Carotid Sinus Baroreceptor Sensitivity in Experimental Heart Failure

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Single-unit carotid sinus baroreceptor activity was recorded in normal and heart-failure (pacing-induced) dogs. The sensitivity of these units was compared between the two groups of dogs. After development of clinical heart failure, the animals were anesthetized, and the left carotid sinus was vascularly isolated and perfused with oxygenated Krebs-Henseleit solution. Single-unit baroreceptor discharge was recorded from the carotid sinus nerve in response to stepwise increases in carotid sinus pressure (CSP). In addition, the carotid sinus diameter was measured with sonomicrometer crystals. In this way, both CSP-discharge and CSP-diameter curves were constructed for both normal and heart-failure dogs. Analysis of these curves demonstrated that the heart-failure group exhibited a significant decrease in peak discharge (48.1±3.0 vs. 22.2±2.2 spikes/sec; p<0.001) and a significant elevation in threshold pressure compared with the normal animals (91.0±5.0 vs. 119.1±4.4 mm Hg; p<0.001). The peak slope of the CSP-discharge curve was also significantly lower in the heart-failure group (0.63±0.06 vs. 0.40±0.09 spikes/sec/mm Hg; p<0.05). In the heart-failure group, perfusion of the carotid sinus with ouabain (0.01 μg/ml) caused a significant decrease in threshold pressure and a significant increase in peak discharge frequency, as well as an increase in slope of the CSP-discharge curve. There were no changes in CSP-diameter relations in response to ouabain. This dose of ouabain had no effect on pressure-discharge relations or carotid sinus diameters in normal dogs. Perfusion of the isolated carotid sinus with a Krebs-Henseleit solution with 50% of the normal potassium ion concentration had no effect on peak discharge or slope, but this perfusion protocol significantly reduced threshold pressure in heart-failure dogs. Low potassium ion concentration had no effect in the normal dogs. From these data, we conclude that there is attenuation of the carotid sinus baroreceptor discharge sensitivity in this model of low-output heart failure. The data are consistent with the view that there is an augmentation of Na⁺,K⁺-ATPase activity in the carotid sinus baroreceptor. (Circulation 1990;81:1959–1966)

The reflex control of the circulation is clearly abnormal in heart failure.1–8 The arterial baroreflex is abnormal in both low- and high-output heart failure in humans3,4 and in animals.5–8 The mechanisms for this reflex abnormality are not completely understood. Derangements in any part of the reflex arc could be responsible for the depression in baroreflex sensitivity that has been observed in heart failure.

Clearly, data indicate that the efferent components of the baroreflex control of heart rate are abnormal,2,4 and it has also been shown that both catecholamine synthesis and responsiveness are depressed in heart failure.9,10 On the other hand, both systemic norepinephrine clearance and spillover are abnormal in heart failure.11

Evidence from this laboratory also suggests that both carotid and aortic baroreceptor discharge sensitivities are depressed in a model of high-output heart failure.7,8 It was found that this abnormality was not due to an alteration in the compliance of the carotid sinus or to gross changes in total vessel sodium, potassium, or water content. The mechanisms for depressed baroreceptor sensitivity in high-output heart failure remain unclear. Furthermore, it is not known to what extent this abnormality is manifested in the more clinically relevant low-output heart failure.

The purpose of the present study was to determine the carotid baroreceptor sensitivity and discharge characteristics in an animal model of low-output congestive heart failure. This was done with the chronic ventricular pacing model.12,13 In addition, we
determined the role of alterations in carotid sinus compliance as a contributing factor to any abnormality observed. Finally, because it has been shown that cardiac glycosides increase the discharge sensitivity of carotid and atrial baroreceptors and enhance the baroreflex control of sympathetic nerve activity in patients with heart failure, we determined if acute, localized administration of ouabain was capable of increasing baroreceptor sensitivity in dogs with low-output heart failure.

The results indicate a depressed baroreceptor discharge sensitivity in heart failure that cannot be explained by alterations in vessel compliance. Oua-bain shifted the pressure-discharge curve toward the normal state. The data strongly support a role for augmented Na⁺,K⁺-ATPase-mediated sodium pumping as a mechanism for the depressed receptor discharge in this model of heart failure.

**Methods**

We performed these experiments on 20 mongrel dogs of either sex. The experiments were approved by the animal review committee of the University of Nebraska Medical Center. Two groups of dogs were studied: normal dogs (n = 12; mean weight, 21.8±0.6 kg) and dogs with heart failure (n = 8; mean weight, 26.5±1.2 kg). Four to 6 weeks before the acute experiment, the dogs with heart failure underwent a left thoracotomy by sterile technique and under pentobarbital anesthesia (30 mg/kg i.v.) for implantation of pacing leads on the left ventricle and left atrium. The left ventricular pacing lead was the screw-in type (model 6197-35T, Medtronic, Minneapolis, Minnesota). The leads were brought out of the chest and tunneled beneath the skin to exit in the midscapular region. After surgery, the dogs were returned to their home cages and allowed to recover for 7–10 days before pacing was started. The dogs were placed on an antibiotic regimen of 1 g cephaloxin/day for the next 5–7 days. All animals were afebrile, healthy, and vigorous at the time pacing was started. The ventricle was paced at a rate of 250 beats/min with an external pacemaker (model 5320, Medtronic). The pacemaker was carried in the pocket of a mesh jacket (Alice-King Chatham, Los Angeles, California) through which the leads were passed. The dogs were examined and weighed daily. The acute experiment was performed when the dogs showed clinical signs of heart failure. These included pulmonary edema, dyspnea, ascites, resting heart rates (with the pacemaker off) above 140 beats/min, and left atrial pressure above 20 mm Hg. The mean number of days from the time of pacing to the acute experiment was 27.6±3.5 days.

**General Experimental Preparation**

At the time of the acute experiment, each dog was anesthetized with sodium pentobarbital (30 mg/kg i.v.), and tracheal intubation was performed. The animals' temperatures were maintained between 37–39°C by external heating. The animals were placed in a dorsal recumbent position, and a femoral artery and vein were cannulated for blood sample acquisition, anesthetic supplement administration, and pressure measurement. A micromanometer-tipped catheter (model PC-350, Millar Instruments, Inc., Houston, Texas) was passed up the contralateral femoral artery into the left ventricle, and left ventricular systolic and end-diastolic (LVEDP) pressures were determined. The catheter was then withdrawn into the aortic arch, and systolic, diastolic, and mean aortic pressures were determined. A 5F thermowell Swan-Ganz catheter (Edwards Laboratories, Santa Ana, California) was inserted into the pulmonary artery through the jugular vein. Cardiac output was determined with 5 ml of 0°C injectate and measuring the resulting values on an Edwards Laboratories cardiac output computer (model 9510).

**Preparation of Isolated Carotid Sinus**

The left carotid sinus region was exposed through a midline incision in the neck. Catheters were placed in the common and external carotid arteries and the lingual artery. Carotid sinus pressure (CSP) was measured from the external carotid catheter, the tip of which was located at the bifurcation of the external and internal carotid arteries. All other branches of the carotid sinus area were ligated carefully to avoid damaging the carotid sinus nerve. All other innervations, including the sympathetic nerve to the carotid sinus, were sectioned. The inflow and outflow perfusion catheters were placed in the common carotid and lingual arteries, respectively. An oxygenated Krebs-Henseleit solution containing (mM): NaCl 129, KCl 4.8, CaCl₂ 1.1, MgSO₄ 2.5, KH₂PO₄ 1.2, NaHCO₃ 25, and dextrose 5.5 was gassed with 95% O₂-5% CO₂. The pH was maintained between 7.35 and 7.45. A heat exchanger in the circuit maintained the perfusate temperature at 38°C. The CSP level was controlled by adjusting a regulator valve connected to a pressurized air source and by adjusting the outflow resistance distal to the pressure catheter with an adjustable tubing clamp.

**Carotid Sinus Diameter Measurements**

A pair of 2-mm piezoelectric crystals (5 MHz) were placed on the medial and lateral aspects of the carotid bifurcation. The crystals were secured with one 5-0 suture placed through the adventitia. This measurement will be called “carotid sinus diameter” although it is not precisely on the carotid sinus. The diameter was measured with a sonomicrometer dimension system (Triton Technology, Inc., San Diego, California).

**Carotid Sinus Nerve Recordings**

The animal was paralyzed with pancuronium bromide (0.05 mg/kg i.v., Organon Inc., West Orange, New Jersey) and ventilated artificially with room air supplemented with 100% O₂ when needed. Supplemental anesthesia was given every hour (3 mg/kg). Arterial blood gases were measured periodically dur-
ing the experiment and were kept within normal limits by adjustments in the ventilation rate, O\textsubscript{2} supplementation, or bicarbonate administration. The carotid sinus nerve was cut at its junction with the glossopharyngeal nerve trunk, covered with warm paraffin oil, and desheathed. Fibers were split and placed on a platinum-iridium unipolar electrode. Activity from a single carotid sinus baroreceptor was recorded. The single-unit discharge was amplified with a Grass DC preamplifier (model P18D Grass Instrs., Quincy, Massachusetts), with the low-frequency cutoff set at 100 Hz, and the high-frequency cutoff set at 3 kHz. The amplified discharge was monitored on a storage oscilloscope (model 121N, Tektronix, Beaverton, Oregon) and connected to a neuronal spike analyzer (model N750, Mentor, Minneapolis, Minnesota). A window discriminator was set so that only one unit was discriminated even if more than one unit was recorded. The discriminator pulses then corresponded only to the desired single-unit baroreceptor discharge. The discriminator pulses were fed into a rate meter (Frederick Haer & Co., Brunswick, Maine) for quantification. The raw nerve activity, rate meter output, discriminator pulses, arterial pressure, CSP, and carotid sinus diameter were all recorded on an FM tape recorder (model D, Vetter, Rebersburg, Pennsylvania) and on an electrostatic strip-chart recorder (model ES1000 B, Gould Inc., Glen Burnie, Maryland).

**Experimental Protocol**

When a single baroreceptor fiber was isolated, perfusion pressure was kept at 100 mm Hg for at least 10 minutes. Then, the sinus was exposed to a slow ramp increase in CSP (2–3 mm Hg/sec) from zero to threshold pressure (i.e., the pressure at which activity was initiated). From the threshold pressure, CSP was increased stepwise, each step being approximately 25 mm Hg and lasting 10–15 seconds. Pressure was increased to a maximum of 250 mm Hg. After a control curve was constructed, the carotid sinus was perfused with one of two solutions, a Krebs-Henseleit solution containing 0.01 \( \mu \text{g/ml} \) ouabain or a Krebs-Henseleit solution containing 50% of the normal potassium ion concentration. The potassium was replaced by equimolar concentrations of NaCl and Na\textsubscript{2}HPO\textsubscript{4}. Several consecutive control curves were constructed, separated in time by 10–15 minutes. There was no effect of time on any parameter of these curves.

**Data Analysis**

CSP, the single-unit discharge rate, and the carotid sinus diameter were sampled during the last 5 seconds of each pressure step with a Tecmar A-D converter (Tecmar Inc. Solon, Ohio) on an IBM XT computer. Pressure-discharge and pressure-diameter curves were constructed from these data. CSP-discharge data and CSP-diameter data were fit with a second-order polynomial equation. The first derivative of this equation for the CSP-discharge data was determined, so that the slope of the curve at any given CSP could be determined. We determined the peak slope from the first derivative. In addition, we determined the pressure at which baroreceptor discharge was 50% of maximal (BP\textsubscript{50}). Saturation pressure was defined as the lowest pressure at which discharge rate remained constant with increases in CSP. The threshold pressure, BP\textsubscript{90}, saturation pressure, and peak slope were obtained for each fiber during the construction of pressure-discharge curves. The tangential strain was determined from the pressure-diameter data with the equation

\[
\text{Strain} = \frac{\Delta \text{radius}}{\text{radius at 50 mm Hg}}
\]

All values are expressed as the mean±SEM. Significant differences were determined with the Student’s t-test for unpaired data for group comparisons and for paired data when we compared the effect of ouabain or potassium on discharge within a given group of dogs. All values were considered statistically significant if \( p \) was less than 0.05.

**Results**

**Hemodynamic Characteristics of Normal and Heart-Failure Dogs**

The mean hemodynamic data of several variables for the two groups of dogs are shown in Table 1. These data were obtained while the dogs were under anesthesia; therefore, resting heart rate is not significantly different between the two groups. The most notable differences between the two groups were those in LVEDP and cardiac output. LVEDP was significantly elevated, and cardiac output was significantly decreased in the heart-failure group. All heart-failure dogs showed signs of pulmonary congestion and ascites.

**Carotid Sinus Baroreceptor Discharge Activity in Normal and Heart-Failure Dogs**

Figure 1 shows a recording from a normal dog. As CSP is increased from subthreshold levels, discharge increases until a saturation level is achieved. In the

| Table 1. Hemodynamics of Anesthetized Normal and Heart-Failure Dogs |
|------------------------|------------------------|------------------------|
| Hemodynamic parameters | Normal \((n=12)\) | Heart failure \((n=8)\) |
| LVSP (mm Hg) | 107.4±4.6 | 112.1±4.9 |
| LVEDP (mm Hg) | 1.3±0.9 | 2.78±2.5 | <0.001 |
| SAP (mm Hg) | 106.0±4.2 | 113.6±5.4 | NS |
| DAP (mm Hg) | 83.9±3.5 | 87.6±4.2 | NS |
| PP (mm Hg) | 22.1±1.2 | 27.3±1.7 | NS |
| MAP (mm Hg) | 91.4±3.7 | 96.0±4.4 | NS |
| HR (beats/min) | 141.3±7.3 | 141.0±9.9 | NS |
| CO (l/min/kg) | 0.26±0.04 | 0.12±0.01 | <0.001 |

LVSP, left ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; PP, pulse pressure; MAP, mean arterial pressure; HR, heart rate; CO, cardiac output.
normal group, 21 fibers were recorded from 12 dogs. In the heart-failure group, 22 fibers were recorded from eight dogs. Figure 2 shows the mean data of the CSP-discharge curves from the two groups of dogs. As shown in Figure 2, the heart-failure group had a significantly lower discharge rate at all pressures above 120 mm Hg. The slope of the CSP-discharge curve was significantly lower at most of the midrange pressures (125–175 mm Hg). The mean data for threshold pressure, BP50, saturation pressure, peak slope, and peak discharge rates are shown for normal and heart-failure dogs in Tables 2 and 3. The threshold pressure and BP50 were significantly higher, and peak slope was significantly lower in the heart-failure group. The saturation pressures were essentially the same in the two groups. In addition, the peak discharge rate was significantly lower in the heart-failure group compared with that of normal dogs (Table 3).

In another three dogs, which had been paced for 3–4 weeks, there were no clinical signs of heart failure, and their hemodynamic data were normal (low LVEDP and normal cardiac output). In these three dogs, carotid sinus baroreceptor discharge parameters were normal, with low threshold values (88.7±4.7), higher peak discharge rates (42.2±2.1), and steeper peak slopes (0.63±0.12). These three dogs were not different from our normal group and can be considered a small sham-paced group.

Figure 3 shows the relation between CSP and carotid sinus diameter in normal and heart-failure dogs expressed as percent of maximal diameter. There was no difference between these two groups of dogs.

Figure 4 shows calculated wall strain–discharge relations from the two groups of dogs. In the heart-failure group, the discharge rate at any given wall strain was significantly lower than in the normal group.

Table 2. Effects of Ouabain on Carotid Sinus Baroreceptor Discharge Properties in Normal and Heart-Failure Dogs

<table>
<thead>
<tr>
<th>Condition</th>
<th>Threshold (mm Hg)</th>
<th>BP50 (mm Hg)</th>
<th>Saturation (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (n=21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before ouabain</td>
<td>91.0±5.0</td>
<td>134.7±4.3</td>
<td>233.9±5.0</td>
</tr>
<tr>
<td>During ouabain</td>
<td>90.0±5.3</td>
<td>134.5±4.5</td>
<td>225.8±4.8</td>
</tr>
<tr>
<td>Heart failure (n=22)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before ouabain</td>
<td>119.1±4.4*</td>
<td>152.9±6.3†</td>
<td>227.9±5.1</td>
</tr>
<tr>
<td>During ouabain</td>
<td>110.2±4.3‡</td>
<td>142.1±4.9</td>
<td>223.7±4.8</td>
</tr>
</tbody>
</table>

* p<0.001, † p<0.05 Compared with the corresponding value in normal dogs.
‡ p<0.01 Compared with the corresponding value before ouabain.
TABLE 3. Effect of Ouabain on Carotid Sinus Baroreceptor Peak Discharge and Peak Pressure–Discharge Slope in Normal and Heart-Failure Dogs

<table>
<thead>
<tr>
<th></th>
<th>Normal (n=21)</th>
<th>Heart failure (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Peak slope</td>
<td>Peak discharge</td>
</tr>
<tr>
<td></td>
<td>(spikes/sec/mm Hg)</td>
<td>(spikes/sec)</td>
</tr>
<tr>
<td>Before ouabain</td>
<td>0.63±0.06</td>
<td>48.1±3.0</td>
</tr>
<tr>
<td>During ouabain</td>
<td>0.64±0.06</td>
<td>44.6±2.6</td>
</tr>
<tr>
<td>Before ouabain</td>
<td>0.40±0.08*</td>
<td>22.2±2.2†</td>
</tr>
<tr>
<td>During ouabain</td>
<td>0.52±0.07†</td>
<td>32.6±2.9§</td>
</tr>
</tbody>
</table>

n, number of fibers analyzed.
* p<0.05, † p<0.01 compared with the corresponding value in normal dogs.
§ p<0.05, § p<0.01 compared with the corresponding value before ouabain.

strain was significantly lower, and by analysis of covariance, the coefficient of the regression line was significantly decreased compared with the normal group (p<0.05).

Effects of Ouabain on Carotid Sinus Pressure–Discharge Relations

In 21 fibers from 12 normal dogs and in 22 fibers from eight heart-failure dogs, we determined the effects of perfusion of the carotid sinus with a Krebs-Henseleit solution containing 0.01 μg/ml ouabain. These data are summarized in Tables 2 and 3 and in Figure 5. In normal dogs (left panel in Figure 5), this dose of ouabain had no significant effect on any of the CSP-discharge curve parameters. However, in the heart-failure dogs, ouabain shifted the curve upward and to the left. As shown in the right panel in Figure 5 and in Tables 2 and 3, the peak slope was increased in the heart-failure group, and the threshold pressure was significantly decreased. The effects of ouabain were completely reversible after perfusion with normal Krebs-Henseleit solution for 10–15 minutes.

Ouabain had no effect on carotid sinus diameter in either normal or heart-failure dogs. The relation be-

tween CSP and diameter is shown in Figure 6 for both groups of dogs before and during ouabain perfusion.

Effects of Low Potassium Ion Concentration on Carotid Sinus Baroreceptor Activity in Normal and Heart-Failure Dogs

The effects of perfusion of the carotid sinus with a Krebs-Henseleit solution containing 50% of normal potassium concentration are shown in Figures 7 and 8. In the normal group (Figure 7), low potassium ion concentration had no significant effect on the CSP-discharge curve. There were no changes in slope, BP50, threshold pressure, and saturation pressure. In the heart-failure group (Figure 8), however, perfusion with a low potassium ion concentration solution resulted in a significant decrease in threshold pressure, from 133.4±4.3 to 119.1±7.0 mm Hg (p<0.05). No significant effects were found, however, in the slope of the CSP-discharge curves.

Discussion

The low-output heart-failure model used in these experiments was originally described by Whipple et al12 and was expanded by Coleman et al.13 In the present study, eight dogs were continuously paced for a mean duration of 27.6±3.5 days. At the time the acute experiment was performed, there was a significant elevation in LVEDP and a significant reduction in cardiac output in the anesthetized dogs. Other parameters were similar in the normal and heart-failure groups. In the conscious state,17 however, there is a significant reduction in left ventricular systolic pressure, arterial systolic pressure, arterial diastolic pressure, mean arterial pressure, and significant tachycardia. Similar data have been presented by Armstrong et al18 using the right ventricular pacing model. These data strongly suggest that anesthesia masks some of the signs of heart failure.

The present study indicates that low-output heart-failure results in a decreased sensitivity of the carotid sinus baroreceptors. The decreased peak slope and the elevated threshold pressure and BP50 suggest that
Figure 5. Curves showing the effects of ouabain (0.01 μg/kg) perfusion of the carotid sinus on carotid sinus pressure (CSP, mm Hg) – discharge (spikes/s) (upper panels) and CSP-slope (spikes/s/mm Hg) (lower panels) relations in normal (left panels) and heart-failure (right panels) dogs. *p<0.05, **p<0.01, ***p<0.001 comparing pre-ouabain vs. post-ouabain.

carotid sinus baroreceptors are not only less sensitive but also that the CSP-discharge curve is shifted to a higher pressure. This is very similar to the results obtained in high-output heart-failure dogs with chronic aortocaval fistulas.7,8

It has been shown that high concentrations of cardiac glycosides can augment baroreceptor discharge sensitivity in normal animals.14,15,19,20 However, perfusion of the isolated carotid sinus regions of cats and rabbits with low concentrations of ouabain caused no significant change in CSP-heart rate relations.21 Cardiac glycosides have been shown to augment the baroreflex in normal and heart-failure patients.16,22 In a recent study by Ferguson et al,16 it was shown that administration of digitalis reduced muscle sympathetic nerve activity in patients with New York Heart Association class III–IV heart failure while there was no such effect in normal individuals. Furthermore, augmentation of cardiac output with dobutamine did not reduce muscle sympathetic nerve activity in either the normal or the heart-failure group. In this latter study, no attempt was made to differentiate between arterial baroreceptor and cardiac receptor involvement.

It is generally well accepted that digitalis is capable of releasing catecholamines from sympathetic nerve
terminals, which thereby contribute to vasoconstriction. Although catecholamine release might have been a potential mechanism in the present study, we can rule out this phenomenon because sympathetic innervation of the carotid was sectioned in these experiments.

In the present study, perfusion of the carotid sinus with a low concentration of ouabain (0.01 μg/ml) resulted in no change in the CSP-discharge curve or the CSP-diameter curve in the normal group. In the heart-failure group, however, ouabain shifted the CSP-discharge curve upward and to the left (right panel in Figure 5), threshold pressure decreased significantly, and the peak discharge frequency as well as the peak slope increased significantly (right panel in Figure 4 and Tables 2 and 3) without a change in the CSP-diameter relation (Figure 6). These data suggest that ouabain can augment the carotid sinus baroreceptor sensitivity in this low-output heart-failure model and that augmentation of the carotid sinus baroreceptor activity is not due to a change in carotid sinus compliance. The mechanism of the effects of ouabain on baroreceptor discharge is probably due to its inhibition of Na⁺,K⁺-ATPase activity at the receptor level. The fact that the dose of ouabain used in these experiments only augmented receptor discharge in the heart-failure group suggests an augmentation of Na⁺,K⁺-ATPase activity in this group. Enhanced sodium pumping at the receptor level would tend to hyperpolarize the membrane and decrease receptor sensitivity.
It is possible that the lack of any dramatic effect after lowering the external potassium ion is due to the fact that we only lowered the concentration to 50% of normal compared with a 100% reduction in other studies. The opposing effects of pump inhibition and hyperpolarization may offset each other, so that minimal effects were seen in these studies.

The beneficial effects of administration of digitalis glycosides in heart failure may be related to their ability to sensitize cardiovascular sensory endings in the aortic arch, carotid sinus, heart, and lungs. Most of the reflex effects of stimulation of cardiopulmonary and arterial baroreceptors are sympathoinhibitory. Reduction in the sensitivity of these endings and thereby the reflexes they mediate may be, in part, responsible for the augmented sympathetic tone in heart failure. The sensitization of these endings by cardiac glycosides may provide reduced sympathetictone, reduced afterload and preload, and increased tissue perfusion in heart failure.

To our knowledge, the data presented here are the first to show a desensitization of single baroreceptor endings in chronic heart failure and its reversal by a cardiac glycoside. These data strongly suggest that carotid baroreceptor sensitivity is depressed in this model of heart failure as a result of augmented Na⁺,K⁺-ATPase activity. It is interesting to speculate that the increase in sodium pump activity may be a generalized phenomenon in heart failure. It is unclear whether this increased pump activity is a response to the volume-expanded state in heart failure or is a central feature in the development of the sequelae of this disease. Acute volume expansion and time-course experiments will help to answer these questions.

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References


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