence for the impaired response of elements of the subendocardial receptor network is compatible with a decrease in the sensitivity of feedback mechanisms responsible for the regulation of sodium and water metabolism.

KEY WORDS cardiac receptors sodium retention infusion congestive heart failure blood volume regulation tricuspid regurgitation hemorrhage central venous pressure

Numerous studies of the control of blood levels of antidiuretic hormone (ADH) point to the role of the complex unencapsulated endings of Nonidez (1–3) located about the orifices of the great veins in approximately equal numbers in the subendocardium of both atria (4). Recent work also indicates that the Nonidez or other receptors in the heart (5) affect the sympathetic outflow to the kidney (6–9). In both cases, an increase in heart chamber filling leads to an increase in afferent activity from the receptors (10); this increase in turn leads to a decrease in ADH levels (1, 2) and a loss of sodium-retaining sympathetic activity (6, 11).

It is a peculiar characteristic of chronic heart failure that so much extravascular fluid is retained despite the pressure rise and the consequent increase in chamber size. The evidence suggests that sympathetic nervous system activity increases (11) and that the mechanisms involved in fluid volume regulation cause water and sodium retention as though effective circulating blood volume had been reduced (12). Zehr et al. (13) recently studied the effects of nonhypotensive hemorrhage in dogs with chronic mitral stenosis. Observing an attenuation of the normal increase in blood levels of ADH together with fibrpsis in the atrial walls, they proposed that these local changes resulted in a "decreased operating gain in the low pressure hypothalamic posterior pituitary axis."

Barger et al. (14) demonstrated reduced sodium excretion in dogs with tricuspid avulsion and pulmonary artery stenosis. The disturbance in electrolyte excretion correlated roughly with the severity of cardiac impairment. Eliahou et al. (15) suspected that the decrease in sodium excretion was associated with diminished pulsation in the atria. Accordingly, they sewed strain gauges made of silicone rubber tubing filled with mercury to the atrial walls. At normal pressures the amplitude of pulsatile movement increased steeply with rising filling pressures. However, at high pressures the pulsation of the stretched atrial wall actually diminished with further increases in filling pressure. In a recent work, Payne et al. (16) made similar observations, using piezoelectric transit-time gauges...
ATRIAL RECEPTORS AND CONGESTIVE HEART FAILURE

By measuring changes in receptor frequency, we used the response of the natural mechanoreceptors within the atrial walls. The responses in normal dogs during acute hemorrhage or massive volume increases were compared with the responses to similar volume changes in dogs chronically suffering from various degrees of tricuspid insufficiency and pulmonary artery stenosis.

Methods

A total of 27 dogs weighing 8–24 kg was employed: 10 successfully underwent surgery, 1 developed spontaneous heart disease, and 16 served as controls. The dogs were subjected to several weeks of veterinary observation and were treated for parasites. They had normal hematocrits and were in good health and well nourished. They were fasted overnight before surgery, and their weights were recorded before and after the operation.

Twelve of the 16 control dogs were subjected to massive increases and the remaining 4 to progressive decreases in blood volume. Central venous pressure and systemic arterial blood pressure were measured. The response of atrial receptors, using slips dissected from the vagus nerve in the neck, was studied in 6 of the dogs subjected to infusion and in the 4 dogs subjected to hemorrhage.

Only ten experimental dogs fulfilled the criteria for successful surgical intervention to induce chronic congestive heart failure and for adequate nerve fiber recordings. The present report is limited to observations made on these successful cases in which the resting central venous pressure stabilized at levels in excess of 7 cm H2O. Various times ranging from 9 days to over 4 months were allowed for the full development of the systemic response to the cardiac lesions. The response of the atrial receptors to acute progressive increases in blood volume was then determined in seven of the experimental dogs and in the one dog with severe blood volume was then determined in seven of the experimental dogs and in the one dog with severe

ANESTHESIA

For heart surgery Demerol (50 mg in 1 ml of saline) was given subcutaneously ½ hour before induction with a fluorothane–nitrous oxide mixture. Nitrous oxide was used for maintenance. Morphine sulfate (1 mg/kg) served as a preanesthetic in the studies of nerve action potentials; it was followed by chloralose (80 mg/kg) dissolved in physiological saline as a 1% solution. A maintenance dose of chloralose (20 mg/kg) was given whenever shivering or spontaneous movements commenced. The dogs were intubated to ensure a clear airway.

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PRESSURE REGISTRATION

Two polyethylene catheters (1.6 mm, i.d.) were inserted at the time of the experiment: one into the right atrium via the right external jugular vein and the other into the thoracic aorta via a femoral artery. Intrapерicardial pressures were monitored by locating catheters with a special tip in the region of the atria before closing the pericardium and the chest following cardiac intervention. An attempt was made to keep the catheter patent until the time for nerve examination. In three of the experimental dogs (dogs 1, 4, and 5) there was no obstruction, and pulsatile pressures were recorded throughout the infusion procedure. The difference between atrial pressure and pericardial pressure is the transmural pressure or the effective pressure distending the atrium. The pressures were recorded by strain gauges of the appropriate range (Statham P23BB and P23Db transducers). The electrocardiogram was monitored by limb leads.

NERVE FIBER ISOLATION

Bipolar 19-gauge platinum-iridium electrodes were used to record action potentials in the vagus nerve in the neck. Dissection in a pool of mineral oil was done according to the method of Paintal (10, 17) with modifications designed to make the dissection and the separation of the fibers easier. The precise procedures have recently been detailed by Sinclair (18).

Single atrial type B afferent fibers were isolated and identified. They fired in late ventricular systole, usually a little after the beginning of the upstroke of the aortic pressure wave and about 200 msec after the QRS complex. Inspiration induced an increase in the impulse activity, and gentle inflation of the lung reduced or abolished it. The discharge sometimes developed in a crescendo and was closely related to the rate of rise of the v wave of the atrial diastolic pressure tracing. The activity of the endings reflected the gradual increase in atrial volume as the atrium filled, and the endings were usually silent during atrial systole. The pressure pulses, which were separately recorded, were corrected for lag time in transmission (19).

RECORDINGS

The electrocardiograms and the neuronal spikes were fed into preamplifiers (Tektronix 122 and Grass P5), and the signals from the pressure transducers were applied to a multichannel signal conditioner. Information was simultaneously stored and displayed. Storage was on a magnetic tape recorder (Sanborn 390TB) which used modulation devices. Nerve action potentials were written out on an oscillograph (Honeywell 1508 Visicorder). They could also be displayed on an oscilloscope (Tektronix 502A) either with the pressures or with the electrocardiogram for timing of events and for identification. A loudspeaker (Grass AM-3 Audio-monitor) permitted discrimination of neuronal spike discharges by ear during dissection. Finally the material stored on the tape could be played back on demand and photographed by a recording camera (Grass Kymograph).
PROCEDURE FOR INFUSION AND HEMORRHAGE

The dogs were maintained at a rectal temperature of 37-38°C by either an electric heating pad or an infrared lamp. All infusions were given at body temperature. The blood volumes of the dogs with heart lesions were determined before and after the operation, using the dye-dilution technique with T1824 Evans blue dye as an indicator. Blood volume reductions were carried out in decrements of 10%. When a measured figure was not available, the volume was assumed to be 90 ml/kg body weight. The rate of bleeding was 2 minutes for each 10% decrement. Recordings were made after 2-3 minutes were allowed for stabilization following the volume reduction. With the exception of dogs 9 and 10, dogs that were studied under conditions of volume reduction were not employed to provide data for the effects of infusion and vice versa. Infusions of 6% clinical dextran were given to both control and experimental dogs. The purpose was to elevate the central venous pressure and thus to stretch the cardiac chambers. Each step in both control and experimental dogs was routinely made in 10% increments with a delay of 2-3 minutes after the step. However, in both control and experimental dogs it was given at a rate of 5 ml/kg min⁻¹ through the right atrial catheter. All dogs were placed on their sides without tension on their legs to avoid respiratory embarrassment.

TRICUSPID AVULSION AND PULMONARY ARTERY STENOSIS

The technique for cardiac intervention has been described by Barger et al. (20). The approach was through the fourth right intercostal space. Pulmonary artery stenosis was most effectively produced by sewing a controlled longitudinal pleat in the conus. Several stitches were added at approximately 5-minute intervals to allow stabilization of each venous pressure increment as the stenosis was progressively increased. With some practice the desired moderate obstruction with venous pressure elevation could be achieved. In the production of tricuspid insufficiency it was important to avulse the medial cusp which lies in the outflow tract; avulsion of this cusp together with one other produced an effective, but not overwhelming, incompetence. The resultant preparations varied in the extent to which they induced cardiac embarrassment. The signs and symptoms of cardiac failure are enumerated in Table 1. Body weight and plasma volume were measured before and after cardiac intervention. The time between surgery and the study of atrial afferent impulse frequency varied because an attempt was made to observe the nerve responses when the dog’s venous pressure and general symptoms of congestive failure had reached a maximum. The condition of some dogs became critical within 1–2 weeks, but for the majority 1–2 months were required.

In one case the response during spontaneous heart failure was determined. The dog, an old boxer, was in severe congestive heart failure despite a relatively low central venous pressure of 7 cm H₂O. At autopsy, verrucae were observed on the tricuspid and mitral valves, and the heart was much enlarged.

Results

EXTENT OF CARDIAC IMPAIRMENT

Although no observations were made of the rate at which a sodium load was excreted, the average gain of 14% in the mean body weight of the experimental dogs was indicative of considerable body fluid accumulation. The mean elevation of central venous pressure was 13 cm H₂O. It ranged from 7 to 20 cm H₂O with more ascites occurring at the higher pressures (Table 1). With a mean elevation of central venous pressure of 10 cm H₂O, Barger et al. (14) reported that the renal response to saline infusion was “sluggish,” resulting in moderate sodium retention. Mean plasma volume for our experimental dogs increased by approximately 33%.

Table 1 presents the observations on the ten dogs with heart lesions whose atrial receptor responses were studied following an increase or a decrease in blood volume. In nine, some degree of pulmonary stenosis was induced together with tricuspid insufficiency. In one, only the tricuspid valve was affected. As has been mentioned, the time at which the vagus nerve was examined varied according to the rate and the extent of deterioration of the dog’s condition.

<table>
<thead>
<tr>
<th>Dog</th>
<th>Days postop</th>
<th>CVP postop (cm H₂O)</th>
<th>Ascites</th>
<th>Dyspnea</th>
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<tr>
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<td>131</td>
<td>7.2</td>
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All dogs except dog 9 were subjected to partial obstruction of the pulmonary artery and avulsion of the tricuspid leaflets. Dog 9 experienced avulsion only. Days postop refers to the time interval between the cardiac intervention and the recording from the atrial fibers in the vagus. CVP postop represents the mean central venous pressure at the time of the nerve analysis. Ascites was estimated post-mortem: a “two plus” score means that only a few hundred milliliters of fluid could be aspirated and a “four plus” means that the effusion exceeded 1 liter. Dyspnea was gauged from the difficulty experienced during normal exercise periods walking from the vivarium to the laboratory.

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The resting heart rate was higher in the dogs with heart lesions, and the tachycardia was more marked in those with severe symptoms; these dogs were also lethargic and dyspneic even at rest. The mean heart rate of the experimental group rose from 155 to 175 beats/min with infusion (Fig. 1). By contrast, in normal dogs the lower resting heart rate of 105 beats/min permitted much larger proportionate changes. Thus with infusion their rate rose from 105 to 155 beats/min. There was also a sharp contrast between the responses of the normal and the heart-damaged dogs to hemorrhage. The curve for heart rate for the dogs with lesions was remarkably stable, whereas the normal dogs actually doubled their rate with the 30% loss of blood volume. The arterial blood pressure records demonstrate that the dogs in heart failure tolerated the fluid volume loss and the overtransfusion without a significant change in this parameter. Indeed the greatest response was in the control dogs (Fig. 1).

**TRANSMURAL PRESSURE**

Figure 2 represents the data from three dogs with heart failure in which atrial and intrapericardial pressures were successfully recorded throughout an infusion. The transmural pressure presented in this figure was calculated by subtracting intrapericardial pressure from central venous pressure. For clarity only the data for the 20%, 40%, 60%, and 80% steps of blood volume increase are presented. Reference to Figure 4 shows that the spike responses of all these dogs (dogs 1, 4, and 5) were severely depressed. This depression might have resulted from a progressive fall in atrial transmural pressure as a result of splinting of the distended atria by the repaired pericardium. The progressive increase in central venous pressure was indeed accompanied by a parallel rise in intrapericardial pressure. However, the plot of transmural pressure shows that the stretch on the atria progressed until, at the higher volume increments, 20 cm H$_2$O was exceeded.

![Figure 1](image1.png)

**FIGURE 1**
Changes in central venous pressure, mean arterial pressure, and heart rate during blood volume increases and decreases. Solid lines and circles = congestive heart failure due to tricuspid avulsion and pulmonary artery stenosis. Broken lines and open circles = normal controls. Vertical bars indicate ±SE.

![Figure 2](image2.png)

**FIGURE 2**
Plot of central venous pressure and pericardial pressure as a function of blood volume. Dextran was infused in dogs in congestive heart failure due to tricuspid avulsion and pulmonary artery stenosis to increase central venous pressure and pericardial pressure (broken lines). The arithmetic difference between these pressures is the transmural pressure (solid line). Circles = dog 1, circles with flags = dog 4, and triangles with flags = dog 5.
ATRIAL RECEPTOR RESPONSES

Figure 3A is a composite record which presents three sets of data from a control dog. In each the right atrial pressure, the electrocardiogram, and the pressure in the thoracic aorta accompany the recordings from an atrial type B fiber. By the appropriate electronic "conditioning" the desired action potentials were separated and presented without interference from unwanted spikes in the tracing. This procedure was merely adopted to demonstrate the activity of the fiber more clearly. However, the spike data were obtained from the original "unconditioned" record by counting the total number of spikes in a 15-second period. The sum was then used to calculate the number of spikes per second and per cycle. The composite record in Figure 3A is typical of a type B atrial fiber in its timing: the fiber commenced firing after the QRS complex and after the aortic pressure had risen. The activity followed the v wave of the venous pressure curve, and there was a change in the number of spikes per cycle as the venous pressure in the resting dog changed with respiration. There was a fivefold increase in the number of spikes per cycle as venous pressure rose from approximately 2 cm H$_2$O to 9 cm H$_2$O with an infusion of about 20% of the total blood volume.

This infusion was given as dextran in two increments of 10% each as described in the Methods. The records in Figure 3 are composites made up from the tape-stored recordings of pressures and action potentials. The third and eighth conditioned action potential bursts for the 20% volume increment in Figure 3A show gaps which do not appear in the original record from which the spike count was obtained. They are artifacts due to brief, random malfunctioning of the oscillograph. By the time the volume had been increased by an estimated 50% and the right atrial pressure had risen to approximately 20 cm H$_2$O, the firing rate had actually declined until it was only double the number of spikes per cycle in the resting period. Data from this control dog are also presented in Figure 4 (solid squares).

The curves in Figure 4A illustrate the changes in the number of spikes per cycle developed by the atrial receptors in the control dogs as central venous pressure increased. To demonstrate the trends, freehand curves were drawn through each set of points obtained for the six control dogs as they were progressively infused. The family of six normal curves rose sharply from a mean resting spike frequency of 10 spikes/cycle. This value is in the normal range for dogs with adequate hydration.
Atrial Receptors and Congestive Heart Failure

A: Plot of atrial spikes per cycle against central venous pressure. Pressure was increased by progressive infusion. The solid lines represent the trends for six control dogs, and the broken lines represent the trends for ten dogs with varying degrees of congestive heart failure. The open symbols represent the actual number of spikes observed per cycle for the different members of the experimental group. The closed symbols are for the control dogs. See also Fig. 5.

B: Plot of the same data shown in A calculated as spikes per second.

The curves reached approximately 20-30 spikes/cycle before turning over between 7 and 10 cm H$_2$O. Thereafter they ran horizontally, dropping off slightly at pressures between 30 and 40 cm H$_2$O.

Figure 3B presents the data from experimental dog 4 in the format used in Figure 3A to present control data. This fiber also had atrial type B characteristics, firing after the onset of the systole as indicated by the QRS complex in the electrocardiogram and by the aortic pressure curve. The central venous pressure was already elevated to about 10 cm H$_2$O, and it approximately doubled with the infusion of 30% of the estimated blood volume. However, the firing rate per cycle was not quite doubled nor was there any further significant increase when the total infusion was increased to 50%. Data from this dog appear in Figure 4 also (open circles with flags).

The overall response to volume expansion shown by the set of curves obtained from the nine successful experimental preparations and the one case of spontaneous heart failure appears in Figure 4. The response differed sharply from that in the control dogs. We took a resting central venous pressure in excess of 7 cm H$_2$O as the arbitrary criterion for successful operative interference. Nevertheless, the mean initial resting spike frequency was actually lower than that in the controls. Although the curves for the individual dogs varied in slope, only four infringed on the lower range of the control data, and there were six flat curves which failed to exceed 12 spikes/cycle even at central venous pressures of 20–30 cm H$_2$O. The data in Figure 4A are presented in their simplest, most direct form as spikes per cycle and demonstrate that the distinction between control and experimental dogs was not due to some change in heart rate as the infusion progressed. However, the significance to the organism of the flow of information from the receptors is probably more closely related to the spike frequency per unit time (21), and Figure 4B presents such plots. The new format resulted in changes in the shapes of the control curves because of some sharp variations in heart rates. However, the general distribution remained the same, i.e., the data from experimental dogs continued to occupy the lower right hand quadrant of the diagram and that from the controls arched over them.

In Figure 5, the data from Figure 4A are presented in condensed form. The central venous pressures for 5-cm H$_2$O increments from zero upwards were grouped together and their means were plotted as single points. The value of these points on the ordinate was determined by taking the mean of the atrial spike data that had been included in that particular 5-cm H$_2$O step, and the standard error was then determined.

![Figure 5](http://circres.ahajournals.org/)

Frequency of atrial receptor discharge in spikes per cycle plotted against mean central venous pressure observations grouped in increments of 5 cm H$_2$O. (See Fig. 4A and B.) Broken line = experimental group, solid line = controls. Vertical and horizontal bars indicate ±SE.
Student’s t-test was used to compare the groups that had opposing sets of data, i.e., the six increments of venous pressure from 5 to 10 cm H$_2$O to 30 to 35 cm H$_2$O. In the first two, $P < 0.001$, and in the remainder $P < 0.01$. Thus, there was a sharp dichotomy between the control and the experimental data.

The effects of blood volume reduction in four control dogs are compared with those in three experimental dogs in Figure 6A. In the controls a sharp fall in the number of spikes per cycle continued until the abscissa was reached, i.e., until the units ceased firing because of the gross reduction in atrial stretch. Inspection shows that the slopes of the curves for the three experimental dogs were less than those for the controls.

In Figure 6B, in which the data from Figure 6A are presented as spikes per second, the slopes of the curves for the experimental dogs were not changed much because of the relative consistency of the pulse rate. However, the sharp cardioacceleration in the normal control dogs, in response to blood volume loss resulted in a significant decrease in the slope of two of the control curves. The data nevertheless still point to a different flatter slope for the experimental dogs.

**Discussion**

**CARDIOVASCULAR RESPONSES**

The rate at which central venous pressure increased with progressive volume expansion and decreased with blood volume loss was essentially the same in dogs experiencing heart failure and in normal control dogs. The major difference was that the curves for dogs with cardiac intervention were displaced upwards (Fig. 1). The question might be raised whether left atrial pressure was elevated in experimental dogs with right heart intervention. On the one occasion when left atrial pressure was followed in an experimental dog, it was elevated both during rest and after infusion. At the routine autopsies the left atria of the experimental dogs were distended and tense. Furthermore, our receptor results were consistent with and supportive of the hormonal data of Zehr et al. (13). In their studies the left heart was directly affected by induction of mitral stenosis. Finally both sides of the heart were involved in our single case of spontaneous heart failure. This dog had a severely impaired receptor response, as can be seen from the lines of open diamonds in Figure 4A and B. From this evidence we would anticipate that pulmonary vascular pressure and left atrial pressure would be elevated when blood volume is increased and overt congestive heart failure occurs and that it would rise still further with massive infusions.

Tricuspid avulsion can lead to a large atriovenous pressure wave due to regurgitation of blood during ventricular contraction. A significant proportion of the observed elevation in mean central venous pressure might have been due to this reflux. Although such a pressure wave could on occasion be recognized, it was not large enough to affect mean pressure significantly. An attempt was made to identify whether the fibers from which recordings were being taken were emanating from receptors in the right or the left atrium. One method was to note the time taken to respond to the sudden infusion of a small bolus of saline into the right atrium. The evidence from this test suggested that the fibers derived from both sides in approximately equal numbers. Those that appeared to be of right atrial origin were studied for any
large burst of atrial action potentials during ventricular systole. In practice only two or three spikes occurred at this point in the cardiac cycle with the majority having the late systolic to early diastolic timing that corresponds to the atrial filling wave. It is thought that reflux was minor, because the extent of intervention with the tricuspid valve was limited and reliance was placed on the added pulmonary artery stenosis to provide the final needed level of cardiac embarrassment. In the example shown in Figure 3B from the records for experimental dog 4, there were no spikes at the time of ventricular systole. It is probable that this fiber was located in the left atrium.

RECEPTOR RESPONSES

As described in Methods, we followed the earlier criteria of Paintal (10, 17), but not those most recently published (22), for the identification of atrial fibers. The location of the fibers was not verified by postmortem local mechanical stimulation, but the evidence indicated that most of the fibers carrying large spikes and identifiable by the criteria outlined earlier were derived from the receptors described by Nonidez (4) and studied by Paintal (22) as atrial type B fibers. The Nonidez receptors are located in the atrial subendocardium in the area of the great veins, and their distribution between the two atria is approximately uniform. Since both vagi carry mixed traffic from the right and left atria, the probability is good that our total of ten dogs provided some fibers from the right atrium and some from the left atrium. Our identification data suggested that in fact they were approximately equally divided. Spikes carried by the nonmedullated fibers studied by Öberg and Thorén (9) are distinguished by their small size, the timing of their discharge, and their response to cardiovascular events.

The curves relating venous pressure to the number of spikes per cycle attained a maximum and then in some cases actually declined with further infusion as the chambers became over-distended (Figs. 4A and 5). Relying on information from externally applied mercury-rubber strain gauges instead of the endocardial receptor network, Eliahou et al. (15) also found a turnover point in dogs subjected to acute overtransfusion. The work of Payne et al. (16) with sonomicrometers installed in the left atrium provided a more accurate comparison of mean left atrial pressure and changes in atrial size during diastolic filling. These researchers presented a measure of left atrial systolic diameter shortening and showed not only that, as the atrial pressure increased to between 20 and 40 cm H2O, the diastolic atrial filling wave decreased to the vanishing point but that the atrial diameter increased less and less with each further increment in pressure (16). This description of the mechanical responses of the atrial wall was important for the present work. The parallelism between the mechanical events during gross distention with progressive overtransfusion and the pattern of atrial spikes per cycle observed in the present study demonstrated that there was an optimal range of pressure for the response of these receptors. This optimum would appear to be at no more than 5-10 cm H2O above resting atrial pressure. Despite the higher pressure in the dogs suffering from cardiac intervention, the arithmetic mean of the resting values of spikes for each heart beat was less (6 spikes/cycle) than it was for the control dogs (10 spikes/cycle). One possible mechanism of this change in receptor response could have been that the altered cardiac sympathetic drive in heart failure affected the discharge. Tachycardia is evidence for this change in drive. A part of the change could have been due to structural alterations in the wall leading to a "resetting" of the receptors in association with the sustained increase in stretch of the atria. Such changes are known to occur in association with the baroreceptors in the course of hypertension (23, 24).

A possible cause of changes in atrial firing rate could have been a failure of pressure transmission across the atrial wall in the dogs with heart failure. It could be that beyond a certain increment in central venous pressure there is no further stretching of the atrial wall because the distended heart chambers are subject to tamponade by the pericardium. But in fact, transmural pressure increased throughout the pressure range studied, remaining at more than half the total pressure differential between the vein and the surrounding atmosphere (Fig. 2). Hence, although there was a decreasing percent elongation of the atrial walls as the distending pressure increased, this elongation with its concomitant progressive distortion of the sensing elements never actually ceased. Furthermore, in two cases, the pericardium was left open following the operation on the heart without eliminating the decrement in receptor response.

Recently Zehr et al. (13) reported on the blood levels of ADH following nonhypotensive hemorrhage in dogs with chronic mitral stenosis. Although the ADH levels increased significantly in both
normal and experimental groups, there was a marked attenuation of this increase in the dogs with mitral stenosis in spite of a fall in atrial pressure that was twice as severe. Our blood volume loss observations confirmed their report of a decrease of 12 cm H2O in mean atrial pressure in dogs with cardiac intervention as compared with 5 cm H2O in normal dogs. Hence, the limited observations presented in Figure 6A and B suggesting a decrease in the falling off of atrial spikes per cycle and to a lesser degree of spikes per second in the dogs with cardiac intervention are consistent with, and indeed help to explain, their results (13). Furthermore, the data of Payne et al. (16) showed that in animals with an elevated atrial pressure the chamber walls are already stretched. Consequently, it is necessary to make a larger change in pressure to achieve the same change in firing rate of the atrial receptors.

In three cases, the atrial receptors scarcely responded to the increasing pressure despite the fact that each dog had a resting venous pressure of no more than 8 cm H2O. This pressure represented a point at which the curve relating spikes per cycle to atrial pressure in the normal dog had not yet reached the stage at which further response was lost. On the other hand, the response of the atrial receptors of the experimental dogs was decreased during volume loss, and considerable falls in central venous pressure were accompanied by little alteration in firing rate (Fig. 6A). These points lead to the idea that, as Zehr et al. (13) have in fact shown, the receptor sites themselves can deteriorate. They reported an endocardial fibrosis which buried the fine networks deep in hypertrophied tissue. They suggested that this change from the normal superficial location of the receptors could lead to a loss of sensitivity.

Working with cats, Arndt et al. (25) presented evidence that atrial type A receptors retain remarkably constant firing patterns despite increases or decreases in blood volume. Since we are reporting impaired fiber response to blood volume changes in congestive heart failure, the question of fiber identification arises. Type A fibers are easily identified. They fire with a few spikes at the time of the a wave of the venous pressure curve, that is, just after the P wave of the electrocardiogram. Furthermore, although atrial A and B fibers are present in the cat in approximately equal numbers, A fibers are rare in the dog and the ratio is 1:15 (22). These two factors support our belief that our vagal action potentials derived from type B atrial receptors.

The responses of other cardiac receptors could be affected by the changes occurring during heart failure. The complex unencapsulated endings of atrial receptors described by Nonidez and Paintal as atrial type A and B are not the only sources of afferent impulses from the heart (5). It has been suggested that the end nets in the atrial walls and the ventricular walls could also have a receptor function (5). Such structures could be affected by the changes occurring during heart failure. This effect is important because, in their studies of the effects of water immersion on renin-aldosterone levels and renal sodium handling in normal man, Epstein and Saruta (26) suggested that these particular cardiac receptors could be involved. In related work Thames et al. (27) and Goetz et al. (28) reached similar conclusions.

It is relevant that Oberg and his co-workers (8, 9) reported left ventricular receptor signaling in nonmedullated vagal afferents that might have a volume regulatory effect and influence the renal vascular bed and that Clement et al. (29) showed that vagal afferents are involved in the control of renal sympathetic nerve activity in response to changes in blood volume. Furthermore Gorfinkel et al. (30) reported that renal blood flow was not reduced in cardiogenic shock but did fall with decreased heart chamber size in hemorrhagic shock.

The data presented in this paper showed that the firing patterns of the classical atrial type B receptors described by Nonidez (4) and Paintal (22) were impaired in congestive heart failure. We do not know whether the response patterns of the other nerve elements, such as the subendocardial plexus recently described in the ventricle by Mikhail (31), were also disturbed. But if they were, then the combined effects could go far in explaining the reduction in electrolyte and fluid excretion in this condition.

References


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