Blood Pressure and Endocrine Responses to Changes in Dietary Sodium Intake in Cardiac Transplant Recipients

Implications for the Control of Sodium Balance

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The role of cardiac extrinsic innervation in the control of sodium balance is controversial. Studies in the 1950s in anesthetized animals suggest an important role for these reflexes because balloon distension within the atrium resulted in natriuresis and diuresis, which was diminished by surgical or chemical cardiac denervation. Atrial stretch results in release from the atria of atrial natriuretic peptide (ANP) in concentrations that have renin effects when reproduced by administration studies or by inhibition of catabolism of ANP. From studies in the denervated dog heart, Goetz suggests that changes in plasma ANP are dissociated from the natriuresis after increases in intracardiac pressure and stretch. However, cardiac denervation may result in reduced renal perfusion pressure, which is an important determinant of the renal actions of ANP. Maintaining adequate renal perfusion pressure is essential for the renal actions of ANP. Taken together, these studies provide evidence that ANP is one of the endocrine components of the cardioenal response to changes in intracardiac hemodynamics.

During cardiac transplantation, the donor heart is anastomosed to a vagally denervated remnant of recipient atrium, with only some residual sympathetic innervation. There is complete denervation of the donor heart and although reinnervation of the donor heart may occur, it usually is only partial, and any functionally important reinnervation usually occurs late after transplantation. Thus, the normal sympathetic and vagal influences on the heart are absent, and studies of cardiac transplant recipients provide a model with which to assess the role in humans of intact cardiac neural reflexes in the regulation of sodium balance. Basal plasma ANP levels are increased in cardiac transplant recipients, but the role of these raised plasma ANP levels in sodium regulation after cardiac denervation is not clear. However, they clearly are not solely explained by excretion from remnant recipient atrium because both ANP and the functionally similar brain natriuretic peptide are synthesized by the donor heart. An important clinical feature after cardiac transplantation is de novo hypertension. We therefore studied the renal and hormonal responses to short-term changes in dietary sodium intake in cardiac transplant recipients compared with two matched control groups—
healthy normotensive subjects and patients with untreated essential hypertension. To assess possible confounding effects on our results of gradual reinnervation of the donor heart, we also looked for possible relations between time after transplant and blood pressure and hormonal findings.

Methods
We studied three groups of outpatients at the Blood Pressure Unit. All subjects gave written informed consent to the studies, each of which was approved by the local ethical committee.

Group 1: Cardiac Transplant Recipients

Twelve healthy male orthotopic cardiac transplant recipients (11 white, 1 black; mean age, 50±3 years [SEM]; range, 26 to 61) were studied, of whom 8 were patients from the Cardiac Transplant Unit at Harefield Hospital and 4 were patients from the Cardiac Transplant Group, St George’s Hospital. Median time after transplantation was 44.5 weeks (range, 18 to 209 weeks), with 7 studied at up to 45 weeks (defined as “early”) and 5 studied at 74, 83, 92, 133, and 209 weeks (defined as “late”). Subjects either had not been treated for hypertension or had been off treatment with blood pressure-lowering drugs for at least 2 weeks before entry to the study. Average supine blood pressure was 146/98±6/4 mm Hg without blood pressure-lowering treatment 12 hours after receiving the usual immunosuppressive treatment with cyclosporin A and azathioprine and with subjects on their usual diet (urinary sodium excretion, 148±18 mmol/24 h). No subjects were receiving corticosteroid treatment, all were free from transplant rejection according to their most recent cardiac biopsy, and none had clinical features of cardiac failure. Blood pressure measurements and blood samples were obtained the morning after the last treatment dose on each of the three study days.

Group 2: Normal Subjects

Twelve healthy white subjects were studied who had normal blood pressure of 113/69±3/2 mm Hg while on their usual diet (urinary sodium excretion, 100±18 mmol/24 h). There were 9 men and 3 women, with an average age of 42±3 years (range, 32 to 55 years).

Group 3: Patients With Essential Hypertension

Twelve patients were studied who had established, uncomplicated essential hypertension. There were 10 men and 2 women (11 white, 1 Asian; average age, 50±3 years; range, 38 to 62 years). Average supine blood pressure without treatment was 158/107±4/2 mm Hg (n=8) with subjects on their usual diet (urinary sodium excretion, 128±14 mmol/24 h [n=11]). Subjects first were studied while on their usual sodium intake and then were entered into the double-blind portion of the study in which the response to two 5-day periods of low-and high-sodium intake was studied in each subject in random order. For the double-blind study, each subject was advised how to maintain a 10 mmol/d sodium diet, which was continued throughout each of the two 5-day parts of the double-blind study. This was achieved by not adding salt to the food when cooking or at the table, by avoiding the use of processed foods containing salt, and by ingesting salt-free bread and margarine. The high-sodium diet (350 mmol sodium/d) was achieved by adding 34 Slow Sodium tablets per day (10 mmol sodium per tablet; CIBA Laboratories) to the 10 mmol sodium diet. During the low-sodium portion of the study, subjects ingested an equal quantity of matching Slow Sodium placebo tablets (CIBA Laboratories) in addition to their low-sodium intake. Subjects were allowed free fluid intake during the studies.

Supine and standing blood pressures were measured in the same arm for each subject with an ultrasound sphygmoma-
TABLE 1. Blood Pressure, Heart Rate, Weight, and 24-Hour Urinary Measurements on the Fifth Day of Low- and Fifth Day of High-Sodium Diet in Cardiac Transplant Recipients, Healthy Subjects, and Patients With Essential Hypertension

<table>
<thead>
<tr>
<th></th>
<th>Cardiac Transplant Recipients</th>
<th>Healthy Subjects</th>
<th>Essential Hypertension</th>
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<tbody>
<tr>
<td></td>
<td>Low Sodium</td>
<td>High Sodium</td>
<td>Low Sodium</td>
</tr>
<tr>
<td>Supine heart rate, beats per minute</td>
<td>93±3</td>
<td>91±3</td>
<td>71±3†</td>
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<tr>
<td>Standing systolic pressure, mm Hg</td>
<td>131.2±8.3</td>
<td>141.4±6.0*</td>
<td>105±3§</td>
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<tr>
<td>Standing diastolic pressure, mm Hg</td>
<td>93.8±4.6</td>
<td>99.5±4.0</td>
<td>77.4±2.7§</td>
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<tr>
<td>Standing heart rate, beats per minute</td>
<td>94±3</td>
<td>95±3</td>
<td>85±3</td>
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<tr>
<td>Supine mean arterial pressure, mm Hg</td>
<td>108.4±4.8</td>
<td>113.9±3.2</td>
<td>82.9±2.9†</td>
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<td>Standing mean arterial pressure, mm Hg</td>
<td>106.3±5.6</td>
<td>113.5±4.2</td>
<td>86.6±2.5§</td>
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<tr>
<td>Weight, kg</td>
<td>77.0±3.0</td>
<td>77.8±2.9†</td>
<td>79.5±4.1</td>
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<tr>
<td>Urinary creatinine, mmol/24 h</td>
<td>11.0±0.8</td>
<td>12.4±0.9</td>
<td>14.5±1.5§</td>
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<td>Urinary potassium, mmol/24 h</td>
<td>64±5</td>
<td>73±5</td>
<td>74±7</td>
</tr>
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<td>Urine volume, L/24 h</td>
<td>1.68±0.12</td>
<td>2.18±0.15†</td>
<td>2.33±0.22§</td>
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</tbody>
</table>

*P<.05, †P<.01 for low- vs high-sodium diet within group.
§P<.05, ‖P<.01, ¶P<.001 for low- or high-sodium diet vs cardiac transplant group.

(increase of 14.4±4 mm Hg, P<.01). There was a much smaller increase in systolic pressure in changing from low- to high-sodium intake in the healthy subjects (increase of 5.2±2 mm Hg, P<.05). Supine diastolic pressure was significantly increased by high-sodium intake in patients with essential hypertension (P<.05, Fig 1) but not in the cardiac transplant recipients or the healthy subjects (Fig 1). There were similar changes in standing blood pressure with altered dietary sodium intake (Table 1). There were no significant differences in heart rate with changes in sodium intake (Table 1). However, resting heart rate was higher in the transplant recipients (Table 1).

Weight was significantly and similarly increased on the high-sodium diet compared with the low-sodium diet in cardiac transplant recipients (0.9±1.0 kg) and in patients with essential hypertension (1.0±0.3 kg, Table 1). The weight increase in changing from low- to high-sodium diet in healthy subjects was 1.6±0.3 kg (not significantly different from the increase in the other two groups).

Plasma ANP, Renin Activity, and Aldosterone

Basal plasma ANP in the cardiac transplant recipients on a normal diet was 64.1±10.4 pg/mL (P=.001 versus healthy subjects; 5.8±1.6 pg/mL). Plasma ANP increased significantly from a low- to a high-sodium intake in each group of subjects (Fig 2). Plasma ANP was 1.6-fold greater (geometric mean; range, 1.1-fold to 3.2-fold) on the high-sodium diet compared with the low-sodium diet in the cardiac transplant recipients. Levels of plasma ANP were significantly higher in the cardiac transplant recipients than in patients with essential hypertension and significantly higher in patients with essential hypertension than in healthy subjects on either high- or low-sodium intake (Fig 2). The proportional increase in plasma ANP levels with dietary sodium intake was not significantly different than the increases in plasma ANP in the healthy (2.1-fold; range, 1.1- to 3.9-fold) or the hypertensive subjects (1.8-fold; range, 1.1- to 3.2-fold) in changing from the low- to high-sodium diet.

Plasma renin activity in the transplant recipients on a normal diet (2.10±0.40 ng·mL⁻¹·h⁻¹) was similar to values in healthy subjects (2.24±0.37 ng·mL⁻¹·h⁻¹). Plasma renin activity increased significantly in all three groups on the low-sodium diet compared with the high-sodium diet (Fig 2). On the low-sodium diet, plasma renin activity in the cardiac transplant recipients was slightly but not significantly higher than that in healthy or hypertensive subjects (Fig 2). Plasma renin activity and aldosterone were significantly less suppressed on the high-sodium diet in cardiac transplant recipients than in the healthy subjects (Fig 2, P<.05).

In the transplant recipients on a normal diet, plasma aldosterone levels (504±82 pmol/L) were comparable to levels in healthy subjects (487±66 pmol/L) and significantly higher than levels in patients with essential hypertension (341±88 pmol/L, P<.05). Plasma aldosterone was slightly but not significantly higher on the low-sodium diet in the cardiac transplant group than in healthy subjects. On the high-sodium diet, plasma aldosterone levels in the cardiac transplant recipients and in the patients with essential hypertension were comparable and significantly less suppressed than levels in the healthy subjects (P<.05 versus healthy subjects, Fig 2).

Urinary Sodium, Potassium, Creatinine, and Water Excretion

On the fifth day of each level of sodium intake, 24-hour urinary sodium excretion was similar in each
group (low-sodium diet: transplant recipients, 39±6 mmol; healthy subjects, 38±8 mmol; patients with essential hypertension, 28±6 mmol; high-sodium diet: transplant recipients, 337±22 mmol; healthy subjects, 355±13 mmol; patients with essential hypertension, 300±17 mmol). The 24-hour urinary potassium excretion was similar both within groups and in each of the three groups on either the low- or the high-sodium diet (Table 1).

The 24-hour urine volume increased significantly in changing from the low- to the high-sodium diet in the cardiac transplant recipients and patients with essential hypertension. There was a small increase in 24-hour urine volume in the healthy subjects that did not reach statistical significance (Table 1). Creatinine clearance was significantly reduced in the cardiac transplant recipients compared with both control groups, decreasing from 65±5 mL/min on the high-sodium diet to 48±4 mL/min on the low-sodium diet (P<.001, Table 1). There were similar changes in creatinine clearance with diet in the subgroup of seven subjects in whom cyclosporin A levels were measured on each diet (see below). There was no significant change in creatinine clearance with dietary sodium intake in either the healthy subjects or patients with essential hypertension (Fig 3).

Cyclosporin A and Dietary Sodium Intake

In 7 of the cardiac transplant recipients, whole-blood cyclosporin A levels were measured 24 hours after treatment. Cyclosporin A levels were significantly higher on the low-sodium diet (180±34 ng/mL whole blood) than in the high-sodium diet (130±16 ng/mL whole blood, P<.05). There were significant changes in creatinine clearance with altered dietary sodium intake in the subgroup of 7 subjects in whom cyclosporin A levels were measured (high-sodium diet, 69±7 mL/min; low-sodium diet, 50±5 mL/min; P=.001).

Other Measurements

There was mild renal impairment in the cardiac transplant recipients (Table 2). In these patients, serum sodium was significantly lower, and hemoglobin, urea, creatinine, total protein, serum calcium, and phosphate were significantly increased on the low-sodium diet compared with the high-sodium diet (Table 2). The pattern of changes in these results with sodium intake was similar in the healthy and hypertensive subjects. In the cardiac transplant recipients, urinary calcium excretion was 1.6±0.3 (low sodium), 1.9±0.3 (normal diet), and 4.0±0.3 mmol/24 h (high sodium) (n=4; one-way ANOVA F=18.9, P<.003, low versus high sodium P<.01 by t test using the variance from the ANOVA; Fig 3).

There were no adverse symptoms or clinical signs in those on the low- or the high-sodium diet.
TABLE 2. Biochemical and Hematological Measurements on the Fifth Day of Low- and Fifth Day of High-Sodium Diet In Cardiac Transplant Recipients, Healthy Subjects, and Patients With Essential Hypertension

<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>Low Sodium</td>
<td>High Sodium</td>
<td>Low Sodium</td>
<td>High Sodium</td>
<td>Low Sodium</td>
</tr>
<tr>
<td>Plasma sodium, mmol/L</td>
<td>136±1</td>
<td>141±1*</td>
<td>139±1§</td>
<td>142±1†</td>
<td>138±1</td>
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<td>Plasma potassium, mmol/L</td>
<td>4.6±0.1</td>
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<td>4.2±1§</td>
<td>4.2±1</td>
<td>3.7±0.2†</td>
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<td>Total protein, g/L</td>
<td>75±2</td>
<td>72±2*</td>
<td>67±2§</td>
<td>64±2§</td>
<td>74±3</td>
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<td>Albumin, g/L</td>
<td>42±1</td>
<td>43±1</td>
<td>46±1§</td>
<td>44±1</td>
<td>45±1</td>
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<td>Urea, mmol/L</td>
<td>12.4±1.3</td>
<td>8.6±0.7†</td>
<td>4.6±0.3§</td>
<td>4.0±0.3§</td>
<td>5.4±0.4§</td>
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<tr>
<td>Plasma creatinine, µmol/L</td>
<td>173±12</td>
<td>140±11‡</td>
<td>94±7†</td>
<td>91±5§</td>
<td>88±4†</td>
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<td>Calcium, mmol/L</td>
<td>2.37±0.02</td>
<td>2.30±0.02†</td>
<td>2.38±0.04</td>
<td>2.29±0.03</td>
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<td>Phosphate, mmol/L</td>
<td>1.04±0.08</td>
<td>0.87±0.07†</td>
<td>1.03±0.06</td>
<td>1.03±0.05*</td>
<td>0.95±0.04</td>
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<td>Hemoglobin, g/dL</td>
<td>12.9±0.4</td>
<td>12.2±0.4*</td>
<td>13.7±0.7</td>
<td>13.0±0.4</td>
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<tr>
<td>Packed cell volume, %</td>
<td>37.6±1.5</td>
<td>36.2±1.1</td>
<td>40.0±2.0</td>
<td>39.0±1.8</td>
<td>40.4±1.2</td>
</tr>
</tbody>
</table>

*P<.05, †P<.01, ‡P<.001 for low- vs high-sodium diet within groups.
§P<.05, ¶P<.01, †P<.001 for low- or high-sodium diet vs cardiac transplant group.

Relation Between Time After Transplantation and Blood Pressure, Heart Rate, Urinary Sodium Excretion, and Hormone Measurements

In transplant recipients on their usual diet, resting supine heart rate, an index of loss of vagal tone, was raised compared with healthy and hypertensive subjects (Table 1) at 89±2 beats per minute in the early group of transplant recipients and did not decrease with time after transplantation (95±6 beats per minute in the late group). Furthermore, the increase in heart rate from supine to standing, an index of reflex neural responses, was similarly blunted early (4±4 beats per minute) and late (4±3 beats per minute) after transplantation compared with healthy (10±2 beats per minute) and hypertensive (9±2 beats per minute) subjects. Blood pressure reduction in changing from high- to low-sodium intake occurred in subjects both early and late after transplantation (early, 155/99±7/5 to 142/95±12/6 mm Hg; late, 139/93±4/4 to 130/93±9/6 mm Hg).

The sodium excretion achieved by 5 days on each diet was similar for early and late groups (Table 3). Hormonal changes occurring when switching from high- to low-sodium intake were similar in pattern in the early and late groups for ANP, plasma renin activity, and aldosterone levels (Table 3).

Cardiac transplantation data by time after transplantation revealed no significant relation between time since surgery and either blood pressure, heart rate, renal function, or hormone levels while on the usual diet or the changes occurring in hormone levels or blood pressure with dietary sodium intake.

Discussion

There were two major findings of this study. First, extensive denervation of the heart in humans as a result of cardiac transplantation does not cause any major abnormality in the regulation of large changes in sodium intake. Second, the mechanisms for regulation of blood pressure in cardiac transplant recipients are very sodium sensitive, with a large decrease in systolic blood pressure occurring when changing from a high- to a low-sodium diet.

Cardiac transplant recipients were able to conserve sodium and came into sodium balance on the high-sodium diet within 5 days without any clinical evidence of sodium and water retention. The weight difference between low- and high-sodium diets was similar to the weight changes in healthy subjects or in patients with essential hypertension, with corresponding changes in dietary sodium intake. Vagal fibers appear to constitute...
the afferent pathway for the neural response to atrial stretch, and orthotopic cardiac transplantation leads to section of these vagal afferent fibers. Our results are in marked contrast to those of the earlier studies of cardiac denervation in anesthetized animals and are consistent with the observation of Blaine that when renal perfusion is maintained after cardiac denervation, the natriuretic response to stretch is preserved. Our findings suggest either that in humans cardiac innervation is of little importance in the control of sodium or that after cardiac transplantation other mechanisms chronically compensate well for the loss of cardiac neural reflexes, with no residual major impairment in the regulation of even very large changes in dietary sodium intake. Our results suggest in particular that loss of cardiac vagal afferent and efferent reflexes has little long-term impact on the regulation of ANP secretion, activity of the renin-angiotensin-aldosterone system, or sodium balance. We were unable to detect evidence in the cardiac transplant recipients for any functional importance of any possible gradual reinnervation of the donor heart as assessed by the lack of change with time after transplantation in the resting heart rate, in heart rate response to change in posture, or in hormonal or hemodynamic responses to altered dietary sodium intake.

Our study confirms previous reports that plasma ANP levels are elevated in cardiac transplant recipients and provides evidence that stimulation of ANP secretion by a high-sodium diet remains a contributory mechanism for regulation of sodium balance despite denervation of the heart by cardiac transplantation. A number of physiological stimuli are associated with an increase in central blood volume, including dietary sodium loading, water immersion, and exercise. All these stimuli have been reported to result in an increase in plasma ANP levels in healthy subjects. In the present study, the proportional increase in plasma ANP levels in response to sodium loading in cardiac transplant recipients was similar to that in healthy subjects and in previous reports on changing from low- to high-sodium intake. This suggests that innervation of the heart is not required for the plasma ANP response to changes in sodium intake. The order of increase in plasma ANP levels with dietary sodium intake in cardiac transplant recipients in the present study was similar to that shown in low-dose ANP administration or neutral endopeptidase inhibition studies to cause significant natriuresis and diuresis. The finding that increased sodium intake is associated with a physiologically significant increase in levels of plasma ANP suggests that ANP plays a role in the regulation of sodium balance when the heart is denervated in humans.

The results of the present study also suggest that the renin-angiotensin-aldosterone system appears to play a role in the response to changes in dietary sodium intake similar to that seen in healthy subjects with intact cardiac innervation. In cardiac transplant recipients, activation of the renin-angiotensin-aldosterone system by a low-sodium diet and suppression of this system by a high-sodium diet, as assessed by measurements of plasma renin activity and aldosterone, were qualitatively similar to the responses in healthy subjects. Furthermore, the absolute levels of plasma renin activity and of aldosterone stimulated by the low-sodium diet were similar to those of healthy subjects of comparable age. This suggests that cardiac denervation in these patients does not influence the effects of baroreceptor adrenergic outflow on renin release by the juxtaglomerular apparatus in the kidney in response to a decrease in sodium intake. In contrast, plasma renin activity and aldosterone were significantly less suppressed by a high-sodium diet in cardiac transplant recipients than in healthy subjects. This may have been the result of reduced central baroreceptor outflow to inhibit renin release from the kidney, although treatment with cyclosporin A could also have been a mechanism for failure to suppress renin normally while on the high-sodium diet.

Basal blood pressure was elevated in both cardiac transplant recipients and patients with essential hypertension. In each of these groups, large decreases in blood pressure occurred when changing from a high- to a low-sodium diet. In the cardiac transplant recipients, there was relatively less suppression of plasma renin activity and aldosterone on the high-sodium diet than in healthy subjects. In contrast, the levels of plasma renin activity and aldosterone were similar in all three groups on the low-sodium diet. One possible mechanism in the cardiac transplant recipients may be that activation of the renin system by cyclosporin A is dependent on sodium intake, with considerable effect on the high-sodium diet but little effect on the low-sodium diet. An alternative explanation is that cardiac neural outflow plays a major homeostatic role in vivo in humans, by other mechanisms, in the response of the renin system to altered intravascular volume. This could explain the contrast between the small decrease in systolic blood pressure in short-term studies of sodium restriction in healthy subjects and the large decrease in systolic pressure with short-term reduction in dietary sodium intake in cardiac transplant recipients.

In the present study, changes in chemical factors were similar to those in healthy subjects in changing from a high- to a low-sodium diet, with decreases in serum sodium and increases in indexes of hemoconcentration. Of particular interest were changes in calcium metabolism with altered dietary sodium intake in the cardiac transplant recipients. Decreased urinary calcium excretion and increased blood calcium levels in humans reducing dietary sodium intake and increased urinary calcium excretion with volume expansion have been reported in healthy humans. Our results indicate that the mechanisms for the effects of altered sodium intake on calcium metabolism are not dependent on cardiac innervation in humans. More speculatively, reducing sodium intake may improve calcium balance in these patients, which is of particular relevance to transplant patients who are receiving corticosteroid treatment or who undergo prolonged reduction in mobility because of intercurrent illness and thus are at high risk of osteoporosis.

The increase in trough postdose blood cyclosporin A levels in changing from a high- to a low-sodium diet was greater than expected from hemoconcentration alone on the low-sodium diet. This finding suggests that cyclosporin catabolism may be influenced by the level of dietary sodium intake, with reduced catabolism of cyclosporin A on the low-sodium diet. In previous studies of similar short-term changes in dietary sodium intake, no significant reduction in creatinine clearance was observed with dietary sodium restriction in healthy subjects.
subjects,26 in essential hypertension,29 or in mild-to-severe chronic renal failure.30 The significant reduction in glomerular filtration rate in the cardiac transplant recipients in changing from the high- to the low-sodium diet, as assessed by creatinine clearance, may therefore have been in part the result of altered metabolism of cyclosporin A with sodium restriction; it is clear that high levels of cyclosporin A are associated with reduced renal function.31 There was little difference in creatinine clearance between the usual diet and the high-sodium diet in this study. There has been recent interest in pharmacological interaction with cyclosporin A by the antihypertensive calcium entry antagonist diltiazem, which reduces catabolism of cyclosporin A by cytochrome P450 and thus the daily dose required32 and costs of treatment. A low-sodium diet may be a non-pharmacological alternative way in which to reduce cyclosporin A requirements and thus to contain costs of treatment in transplant recipients.

This study showed that denervation of the heart achieved by cardiac transplantation in humans does not result in any major abnormality in the regulation of large changes in sodium intake; in particular, subjects were able to conserve sodium. Our study also suggests that normal extrinsic innervation of the heart is not required for the plasma ANP response to physiological stimuli associated with changes in central blood volume and thus atrial stretch. The results of the present study are consistent with a role both for ANP and for the renin-angiotensin-aldoosterone system in the regulation of sodium balance in humans after cardiac denervation. After cardiac denervation, blood pressure was sensitive to reduced dietary sodium intake, which should be considered a possible nonpharmacological measure in the management of hypertension in these patients.

Acknowledgments
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References
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