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Differential Effect of Acute Baroreceptor Unloading on Cardiac and Systemic Sympathetic Tone in Congestive Heart Failure

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Objectives. **The present study was designed to identify the hemodynamic factor or factors that reflexly contribute to activation of the cardiac sympathetic nerves in patients with severe congestive heart failure (CHF).**

Background. **We and others have previously shown that activation of the sympathetic nervous system is a key feature of CHF in humans. Furthermore, the degree of sympathetic activation shows marked regional heterogeneity and is most pronounced in the heart. Recent studies have shown a significant positive relation between pulmonary artery pressure and the magnitude of cardiac sympathetic activation. Of particular importance, the degree of cardiac sympathoexcitation has also been shown to be strongly associated with mortality in CHF.**

Methods. **We assessed total systemic and cardiac sympathetic activity (norepinephrine [NE] spillover method) in nine patients with severe CHF and significantly elevated pulmonary artery pressure (mean [±SEM] pulmonary artery pressure 46 ± 3 mm Hg) at rest and during a titrated infusion of sodium nitroprusside (SNP).**

Results. **SNP infusion significantly reduced mean arterial blood pressure, pulmonary artery pressure and pulmonary capillary wedge pressure. During SNP infusion, the total body NE spillover rate (NESR) increased (from 7.9 ± 1.7 to 11.2 ± 3.1 nmol/min, $p < 0.01$), whereas the cardiac NESR decreased (from 522 ± 86 to 409 ± 71 pmol/min, $p < 0.05$). The ratio of cardiac/total NE spillover was also substantially reduced (from 7.8 ± 1.3 to 4.9 ± 0.9%, $p < 0.001$).**

Conclusions. **There is a directionally opposite change in whole-body (increase) and cardiac (reduction) sympathetic nervous activity during SNP infusion, most likely due to unloading of arterial baroreceptors and specific cardiopulmonary baroreceptors, respectively, in severe CHF. These observations support the concept of a positive feedback relation between pulmonary artery pressure/filling pressure and cardiac sympathetic tone in CHF and serve to reinforce the importance of vasodilator therapy in this condition.**

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Neurohormonal activation is a well characterized and important pathophysiologic component of congestive heart failure (CHF). Moreover, many of the systems that are reflexly activated in the setting of reduced cardiac performance are currently receiving intense attention as targets for pharmacologic intervention (1–3). Sympathetic nervous activation has been demonstrated both in CHF in patients and in experimental models of heart failure by multiple means, including biochemical and neurophysiologic approaches (4–6). The potentially adverse prognostic implications of sympathetic overactivity in CHF are also becoming increasingly apparent (7,8).

Despite the extensive documentation of sympathetic overactivity in CHF, the reflex mechanisms responsible for this process remain unclear. Moreover, the spatial heterogeneity of sympathetic outflow in CHF (4) invalidates any assumptions about generalized reflex control of sympathetic tone in this condition. Activation of cardiac sympathetic nerves occurs early in the course of CHF (9), and our group has demonstrated (5) a positive correlation between pulmonary artery pressures and the extent of cardiac sympathetic activation, as reflected by the cardiac norepinephrine spillover rate (NESR). We have also observed (10) a positive correlation between monoamine turnover in the brain and the cardiac NESR in CHF that is thought to reflect the central nervous system mechanism linking afferent neural traffic from the cardiopulmonary receptors to selective control of sympathetic outflow. Taken together, these data suggest a direct reflex link between pulmonary pressure and sympathetic efferent outflow to the heart.

The aim of the present study, therefore, was to further investigate the reflex control of cardiac sympathetic activity in CHF in patients. Total systemic and cardiac sympathetic activity were investigated by radiotracer methodology. To specifically investigate the relation between pulmonary artery pressure and cardiac NESR, we selected a group of patients with severe pulmonary hypertension and examined the effect

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
CHF = congestive heart failure
NE = norepinephrine
NESR = norepinephrine spillover rate
SNP = sodium nitroprusside

of lowering pulmonary artery pressure with a titrated infusion of sodium nitroprusside (SNP) on sympathetic tone.

Methods

Study patients. Nine patients with CHF and significant pulmonary hypertension form the basis of this study. All patients had New York Heart Association functional class III to IV symptoms and had been referred to the Alfred Hospital Heart Failure Center for consideration for heart transplantation. Mean (±SEM) left ventricular ejection fraction for the group was 16 ± 3% (Table 1). All patients were treated with angiotensin converting-enzyme inhibitors, digoxin and diuretic drugs (Table 1), and these medications were continued throughout the study period to avoid hemodynamic decompensation secondary to withdrawal of antifailure therapy. All patients gave written informed consent, and the study was performed with the approval of the Alfred Hospital Ethics Review Committee.

Inclusion criteria and catheterization protocol. All catheterization studies were performed in the morning, and patients were asked not to consume caffeinated beverages on the study day to avoid additional sympathoexcitation. A thermodilution catheter (7F, Arrow International) was inserted percutaneously under local anesthesia through a right internal jugular venous introducer sheath for the determination of pulmonary artery pressures, pulmonary capillary wedge pressure, right atrial pressure and cardiac output. Cardiac output was determined from the average of three cardiac output measurements that varied by <10%. Arterial blood pressure was determined invasively through a radial artery cannula. The criteria for inclusion in the present study were a pulmonary artery systolic pressure >50 mm Hg or a transpulmonary gradient (mean pulmonary artery pressure minus mean wedge pressure) >12 mm Hg, or both, with an arterial systolic blood pressure of at least 90 mm Hg.

At the completion of the hemodynamic assessment, a coronary sinus thermodilution catheter (Webster Laboratories) was positioned in the coronary sinus under fluoroscopic control. The tip of the thermodilution catheter was carefully noted and confirmed to lie at least 2 cm proximal to the coronary sinus orifice in all cases by injection of radiographic contrast medium. In three subjects two right internal jugular venous sheaths were inserted to allow simultaneous pulmonary artery pressure recording and coronary sinus catheterization. Coronary sinus blood flow was subsequently determined as previously described (11), and simultaneous arterial and coronary sinus blood sampling was performed. Coronary sinus plasma flow was calculated after determination of each patient's hematocrit.

Radiotracer assessment of sympathetic function. A neurochemical approach to measuring total systemic and cardiac sympathetic activity and neuronal biochemical integrity was used, as previously described by our group (5). In brief, radiolabeled L-[7-^{3}H]norepinephrine was continuously infused (0.5 to 1 μCi/min) through a peripheral vein to achieve a steady state plasma concentration. The rate of appearance rate of norepinephrine (NE) in plasma was measured as an indirect index of "global" sympathetic nervous activity and calculated as the ratio of the infusion rate for tritiated NE to the plasma specific activity of NE in plasma, as previously described (12,13). The cardiac NESR was calculated from the relation

$$\text{Cardiac NESR} = [(NE_{CS} - NE_{art}) \times NE_{ex} \times NE_{art})] \times \text{CSPF},$$

where NE_{CS} and NE_{art} are the plasma NE concentrations in the coronary sinus and arterial blood; NE_{ex} is the fractional extraction of tritiated NE across the heart; and CSPF is coronary sinus plasma flow.

Table 1. Study Group Characteristics

Pt No./ Gender	Age (yr)	Diagnosis	LVEF (%)	PAP (mm Hg)*	Medications
1/M	45	IHD	13	109/48 (66)	ACEI, dig, furo, prazosin
2/M	54	IHD	35	55/10 (38)	ACEI, dig, furo
3/M	62	IHD	11	81/28 (47)	ACEI, furo, Ca
4/M	65	IHD	18	74/20 (44)	ACEI, furo, Ca, nitrate
5/M	45	IHD	9	98/37 (54)	ACEI, dig, furo
6/M	64	IDCM	12	59/30 (42)	ACEI, dig, furo
7/M	45	EtOH	12	56/19 (34)	ACEI, dig, furo, metoprolol, Ca
8/F	61	IHD	18	84/44 (55)	ACEI, dig, furo, hydrochlorthiazide
9/M	56	IHD	19	63/23 (37)	ACEI, dig, furo, Ca, nitrate

*Systolic/diastolic (mean). ACEI = antiotensin-converting enzyme inhibitor; Ca = calcium antagonist; dig = digoxin; EtOH = alcoholic cardiomyopathy; F = female; furo = furosemide; IDCM = idiopathic dilated cardiomyopathy; IHD = ischemic heart disease; LVEF = left ventricular ejection fraction; M = male; PAP = pulmonary artery pressure; Pt = patient.

SNP infusion. After the completion of baseline hemodynamic measurements, coronary sinus blood flow determination and blood sampling, an intravenous infusion of SNP was commenced. SNP was administered through a peripheral vein at an initial rate of 0.5 μg/kg body weight per min. The infusion rate was increased at 5-min intervals, titrated to achieve a stable reduction in arterial systolic blood pressure of 20 mm Hg or a minimal systolic blood pressure of 90 mm Hg. At the maximal SNP infusion rate, hemodynamic measurements, coronary sinus blood flow determination and blood sampling were again performed after 5 min of stable arterial blood pressure. In subjects where simultaneous hemodynamic and coronary sinus catheterization was not performed, great care was taken to ensure that the position of the coronary sinus catheter was identical to that of the baseline study and that the arterial blood pressure remained stable during repositioning of the coronary sinus catheter.

Biochemical assays. On collection, blood samples were immediately transferred to ice-chilled tubes containing EGTA and reduced glutathione. Samples were stored on ice and subsequently separated by centrifugation at 4°C. Plasma samples were stored at −70°C until assay. The plasma norepinephrine concentrations were determined by high performance liquid chromatography with electrochemical detection (14). The plasma specific activity of tritiated NE and dihydroxyphenylglycol was determined by performing timed collections of the detector cell eluant. Radioactivity was measured by liquid scintillation spectroscopy.

Statistical methods. Results are presented as the mean value ± SEM. Where normally distributed, between-group comparisons were performed by an unpaired Student *t* test. Data that were not normally distributed were compared using the Wilcoxon rank-sum test. The null hypothesis was rejected at $p < 0.05$.

Results

Baseline hemodynamic variables and response to SNP. The baseline hemodynamic characteristics of the study patients were consistent with their moderate to severe clinical profile and degree of left ventricular dysfunction. Baseline hemodynamic variables and the hemodynamic profile during the maximal dose of the SNP infusion are detailed in Table 2. By design, the patients included in this report were characterized by moderate to severely impaired left ventricular function, with attendant markedly elevated pulmonary artery and pulmonary capillary wedge pressures. During SNP infusion, there were significant reductions in systemic arterial, pulmonary artery and mean pulmonary capillary wedge pressures. In conjunction, there was a significant increase in cardiac output. In response to the SNP infusion there was a modest reduction in coronary sinus blood flow (baseline vs. SNP: 240 ± 42 vs. 206 ± 31 ml/min, $p = 0.07$).

Sympathetic responses to SNP. The arterial plasma NE concentration was unchanged during SNP infusion (Fig. 1). This observation was explained by the counterbalancing effects of a substantial increase in the total systemic NESR (7.9 ± 1.7 vs. 11.2 ± 3.1 nmol/min, $p < 0.01$) and an increase in the total systemic clearance rate for NE from plasma (1.9 ± 0.3 vs. 2.6 ± 0.5 liters/min, $p < 0.05$).

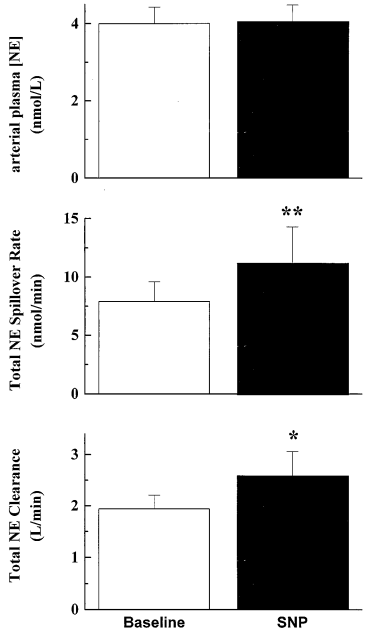
In contrast, the administration of SNP significantly reduced the NESR to plasma across the heart (baseline vs. SNP: 522 ± 86 vs. 409 ± 71 pmol/min, $p < 0.05$), as shown in Figure 2. The extraction of tracer NE across the heart was not altered by the SNP infusion (baseline vs. SNP: 0.47 ± 0.05 vs. 0.48 ± 0.05%, p = NS). At rest, cardiac NESR accounted for 7.8 ± 1.3% of the total systemic NESR, and this fell to 4.9 ± 0.9% ($p < 0.001$) during SNP infusion (Fig. 2).

Table 2. Baseline Hemodynamic Variables and Responses to Nitroprusside

	Baseline (mean ± SEM)	Nitroprusside (mean ± SEM)	p Value
Heart rate (beats/min)	98 ± 4	93 ± 4	< 0.05
$Arterial_{SYS}$ (mm Hg)	131 ± 6	112 ± 8	< 0.001
$Arterial_{MEAN}$ (mm Hg)	91 ± 4	77 ± 5	< 0.001
RA (mm Hg)	11 ± 1	8 ± 1	< 0.001
PA_{SYS} (mm Hg)	75 ± 6	55 ± 6	< 0.001
PA_{MEAN} (mm Hg)	46 ± 3	31 ± 4	< 0.001
PCWP (mm Hg)	30 ± 2	18 ± 2	< 0.001
CO (liters/min)	4.0 ± 0.4	4.6 ± 0.4	< 0.05

$Arterial_{MEAN}$ = mean arterial pressure; $Arterial_{SYS}$ = arterial systolic pressure; CO = cardiac output; PA_{MEAN} = mean pulmonary artery pressure; PA_{SYS} = pulmonary artery systolic pressure; PCWP = pulmonary capillary wedge pressure; RA = right atrial pressure.

Figure 1. Effect of SNP infusion on arterial plasma NE concentration, total NESR and total NE clearance rate. *p < 0.05, **p < 0.01, baseline versus SNP.



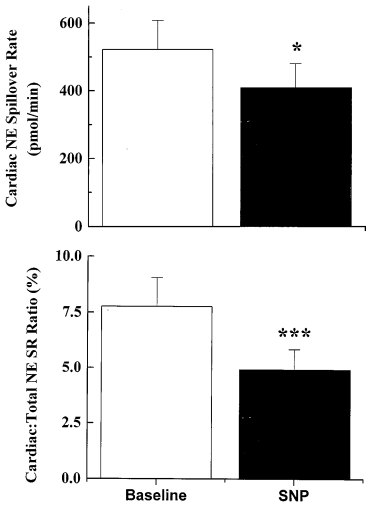


Figure 2. Effect of SNP infusion on cardiac NESR and cardiac/total systemic NESR ratio. *$p < 0.05$, ***$p < 0.001$, baseline versus SNP.

Discussion

Activation of cardiac sympathetic nerves has been well documented in human cardiac failure and has recently been shown (9) to be an early feature of even mild to moderate CHF failure. Although generalized sympathetic activation is a hallmark of CHF, the degree to which cardiac sympathetic activity increases appears to be considerably greater than that measured at other sites (4,9). In a previous study (5), we observed a statistically significant, positive correlation between mean pulmonary artery pressure and the cardiac norepinephrine spillover rate. A similar relation between pulmonary artery/left ventricular filling pressures and muscle sympathetic nerve activity has also been reported (6,15). Accordingly, in the present study we aimed to further explore the relation between pulmonary artery pressures and cardiac sympathetic activity.

The major new finding of the present study is the demonstration that acute systemic and pulmonary vasodilation induced by SNP results in directionally opposite changes in cardiac and systemic sympathetic activity in patients with severe CHF and pulmonary hypertension. As expected, in our study a fall in arterial blood pressure was associated with a 42% increase in the total systemic NSR. In conjunction, there was a substantial fall in pulmonary artery pressure and a 22% fall in the cardiac NESR.

To date, the processes involved in the reflex control of cardiac sympathetic nerves remain incompletely understood. In the context of cardiac sympathetic regulation specifically, most studies, both in healthy subjects and patients with CHF, have concentrated on the relation between alterations in baroreceptor loading or unloading and heart rate (16–18). Although these studies consistently demonstrate a reduction in the gain of the blood pressure–heart rate relation, one potential confounding factor is the reduced chronotropic response of the heart to directly infused catecholamines (19), thereby limiting the usefulness of heart rate changes as a direct reflection of alterations in cardiac sympathetic nerve activity. The difficulty in studying cardiac sympathetic function indirectly in CHF in patients by means of heart rate spectral analysis has also been recently highlighted (20).

In a recent study, Newton and Parker (21) examined the effect of SNP-induced vasodilation on whole-body and cardiac NESR in healthy subjects and patients with CHF. As in our study, acute vasodilation was associated with a substantial increase in total systemic NESR, although there was little change in the peripheral plasma NE concentration because of a coincident cardiac output-dependent rise in the clearance rate of NE from plasma. Unlike the present study, Newton and Parker (21) demonstrated that acute vasodilation was associated with a small, nonsignificant increase in the cardiac NESR in patients with CHF, that was significantly less than that observed in subjects with normal left ventricular function. This observation led Newton and Parker to conclude that this was a reflection of impaired baroreceptor function. Our study group differs in two important ways from that of Newton and Parker (21). By selection, our patients had 1) significantly higher pulmonary artery and wedge pressures, and 2) in association, a higher cardiac NESR. Consistent with the reduction in cardiac NESR seen in the present study, we also observed a significant reduction in heart rate during SNP infusion. Again, this was directionally opposite to that observed by Newton and Parker (21).

Our study therefore suggests that the more marked degrees of cardiac sympathetic activation observed in severe CHF may be a direct, reflex consequence of substantially elevated filling pressures. Under normal circumstances, cardiac sympathetic tone measured in humans by isotope dilution is increased in the setting of arterial baroreceptor unloading (21). The effects of selective cardiopulmonary baroreceptor unloading on cardiac sympathetic function have not been examined directly to date. Furthermore, studies addressing the influence of nonhypotensive lower body negative pressure on heart rate have yielded conflicting results (22,23). Consistent with the findings of our study, previous experimental studies have also suggested that distention of certain cardiopulmonary baroreceptor groups may actually increase cardiac sympathetic tone. A number of studies (24–26) have demonstrated that distention of the left atrium or pulmonary veins increases heart rate through a vagal afferent, sympathetic efferent pathway. More recently, Kurz et al. (27) also showed that left atrial and pulmonary distention was also associated with a sympathetically mediated increase in left ventricular contractility.

Clinical implications. In a previous report from our group (8), we examined the clinical implications of elevated cardiac sympathetic activity in patients with severe CHF. Using a multivariate Cox proportional hazards model, we showed that the cardiac NESR was the most powerful marker of outcome. Given the apparent reflex influence of pulmonary artery pressures on cardiac sympathetic activity, it could therefore be hypothesized that a therapeutic intervention that reduced filling pressures would potentially impart a beneficial effect on survival, in part mediated by a reduction in sympathetic drive to the heart. In this context, Stevenson et al. (28) showed that

patients with severely impaired left ventricular function and persistently elevated filling pressures had a substantially poorer prognosis than patients whose pulmonary capillary wedge pressure could be lowered to <16 mm Hg by tailored antifailure therapy. However, not all vasodilators have been shown to improve outcome in patients with CHF.

The well known beneficial effect of angiotensin-converting enzyme (ACE) inhibition in heart failure (1,2) may also be partly mediated by a reflex reduction in cardiac sympathetic drive. This hypothesis is supported by a follow-up study from the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial (29), in which it was observed that the beneficial effects of enalapril were seen only in patients with neurohormonal activation. In a study of the effect of ACE inhibition on cardiac sympathetic function, Gilbert et al. (30) showed that lisinopril significantly reduced the concentration of NE in the coronary sinus, in association with a reduction in pulmonary artery pressure (30). Moreover, when patients were stratified according to their baseline coronary sinus NE concentration, the apparent antiadrenergic effect of lisinopril was only evident in patients with a high coronary sinus NE concentration. This patient group was also characterized by having a trend toward higher pulmonary artery and wedge pressures.

Conclusions. Cardiac sympathoexcitation is a hallmark of CHF and has been implicated as a key adverse pathophysiologic factor. We previously observed a significant positive correlation between pulmonary artery pressure and cardiac NESR. In the current study we showed that acute vasodilation resulted in a reduced cardiac NESR in patients with poor left ventricular function and high pulmonary pressures. This study therefore further supports the notion that the distention of certain intracardiac baroreceptors results in increased sympathetic drive to the failing human heart.

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