Changes in Hemodynamics and Myocardial Contractility During Chronic Sodium Depletion in Conscious Dogs

TAKANOBU NII, FETNAT M. FOUAD-TARAZI, CARLOS M. FERRARIO, EMMANUEL L. BRAVO, AND BARBARA CZERSKA

SUMMARY Chronic sodium depletion has been reported to decrease ejection fraction in anesthetized dogs. We tested the hypothesis that this reduction in cardiac performance is due to either hemodynamic or humoral factors. Seven mongrel dogs were fed a low sodium diet (<2 mEq Na\(^+\) per day) for 5 weeks. Echocardiographic and radionuclide techniques were used to monitor cardiac function. There was a gradual but significant \((p<0.01)\) decrease in ejection fraction from \(61 \pm 7\%\) (SD) at baseline to \(47 \pm 8\%\) after 5 weeks of sodium depletion in association with a fall in left ventricular end-diastolic volume. Ejection fraction did not change in five control dogs fed 55 mEq Na\(^+\) per day throughout the 5-week follow-up period. Myocardial contractility did not change in either salt-depleted or control dogs. Plasma norepinephrine levels in the coronary sinus were twice as high in salt-depleted as in control dogs, but there were no significant differences in arterial norepinephrine concentration between the two groups. Therefore, we concluded that reduced ejection fraction during sodium depletion resulted from hemodynamic changes (decreased preload). The excess available norepinephrine failed to increase myocardial contractility, suggesting a dysfunction at the cardiac adrenergic neuroeffector junction. (Hypertension 9 [Suppl III]: III-176-III-180, 1987)

KEY WORDS • sodium • ejection fraction • myocardial contractility • norepinephrine • blood volume

T

HOUGH the peripheral vascular effects of sodium restriction have been studied extensively,\(^1\) the direct effects of chronic sodium depletion on the myocardium have not been fully investigated. However, Lynn et al.\(^4\) reported a reduction of left ventricular (LV) ejection fraction in anesthetized, salt-depleted dogs, and Szilagyi et al.\(^5\) reported a reduction in stroke volume in salt-deprived anesthetized dogs. Given that ejection fraction and stroke volume are both load-dependent indices of cardiac function, it is not clear from these studies whether the reductions in LV ejection volume and stroke volume were due to hemodynamic changes or to alterations in myocardial contractility. Moreover, it cannot be determined whether the observed reductions were related to changes in extrinsic adrenergic support to the heart. The present study was designed to assess cardiac performance in the conscious dog in relation to hemodynamic changes and the presence of myocardial catecholamines during regular and low sodium intake.

Methods

Animal Preparation and Protocols

Twelve trained male mongrel dogs (20–27 kg) were studied in the conscious state 2 to 3 weeks after the placement of chronic iliac artery catheters. Baseline studies were carried out after equilibration on a regular sodium diet (Lab Canine Diet 5006, Ralston Purina, St. Louis, MO, USA), providing 55 mEq Na\(^+\) per day. Then, seven of the dogs were placed on a low sodium diet (Prescription h/d, Hill’s Pet Products, Topeka, KS, USA), providing <2 mEq Na\(^+\) per day for 5 weeks; the other five dogs continued on the regular sodium diet. Studies were repeated 3 and 5 weeks later. Blood pressure and heart rate were followed weekly. The protocol involved recording baseline indices of LV function (ejection fraction measured by radionuclide technique, and fractional shortening measured by echocardiography). Then a phenylephrine infusion was started to determine myocardial contractility \((E_{max})\) as described below (see Techniques).
To assess the relationship between cardiac catecholamines and function, two of these dogs (from the low sodium group) and 10 others were subjected to an additional procedure as described below. The 10 new dogs followed the same dietary protocol and had the same surgical instrumentations but were not subjected to the E\text{\textsuperscript{max}} study. This group of 12 dogs included six on regular sodium diet and six on low sodium diet. At the end of the dietary manipulation, a chest operation was performed under sterile techniques and general anesthesia. Through a thoracotomy in the fourth right intercostal space, a Tygon catheter was chronically implanted into the left ventricle via a stab wound at the apex, and a wide-bore cannula was implanted in the coronary sinus via the azygos vein during the same procedure. The tips of two catheters were exteriorized on the back of the neck. Three days after recovery from surgery, LV pressure, electronically derived rate of change of pressure (dP/dt), and concentrations of plasma catecholamines simultaneously drawn from the coronary sinus and aorta were measured while the conscious dogs lay quietly in a darkened room. Net cardiac catecholamine influx was estimated by subtracting arterial from coronary sinus plasma catecholamine concentrations.

All surgical procedures were done with aseptic techniques, with the dogs under general anesthesia (morphine, 2 mg/kg, and sodium pentobarbital, 15 mg/kg i.v.), and with mechanical ventilation. The experimental protocols were approved by our Institutional Animal Biomedical Research Review Committee.

Techniques

Plasma volume was measured at the beginning of each study following intravenous injection of 3 mg Evans blue dye and a 10-minute equilibration period.

With the animal lying on its right side, the scintillation camera was positioned facing the left side of the chest for optimal visualization of each cardiac chamber. The first-pass technique was used to calculate the cardiac flow index and pulmonary mean transit time (MTT) using \textsuperscript{99}Te-human serum albumin (25 mCi). An index of venous distensibility equivalent to the ratio of cardiopulmonary blood volume to total blood volume (previously reported\textsuperscript{6}) was derived from measurements of cardiac flow index and MTT. The index is independent of the absolute value of total blood volume. Following these determinations, gated blood pool scanning was done to measure the LV ejection fraction.

With the animal in the same position, an M-mode echocardiogram was made using two-dimensional monitoring achieved by directing the ultrasonic transducer upward across a hole in the padded table. Recordings were obtained from a "window" on the right chest wall, just proximal to the maximal apical pulsation, using a Hewlett-Packard electrocardiograph (Model 77020 AC) and a 3.5-MHz transducer at a speed of 100 mm/sec. Left ventricular chamber dimensions were recorded at the level of the tip of the mitral valve. Following baseline imaging and blood pressure recording, phenylephrine was infused intravenously at a rate of 13 to 33 \mu g/min to increase systolic pressure from baseline values by 20, then 40, mm Hg; LV echocardiogram was recorded at each level of systolic pressure. To avoid reflex slowing of heart rate during this procedure,\textsuperscript{7} the dogs were premedicated with atropine (0.2–0.3 mg i.v.).

The left ventricular end-diastolic dimension was measured at the beginning of the QRS, using the leading edge method.\textsuperscript{8} To determine LV end systole, the time from the start of the QRS to the end point of aortic valve closure was measured for several cycles and the average time applied to the LV M-mode echocardiogram. Thus, variations in end-systolic dimensions were minimal. Measurements were made on 10 consecutive cardiac cycles using a programmable calculator (Model 1239, Numonics). End-systolic and end-diastolic volumes were calculated from end-systolic and end-diastolic dimensions, respectively, according to the cube formula.\textsuperscript{9}

Echocardiographic indices of LV systolic function included fractional shortening, myocardial contractility (E\text{\textsuperscript{max}}),\textsuperscript{10} and cardiac output. E\text{\textsuperscript{max}} was calculated as the slope of the aortic peak-systolic pressure/end-systolic volume relationship. In addition, we calculated E\text{\textsuperscript{max}} by using the dicrotic notch of the pressure waveform recorded in the abdominal aorta for end-systolic pressure.\textsuperscript{11} These measurements were made from simultaneously recorded pressures and echocardiographic LV dimensions obtained during 7 to 10 cardiac cycles at each pressure level. LV fractional shortening was derived by the formula LVFS = EDD - ESD/EDD, where EDD = end-diastolic dimension, and ESD = end-systolic dimension. Cardiac output was calculated as stroke volume times heart rate. Plasma catecholamines were analyzed by radioenzymatic assay, and renin activity was analyzed by radioimmunoassay as described previously.\textsuperscript{12, 13}

Statistical Analysis

Data are presented as means ± SD. Differences were considered significant at \( p < 0.05 \). Data were analyzed with PROPHET, a computer system supported by the National Institutes of Health. Two-way analysis of variance for repeated measures was used. Alternatively, a nonparametric analysis (Newman-Keul’s test) or the unpaired \( t \) test was used as appropriate.\textsuperscript{14}

Results

Body weight and blood biochemical and volume changes are summarized in Table 1. Sodium depletion caused a significant reduction in body weight and increased plasma renin activity at 3 but not at 5 weeks, whereas changes in plasma volume and the ratio of cardiopulmonary blood volume to total blood volume were not statistically significant. There were no differences within or between the two dietary groups with respect to serum sodium and potassium concentrations. Arterial plasma catecholamine concentrations

---

**Table 1:** Sodium depletion caused a significant reduction in body weight and increased plasma renin activity at 3 but not at 5 weeks, whereas changes in plasma volume and the ratio of cardiopulmonary blood volume to total blood volume were not statistically significant. There were no differences within or between the two dietary groups with respect to serum sodium and potassium concentrations.

**Cardiac Flow Index and MTT**

<table>
<thead>
<tr>
<th>Group</th>
<th>Cardiac Flow Index</th>
<th>MTT (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Sodium</td>
<td>0.9 ± 0.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Regular Sodium</td>
<td>1.1 ± 0.2</td>
<td>0.9</td>
</tr>
</tbody>
</table>

**Cardiac Output**

<table>
<thead>
<tr>
<th>Group</th>
<th>Cardiac Output (L/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Sodium</td>
<td>2.5 ± 0.3</td>
</tr>
<tr>
<td>Regular Sodium</td>
<td>2.8 ± 0.4</td>
</tr>
</tbody>
</table>

**Echocardiographic Indices**

<table>
<thead>
<tr>
<th>Group</th>
<th>Fractional Shortening</th>
<th>E\text{\textsuperscript{max}} (mm Hg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Sodium</td>
<td>0.3 ± 0.1</td>
<td>20 ± 2</td>
</tr>
<tr>
<td>Regular Sodium</td>
<td>0.4 ± 0.2</td>
<td>22 ± 3</td>
</tr>
</tbody>
</table>

**Plasma Catecholamines**

<table>
<thead>
<tr>
<th>Group</th>
<th>Norepinephrine (ng/mL)</th>
<th>Epinephrine (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Sodium</td>
<td>120 ± 20</td>
<td>50 ± 10</td>
</tr>
<tr>
<td>Regular Sodium</td>
<td>180 ± 25</td>
<td>75 ± 15</td>
</tr>
</tbody>
</table>

---

To summarize, sodium depletion caused significant changes in body weight and plasma renin activity, but not in plasma volume or the ratio of cardiopulmonary blood volume to total blood volume.
tended to be higher in salt-depleted dogs than in dogs on the regular sodium diet (see Table 1), but differences were not significant.

Changes in hemodynamics and cardiac function indices are summarized in Table 2 and Figure 1. The differences in heart rate and mean arterial pressure between the two dietary groups were not significant during the 5 weeks of follow-up. LV ejection fraction and fractional shortening were similar in dogs on regular sodium intake (see Figure 1), where both functional indices decreased (from 61 ± 7 to 50 ± 7% at 3 weeks, and to 53 ± 6% at 5 weeks, p < 0.01 for both; and from 28 ± 3 to 22 ± 4% at 3 weeks, and to 23 ± 4% at 5 weeks, p < 0.01 for both, respectively) together with a reduction in LV end-diastolic diameter. Since there was no concomitant change in LV end-systolic diameter, LV stroke volume and cardiac output decreased. On the other hand, the load-independent index E_max was unchanged during both sodium depletion and regular sodium intake.

The effects of the two diets on cardiac catecholamines and hemodynamics are listed in Table 3. Resting heart rate, aortic pressure, and LV end-diastolic pressure were not significantly different between the two dietary groups. Under conditions of similar preload and afterload, LV pressure and LV dP/dt were also similar. On the other hand, sodium-depleted dogs showed a striking increase (p<0.01) in coronary sinus plasma norepinephrine concentration compared to control dogs, although arterial plasma norepinephrine was unchanged. The calculated norepinephrine gradient across the heart in sodium-depleted dogs was therefore significantly higher (p<0.005) than in the control group.

Discussion

Inasmuch as cardiac pump function is influenced by the intrinsic properties of the myocardium as well as by the loading conditions of the heart and norepinephrine release from cardiac sympathetic nerve endings, we
TABLE 3. Effects of Chronic Sodium Depletion on Norepinephrine Release from the Heart in Conscious Dogs

<table>
<thead>
<tr>
<th>Effect</th>
<th>Regular sodium (n = 6)</th>
<th>Low sodium (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic systolic pressure (mm Hg)</td>
<td>135 ± 10</td>
<td>139 ± 14</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>112 ± 12</td>
<td>112 ± 20</td>
</tr>
<tr>
<td>Left ventricular peak-systolic pressure (mm Hg)</td>
<td>118 ± 9</td>
<td>123 ± 12</td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure (mm Hg)</td>
<td>9 ± 4</td>
<td>6 ± 4</td>
</tr>
<tr>
<td>Left ventricular dP/dt (mm Hg/sec)</td>
<td>1804 ± 398</td>
<td>2033 ± 494</td>
</tr>
<tr>
<td>Aortic plasma norepinephrine (pg/ml)</td>
<td>380 ± 106</td>
<td>265 ± 127</td>
</tr>
<tr>
<td>Coronary sinus plasma norepinephrine (pg/ml)</td>
<td>297 ± 70</td>
<td>735 ± 298†</td>
</tr>
<tr>
<td>Net release of norepinephrine from the heart (pg/ml)*</td>
<td>-83 ± 111</td>
<td>444 ± 213‡</td>
</tr>
</tbody>
</table>

Data are presented as means ± SD.
*Net obtained by subtracting arterial from coronary sinus plasma norepinephrine concentrations.
†p < 0.01; ‡p < 0.005 (unpaired t test) compared to dogs on the regular sodium diet.

postulated that the previously reported reduction in ejection fraction and stroke volume in sodium-depleted dogs may be due to an alteration of either intrinsic myocardial contractility or neurohormonal and hemodynamic factors. In this study, both the end-systolic pressure/volume relationship and the peak-systolic pressure/end-systolic volume relationship were preserved during both sodium depletion and regular salt intake. These data suggested that intrinsic myocardial contractility was normal in salt-depleted dogs. However, the end-systolic pressure/volume relationship in the sodium-depleted group of dogs, resulting in net stability of myocardial contractility. It is possible that in our study the increase in myocardial catecholamines just counterbalanced the effect of decreased preload on the peak-systolic pressure/end-ejection volume relationship in the sodium-depleted group of dogs, resulting in net stability of our findings did not agree with those of Suga and colleagues, who demonstrated that the end-systolic pressure/volume relationship depends partially on preload in the isolated canine ventricle. Though such an effect was not validated in our closed-chest animal model, we took it into consideration in evaluating the relationship between changes in myocardial catecholamines and changes in indices of myocardial contractility. It is possible that in our study the increase in myocardial catecholamines just counterbalanced the effect of decreased preload on the peak-systolic pressure/end-ejection volume relationship in the sodium-depleted dogs. This observation supports the hypothesis that the lack of increase in contractility indices is due to diminished responsiveness to adrenergic influences rather than to a concomitant decrease in preload.

Our findings might have been affected by experimental conditions. In our study, the dogs' average heart rate was higher during the experiments designed to assess myocardial catecholamine release than in experiments designed to assess cardiac performance. We do not think, however, that these differences in heart rate should alter the conclusions drawn from our study. The higher heart rate during assessment of myocardial catecholamines was observed equally in the two dietary groups and could be explained by the lingering effects of anesthesia and surgical intervention.

Hemodynamic factors do, however, seem to have played a role in the reduction of LV ejection fraction and fractional shortening, as demonstrated by the concomitant reduction of end-diastolic LV cavity size.
The mechanism of reduction of LV end-diastolic dimensions requires explanation. It could have resulted from venodilation. However, our data in the conscious dog showed no significant change in the ratio of cardiopulmonary blood volume to total blood volume, whereas studies by Lynn et al. of the anesthetized, sodium-depleted dog revealed a significant increase in this ratio. These discrepancies may be related to the experimental conditions, such as the use of diuretics or anesthesia, the animals’ posture during the study, and the intrathoracic distribution of central blood volume.

In summary, we observed that chronic sodium depletion in conscious dogs caused a reduction of load-dependent indices of cardiac performance in association with a diminution of LV end-diastolic cavity dimension. Moreover, the preservation of E\(^{\text{max}}\) in the presence of increased available plasma norepinephrine denotes inadequate myocardial contractility. It may be explained by one of the following mechanisms: 1) inability of the normal myocardium to respond to norepinephrine excess, possibly due to a dysfunction at the neuroeffector junction; 2) normalization of an initially decreased E\(^{\text{max}}\) by an increase in available norepinephrine; 3) offsetting of an adequate myocardial response to norepinephrine by in vivo inhibitory neural or humoral factors; or 4) the possibility that E\(^{\text{max}}\) is not completely load-independent.

References

Changes in hemodynamics and myocardial contractility during chronic sodium depletion in conscious dogs.
T Nii, F M Fouad-Tarazi, C M Ferrario, E L Bravo and B Czerska

Hypertension. 1987;9:III176
doi: 10.1161/01.HYP.9.6_Pt_2.III176

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1987 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/9/6_Pt_2/III176

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/