Cardiorenal and Neurohumoral Function in a Canine Model of Early Left Ventricular Dysfunction

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Background. Recent studies have reported that asymptomatic left ventricular dysfunction (ALVD) in humans is characterized by early neurohumoral activation. Specifically, atrial natriuretic factor (ANF) and norepinephrine are activated without activation of the renin-angiotensin-aldosterone system (RAAS). The current study describes hemodynamic and renal function associated with this neurohumoral profile in a canine model of early and presumably “asymptomatic” ventricular dysfunction. We hypothesized that the neurohumoral profile observed in ALVD is associated with preservation of renal function despite significant hemodynamic compromise.

Methods and Results. ALVD was produced by ventricular pacing at 180 beats per minute for 10 days. Intravascular volume expansion was performed before and after producing ALVD in eight conscious dogs. The model of ALVD was characterized by decreases in ejection fraction (48±2 to 29±4%), cardiac output (4.64±0.29 to 2.89±0.17 L/min), and mean arterial pressure (119±4 to 108±4 mm Hg). Atrial pressures and systemic vascular resistance were increased. ANF (60±19 to 165±27 pg/mL) and norepinephrine (382±127 to 690±211 pg/mL) were activated, whereas the RAAS was not. Creatinine clearance and sodium excretion (UNa V) were unchanged after producing ALVD. The natriuretic response to volume expansion in ALVD was completely intact, with increases in UNa V similar to that observed with volume expansion before producing ALVD.

Conclusions. The current study demonstrates that significant ventricular dysfunction with peripheral vasoconstriction can be associated with normal renal function and thus suggests an important functional role for the neurohumoral profile of ALVD in preserving sodium balance. (Circulation 1993;87:2016–2022)

KEY WORDS: atrial natriuretic factor • renal function • hemodynamics • congestive heart failure

Whereas heart failure is initiated by a primary abnormality in ventricular function, the syndrome of chronic congestive heart failure (CHF) is characterized by complex neurohumoral and renal perturbations that are associated with peripheral vasoconstriction and avid renal sodium retention. These perturbations are postulated to contribute to the progression of symptomatic CHF. To improve mortality in CHF, clinical studies have recently focused on early heart failure. In the Studies of Left Ventricular Dysfunction (SOLVD) study, Francis et al described patients with asymptomatic left ventricular dysfunction (ALVD) who had significant ventricular dysfunction without symptoms of heart failure. Despite a lack of symptoms of CHF, neurohumoral activation was demonstrated that was characterized by an increase in the vasodilator–natriuretic cardiac hormone atrial natriuretic factor (ANF) in the absence of activation of the renin-angiotensin-aldosterone system (RAAS).

Although these important human studies of ALVD demonstrated neurohumoral activation, the functional significance, specifically regarding associated cardiovascular hemodynamics and renal function, were not defined. Therefore, the current study was undertaken to provide new insight into the biological significance of neurohumoral activation in ALVD. To accomplish this objective, studies were performed in a conscious canine model of early experimental heart failure that mimics human ALVD. Specifically, this experimental model is characterized by decreased left ventricular function and increased plasma ANF and plasma catecholamines with the absence of activation of the RAAS. Functional status was not formally determined in this canine model: This model is characterized by mild to moderate hemodynamic derangement and the absence of signs of heart failure such as ascites, lethargy, and decreased food intake that are normally observed with the pacing model of severe CHF. We sought to define renal and cardiovascular function and associated neurohumoral function before and after intravascular saline volume expansion in experimental ALVD, a maneuver that results in a markedly impaired cardiorenal response in symptomatic CHF. We specifically tested the hypothesis that the cardiovascular and renal responses to volume expansion are intact in this animal model of ALVD or early left ventricular dysfunction and are related to a normal neurohumoral response.
Methods

Experimental Protocol

An experimental model of asymptomatic left ventricular dysfunction was produced in eight conscious male mongrel dogs by rapid ventricular pacing at 180 beats per minute for 10 days. Acute intravascular volume expansion with saline was performed before and after the production of ALVD. All dogs weighed between 18 and 21 kg and were fed normal dog chow (Lab Canine Diet 5506; Purina Mills, St. Louis, Mo.) and were allowed free access to tap water. All studies were conducted in a manner consistent with the guiding principles of the American Physiological Society. The experimental protocol was approved by the Institutional Animal Care and Use Committee.

Programmable cardiac pacemakers (model 8426, Medtronic, Minneapolis, Minn.) were implanted. Under pentobarbital sodium anesthesia (30 mg/kg) and via a left thoracotomy and 1–2-cm pericardotomy, the heart was exposed and a screw-in epicardial pacemaker lead was implanted into the right ventricle. The pacemaker lead was connected to a pulse generator that was implanted subcutaneously in the chest wall. The pericardium was sutured closed with great care not to disturb the anatomy of the pericardium. This procedure leaves the pericardium intact without significant perturbation. The incision was closed in layers. The dogs were allowed to recover for 5–7 days, during which time they received antibiotics for the first 3 days. The animals also underwent implantation of a subcutaneously placed chronic femoral artery catheter (Access Technologies, Skokie, Ill.). This was implanted via the right femoral artery with the access well tunneled subcutaneously and placed subcutaneously on the right upper hind limb. The catheter was flushed biweekly with heparinized saline. Dogs to be used for chronic conscious studies were carefully selected, and only the more docile and kennel-acclimated dogs were used. Dogs were handled daily for inspection of incisions, antibiotic administration, pacemaker checks, echocardiography, and catheter flushes. Dogs were acclimated to the sling, which allows the dog to stand quietly in a minimally restrained fashion.

The rapid ventricular pacing model (at 240–250 beats per minute) has been used extensively by our laboratory and others to produce a model of severe CHF with marked depression of cardiac function and activation of the RAAS. The current study uses a modification of this model in the conscious state with a lower pacing rate, which produces a milder form of tachycardia-related cardiomyopathy as described below. Although sinus tachycardia in the dog may reach 180 beats per minute intermittently, the animals were paced for the majority of beats whenever an ECG was monitored to confirm pacemaker function or at the time of echocardiography.

The acute experiment was performed 5–7 days after pacemaker implantation. The night before the acute experiments, the animals were fasted and given 300 mg of lithium carbonate. The dogs were allowed access to water ad lib. The day of the acute experiment, the animals were briefly anesthetized with thiopental sodium (15 mg/kg) to allow percutaneous placement of a flow-directed balloon tip pulmonary artery catheter (model 93131-7F; American Edwards Laboratories, AHS del Caribe, Anasco, P.R.) via an external jugular vein for measurement of cardiac output and atrial pressures. A second balloon-tip catheter was inserted in the urinary bladder to allow urine collection. The animals were placed in a minimally restraining sling and allowed to regain consciousness and equilibrate for 90–120 minutes. The femoral artery catheter was connected to a pressure monitor during this period for on-line measurement of aortic pressure.

At the conclusion of the equilibration period, two 30-minute baseline urinary clearances were performed. Midway through each urinary clearance period, cardiac hemodynamics were measured and arterial blood was drawn for hormonal and electrolyte analysis. After the two 30-minute baseline urinary clearances, the animals were volume expanded with normal saline. Normal saline was infused at 2 mL·kg⁻¹·min⁻¹. This was equivalent to approximately 5% body weight volume expansion over 30 minutes. A 15-minute urinary clearance was performed during the second half of volume expansion. The pulmonary artery and urinary catheters were then removed, the subcutaneous arterial catheter was flushed, and the dogs were returned to the kennels.

The next morning, the pacemaker was programmed at 180 beats per minute. On the 10th day of pacing, after an overnight fast and after receiving lithium carbonate (300 mg), the acute volume expansion was performed in the exact same manner as it was before the induction of ALVD. At the end of the acute experiment, the catheter was flushed, and the dog was returned to the kennel.

A two-dimensional echocardiogram was performed at baseline and after the induction of ALVD on the 11th day of pacing. Echocardiograms were performed in the conscious state with the dog unrestrained and standing quietly. Each time, the echocardiogram included measurements of the left ventricular dimensions in the short-axis view at the midventricular level, and cross-sectional left ventricular area at this level was determined by tracing the endocardium (Dextra D-200, Dextra Medical Incorporated; Lakewood, Calif.). During the ALVD phase, the pacemaker was reprogrammed to 30 beats per minute and the echocardiogram was taken within 10 minutes of reprogramming. Five cardiac cycles were measured, and the average of the five measurements was taken. No cycles after a premature or paced premature beat were used for analysis. The ejection fraction (EF) was calculated using the formula

\[
\text{EF} = \frac{\text{end-diastolic area} - \text{end-systolic area}}{\text{end-diastolic area}}
\]

Cardiac hemodynamic parameters measured during each clearance period included right atrial pressure (RAP), pulmonary capillary wedge pressure (PCWP), cardiac output (CO), and mean arterial pressure (MAP). CO was determined by thermodilution (cardiac output model 9510-A computer, American Edwards Laboratories, Irvine, Calif.). CO was measured five times during each clearance period, and the average of these readings was used. Systemic vascular resistance (SVR) was calculated using the formula

\[
\text{SVR} \left(\frac{\text{dyne} \cdot \text{sec} \cdot \text{cm}^{-2}}{\text{L} \cdot \text{minute}^{-1}}\right) = \frac{\text{MAP} - \text{RAP}}{\text{CO}} \times 80
\]
All voided urine was measured using a graduated cylinder and allocated for measurements of sodium, creatinine, and lithium. Urine samples for sodium, creatinine, and lithium determinations were refrigerated until analysis. Fractional excretion of lithium (FELi) was used as a measure of whole kidney proximal tubule delivery of sodium.\(^3\,^4\) Arterial blood for sodium, lithium, and creatinine determinations was collected in heparinized tubes, placed on ice, and centrifuged at 2,500 rpm at 4°C. After centrifugation, plasma was decanted and refrigerated until it was analyzed. Plasma and urinary sodium concentrations were measured using ion-selective electrodes (Beckman Instruments, Brea, La.). Glomerular filtration rate was determined by creatinine clearance. Plasma and urinary creatinine concentrations were measured by the Jaffe reaction (Beckman Instruments). Plasma and urine lithium levels were determined by flame emission spectrophotometry (model 357, Instrumentation Laboratory, Wilmington, Mass.).

Arterial blood samples for hormones and cGMP analysis were placed in EDTA tubes, immediately placed on ice, and centrifuged at 2,500 rpm at 4°C. After extraction, plasma levels of ANF were measured by radioimmunooassay to \(\alpha\)-human ANF as previously described.\(^1\) Plasma renin activity was determined by radioimmunoassay using the method of Haber et al.\(^1\) Plasma samples for cGMP were extracted with ethanol. Plasma cGMP was measured by radioimmunoassay using the method of Steiner et al.\(^1\) Plasma catecholamines were measured by high-pressure liquid chromatography (Mayo Laboratories, Rochester, Minn.) at baseline, before, and after production of left ventricular dysfunction.

As hematocrit decreased markedly because of intravascular volume expansion, plasma ANF and plasma cGMP were corrected for the increase in plasma volume (PV) with volume expansion. Percent change of plasma volume was calculated using the formula

\[
\%\text{PV} = \frac{100}{100 - H_c} \times \left[100 \left(\frac{H_1 - H_2}{H_2}\right)\right]
\]

(Reference 14).

**Statistics**

All data are presented as mean±SEM. Comparisons between the baseline period of the normal phase and ALVD phase were analyzed by the paired Student’s \(t\) test for ejection fraction and norepinephrine levels. Statistical significance was defined as \(p<0.05\). Comparisons for the remainder of data analysis were performed by ANOVA for repeated measures analysis followed by the Student-Newman-Kuels test for significance in individual comparisons.

**Results**

The hemodynamic characteristics of this model of ALVD are depicted in Figure 1. There was a 38% reduction in CO; MAP decreased by 9%; RAP increased by 81%; PCWP increased by 52%; and SVR increased by 55%.

The neurohumoral profile of this model of ALVD is depicted in Figure 2. ANF and its second messenger plasma cGMP (pcGMP) were both elevated. The circulating RAAS was not activated, as there was no significant change in plasma renin activity or plasma aldosterone. Plasma norepinephrine was measured in four dogs and was significantly increased after 10 days of pacing (382±127 to 690±211 pg/mL, \(p=0.046\)).

As depicted in Figure 3, basal renal hemodynamic and excretory function were not different from normal. Specifically, there was no change in creatinine clearance, urinary sodium excretion, fractional excretion of sodium, FELi, or urinary cGMP excretion.

Ejection fraction was measured by two-dimensional echocardiography in five dogs and decreased from 48±2% in the normal phase to 29±4% after 10 days of pacing. No dog developed ascites, edema, decrease in appetite, muscle wasting, or lassitude.

Table 1 presents the hemodynamic, hormonal, and renal parameters before and during intravascular saline volume expansion in the normal and ALVD phases of the protocol. In both the normal phase and the ALVD phase, volume expansion resulted in increases in cardiac output and mean arterial pressure and was associated with an increase in atrial pressure and a decrease in SVR. The peak CO and MAP achieved in the ALVD phase were significantly lower than that obtained in the normal phase. The peak wedge pressure was also higher in the ALVD phase.

Hematocrit decreased from 39.0±1.5 at baseline to 26.4±12 with volume expansion. The percent change in plasma volume was 69±8%. When corrected for the change in plasma volume, plasma ANF and its second messenger cGMP both increased with volume expansion in the normal phase. Plasma ANF also increased with volume expansion in the ALVD phase, and this was associated with a strong trend toward an increase in
plasma cGMP. Plasma renin activity and aldosterone decreased with volume expansion in both phases. The effect of volume expansion on creatinine clearance and renal excretory function during the normal and ALVD phases of the experiment are depicted in Table 1. There was a trend toward an increase in creatinine clearance with volume expansion in each group, but this was not significant. There were similar increases in urinary volume, urinary sodium excretion, and fractional excretion of sodium with volume expansion in the normal and ALVD phase of the experiment. Whole kidney proximal tubule reabsorption of sodium as measured by FELi decreased to similar levels with volume expansion in the normal and ALVD phases of the experiment.

Discussion

Recent investigations have reported early neurohumoral activation in humans with ALVD. Specifically, ALVD was characterized by elevations in ANF and norepinephrine without activation of the circulating RAAS.\(^1\) The current study in a canine model of ventricular dysfunction that mimics the humoral profile observed in ALVD provides insight into the biological significance of such endocrine activation in the control of cardiorenal function in early heart failure. In the current model of ALVD, decreased ventricular function was associated with increases in plasma norepinephrine. Despite significant ventricular dysfunction and peripheral vasoconstriction, sodium excretion was maintained at normal levels and the natriuresis associated with intravascular volume expansion was intact. Such a renal response occurred in association with chronic elevation of plasma ANF and with increased release of ANF with volume expansion. Moreover, despite significant hemodynamic compromise, there is no activation of the circulating RAAS with suppression of this normal activity with volume expansion. Whereas exercise capacity was not formally assessed in this model of early left ventricular dysfunction, the moderate hemodynamic derangements were not associated with signs of CHF observed in the pacing model of severe CHF and were associated with intact renal excretory function. Thus, the early left ventricular dysfunction described in the current study provides an animal model of asymptomatic ventricular dysfunction or early heart failure.

In the current conscious canine model of experimental ALVD, decreased ejection fraction and CO and increased filling pressures were associated with mild but significant decreases in MAP and moderate increases in SVR. Although the baseline values for MAP and CO described in the current study are higher than previously reported by some investigators, they are consistent with values obtained in the conscious and anesthetized dog reported in numerous studies from this and other laboratories.\(^5,6,15-20\) Although some investigators have reported preservation of contractility, CO, or SVR until the very late phases of rapid pacing-induced heart failure,\(^21-23\) most studies have reported an early decrease in CO and increase in SVR.\(^2,5,6,8,16,19,20\) Previous studies have also demonstrated decreases in arterial compliance\(^24\) and evidence of impairment in endothelium-dependent vascular relaxation after 10–30 days of rapid ventricular pacing.\(^25,26\) The current study demonstrates that experimental ALVD is characterized by early peripheral vasoconstriction and suggests that al-
Table 1. Hemodynamic, Hormonal, and Renal Parameters Before and After Volume Expansion

<table>
<thead>
<tr>
<th>Hemodynamic data</th>
<th>Normal phase</th>
<th>ALVD phase</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>VE</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>4.6±0.3</td>
<td>7.8±0.6*</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>119±4</td>
<td>131±4*</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>2.7±0.4</td>
<td>10.1±0.7*</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>6.5±0.4</td>
<td>16.9±1.4*</td>
</tr>
<tr>
<td>SVR (dyne·sec·cm⁻²)</td>
<td>1,944±151</td>
<td>1,282±95*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hormonal data</th>
<th>Normal phase</th>
<th>ALVD phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANF (pg/mL)</td>
<td>60±19</td>
<td>158±24*</td>
</tr>
<tr>
<td>pcGMP (pmol/mL)</td>
<td>3.91±0.37</td>
<td>9.14±1.00*</td>
</tr>
<tr>
<td>PRA (ng/mL/hr)</td>
<td>0.83±0.37</td>
<td>&lt;0.1*</td>
</tr>
<tr>
<td>Aldo (ng/dL)</td>
<td>4.09±0.88</td>
<td>&lt;2.5*</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Renal data</th>
<th>Normal phase</th>
<th>ALVD phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crt Cl (mL/min)</td>
<td>58±3</td>
<td>110±32</td>
</tr>
<tr>
<td>V (mL/min)</td>
<td>0.40±0.11</td>
<td>5.59±0.68*</td>
</tr>
<tr>
<td>UNa V (mEq/min)</td>
<td>44±22</td>
<td>693±93*</td>
</tr>
<tr>
<td>FENa (%)</td>
<td>0.49±0.26</td>
<td>5.77±1.05*</td>
</tr>
<tr>
<td>FELi (%)</td>
<td>13±3</td>
<td>36±7*</td>
</tr>
</tbody>
</table>

ALVD: asymptomatic left ventricular dysfunction; VE, volume expansion; CO, cardiac output; MAP, mean arterial pressure; RAP, right atrial pressure; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance; ANF, atrial natriuretic factor; pcGMP, plasma cyclic guanosine monophosphate; PRA, plasma renin activity; Aldo, aldosterone; Crt Cl, creatinine clearance; FENa, fractional excretion of sodium; FELi, fractional excretion of lithium; V, urinary flow rate; UNa V, urinary sodium excretion.

*Baseline vs. VE (either phase); †ALVD vs. normal at baseline; ‡ALVD vs. normal at VE. Levels reported as < are below the limits of detection of the assay.

Deposition in vascular tone occur early in the natural history of evolving CHF and precede activation of the circulating RAAS. The mechanisms underlying the peripheral vasoconstriction are probably multifactorial. The current findings and those of Francis et al in humans would support a role for early suppressive activation in the peripheral vasoconstriction of early heart failure. The absence of activation of the circulating RAAS does not exclude a possible role for activation of tissue RAAS in modulating vascular tone early in heart failure.27 Elevation of plasma endothelin has been reported in humans with severe CHF and in the pacing model of severe CHF.23,28 Whether endothelin is activated at a tissue or circulating level in early heart failure remains unclear.

Despite the significant hemodynamic compromise present in this model of ALVD, sodium excretion before and after volume expansion is preserved. This may be a fundamental characteristic of ALVD. Indeed, the onset of sodium retention or altered response to volume expansion may mark the critical progression of ALVD to overt CHF. The finding of an intact response to volume expansion in this model of ALVD differs from previous findings reported by Hostetter et al29 in rats with mild ventricular dysfunction produced by experimental myocardial infarction that displayed an attenuated natriuretic response to acute volume expansion. In this previous report, the activity of the RAAS was not assessed. More recently, Volpe et al34 reported a blunted natriuretic response to volume expansion in a group of patients with dilated cardiomyopathy and mild CHF. These patients displayed a heterogeneous pattern of RAAS activation and an inability to increase stroke volume with volume expansion. These responses were also associated with an inability to increase plasma ANF.

In the current study, the ability to maintain a natriuretic response to volume expansion was associated with an increase in CO and MAP and decreases in SVR and plasma renin activity. While CO and MAP did not reach levels achieved in the normal phase, there were physiologically significant increases in CO and MAP with a marked decrease in SVR. This is in contrast to previous findings in severe CHF characterized by an absent natriuretic response to volume expansion associated with an inability to improve cardiac hemodynamics and with persistent activation of the RAAS.4 Thus, a critical degree of cardiac reserve and a complete lack of activation of the RAAS may play important roles in preserving sodium balance in early heart failure. Although the study of Hostetter et al demonstrated sodium retention despite increases in CO with volume expansion, Hollander and Judson30 studied patients with heart failure and found that patients who maintained their ability to respond to a sodium load increased their CO with exercise to a greater degree than those who retained sodium, which is consistent with the current observations.

Proximal tubule sodium reabsorption was normal in the presence of ALVD and decreased with volume expansion, as was observed with volume expansion in the normal phase. Previous studies have demonstrated an inability to decrease proximal tubule sodium reabsorption and suppress plasma renin activity with volume expansion in severe CHF.4 Cody et al31 postulated that the inability to suppress plasma renin activity in response to chronic oral sodium loading in a series of patients with CHF may be linked to a failure to enhance...
distal delivery of sodium to the macula densa. The current study would support such a hypothesis. Specifically, volume expansion in ALVD resulted in an increased delivery of sodium from the proximal tubule as determined by the increase in FELi. Such a response was associated with a decrease in plasma renin activity. As angiotensin II is known to stimulate and ANF to decrease sodium reabsorption by the proximal tubule, the neurohumoral milieu present in ALVD may preserve proximal tubule function in ALVD.

Previous studies from this laboratory and others have reported an inability to increase ANF levels with volume expansion in experimental chronic severe CHF. The current study demonstrates that in this model of early left ventricular dysfunction that mimics the neurohumoral activation reported in humans with ALVD, circulating ANF increased in response to volume expansion when corrected for changes in plasma volume with volume expansion. Thus, an increased amount of ANF must be released into the plasma as reflected by the increase in plasma level of ANF corrected for the increase in plasma volume. This increased ANF was associated with a strong trend toward an increase in the plasma cGMP levels. This increase in ANF occurred in response to appropriate and equivalent increases in cardiac filling pressures, which in part differs from the findings of Volpe et al4 in mild CHF where there was an attenuated increase in estimated left ventricular end-diastolic pressure associated with a blunted increase in plasma ANF. Thus, in this model of ALVD, a fundamental characteristic is an intact ANF response to increases in cardiac filling pressure produced by intravascular volume expansion. It is tempting to speculate that this intact response is responsible for the preserved renal natriuretic response and maintenance of body fluid hemostasis. Indeed, the elegant studies by Volpe et al4 would support such a speculation because an attenuated renal response to volume expansion was observed in patients with mild CHF and was associated with an attenuated increase in plasma ANF. Although the elevation in plasma ANF is a marker for ventricular dysfunction, previous studies by Lee et al3 strongly support a role for ANF in maintaining renal function and preventing activation of the RAAS in acute CHF. Anti-ANF antibody studies by Drexler et al4 in rats with chronic CHF strongly support a role for ANF in preserving renal function and favorably affecting SVR. The current study extends these previous studies by demonstrating activation of ANF, suppression of the RAAS, and preservation of sodium excretion in the face of significant reduction in ventricular function and systemic hemodynamics. The current study provides insights into this preservation of renal function by demonstrating preservation of the proximal tubule response to acute volume expansion as discussed above.

Summary

The significance of the current study is that an experimental model of ALVD or very early heart failure has been developed and characterized in which ventricular dysfunction and peripheral vasoconstriction are observed but sodium homeostasis is preserved in the presence and absence of intravascular volume expansion. The neurohumoral profile that this model mimics is that of patients with ALVD. Because patients with ALVD remain asymptomatic in the absence of diuretics, an ability to maintain sodium balance is strongly implied. The current model demonstrates that significant ventricular dysfunction can be associated with an intact ability to maintain sodium balance. Thus, the neurohumoral profile observed in this model and in patients with ALVD may be importantly related to these physiological characteristics. Specifically, increased norepinephrine may be an indicator of activation of the sympathetic nervous system that contributes to the peripheral vasoconstriction, and increased ANF may be a marker for cardiac volume overload that contributes to the maintenance of sodium excretion and inhibition of the RAAS. As evidenced by recent studies, therapeutic strategies that maintain such neurohumoral adjustments may prolong the asymptomatic phase of ventricular dysfunction.

References


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