Reducing Cardiac Filling Pressure Lowers Norepinephrine Spillover in Patients With Chronic Heart Failure

Eduardo R. Azevedo, MD; Gary E, Newton, MD; John S. Floras, MD, DPhil; John D. Parker, MD

Background—We studied the cardiac sympathetic response to selective unloading of cardiopulmonary baroreceptors in subjects with normal left ventricular (LV) function and congestive heart failure (CHF).

Methods and Results—Eight patients with normal LV function (age 57±5 years, ejection fraction 58±2%) and 8 patients with CHF (age 60±2 years; ejection fraction 19±2%) were studied. Instrumentation consisted of an arterial line, a pulmonary artery catheter, and a coronary sinus thermodilution catheter. The radiotracer technique was used for measurement of cardiac norepinephrine spillover (CANESP) and total-body norepinephrine spillover. Lower-body negative pressure (LBNP) was applied at 2 levels: nonhypotensive and hypotensive LBNP. Nonhypotensive LBNP reduced filling pressures significantly in both groups. Arterial pressure did not change. This reduction in filling pressures caused a significant reduction in CANESP in the CHF group (from 167±53 to 125±37 pmol/min, P<0.05) but no change in the normal LV function group. Hypotensive LBNP caused a significant increase in CANESP in the normal group (73±13 vs 122±27 pmol/min, P<0.05) but no significant change in those with CHF.

Conclusions—We conclude that selective reduction in filling pressures lowers cardiac norepinephrine spillover in patients with CHF. These findings suggest that a goal of CHF management should be to reduce cardiac filling pressures while avoiding systemic hypotension. (Circulation. 2000;101:2053-2059.)

Key Words: norepinephrine • sympathetic nervous system • autonomic nervous system

Cardiac norepinephrine spillover is increased in the setting of chronic congestive heart failure (CHF), and this increase has been shown to have an important impact on survival.1 The mechanisms underlying cardiac sympathetic activation remain unclear and may involve abnormalities in afferent control, local prejunctional modulation, and/or central processing. Sympathetic activation in CHF is not a generalized process and has been shown to be organ specific.2,3 Cardiac sympathetic activation occurs early during the course of CHF, and the greatest increase in sympathetic activity in this disease is directed at the heart.2,3 Importantly, recent studies have demonstrated that the response to modulation of the sympathetic nervous system is often cardiac specific.3–5 These findings emphasize the need to measure cardiac sympathetic activity because cardiac responses cannot be inferred from systemic or noncardiac responses. Furthermore, these observations suggest that some mechanisms involved in cardiac sympathetic activation may involve local afferent or central integrative responses that are specific to the heart and the heart failure state.

Kaye and colleagues6 have documented a positive correlation between cardiac norepinephrine spillover and pulmonary artery pressures in patients with CHF. Therefore, it has been suggested that in the setting of CHF, increased cardiac filling pressures and/or pulmonary arterial pressures may cause a direct reflex increase in sympathetic efferent outflow to the heart. This has led to the hypothesis that a reduction in cardiac filling pressure might have sympathoinhibitory effects. In a previous study, we demonstrated that generalized baroreceptor unloading caused by an infusion of nitroprusside had no effect on cardiac norepinephrine spillover in patients with CHF despite causing large increases in sympathetic outflow to the periphery.4 Although a reduction in cardiac norepinephrine spillover was not observed, this effect may have been masked by the stimulus to sympathoactivation invoked by arterial baroreceptor unloading.7 More recently, Kaye et al8 demonstrated that an infusion of nitroprusside caused a reduction in cardiac norepinephrine spillover in a selected group of patients with CHF and severe pulmonary hypertension. In the present investigation, we used a lower-body negative pressure (LBNP) chamber in an effort to unload cardiopulmonary baroreceptors in the absence of measurable changes in systemic arterial blood pressure. We hypothesized that such selective unloading of cardiac filling and pulmonary pressures would have cardiac sympathoinhibitory effects in patients with CHF.

Methods

Patient Characteristics
A total of 16 patients referred for angiography participated in this study. Eight subjects had normal LV function (ejection fraction 58±2%, mean age 57±5 years) and 8 patients had CHF (ejection
fraction 19% ± 2%, mean age 60 ± 2 years). In the group with normal LV function, all subjects had a chest pain syndrome and some degree of coronary artery disease. Among the CHF group patients, all were in New York Heart Association class II or III, and the underlying cause of the cardiomyopathy was ischemic in 6 and idiopathic in 2. Medical therapy in the normal LV function group included β-blockers (n = 4), calcium channel blockers (n = 3), ACE inhibitors (n = 1), furosemide (n = 1), transdermal nitroglycerin (n = 1), and amiodarone (n = 1). In the CHF group, medical therapy consisted of ACE inhibitors (n = 6), furosemide (n = 6), digoxin (n = 3), β-blockers (n = 3), amiodarone (n = 2), and transdermal nitroglycerin (n = 1). All medical therapy was held on the morning of the study. This protocol was approved by the Ethical Review Committee for Human Experimentation of the University of Toronto. Written informed consent was obtained from all patients.

**Hemodynamic and Coronary Flow Measurements**

A diagnostic right and left heart catheterization was performed without sedation. The pulmonary artery catheter was left in place after completion of the diagnostic procedure. A 7F coronary sinus thermodilution flow catheter (type CCS-7U-90B, Webster Laboratories) was then inserted from an antecubital vein and positioned in the coronary sinus for flow measurements and blood sampling. Systemic arterial pressure was monitored from an 8F sidearm sheath (Cordis Laboratories). Cardiac output was assessed by the Fick method. The ECG, right atrial pressure, pulmonary artery pressure, and pulmonary capillary wedge pressure were recorded on a strip-chart recorder. For each variable, the results were expressed as an average of measurements of 15 cardiac cycles. Coronary sinus blood flow measurements were performed in duplicate at each measurement point according to the method of Ganz et al. 8

**Norepinephrine Spillover Measurements**

Sympathetic outflow was estimated by the measurement of cardiac and total-body norepinephrine spillover, with the use of techniques that are well established in our laboratory. 4,9 For these measurements, tritiated norepinephrine (1.6 μCi/min with a 16-μCi priming bolus of L-[2,5,6-3H]norepinephrine; New England Nuclear) was infused into the femoral vein through a Harvard pump (model 33, Harvard Apparatus Canada) to steady-state concentration in plasma. Norepinephrine spillover rates were calculated as follows:

\[
\text{Total-Body Norepinephrine Spillover (nmol/min)} = \frac{[\text{H}]\text{NE} \text{infusion rate}}{\text{Plasma NE specific activity}}
\]

\[
\text{Cardiac Norepinephrine Spillover (pmol/min)} = (\text{N}_{\text{ECS}} - \text{NE}_{\text{art}} + (\text{NE}_{\text{art}} \times \text{NE}_{\text{art}})) \times \text{CSFP}
\]

where [H]NE indicates tritium-labeled norepinephrine; NEart, transcardiac fractional extraction of tritium-labeled norepinephrine; NEC, and NEart, coronary sinus and arterial plasma norepinephrine concentrations, respectively, and CSFP, coronary sinus plasma flow.

**Analysis of Plasma Catecholamines**

Plasma catecholamine concentrations were measured by high-performance liquid chromatography with electrochemical detection. Fractions from the high-performance liquid chromatography effluent containing tritium-labeled norepinephrine were assayed by liquid scintillation spectroscopy. 4,9 The biochemical analysis was performed by personnel blinded to patient status.

**Study Protocol**

After the diagnostic heart catheterization and insertion of catheters for hemodynamic monitoring, all patients in both groups were carefully transferred from the catheterization table to an LBNP chamber. The LBNP chamber was specially designed for use in patients with arterial and venous access from the femoral site. The chamber was made of Plexiglas with a sliding top to allow continuous observation of the groin and guarantee fast access in case of bleeding or other complications. Once the patient was in the LBNP chamber, a neoprene skirt was adjusted around the waist to assure adequate air seal. The patient was left undisturbed for a minimum of 20 minutes for tritium-labeled norepinephrine to reach steady-state concentration in plasma. Hemodynamic measurements were then performed, and total-body and cardiac norepinephrine spillover were assessed (control measurements). Subsequently, negative pressure was applied and slowly decreased to achieve a significant reduction in filling pressures without affecting arterial pressure (nonhypotensive LBNP). Our goal was to obtain a 30% to 40% reduction in mean pulmonary artery pressure, as long as there were no detectable changes in arterial pressure. None of the patients enrolled in this study demonstrated a significant change in arterial pressure during nonhypotensive LBNP, and the hemodynamic end point was achieved without difficulties. Measurements were repeated and the negative pressure was further titrated, this time to obtain a 10% reduction in systolic arterial pressure (hypotensive LBNP). After hemodynamic measurements and catecholamines were reassessed, the negative pressure was discontinued and patients were monitored until all pressures returned to baseline (recovery measurements).

**Statistical Analysis**

All data are presented as mean ± SEM. Between-group comparisons of baseline characteristics were performed with an unpaired t test. Within-group comparisons of the effects of nonhypotensive and hypotensive LBNP on hemodynamics, catecholamine concentrations, and norepinephrine kinetics were made by 1-way repeated measures ANOVA with the use of the Student-Newman-Keuls test for post hoc comparisons. Between-group comparisons of the effects of LBNP were performed with the use of ANCOVA. A value of P < 0.05 was required for statistical significance.

**Results**

**Baseline Characteristics**

In the normal left ventricular (LV) function group, cardiac filling pressures were significantly lower than in the CHF group. Despite the severity of the LV dysfunction in the CHF group, they were fairly compensated, with a wedge pressure of only 15 ± 3 mm Hg. Total-body and cardiac norepinephrine spillover were increased in the CHF group when compared with the normal LV function group (Table 1).

**Hemodynamic Responses**

**Nonhypotensive LBNP**

In the group with normal LV function, there was a highly significant reduction in right atrial, pulmonary arterial, and capillary wedge pressures but no change in systemic arterial blood pressure. Nonhypotensive LBNP caused very similar hemodynamic responses in the CHF group characterized by consistent reductions in filling pressures and no significant change in arterial blood pressure. A significant reduction in cardiac index was seen in the normal LV function and CHF groups. The analysis of covariance revealed that the hemodynamic effects of nonhypotensive LBNP were similar in the 2 groups (Tables 2 and 3).

**Hypotensive LBNP**

With the application of hypotensive LBNP, the group with normal LV function demonstrated further reduction in filling pressures and cardiac index. Similar responses were observed in the CHF group for all the hemodynamic parameters mentioned above. In the normal LV function group, there was a significant reduction in systolic arterial pressure, but the
changes in systolic, diastolic, and mean arterial pressures were not significant. In the CHF group, despite similar levels of negative pressure, we were able to cause a significant reduction in systolic, diastolic, and mean arterial pressures.

**Cardiac Sympathetic Responses**

**Nonhypotensive LBNP**

Nonhypotensive LBNP caused no change in cardiac norepinephrine spillover in the group with normal LV function (73±13 vs 71±14 pmol/min, P=NS). However, in the CHF group, there was a significant reduction in cardiac norepinephrine spillover with the application of nonhypotensive LBNP (167±53 vs 125±37 pmol/min, P<0.05). ANCOVA revealed that the decrease in cardiac norepinephrine spillover observed in the CHF group was significantly different from the change observed in the normal LV function group (Tables 2 and 3 and Figure 1).

**Hypotensive LBNP**

In the group with normal LV function, there was a significant increase in cardiac norepinephrine spillover with hypotensive levels of LBNP. This effect was not seen in the CHF group, in which cardiac norepinephrine spillover only increased back to baseline levels.

**Generalized Sympathetic Responses**

**Nonhypotensive LBNP**

Nonhypotensive LBNP was associated with a significant increase in total-body norepinephrine spillover in the group with normal LV function (from 1.8±0.2 to 2.7±0.3 nmol/min, P<0.05). In the CHF group, similar levels of nonhypotensive LBNP did not significantly alter total-body norepinephrine spillover (3.4±0.6 vs 3.9±0.6 nmol/min, P=NS) (Tables 2 and 3 and Figure 2).

**Hypotensive LBNP**

With the application of hypotensive levels of LBNP, there was a significant increase in whole-body sympathetic neuronal activity as measured by total-body norepinephrine spillover in both the normal LV function and CHF groups.

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Normal LV</th>
<th>CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>57±5</td>
<td>60±2</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>58±2</td>
<td>19±2*</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>68±5</td>
<td>72±5</td>
</tr>
<tr>
<td>RA, mm Hg</td>
<td>4±1</td>
<td>7±2*</td>
</tr>
<tr>
<td>PAmean, mm Hg</td>
<td>11±1</td>
<td>27±4*</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>5±1</td>
<td>15±3*</td>
</tr>
<tr>
<td>FAM, mm Hg</td>
<td>88±2</td>
<td>80±4</td>
</tr>
<tr>
<td>Cl, L·min⁻¹·m⁻²</td>
<td>3.2±0.2</td>
<td>2.5±0.2*</td>
</tr>
<tr>
<td>CSBF, mL/min</td>
<td>120±23</td>
<td>111±12</td>
</tr>
<tr>
<td>TBNESP, nmol/min</td>
<td>1.8±0.2</td>
<td>3.4±0.6*</td>
</tr>
<tr>
<td>CANESP, pmol/min</td>
<td>73±13</td>
<td>167±53*</td>
</tr>
</tbody>
</table>

LVEF indicates LV ejection fraction; HR, heart rate; RA, right atrial pressure; PAmean, pulmonary artery mean pressure; PCWP, pulmonary capillary wedge pressure; FAM, femoral artery mean pressure; CI, cardiac index; CSBF, coronary sinus blood flow; NEart, arterial plasma norepinephrine; NEcs, coronary sinus plasma norepinephrine; TBNESP, total-body norepinephrine spillover; NEext, norepinephrine extraction rate; and CANESP, cardiac norepinephrine spillover.

Data are mean±SEM.

### Table 2. Responses to LBNP in Normal LV Group

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>NH-LBNP</th>
<th>HP-LBNP</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chamber pressure, mm Hg</td>
<td>0±0</td>
<td>-16±1*</td>
<td>-35±2*</td>
<td>0±0</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>68±5</td>
<td>67±5</td>
<td>73±6*</td>
<td>67±5</td>
</tr>
<tr>
<td>RA, mm Hg</td>
<td>3.8±0.7</td>
<td>0.4±0.5*</td>
<td>-1.8±0.7*</td>
<td>2.8±0.8</td>
</tr>
<tr>
<td>PAmean, mm Hg</td>
<td>11±1</td>
<td>3.7±1*</td>
<td>4±1*</td>
<td>10±1</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>5±1</td>
<td>1±1*</td>
<td>-1±1*</td>
<td>5±1</td>
</tr>
<tr>
<td>FAS, mm Hg</td>
<td>132±2</td>
<td>132±3</td>
<td>121±3*</td>
<td>132±4</td>
</tr>
<tr>
<td>FAD, mm Hg</td>
<td>65±3</td>
<td>66±3</td>
<td>64±2</td>
<td>66±3</td>
</tr>
<tr>
<td>Cl, L·min⁻¹·m⁻²</td>
<td>3.2±0.2</td>
<td>2.7±0.1*</td>
<td>2.4±0.1*</td>
<td>3.0±0.2</td>
</tr>
<tr>
<td>CSBF, mL/min</td>
<td>120±23</td>
<td>94±18</td>
<td>99±25</td>
<td>119±28</td>
</tr>
<tr>
<td>NEart, nmol/L</td>
<td>0.9±0.1</td>
<td>1.4±0.1*</td>
<td>2.3±0.3*</td>
<td>1.2±0.2</td>
</tr>
<tr>
<td>NEcs, nmol/L</td>
<td>1.3±0.2</td>
<td>1.6±0.2</td>
<td>2.7±0.8*</td>
<td>1.4±0.3</td>
</tr>
<tr>
<td>TBNECL, L/min</td>
<td>2.1±0.1</td>
<td>1.9±0.1</td>
<td>1.6±0.1*</td>
<td>2.0±0.2</td>
</tr>
<tr>
<td>TBNESP, nmol/min</td>
<td>1.8±0.2</td>
<td>2.7±0.3*</td>
<td>3.5±0.3*</td>
<td>2.3±0.3*</td>
</tr>
<tr>
<td>NEext, %</td>
<td>76±3</td>
<td>79±2</td>
<td>82±2</td>
<td>74±3</td>
</tr>
<tr>
<td>CANESP, pmol/min</td>
<td>73±13</td>
<td>71±14</td>
<td>122±27*</td>
<td>65±11</td>
</tr>
</tbody>
</table>

NH-LBNP indicates nonhypotensive LBNP; HP-LBNP, hypotensive LBNP; HR, heart rate; RA, right atrial pressure; PAmean, pulmonary artery mean pressure; PCWP, pulmonary capillary wedge pressure; FAS, femoral artery systolic pressure; FAD, femoral artery diastolic pressure; CI, cardiac index; CSBF, coronary sinus blood flow; NEart, arterial plasma norepinephrine; NEcs, coronary sinus plasma norepinephrine; TBNESP, total-body norepinephrine spillover; NEext, norepinephrine extraction rate; and CANESP, cardiac norepinephrine spillover.

Data are mean±SEM.

*P<0.05 vs control.
Discussion

This is the first human study to measure cardiac norepinephrine spillover in response to LBNP. Data obtained from both the normal LV function and CHF groups are novel, providing new insights into the control of the sympathetic nervous system. The LBNP chamber has important advantages over other methods that have been used to explore the effect of changes in cardiac filling pressure on sympathetic activity. First, predictable and relatively selective cardiopulmonary baroreceptor unloading can be achieved, something that is not possible with other approaches. Second, since no pharmacological intervention is involved, we were able to avoid potential confounding effects such as might be observed when a nitric oxide donor (eg, nitroprusside) is used. It is recognized that nonhypotensive LBNP, although not causing a measurable decrease in systemic arterial blood pressure, may well have some impact on arterial baroreceptors. Nevertheless, the use of nonhypotensive LBNP does provide an opportunity to decrease cardiopulmonary filling pressures without fully engaging reflex sympathetic responses to systemic hypotension.

It is recognized that patients with chronic CHF have abnormal autonomic neuronal reflex responses to changes in cardiopulmonary loading conditions. In 1950, Brigden and Sharpey-Schafer demonstrated that upright tilt was associated with forearm vasodilation in patients with CHF. More than 30 years later, in a better-characterized population of patients with CHF, Ferguson et al reported that some patients with severe CHF develop forearm vasodilation in response to LBNP. These responses are abnormal because reductions in cardiopulmonary filling pressures should cause sympathoexcitation. It is also clear that patients with CHF have abnormal responses to increases in cardiac filling pressures. Positive correlation between measures of sympathetic activity and increased cardiac filling pressures have been recognized for several years. In 1994, Kaye and colleagues demonstrated that mean pulmonary artery pressure was an independent predictor of cardiac sympathetic activity in patients with chronic CHF. This relation is paradoxical, since in the setting of normal physiology, increases in cardiopulmo-
nary pressures have sympathoinhibitory effects reflected by peripheral vascular resistance responses.17

This series of observations led to the hypothesis that reductions in cardiopulmonary pressures would lead to reductions in cardiac sympathetic activity. Subsequently, our laboratory reported that nitroprusside, given to patients with moderately severe CHF, caused increases in total-body norepinephrine spillover but had no significant effects on cardiac norepinephrine spillover.4 As expected, in patients with normal ventricular function, an infusion of nitroprusside that had similar hemodynamic effects caused marked increases in both systemic and cardiac sympathetic activity. These results demonstrate that cardiac sympathetic responses to generalized arterial and cardiopulmonary baroreceptor unloading are abnormal in chronic CHF. A cardiac sympathoinhibitory effect of preload reduction was not observed, presumably because of the simultaneous decrease in systemic arterial pressure with subsequent arterial baroreceptor–mediated increases in sympathetic output, some of which may be directed to the heart.7 More recently, Kaye et al5 have reported that the acute administration of nitroprusside was associated with decreases in cardiac sympathetic activity in patients with CHF and severe pulmonary hypertension. This sympathoinhibitory cardiac response occurred despite significant increases in total-body norepinephrine spillover. On the basis of these findings, the authors concluded that increased cardiopulmonary filling pressure in patients with CHF evokes an increase in cardiac sympathetic activity by a direct reflex mechanism. Although these findings are important, the administration of nitroprusside to these patients with CHF and severe pulmonary hypertension was associated with significant increases in cardiac output, and it is not possible to conclude that the observed cardiac sympathoinhibition occurred only as a result of a reduction in filling pressures.

In the present study, patients were well compensated despite having severe ventricular dysfunction. In this regard, they are representative of a broad range of patients with LV dysfunction and symptomatic CHF. The application of nonhypotensive LBNP in these patients caused significant reductions in cardiopulmonary filling pressure but had no effect on systemic arterial pressure. Despite the associated reduction in cardiac output, a significant decrease in cardiac norepinephrine spillover was observed. On the basis of these responses, we conclude that a selective reduction in cardiac filling and pulmonary artery pressure in patients with chronic CHF leads to a decrease in efferent cardiac sympathetic outflow. It is important to emphasize that this decrease in cardiac sympathetic activity occurred despite a tendency for total-body norepinephrine spillover to increase, a finding indicative of increased sympathetic activity in other, noncardiac, vascular beds.2 In the CHF group, there was no change in heart rate with nonhypotensive LBNP despite a significant reduction in cardiac norepinephrine spillover. Previous studies have shown a poor correlation between heart rate responses and adrenergic markers such as plasma norepinephrine or muscle sympathetic nervous activity.18 Potential mechanisms for this discrepancy include (1) sinus node dysfunction in the setting of CHF,19 (2) parasympathetic modulation of sinus node responses, (3) sympathetic drive to the heart muscle may be different from central outflow to the sinus node, and (4) concomitant use of chronotropically active drugs.

In patients with normal LV function, nonhypotensive LBNP caused a significant increase in generalized sympathetic activity as measured by an increase in total-body norepinephrine spillover but had no effect on cardiac norepinephrine spillover. Increases in sympathetic outflow to the periphery, as measured by increases in limb vascular resistance or direct microneurographic recordings, are consistently reported in response to nonhypotensive LBNP.13,20 In contrast, a number of studies performed with norepinephrine kinetics have not found the significant increase in total-body norepinephrine spillover that we report here.21,22 This difference probably is secondary to the fact that in previous studies, fixed levels of LBNP (ie, −15 mm Hg) were applied instead of being titrated until a hemodynamic goal was attained. Furthermore, patients in the present study were considerably older (57 ± 5 years) than the normal volunteers exposed to nonhypotensive LBNP in previous reports, and this may have contributed to differences in the observed response.

In patients with normal LV function, a number of studies,14,23,24 have reported conflicting results regarding the effects of LBNP on sympathetic outflow to the heart despite evidence of increased sympathetic outflow to the periphery. In these reports, changes in heart rate were used as a surrogate marker for cardiac sympathetic responses. The present investigation confirms that nonhypotensive LBNP does not increase sympathetic outflow to cardiac muscle despite evidence of increased sympathetic outflow to a number of organ beds. This is important because it provides another example in which observations made in the periphery cannot predict cardiac sympathetic responses.

As would be expected, hypotensive LBNP was associated with significant increases in cardiac norepinephrine spillover in patients with normal LV function. This is similar to what was observed in response to combined cardiopulmonary and arterial baroreceptor unloading with nitroprusside in patients.
with normal LV function. Patients with CHF displayed abnormal cardiac norepinephrine spillover responses to hypotensive LBNP. In this group, systemic hypotension during hypotensive LBNP did not lead to an increase in cardiac norepinephrine spillover. In response to hypotensive LBNP, cardiac sympathetic responses returned to control levels from what was observed during nonhypotensive LBNP but did not increase above baseline values. This finding is consistent with our previous report in which a nitroprusside infusion caused no change in cardiac norepinephrine spillover despite causing systemic hypotension and increases in total-body norepinephrine spillover. The mechanism of the specific reduction in cardiac norepinephrine spillover during nonhypotensive LBNP in patients with CHF remains uncertain. The findings suggest that a reduction in cardiopulmonary filling pressures, in the absence of reductions in systemic blood pressure, has a specific effect on afferent signaling pathway(s) that leads to a reduction in cardiac sympathetic efferent neuronal activity. This, in turn, would imply that increases in cardiopulmonary filling pressures engage afferent signals that lead to cardiac sympathoexcitatory effects. This possibility is consistent with a number of animal studies in which distension of the left atrium or pulmonary veins was associated with a sympathetically mediated increase in heart rate or increased LV contractility. It is important to recognize that this explanation rests on the assumption that LBNP caused a reduction in the dimensions of right and left heart chamber pressures and/or volume. This assumption may not be true, since a recent report by Atherton et al demonstrated that in some patients with CHF, the application of LBNP was associated with paradoxical increases in LV end-diastolic volume. This effect was observed in a subset of patients with severe CHF that had marked increases in right-sided filling pressures, and the authors conclude that the increase in LV diastolic volumes during LBNP was attributable to relief of pericardial constraint and a favorable effect on ventricular interaction. In a subsequent report, they demonstrate that in patients in whom ventricular interaction was present, LBNP was not associated with reflex increases in forearm vascular resistance. In the present study, it seems unlikely that a favorable effect on ventricular interaction provides an explanation for the observed cardiac sympathetic inhibitory effect in the CHF group. These patients had only modest increases in right and left heart filling pressures, and nonhypotensive LBNP led to a fall in cardiac index in 7 of 8 patients, a finding that would seem inconsistent with an LBNP-induced increase in LV end-diastolic volume and improved cardiac performance.

In summary, these results demonstrate that a reduction in cardiopulmonary filling pressures, in the absence of a decrease in systemic arterial pressure, is associated with a reduction in cardiac norepinephrine spillover in patients with chronic CHF. These findings have clinical implications and suggest that a goal of CHF management should be to reduce cardiac filling pressures toward normal while avoiding systemic hypotension. Although this may be stating the obvious, it is still very common to see patients with treated CHF who have poorly controlled pulmonary pressures. Since cardiac sympathetic activity has been shown to be an independent predictor of death in CHF, our findings suggest that therapy aimed at normalizing filling pressures may have a beneficial effect on this important risk factor.

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References
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