

The Mechanism of Adaptation of Left Atrial Stretch Receptors in Dogs with Chronic Congestive Heart Failure

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ABSTRACT Chronic congestive heart failure (CHF) was induced in dogs by the construction of an aorto-caval fistula below the level of the renal arteries. Aorto-caval fistula dogs showed signs of CHF which included ascites, hind limb edema, and pulmonary congestion. Ventricular catheterization indicated a significantly higher left ventricular end diastolic pressure and lower maximum velocity of left ventricular pressure development/left ventricular end diastolic pressure in CHF dogs when compared to sham-operated controls. Heart weight/body weight ratios were significantly higher in CHF dogs. Electrophysiological recordings from medullated left atrial type B receptors from the cervical vagus indicated a depressed sensitivity of these receptors in CHF dogs when compared to sham-operated control dogs. For any given change in left atrial pressure, the discharge of left atrial receptors was significantly reduced in CHF dogs compared with sham-operated controls. The mechanism for this depressed sensitivity was investigated. Sonomicrometry of the left atrial appendage indicated a decreased compliance of the left atrial appendage in the dogs with chronic CHF. In addition, microscope examination of the complex unencapsulated receptor endings taken from the left atrial endocardium indicated a marked alteration in receptor morphology. A loss of the end arborization was the most typical finding. It is concluded that chronic CHF brought about by an aorto-caval fistula results in a depressed left atrial stretch receptor response and that both decreased left atrial compliance and

structural alterations in the receptor endings may account for this depressed sensitivity.

INTRODUCTION

Alterations in salt and water metabolism during congestive heart failure (CHF)¹ are well known sequelae of this disease process (1-4). The etiology of the altered fluid balance in CHF can be attributed to both hemodynamic (1, 3, 5, 7) and hormonal factors (4, 8-11). Evidence has been presented by several investigators that the secretion of antidiuretic hormone (ADH) may be altered during CHF or related disease states (12-19).

Wood (20) suggested in 1963 that the polyuria which often accompanies attacks of paroxysmal atrial tachycardia may be related to the activity of left atrial stretch receptors. He noted that the polyuria was absent in patients with chronic heart failure or mitral valve disease.

Although the response of atrial stretch receptors has been studied under a variety of acute situations (21-29), little is known about the discharge properties of these receptors under conditions in which the atria are chronically distended. Greenberg et al. (30) demonstrated a depressed electrophysiological response of atrial stretch receptors in dogs with tricuspid avulsion and pulmonary artery stenosis. They concluded that in CHF, impairment of salt and water homeostasis is due, at least in part, to a decrease in type B atrial receptor sensitivity. No attempt was made in their study to delineate the mechanism of altered discharge

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¹Abbreviations used in this paper: ADH, antidiuretic hormone; A-V, aorto-caval; CHF, congestive heart failure; dp/dt max, maximum velocity of left ventricular pressure development; LVEDP, left ventricular end diastolic pressure.

responsiveness nor were adequate sham-operated controls employed.

Because of the potential clinical importance of atrial receptors in the control of salt and water balance, we decided to investigate receptor discharge during chronic CHF in the dog. Using a model of high output cardiac failure, left atrial stretch receptor activity was analyzed electrophysiologically. We also undertook a study of atrial receptor morphology and atrial compliance in an attempt to ascertain a possible mechanism by which atrial receptor sensitivity is altered.

METHODS

Mongrel dogs of either sex averaging 20.3 ± 0.63 kg in weight were used. They were anesthetized with intravenous pentobarbital sodium and divided into two groups. Group I consisted of 11 dogs which survived the establishment of an aorto-caval fistula below the level of the renal arteries whereas group II consisted of 8 dogs which were sham-operated.

A laparotomy was performed under sterile conditions, the intestines retracted, and the abdominal aorta and inferior vena cava dissected and isolated. After clamping the aorta and vena cava, an oval window varying in length between 10 and 15 mm was cut in each vessel, and anastomosed using 5-0 Ethaflex suture (Ethicon, Inc., Somerville, N. J.). The vessels were occluded between 20 and 30 min. Sham-operated dogs were subjected to an identical procedure except that each vessel was opened and sutured closed without establishing an anastomosis. After surgery, each dog was treated with 1.2 million U of Wycillin (Wyeth Laboratories, Philadelphia, Pa.) intramuscularly for 3 days. Of those animals in group I which survived the first 24-h recovery period, the postoperative recovery course was uneventful except for the slow development of CHF. All animals in group II survived with an uneventful postoperative course. Animals were weighed daily and checked for signs of pulmonary congestion, ascites, and peripheral edema. Animals were housed in outdoor runs adjoining indoor cages, and fed standard lab chow and given water ad lib.

Before surgery, a left ventricular catheterization was performed. A high gain recording of left ventricular end diastolic pressure (LVEDP) and the maximum velocity of left ventricular pressure development (dp/dt max) were obtained. A similar catheterization was done at the time the acute experiment to be described below was performed. Cardiac output was measured by thermal dilution using the IL 601 cardiac output computer (Instrumentation Laboratory, Inc., Lexington, Mass.) with a 5-French, flow-directed catheter in seven animals before surgery and at the time of the acute experiment.

When clinical signs of CHF were evident in the dogs of group I and after a similar length of time for the dogs in group II, each animal was prepared for recording atrial receptor activity as described by us previously (25). A transverse thoracotomy was performed in the fourth intercostal space. The animal was placed on positive-pressure respiration using room air supplemented with 100% oxygen. Left atrial pressure was measured using a catheter-tipped transducer (Millar, Houston, Tex.) placed into the left atrium through a small pulmonary vein. Aortic pressure was similarly recorded in the ascending aorta via a femoral artery.

Left atrial contractile force was measured using a Walton-Brodie strain gauge arch sutured to the left atrial appendage. A standard limb lead ECG was also recorded. Blood gases were periodically monitored (Radiometer Co., Copenhagen, Denmark) and kept within normal limits. The left cervical vagus was isolated, placed upon a black plastic platform under warm mineral oil, and desheathed. Slips of the vagus were cut centrally and placed upon bipolar platinum-iridium recording electrodes. The neural activity was appropriately amplified and the fiber continuously split until a recording was obtained from a single unit.

Each receptor was identified initially as an atrial receptor by its discharge pattern in relation to the aortic and left atrial pressure pulse, the ECG, and left atrial contractile force tracing. The response to occlusion of the aortic root and pulmonary artery further identified the receptor as being in the left or right atrium.

When the activity from an atrial receptor was identified, left atrial pressure was increased by intravenous infusion of warm isotonic saline in 50-ml increments. Recordings were taken continuously during volume expansion. Usually two volume expansions were performed for each receptor. The animal was hemorrhaged back to the control left atrial pressure between the first and second volume expansions.

The conduction velocity was measured in several animals as follows: at the conclusion of the experiment, stimulating electrodes were placed around the left vagus in the chest above the heart while recording from the unit in the neck. The vagus was stimulated at a frequency far in excess of the natural frequency of the receptor. Since several units were usually evoked by this stimulation, a fast oscillographic trace indicated which of the several evoked potentials became occluded as the natural and stimulating pulses collided. The latency between stimulus artifact and evoked potential was calculated as the conduction time. A length of thread placed along the nerve between the stimulating and recording electrodes was measured to obtain the conduction distance. After determination of conduction time, the animals were bled, the heart opened, and the last receptor recorded from in each animal was localized by punctate probing. In some animals two receptors were studied. The first receptor was localized using vessel occlusion and selective probing in the beating heart. 16 receptors were studied in the 11 CHF dogs and 14 receptors were studied in the 8 sham-operated dogs.

Receptor discharge was counted directly from the oscillographic recording (Visacorder 1858, Honeywell, Inc., Minneapolis, Minn.) and atrial and aortic pressures were analyzed from the original record. The change in receptor discharge was correlated with the change in left atrial peak v wave pressure for spikes/cardiac cycle and spikes/minute with the use of an IBM 1800 computer program (IBM Corp., White Plains, N. Y.). Student's *t* test and regression analyses were employed for statistical evaluation.

Measurements of left atrial appendage diameter were obtained in four animals using 5 MHz piezoelectric crystals (kindly supplied by Dr. H. L. Stone, University of Texas at Galveston) which were sutured on to the left atrial appendage as close to the body of the atrium as possible. The ultrasound transit time between the crystals was measured using a sonomicrometer (kindly supplied by Dr. A. M. Scher, University of Washington at Seattle). The change in left atrial pressure was plotted against the left atrial appendage diameter. The slopes of the regression equation for these points were compared for sham-operated and CHF dogs.

At the end of the experiment the heart was removed, washed in saline, blotted, and then weighed. Blocks of

cardiac tissue, including the junction of the pulmonary vein and the left atrium, were stained with methylene blue according to the Schabadasch procedure as described by Mitchell (31). The tissue samples were coded so that the histologist did not know from which group of dogs they had been obtained. Frozen, tangential sections of endocardium were cut at 40 μ m. Sections were mounted on slides using gelatin-alcohol (32), dehydrated, and then covered to facilitate microscope examination.

RESULTS

The average length of time from establishment of the aorto-caval shunt to the recording of receptor activity from the dogs in group I was 57.8 ± 7.6 days and 31.5 ± 3.5 days for the dogs in group II. All CHF dogs showed signs of either ascites or peripheral edema and severe pulmonary congestion. All dogs in group II appeared healthy with no signs of ascites, edema, or pulmonary congestion.

Table I compares the hemodynamic data of CHF and sham-operated dogs. Some of the parameters shown in Table I were obtained from aorto-caval (A-V) fistula or sham-operated animals which were not used for recording atrial receptor discharge. LVEDP was significantly elevated in CHF dogs,

whereas mean aortic pressure was significantly lower in the CHF group. dp/dt max and dp/dt max/LVEDP were used as indices of contractility. Although dp/dt max was not significantly different in the two groups of dogs, dp/dt max/LVEDP was significantly altered, being greatly reduced in the CHF dogs. Postmortem heart weights were significantly heavier in CHF than in sham dogs, indicating some degree of cardiac hypertrophy. Heart shadows analyzed from X rays taken before and after establishment of the A-V fistula in two dogs showed marked cardiac dilatation. The data presented in Table I along with the clinical data observed, describe a picture of chronic cardiac dilatation and hypertrophy with a decrease in contractility.

Fig. 1 illustrates the response of a type B left atrial receptor in a CHF dog (top) and a sham-operated dog (bottom). Panel A represents the control state, and panel B the volume-expanded state. In the CHF dog, resting left atrial pressure is high and aortic pulse pressure is elevated due to the low resistant A-V fistula. Atrial receptor discharge occurs during atrial filling (v wave of the atrial pulse) and ceases before atrial contraction. In the CHF dog

TABLE I
Hemodynamics of CHF and Sham-Operated Dogs

	CHF	Sham	
Body weight, kg	$20.0 \pm 0.96^*$ (11)†	20.6 ± 0.73 (8)	NS
Heart weight, g	212.7 ± 10.8 (11)	152.0 ± 7.2 (8)	$P < 0.0005$
Heart weight/kg body weight	10.8 ± 0.66 (11)	7.4 ± 0.35 (8)	$P < 0.0025$
Mean arterial blood pressure, mm Hg	98.3 ± 6.8 (11)	121.4 ± 7.2 (8)	$P < 0.025$
LVEDP, mm Hg	24.4 ± 8.6 (7)	4.8 ± 0.93 (6)	$P < 0.025$
dp/dt max, mm Hg/s	$2,150.8 \pm 206.6$ (7)	$1,920.7 \pm 130.8$ (6)	NS
dp/dt max/LVEDP, per s	90.5 ± 16.3 (6)	659.5 ± 282.4 (6)	$P < 0.05$
Cardiac output			
Before A-V fistula or sham operation, liters/min	2.80 ± 0.81 (5)	2.53 ± 0.31 (2)	NS
After A-V fistula or sham operation, liters/min	4.37 ± 0.83 (5)	1.92 ± 0.26 (2)	$P < 0.0025$

* ± 1 SEM.

† Numbers in parentheses refer to the number of animals on which each measurement was made.

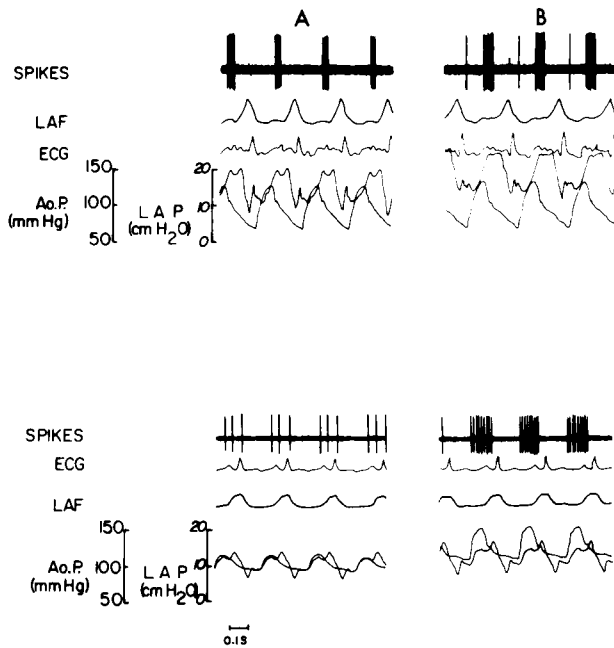


FIGURE 1 Recording of a type B left atrial receptor from a CHF dog (top) and from a sham-operated dog (bottom). SPIKES, neurogram; LAF, left atrial force tracing; ECG, electrocardiogram; Ao.P., aortic pressure; LAP, atrial pressure.

depicted in Fig. 1, control atrial receptor discharge is 5 spikes/cardiac cycle. After raising left atrial pressure by approximately 5 cm H₂O (from 20 to 25 cm H₂O), atrial receptor discharge increased to 10 spikes/cardiac cycle. The sham-operated dog depicted in Fig. 1 had a control left atrial pressure of about 12 cm H₂O, and atrial receptor discharge increased from 3 to 9 spikes/cardiac cycle, with an increase in left atrial pressure of only 2 cm H₂O. The control left atrial pressures shown in Fig. 1 and those recorded in each animal are not necessarily the control left atrial pressures which existed in the closed-chest animal. Since various amount of fluid were administered to each animal in the process of identifying the volume responsiveness of the units isolated, it is felt that the LVEDP obtained in the closed-chest, nonfluid-loaded animals (Table I) is a better indication of the true resting left atrial pressure. The mean change in discharge/cardiac cycle versus the mean change in left atrial v wave pressure is shown in Fig. 2. Note that for any given change in left atrial pressure, the sham-operated dogs had a substantially higher change in discharge when compared to the CHF dogs. These two curves are significantly different from each other at each point depicted. Conduction velocity was measured in five fibers, four from CHF animals and one from a sham animal. Mean conduction velocity was 18.9 ± 2.9 m/s (range

9.8–25.8 m/s for all fibers, agreeing with previous values obtained by Paintal (33) for myelinated type B atrial receptors.

Fig. 3 shows the relationship between left atrial appendage diameter and the change in left atrial filling pressure over a wide range of pressures. Two normal dogs are compared with two CHF dogs. The slope of the regression lines for the two normal dogs and the slopes of the regression lines for the two CHF dogs are not significantly different from each other. However, the common slopes for the two normal animals are significantly different from the common slopes of the two CHF animals ($P < 0.001$) using a *t* analysis for the comparison of slopes (34).

Fig. 4 shows six representative receptors from sham-operated (A) and CHF dogs (B). The receptors from sham-operated dogs show the characteristic complex unencapsulated endings originally described by Nonidez (35). Each ending appears as an arborization extending as a ball-like structure from its axon. In contrast, the endings obtained from CHF dogs show a loss of the typical complex unencapsulated ending seen in the normal or sham-operated dog. The axons appear prominent but the ball-like arborization is either completely absent or appears as compressed and disoriented structures. A receptor ending such as those displayed here from the sham-operated group was never seen in any CHF dog.

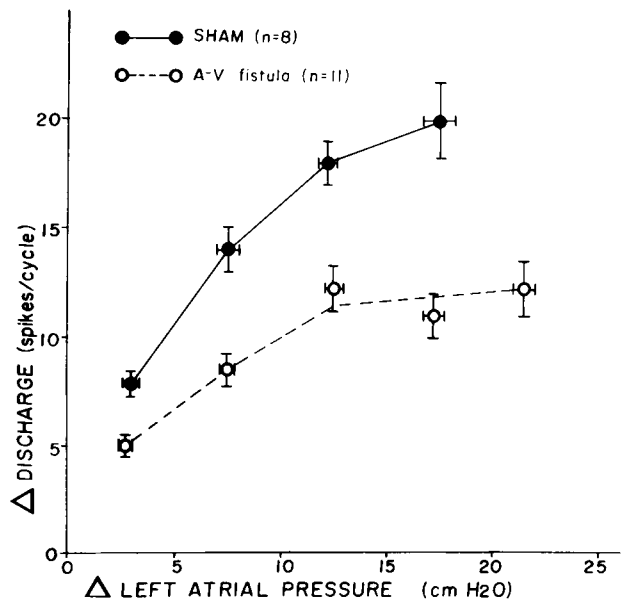


FIGURE 2 The relationship between the change in discharge in spikes/cardiac cycle and the change in left atrial peak v wave pressure. ●—●, sham-operated dogs; ○---○, CHF dogs. Vertical and horizontal bars are \pm SEM. The data has been accumulated on 16 receptors from 11 CHF dogs and 14 receptors from 8 sham dogs.

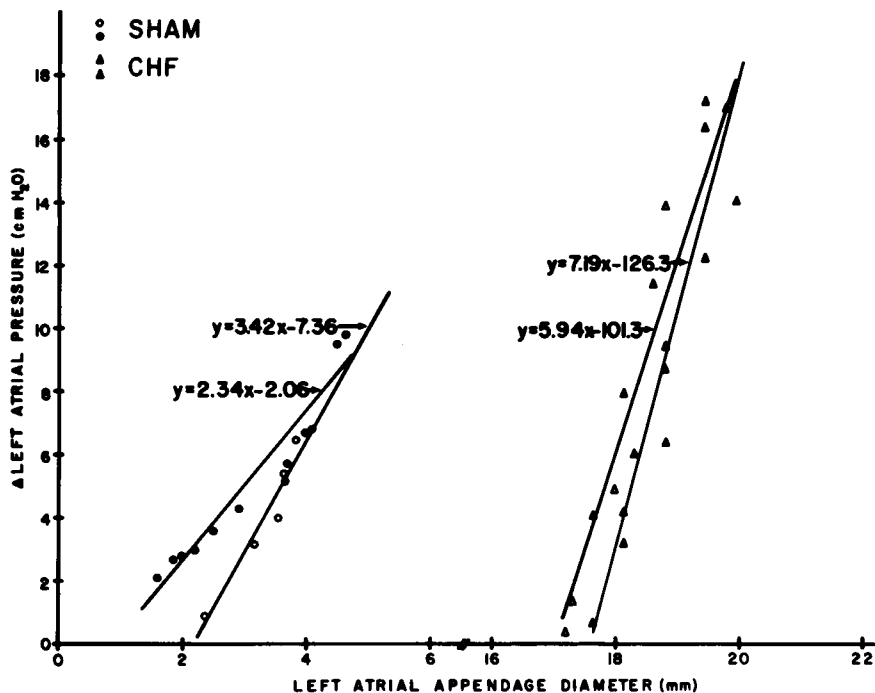


FIGURE 3 The relationship between the change in left atrial end diastolic (peak v wave) pressure and the diameter of the left atrial appendage. (Circles represent two separate sham-operated dogs; triangles represent two separate CHF dogs).

DISCUSSION

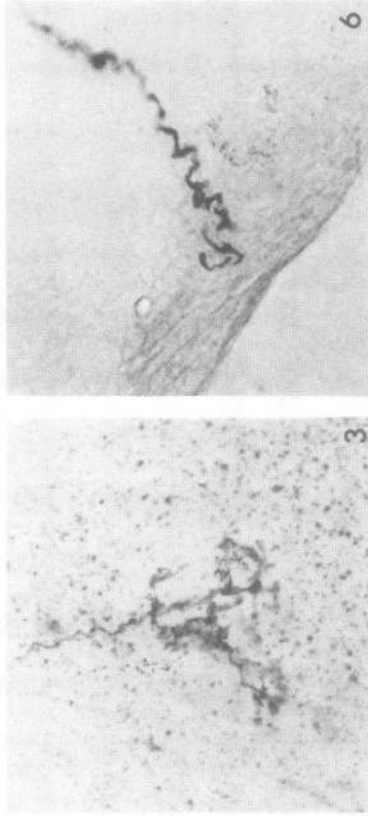
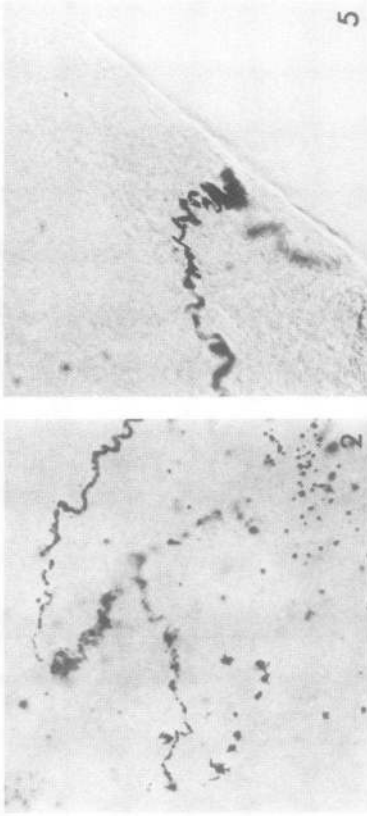
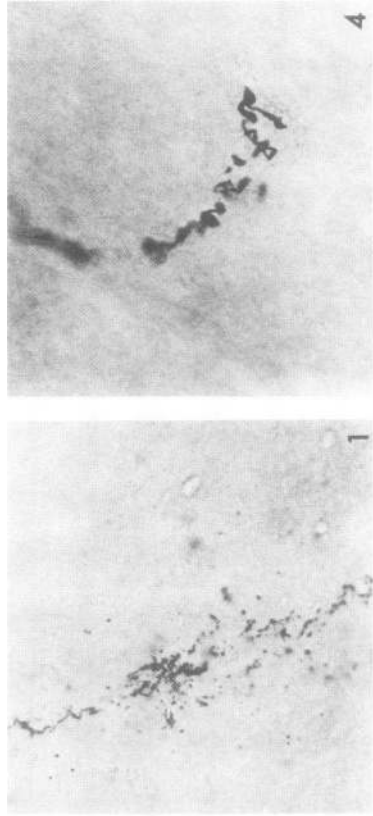
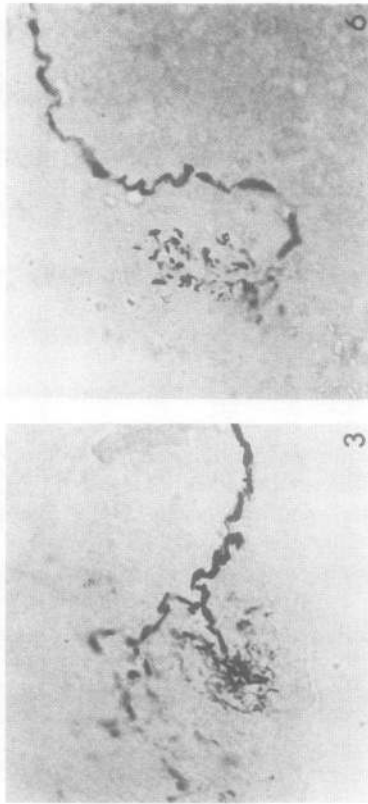
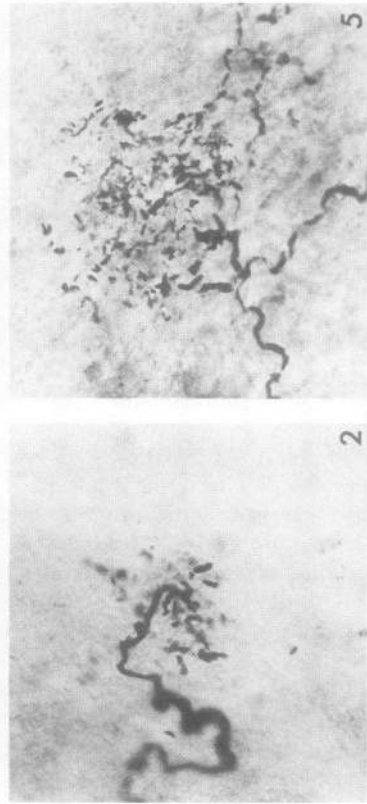
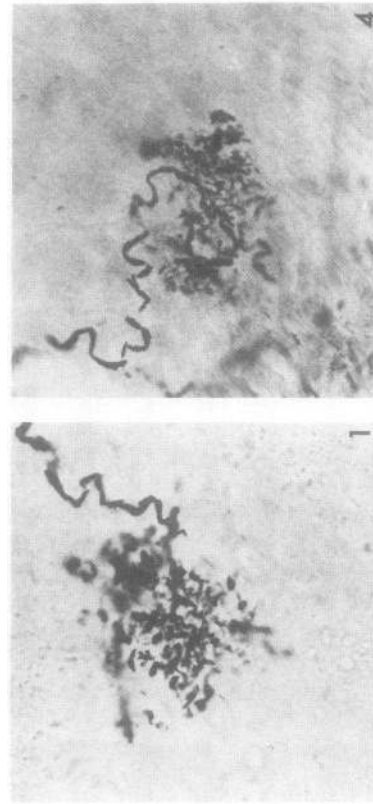
The A-V fistula model used in the present experiments resulted in the production of consistent CHF as evidenced by the high LVEDP, cardiac hypertrophy, and dilatation as well as the clinical evidence cited previously. In addition to the hemodynamic alterations presented here, the animals in the present study were retaining sodium markedly and were unable to excrete a volume load (unpublished observation).

In the present experiment, the ability of left atrial stretch receptors in CHF dogs to respond to elevations of left atrial pressure was reduced compared to sham-operated controls (Figs. 1-2). We have previously demonstrated (25) an exquisite sensitivity of left atrial stretch receptors in the dog. This sensitivity was not reduced by acute induction of heart failure produced by administration of propranolol or pentobarbital sodium or by acute coronary artery occlusion (26).

The present experiments extend the findings of Greenberg et al. (30). Their studies showed a depressed atrial receptor responsiveness to increases in central venous pressure during volume expansion in dogs with tricuspid avulsion and pulmonary artery stenosis as compared to normal dogs. Sham-operated controls were not used in the above study so that

the nonspecific effects of surgery could not be ruled out as a causative factor. In addition, no attempt was made to locate the receptors from which these workers recorded. Although the mechanism of the depressed atrial responsiveness was not investigated, the authors indicated that a possible explanation is the failure of the atrium to stretch beyond a certain point because of pericardial tamponade. This obviously cannot be a causative factor in the decreased sensitivity of atrial receptors in the present experiments since our dogs were open chest with the pericardium removed at the time atrial receptor activity was recorded. Greenberg et al. (30) also raise the possibility that altered sympathetic drive in CHF might have influenced the sensitivity of atrial receptor discharge. Again, we must reject this hypothesis since we have previously shown that efferent cardiac sympathetic nerve stimulation has no direct effect on type B left atrial receptor discharge (24).

One obvious mechanism by which the sensitivity of left atrial stretch receptors can be reduced in CHF is by loss of atrial compliance. Zehr et al. (19) reported that ADH levels fail to rise when dogs with experimental mitral stenosis were subjected to a non-hypotensive hemorrhage. Histological sections of the left atrium indicated endocardial hypertrophy and ossification. The consequence of these changes would most likely be a stiffer and less compliant atrium.



50 μ m

50 μ m

Using Whitney strain gauges Eliahou et al. (36) demonstrated a decrease in atrial pulsation at a high filling pressure. These observations were confirmed by Payne et al. (37) using sonomicrometry. Paintal has suggested that atrial stretch receptors respond to the amplitude or atrial pulse pressure rather than the peak or static pressure reached during atrial filling (21). We could not confirm this finding in our previous work which showed that the best correlate to type B atrial receptor discharge is the peak v wave pressure (25). This is in agreement with the study of Arndt et al. (38) who could demonstrate a velocity component to atrial receptor discharge only at high levels of stretch and at rapid frequencies of stretch *in vitro*. Even though atrial pulsations decrease with progressive volume expansion (37), the static levels of atrial stretch also increase and one would expect receptor discharge to increase up to some plateau as indeed it does in the normal animal. Payne et al. (37) plotted the relationship between left atrial end diastolic diameters and the change in the left atrial pressure for two conscious dogs on two separate occasions. At low end diastolic diameters the change in left atrial end diastolic pressure was low and it increased sharply at high end diastolic diameters. One would expect that at a high atrial end diastolic diameter the compliance of the atrium would be diminished.

In the present experiments, sonomicrometry of left atrial appendage diameter in two thoracotomized, sham-operated dogs and two thoracotomized CHF dogs indicated that the appendage was less compliant in the CHF dogs compared to the sham-operated dogs (Fig. 3). This diminished compliance could explain the high left atrial pressures and the altered receptor discharge in CHF.

In a recent study published in Russian, Anjuhovskij et al. (39) observed a depression of right atrial type-B receptor discharge in cats with CHF due to pulmonary artery stenosis. Based upon pressure diameter measurements of the right atrium, these workers concluded that the depression of receptor discharge was most likely brought about by a decrease in right atrial compliance, an observation essentially confirmed in the present investigation.

Several groups have recently described the response of atrial stretch receptors whose activity travels up small diameter (c fiber) fibers in the vagus nerve. These fibers have low conduction velocities (less than 2 m/s) and are relatively unresponsive to changes in atrial pressure (40, 41). Since we measured conduction velocity in several fibers and all were far above 2 m/s and averaged very close to

that reported for myelinated atrial receptors by others (21), it does not appear that we were selectively recording from c fibers in our CHF dogs.

The study of Greenberg et al. (30) eludes to the fact that a change in the sensitivity of atrial receptor discharge could have come about by a structural resetting of receptor endings. A precedence has been established for morphological alterations in cardiovascular stretch receptors under sustained stretch by the work of Angell-James (42). She found degeneration and fragmentation of aortic baroreceptor endings in several rabbits with sustained renal hypertension. These results confirm those of Ábrahám (43) and Hilgenberg (44). In the present study, vital staining of left atrial receptors indicated similar degeneration and fragmentation of the receptor ending in CHF. The chronic stretch that these endings were subjected to is a similar condition to the sustained hypertension of the aortic baroreceptor studies cited above. The histology of the receptor endings from our sham-operated dogs is similar to that described in a variety of species by Miller and Kasahara (45). The morphology of atrial receptors in the human described by Johnston (46) is similar to that seen in the present study for the CHF group of dogs; that is, the distinct end arborization is absent and the endings appear more diffuse than those described by Miller and Kasahara for monkey, dog, cat, and lamb (45) and those observed in the sham-operated group in the present study. Although Johnston used post-mortem material, he did not state whether or not any cardiac pathology was present in these patients, an important consideration in view of the present findings. Diffuse endocardial nerve nets have also been described in the atrium (45, 47). The receptors that we observed in the dogs with CHF do not have the interlacing appearance characteristic of nerve end nets. It is therefore most likely that the endings shown in the present experiments are single degenerated unencapsulated left atrial receptors.

Since the secretion of ADH under normal conditions appears to be in part governed by mechanoreceptors located on both the high and low pressure side of the circulation (48–53), alterations in the activity of these receptors could potentially alter the secretion of ADH.

Cardiac dilatation and hypertrophy are the hallmarks of both high and low cardiac output chronic CHF. According to the schema proposed by Gauer and Henry (54) and others, increased left atrial pressure increases left atrial stretch, thereby stimulating left atrial stretch receptors of the type first described by

FIGURE 4 Light micrographs of left atrial receptors from sham-operated dogs (A) and from CHF dogs (B).

Nonidez (35) and subsequently characterized by many others (45–47). The increased activity of these receptors would enter the brain via the vagi and reflexly inhibit the release of ADH, thereby increasing water excretion, which in turn would cause a decrease in plasma volume returning left atrial pressure to normal. In addition to the modulation of ADH secretion, enhanced left atrial stretch receptor activity has been shown to depress renal efferent sympathetic nerve activity (55, 56), an effect that would increase renal blood flow and glomerular filtration rate, thereby enhancing the ability of the kidney to reduce plasma volume. In spite of the potent stimulus on left atrial stretch receptors in CHF, ADH titers remain high and renal blood flow remains low (12, 14–19).

It is concluded from the present study that the decreased sensitivity of left atrial stretch receptors in dogs with CHF is the result of alterations in atrial compliance and of morphological changes in the receptor endings themselves. Atrial receptor adaptation may be responsible for the inappropriately high plasma ADH levels and may contribute to the peripheral edema, ascites, and hyponatremia often seen in patients with chronic CHF.

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