Impaired Baroreceptor Control of Renal Sympathetic Activity in Human Chronic Heart Failure

Abdul Al-Hesayen, MD; John D. Parker, MD

Background—The regulation of renal sympathetic activity in the setting of heart failure is largely unexplored. We used the norepinephrine spillover method to address the hypothesis that baroreflex control of renal sympathetic activity is blunted in heart failure.

Methods and Results—Twenty-two patients were studied, 11 in a group with heart failure and 11 in a group with normal ventricular function. In both groups, renal norepinephrine spillover was assessed in response to sodium nitroprusside infused to steady-state conditions. Sodium nitroprusside resulted in significant reductions in mean systemic arterial pressure (normal group, −13±1% [mean±SEM]; heart failure group, −12±1%). In response to nitroprusside, there was an 85±34% increase in renal norepinephrine spillover in the normal group (from 537±84 to 840±140 pmol/min, P<0.05). Despite similar hemodynamic responses to nitroprusside in the heart failure group, renal norepinephrine spillover was unchanged (from 1420±153 to 1387±161 pmol/min, P=NS), a response that was significantly different from that seen in the normal group.

Conclusions—In patients with heart failure, compared with those with normal ventricular function, renal sympathetic activity did not change in response to a steady-state infusion of sodium nitroprusside. This result provides evidence for reduced baroreflex control of renal sympathetic activity in heart failure. (Circulation. 2004;109:2862-2865.)

Key Words: baroreceptors ■ heart failure ■ vasodilation

Chronic heart failure (CHF) is a characterized by early activation of multiple neurohormonal systems in an effort to maintain cardiac output, blood pressure, and effective circulating arterial blood volume. The kidney plays a central role in homeostasis and is an important target of the neurohormonal activation that occurs in the setting of CHF. Indeed, CHF is characterized by reductions in renal plasma flow (RPF) and glomerular filtration rate (GFR) and is a state of avid sodium and water retention.1 Along with contributing to the symptomatic status in these patients, renal dysfunction is an independent predictor of mortality in the setting of heart failure.2

CHF is associated with generalized and organ-specific increases in efferent sympathetic nerve activity, with the greatest activation directed at the heart and kidneys.3 This sympathetic activation contributes to the alterations in renal function that are well described in patients with CHF. These effects are mediated through α1-, β1-, and β2-adrenergic receptors on renal blood vessels, glomerular mesangium, and proximal tubules.4 However, the control of efferent renal sympathetic activity in the setting of human CHF remains largely unexplored.

Animal models of CHF suggest that baroreceptor reflex control of renal sympathetic tone might be impaired.5,6 In human CHF, we demonstrated that baroreflex impairment is organ specific, with preserved responses of total-body norepinephrine spillover to generalized baroreceptor unloading but impaired responses of cardiac norepinephrine spillover in CHF patients.7 To date, there is little information in the setting of human CHF about the impact of baroreceptor unloading on efferent renal sympathetic activity.

We hypothesized that baroreflex control of renal sympathetic activity is impaired in the setting of human CHF. We measured renal norepinephrine spillover responses to generalized baroreceptor unloading using an infusion of sodium nitroprusside (SNP).

Methods

Patients

The study population consisted of 22 patients. Eleven subjects with normal left ventricular (LV) function as assessed by 2D echocardiography (mean age, 56±3 years) underwent coronary angiography to investigate a chest pain syndrome. Six of these had coronary artery disease. Medical therapy in these patients included a β-blocker (n=7), calcium channel blocker (n=4), ACE inhibitor (n=2), and angiotensin-receptor blocker (n=1). Eleven patients had CHF (LV ejection fraction by radionuclide angiography of 21±2%); LV end-diastolic dimension, 73±2 mm; mean age, 58±2 years) and underwent cardiac catheterization as part of a heart failure assessment. The mean serum sodium concentration was 135±1 mmol/L. The pathogenesis of the heart failure was ischemic in 8 patients and idiopathic in 3 patients. The medical therapy consisted of a β-blocker (n=5), digoxin (n=6), amiodarone (n=6), and ACE inhibitor (n=11). All patients had NYHA class III symptoms.
Procedure
A diagnostic left and right heart catheterization from the femoral approach was performed without sedation. After the diagnostic procedure, the pulmonary artery catheter was left in place. A 6F Judkins left diagnostic catheter was inserted via the femoral vein and positioned under fluoroscopic guidance in the right renal vein for blood sampling. Femoral artery pressure was monitored via a 6F side-arm sheath (Cordis Laboratories).

Norepinephrine Spillover Measurements
Sympathetic activity was estimated by the measurement of renal and total-body norepinephrine spillover. For these measurements, tritiated norepinephrine (1 to 1.2 μCi/min with a 16 μCi priming bolus of 1-[2,5,6-3H]norepinephrine; New England Nuclear) was infused into a peripheral vein to steady-state concentration in plasma. Norepinephrine clearance and spillover rates were calculated as previously described.6,9

RPF and GFR
RPF was measured by use of the p-aminohippurate clearance technique. GFR was measured by use of inulin clearance. p-Aminohippurate and inulin priming bolus was followed by a steady-state infusion into a peripheral vein. Arterial versus renal vein concentrations of p-aminohippurate and inulin were determined to measure RPF and GFR, respectively.5

Biochemistry
Plasma catecholamine concentrations were measured by high-performance liquid chromatography (HPLC) with electrochemical detection. Fractions from the HPLC effluent containing tritium-labeled norepinephrine were assayed by liquid scintillation spectroscopy. These analyses were performed by established methods in our laboratory by personnel blinded to patient status.6,9

Study Protocol
After the diagnostic heart catheterization and insertion of catheters for hemodynamic monitoring, the patient was left undisturbed for a period of 60 minutes to achieve steady state. Baseline hemodynamic measurements were obtained, along with measures of total-body and renal norepinephrine spillover. Subsequently, an intravenous infusion of SNP was initiated, starting at 10 μg/min. The SNP infusion rate was increased until the mean arterial pressure had decreased by 10%. Hemodynamic and total-body and renal norepinephrine spillover were reassessed 30 minutes after this reduction in mean arterial pressure had been achieved.

Statistical Analysis
Data are presented as the mean±SEM. Between-group comparisons of baseline characteristics were performed with unpaired t test. Within-group comparisons of the effects of SNP on hemodynamics, catecholamine concentration, and norepinephrine kinetics were made by a paired t test. Between-group comparisons of the effects of SNP were performed with the use of ANCOVA. A value of P≤0.05 was required for statistical significance.

Results
Baseline Characteristics
The heart failure (CHF) patients had significantly higher cardiac filling pressures than the normal LV function subjects. Total-body and renal norepinephrine spillover were elevated in the CHF group compared with the normal LV function group. Similarly, arterial and renal vein norepinephrine levels were higher in the CHF group (Table).

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<th>Procedure</th>
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<td>A diagnostic left and right heart catheterization from the femoral approach was performed without sedation. After the diagnostic procedure, the pulmonary artery catheter was left in place. A 6F Judkins left diagnostic catheter was inserted via the femoral vein and positioned under fluoroscopic guidance in the right renal vein for blood sampling. Femoral artery pressure was monitored via a 6F side-arm sheath (Cordis Laboratories).</td>
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NLV indicates normal ventricular function; HR, heart rate; RAP, right atrial pressure; PAwedge, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; MAP, mean arterial pressure; CO, cardiac output; NEarter, arterial norepinephrine; NErenal, renal vein norepinephrine; TBESP, total body norepinephrine spillover; and RNESP, renal norepinephrine spillover. *P<0.05 vs CHF, †P<0.05 vs baseline.

Hemodynamic Responses
SNP caused a significant reduction in systemic arterial and central filling pressures in both groups. By design, the magnitude of change in systemic arterial pressure was similar (−13±1% versus −12±2%, normal versus CHF, P=NS). There were no significant differences between the 2 groups in the effects of SNP on mean pulmonary arterial pressure (−41% versus −31%, P=NS) or pulmonary capillary wedge pressure (−53% versus −46%, P=NS). SNP reduced the cardiac output in the normal LV function group and increased it in CHF patients (−8% versus +19%, normal versus CHF, P<0.001). Heart rate increased significantly in the normal LV function group in response to SNP (65±3 versus 71±4 bpm, P<0.05). In both groups, RPF and GFR remain unchanged during the infusion of SNP (Table).

Renal Sympathetic Responses
Renal norepinephrine spillover was unchanged during SNP infusion in the CHF group (1420±153 versus 1387±161 pmol/min, P=NS). By contrast, SNP infusion was associated with a significant increase in renal norepinephrine spillover in the normal LV function group (537±84 versus 840±140 pmol/min, P<0.05). In comparing the 2 groups, the renal norepinephrine spillover responses to SNP were significantly different (+85±34% versus +1.6±5%, normal versus CHF, P<0.02). The changes in renal vein norepinephrine levels reflected the changes observed in renal norepinephrine spillover (Table and Figure).

Systemic Sympathetic Responses
In both groups, SNP infusion was associated with a significant increase in total-body norepinephrine spillover (Table).
studies have documented an abundance of neuroeffector junctions in the proximal convoluted tubules and the presence of renal dysfunction in this patient population. Anatomic efferent sympathetic activity plays a major role in the level of activation of renal sympathetic tone was required before changes in renal hemodynamics were observed. The major findings of this study are that (1) generalized baroreceptor unloading produced by SNP is associated with a reflex increase in renal efferent sympathetic nerve activity in subjects with normal LV function; (2) the same stimulus did not change renal norepinephrine spillover in CHF subjects; and (3) in both groups, steady-state vasodilation had no effect on RPF or GFR.

Heart failure is characterized by early activation of the sympathetic nervous system, with the greatest activation directed at the heart and kidneys. The increase in renal efferent sympathetic activity plays a major role in the sodium-avid state that characterizes CHF and is a contributor to renal dysfunction in this patient population. Anatomic studies have documented an abundance of neureffector junctions in the proximal convoluted tubules and the presence of \( \alpha \)-, \( \beta \)-, and \( \gamma \)-adrenergic receptors. Bello-Reuss et al have shown that acute renal denervation caused a marked depression of sodium and water resorption in the proximal tubule in whole-kidney and single-nephron studies in the absence of any alteration in RPF. This dissociation between proximal tubular functions and hemodynamic alterations has been confirmed by other animal studies showing that a higher level of activation of renal sympathetic tone was required before changes in renal hemodynamics were observed.

In the present investigation, SNP infusion resulted in an 85% increase in renal norepinephrine spillover in the normal LV function group. This finding is consistent with animal data showing an increase in renal nerve firing rate with unloading of carotid baroreceptors. Our findings corroborate the report from Tidgren et al in which an increase in renal vein norepinephrine levels occurred in response to hypotensive lower-body negative pressure in normal subjects. We observed no change in RPF or GFR with this increase in renal norepinephrine spillover. This finding might seem contradictory to a report by Middelkaufl et al describing a reduction in renal cortical blood flow during phlebotomy in healthy humans. However, renal sympathetic tone was not measured in that study, and different degrees of renal sympathetic activation cannot be ruled out. It is possible that the level of activation achieved with SNP was below the threshold required to alter RPF. Furthermore, the differences in the interventions used in the experimental protocols might explain this observation. Indeed, SNP infusion in normal subjects has previously been shown to have a neutral effect on RPF.

In CHF patients, renal norepinephrine spillover was unchanged during SNP infusion. This observation might be related to maximal stimulation of renal sympathetic activity at baseline with a failure to achieve any further activation with baroreceptor unloading. This seems unlikely, because previous studies have shown an increase in renal norepinephrine spillover in response to exercise in patients with CHF. Therefore, we believe that these findings are more likely to represent an impairment in the baroreceptor control of renal sympathetic nerves. Attenuated baroreceptor control of efferent cardiac sympathetic activity has been documented in the setting of CHF. Our findings confirm that this attenuated response is not restricted to the heart in CHF patients. Three mechanisms could potentially explain this attenuated response in efferent renal sympathetic activity. First, reduced baroreceptor sensitivity, which has been demonstrated in animal models of CHF, could account for impaired renal sympathetic responses to baroreceptor unloading. Another potential explanation is a change in the operational point of the baroreflex stimulus—renal response relation toward the threshold for baroreceptor firing in CHF. A third possibility involves unique sympathoexcitatory reflexes that appear to be operative in the setting of CHF. In animal models of CHF, it has been documented that increases in left atrial pressure are associated with paradoxical increases in renal sympathetic nerve traffic, whereas reductions in atrial pressure have the opposite effect. Such reflexes are paradoxical, because increases in left atrial pressure normally cause a reduction in renal sympathetic nerve traffic with an associated increase in sodium excretion, whereas a reduction in left atrial pressure has the opposite effect. This abnormal sympathoexcitatory reflex associated with increased cardiac filling pressures has been documented in human CHF, in which reductions in filling pressure cause cardiac-specific decreases in sympathetic outflow. In light of this, the hypothesis is raised that nitroprusside had had neutral effects on renal sympathetic activity in patients with CHF because of a balanced effect of a reduction in sympathetic outflow mediated by a reduction in cardiac filling pressures and the expected increase in sympathetic tone caused by arterial baroreceptor unloading. Therefore, different responses might have been observed with direct cardiopulmonary or arterial baroreceptor manipulations.

The present data are not inconsistent with a recent report from Brunner-La Rocca et al. They report that an infusion of brain natriuretic peptide in patients with CHF, an intervention that reduced diastolic systemic arterial pressure as well as pulmonary capillary wedge pressure, was associated with a reduction in renal norepinephrine spillover. Although we did not observe a renal sympathetic inhibitory effect, despite similar hemodynamic changes, the differential effect on sympathetic outflow to the kidney may be explained by the specific sympathetic inhibitory effects of natriuretic peptides.
Despite a 19% increase in cardiac output, no changes were observed in RPF or GFR. This might seem contradictory to a report by Cogan et al., who report a 33% increase in renal blood flow with SNP in patients with heart failure. However, a larger increase in cardiac index (35%) in response to SNP in their patient population could explain these differences. Furthermore, our data are consistent with other reports in patients with CHF and normal subjects describing constant renal blood flow in response to SNP infusion.\(^{16,27}\) This observation speaks to the ability of the kidney to autoregulate its blood flow despite alteration in perfusion pressure.\(^{28}\)

These findings document that the acute infusion of SNP, although effective in lowering filling pressures and increasing cardiac output, did not cause an increase in RPF and GFR. This negative result was observed even though these patients had severe CHF with markedly depressed LV function and high pulmonary capillary wedge pressure. These findings suggest that vasodilators alone are not an effective mechanism for improving renal function in patients with CHF (we recognize that SNP might have had a beneficial effect on renal sodium handling, an end point we did not measure). The fact that SNP did not cause a reduction in renal sympathetic activity may provide an explanation for the lack of its effect on GFR and RPF. With this in mind, vasodilators that inhibit the renin-angiotensin axis have been shown to improve renal function in patients with CHF.\(^{29}\) These agents can also lower filling pressures and increase cardiac output. Although their impact on renal sympathetic tone in the setting of human CHF has never been described, they have been shown to reduce sympathetic activity in the situations of elevated sympathetic drive.\(^{30–32}\)

In conclusion, we have described the response of the renal norepinephrine spillover to generalized baroreceptor unloading. We have documented an attenuation in the baroreflex control of efferent renal sympathetic activity in heart failure patients with lack of a beneficial effect on RPF and GFR. This observation is clinically relevant, given the frequency of SNP infusion use in the setting of compensated CHF.

**Acknowledgments**

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**References**

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