Cardiac Sympathetic Activation in Patients With Pulmonary Arterial Hypertension

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Abstract

Patients with congestive heart failure (CHF) due to left ventricular (LV) dysfunction have sympathetic activation specifically directed to the myocardium. Although pulmonary arterial hypertension (PAH) is associated with increased systemic sympathetic activity its impact on sympathetic drive to ventricular myocardium is unknown. Fifteen patients with PAH (9 women; 54±12 years) were studied; 10 with idiopathic PAH and 5 with a connective tissue disorder. We measured haemodynamics as well as radiolabelled and endogenous concentrations of arterial and coronary sinus norepinephrine (NE). These measures were repeated after inhaled nitric oxide (NO). Measurement of transcardiac NE concentrations and the cardiac extraction of radiolabelled NE allowed calculation of the corrected transcardiac gradient of NE (CTCG of NE). Comparative data were collected from 15 patients (9 women; 55±12 years) with normal LV function and 15 patients with CHF (10 women; 53±12 years). PAH patients had elevated arterial NE concentrations as compared with those with normal LV function but were similar to those with CHF. The CTCG of NE was higher in those with PAH than in the normal LV group (3.6±2.2 versus 1.5±0.9 pmol/ml; P<0.01) but similar to that seen in those with CHF (3.3±1.4; P=NS). Inhaled NO, which reduced pulmonary artery pressure and increased cardiac output, had no effect on cardiac sympathetic activity. Therefore cardiac sympathetic activation occurs in PAH. The mechanism of this activation remains uncertain but does not involve elevations in left heart filling pressure.
Background

Pulmonary hypertension is defined as a mean pulmonary artery pressure of more than 25 mmHg at rest and is classified into five groups based upon aetiology. (42, 43) Idiopathic pulmonary arterial hypertension (IPAH) and other forms of pulmonary hypertension due to abnormalities in the pulmonary vasculature (pulmonary arterial hypertension (PAH)) require the exclusion of other causes, particularly abnormalities of left heart function. Recent registries of patients with PAH have confirmed the heterogeneous nature of this clinical syndrome, both in terms of etiology and prognosis. Recent advances in diagnosis, clinical management and pharmacologic therapy have improved the prognosis for patients with IPAH. Nevertheless, this disease continues to be associated with marked morbidity and mortality, emphasizing the need for a better understanding of the pathophysiology and improvement in therapeutic approaches. (6, 7, 14)

Patients with chronic congestive heart failure due to left ventricular (LV) systolic dysfunction have sympathetic activation. Cardiac sympathetic activation plays an important pathophysiologic role in the progressive nature of heart failure, (20) with measures of cardiac sympathetic activity correlating with disease severity and prognosis. (12, 26, 30) To date, no study has examined cardiac sympathetic activity in patients with PAH. Some investigations have documented peripheral sympathetic activation in patients with PAH including elevations in peripheral plasma NE, increased sympathetic activity directed to skeletal muscle as well as changes in the autonomic regulation of heart rate. (10, 11, 28, 31, 36, 44) Importantly, with respect to the findings presented here, is the fact that sympathetic outflow is regional and organ specific with certain organs experiencing the greatest degree of sympathetic
activation.(18, 23, 40) Therefore, although sympathetic activation to the periphery has been demonstrated in patients with PAH, the state of cardiac sympathetic activity in PAH remains an important, unanswered question.

The aim of the current study was to measure haemodynamics and cardiac sympathetic activity in patients with PAH, comparing the findings in this population with those observed in patients with normal LV function and those with CHF secondary to LV systolic dysfunction. We also examined the effects of lowering pulmonary artery pressure (PAP) with inhaled nitric oxide (NO) on measures of sympathetic activity.

**Methods**

We enrolled patients with PAH (mean pulmonary artery pressure ≥ 25mmHg) all of whom had been referred for a diagnostic heart catheterization. All patients had previously undergone echocardiography to exclude LV systolic dysfunction and significant primary valvular disease. None of these patients had primary lung disease and none had evidence of pulmonary thromboembolic disease. Patients with any of these conditions were excluded from the study. Patients on medications that interfere with norepinephrine (NE) neuronal uptake, including tricyclic antidepressants and monoamine oxidase inhibitors, along with those taking calcium channel blocking agents or other directed pulmonary vasodilator therapy such as prostanoids, endothelin receptor antagonists, and phosphodiesterase inhibitors were also excluded.

Findings in patients with PAH were compared with similar endpoints derived from patients with normal LV systolic function as well as a group of patients with congestive heart failure.
secondary to LV systolic dysfunction. Data from patients with normal LV function (and normal haemodynamics) as well as from patients with CHF were derived from patients who had participated in previous studies within our research cardiac catheterization laboratory program. The normal and CHF groups were age matched. Patients with CHF had NYHA class II and III symptoms. The normal group was taking a number of cardiac medications including (in some combination) calcium channel antagonists, beta-blockers, and angiotensin converting enzyme inhibitors. The patients with CHF were taking digoxin, diuretics, beta-blockers, and/or angiotensin converting enzyme inhibitors. Cardiac medications in all groups were held on the morning of the cardiac catheterization. We did not enroll patients with impaired renal function (creatinine > 150\(\mu\)mol/L) and women of child bearing potential. All patients gave informed, written consent. The institutional ethics review board of Mount Sinai Hospital approved the study protocol.

**Neurochemical measurements**

Cardiac and total body sympathetic activity was estimated using radiotracer methodology.(19) For these measurements, tritiated NE (New England Nuclear, Boston, Massachusetts) was infused into a peripheral vein to steady state concentration in plasma. Our laboratory has employed this technique in multiple previous investigations.(3-5, 32, 34, 35) Total body norepinephrine spillover (TBNESP), an index of the total amount of NE presenting to the plasma compartment over time was calculated as:

\[
TBNESP = \frac{[\text{\(^3\)H}]\text{ infusion rate}}{\text{Plasma NE specific activity}}
\]
Cardiac NE production was estimated by calculating the corrected transcardiac gradient of NE (CTCG of NE) as below:

\[
\text{CTCG of NE} = \left[ (C_v - C_a) + C_a \times (\text{NE}_{\text{extr}}) \right]
\]

where \( C_v \) is the venous (coronary sinus) NE concentration, \( C_a \) is the arterial concentration, and \( \text{NE}_{\text{extr}} \) is the extraction across the heart. NE extraction is calculated as:

\[
\text{NE}_{\text{extr}} = \frac{[\text{H}]\text{NE}_{\text{art}} - [\text{H}]\text{NE}_{\text{cs}}}{[\text{H}]\text{NE}_{\text{art}}}
\]

where \([\text{H}]\text{NE}_{\text{cs}}\) is the concentration of tritiated NE in the coronary sinus and \([\text{H}]\text{NE}_{\text{art}}\) is the arterial concentration of tritiated NE. This radiotracer methodology has important advantages as an index of organ specific sympathetic activity since it allows for the direct measurement of transorgan NE extraction that could explain differences in transorgan NE concentrations in a disease state or in response to an intervention. Endogenous and radiolabelled catecholamines were measured using standard techniques that have been published elsewhere,(18, 33, 35) and are based on the radiotracer method established by Esler et al.(17)

**Catheterization protocol**

The procedure was conducted through the right femoral artery and vein without sedation. Following the clinical component of the procedure, the pulmonary artery and femoral artery catheters were left in place for hemodynamic monitoring. Cardiac output was calculated using the Fick method. Systemic and pulmonary arterial pressures were recorded and for each variable and measurement time point the results were expressed as an average of 10 cardiac cycles. Through a second femoral vein puncture, a 6F Simmonds catheter (Cordis Laboratories) was positioned into the coronary sinus (CS) for blood sampling. The CS catheter was advanced until it was at least two centimeters in from the os to avoid the possibility of
including right atrial blood in the CS samples. This position was also confirmed by measuring coronary sinus blood oxygen saturation (confirmed by an oxygen saturation of less than 40 per cent) prior to each measurement time point.

Subsequently, a bolus and a maintenance infusion of tritiated NE was started peripherally to allow measurements of NE kinetics. Twenty minutes later, at steady state, right atrial, pulmonary artery, pulmonary capillary wedge pressures (haemodynamics) were measured along with cardiac output. Hemodynamic and cardiac output measurements were repeated 5 minutes later to confirm hemodynamic stability. Blood samples were drawn from the femoral arterial catheter and the CS catheter.

**Administration of Inhaled NO**

In patients with PAH NO was administered after control measurements (through a sealed face mask) at a rate of 40 ppm and maintained for 20 minutes. At the end of this period, haemodynamic and cardiac output measurements were repeated, and blood was drawn as described above. NO was then discontinued, and after a further 20 minutes, recontrol hemodynamic data and blood samples were collected.

**Statistics**

All data are presented as means (SD). A one-way ANOVA was used for comparison of baseline variables between groups. The effect of inhaled NO on haemodynamics and neurochemical variables was analyzed using repeated measures ANOVA. The Bonferroni correction was used for multiple comparisons. Univariate and stepwise linear regression
analysis procedures were used to explore the relationships between haemodynamic variable and the CTCG of NE.

Results

Patient Characteristics

A total of 15 patients with PAH were studied. Ten patients had IPAH and 5 had PAH in association with a connective tissue disorder. There were 9 women and 6 men. Their mean age was 54±12 years. Patients with normal LV systolic function included 9 women and 6 men with a mean age of 55±12 years. Of these 8 had normal coronary anatomy and 7 had significant coronary artery disease. The group with CHF included 5 women and 10 men all with a LV ejection fraction of less than 40%. Their mean age was 53±12 years. Of this group 5 had significant coronary artery disease and 10 were felt to have a nonischemic cardiomyopathy.

Hemodynamic Characteristics

Table 1 summarizes the baseline haemodynamic characteristics of the 3 patient groups. In comparison to the group with normal LV function patients with PAH had increased right atrial, mean pulmonary artery pressure and markedly elevated pulmonary vascular resistance. In contrast they had similar pulmonary wedge pressures as compared to the normal group. In comparison to the CHF group, patients with PAH had lower pulmonary wedge pressures but similar right atrial and mean pulmonary artery pressures. CHF patients had elevated pulmonary vascular resistance as compared with the normal LV group but this value was lower than that seen in the PAH group. The mean systemic arterial blood pressure and cardiac index in the CHF group were lower than in both the normal LV function and PAH group.
Neurochemical characteristics

Table 1 also summarizes the baseline neurochemical data. Arterial NE levels were higher in both the PAH and CHF groups as compared to the normal group (P < 0.01 for both). Although TBNESP was significantly elevated in the CHF group it was significantly higher in the PAH group (9812 ± 6033 versus 4609 ± 2279 pmol/min, PAH versus CHF; P< 0.01) Patients with PAH and CHF also had significantly higher concentrations of NE in the coronary sinus and greater CTCG of NE values than controls. There was no difference in this measure of cardiac sympathetic activity between the PAH and CHF group indicating similar levels of sympathetic activity in these 2 populations.

Regression analysis did not demonstrate a significant correlation between any hemodynamic variable and the CTGC of NE in the patients with PAH (data not shown).

Responses to nitric oxide in patients with PAH

Table 2 shows the haemodynamic data at rest and in response to inhaled NO. There was no change in mean arterial pressure with inhaled NO. Inhaled NO caused a decrease in pulmonary artery pressure and pulmonary vascular resistance, an increase in cardiac output but no change in pulmonary wedge pressure. Administration of NO did not significantly alter measures of cardiac or systemic sympathetic activity (Table 2).
Discussion

The present data demonstrate that patients with PAH have both systemic and cardiac sympathetic activation. There is a clear physiologic rationale supporting a role for the sympathetic nervous system in the pathophysiology of PAH. The pulmonary circulation has extensive sympathetic innervation\(^\text{(8, 13, 41)}\) and \(\alpha\)-receptor blockers have been shown to reduce pulmonary vascular resistance,\(^\text{(13)}\) observations that point to some role of sympathetic activation in pulmonary vasoconstriction.

Chronic heart failure due to systolic LV dysfunction is characterized by generalized and organ specific (cardiac and renal) increases in sympathetic activity, a phenomenon that is the pathophysiologic basis for the beneficial effects of beta-adrenergic blocking agents in that clinical syndrome\(^\text{(17, 26, 40)}\) To date, studies examining the sympathetic nervous system in patients with PAH have employed measures of systemic catecholamine concentrations, recordings of peripheral sympathetic nerve firing rate as well as heart rate variability analysis. Some studies describe an increase in circulating catecholamine levels,\(^\text{(24, 31, 36)}\) but this has not been a consistent finding,\(^\text{(39, 44)}\) These contradictory findings are not surprising; circulating NE plasma levels are an imperfect measure of sympathetic tone since they are not only the result of NE release, but also uptake, metabolism, and clearance. Increases in sympathetic nerve traffic have also been described in patients with PAH,\(^\text{(11, 28, 44)}\) with recent findings suggesting that MSNA has prognostic significance, predicting episodes of clinical deterioration.\(^\text{(10)}\) Finally, patients with PAH have decreased heart rate variability\(^\text{(21, 28, 45)}\) and in patients with congenital heart disease the reduction in heart rate variability...
correlates with the severity of right ventricular dysfunction. (15) However, heart rate variability is representative of the balance of vagal input and sympathetic tone directed at the sinus node and is therefore not a specific measure of sympathetic activity directed at the myocardium. (27) Indeed, in patients with PAH there was an inverse rather than a positive relationship between direct measures of peripheral sympathetic nerve activity and indirect (heart rate variability) estimates of sympathetic modulation of heart rate. (28)

The presence of cardiac activation of the sympathetic nervous system in patients with PAH has important implications. Enhanced cardiac sympathetic stimulation in patients with LV systolic dysfunction is associated with adverse remodeling, an increased risk of malignant ventricular dysrhythmias and adverse clinical outcome. (26, 30) Beta-blockers in patients with LV systolic dysfunction have dramatic effects on both adverse remodeling, and outcomes including sudden death. (1, 37, 38) In the setting of PAH elevated cardiac sympathetic activation may contribute to progressive abnormalities in right ventricular dysfunction and associated clinical deterioration. This cardiac sympathetic activation might also be related to the sudden death seen in these patients as has been demonstrated in patients with LV systolic dysfunction. (30) Although their use in humans with PAH remains both uncertain and controversial, animal models of PAH have suggested that beta-blockers can have beneficial effects. (9, 16)

In patients with PAH the marked increases in cardiac sympathetic activity occur despite the presence of normal left ventricular filling pressures. The mechanism of the increase in systemic and cardiac sympathetic activity in patients with PAH remains unclear. In patients
with heart failure due to left ventricular systolic dysfunction, the magnitude of cardiac sympathetic activation is positively correlated with left heart filling pressure and increased filling pressures are felt to be an important afferent contributor to cardiac sympathetic activation. (25) In the current cohort of patients with PAH, no haemodynamic variable was significantly correlated with cardiac or systemic sympathetic activity. Further, the acute reduction of pulmonary vascular resistance, mean pulmonary artery and right atrial pressures with inhaled NO did not reduce the CTCG of NE. This finding does not support the concept that pulmonary and/or right heart pressures are a causal stimulus for increased cardiac sympathetic activity in PAH. It is worth noting that the control of cardiac sympathetic activity and its response to changes in loading conditions appears to be complex. In patients with congestive heart failure secondary to left ventricular dysfunction both cardiac and renal sympathetic activation have been shown to be unresponsive to acute reductions in cardiac filling pressures induced by nitroprusside. (2, 34) However, the magnitude of the decrease in pulmonary arterial pressures and resistance in response to inhaled NO in the current study was modest and a larger change might modify the level of cardiac sympathetic activation. Further, the reductions in he lack of a baseline correlation could result from the small sample size and type II error.

**Perspectives and Significance**

The current findings raise the important question of whether beta-adrenergic receptor blockers should be considered in the therapy of PAH. Unlike their established utility in CHF secondary to left ventricular systolic dysfunction beta-blockers have not been extensively studied with respect to their hemodynamic and clinical effects in patients with PAH. The most recent
guidelines concerning the diagnosis and management of pulmonary hypertension make no mention of the use of these agents except to point out a report of their apparent deleterious effect in patients with portopulmonary hypertension.(22, 29) There is, however, recent animal data suggesting that they may have beneficial effects on the right ventricular function response to increases in pulmonary artery pressure.(9, 16) The current observations should provoke some discussion of the potential utility of beta-blockers in the setting of PAH, particularly in those with established but not advanced disease. Importantly we provide the first evidence that PAH is associated with sympathetic activation directed at heart muscle. Despite this, there are many uncertainties. Norepinephrine concentrations in blood sampled from the main coronary sinus is most representative of blood draining from LV myocardium, particularly the interventricular septum. Venous drainage from the RV is complex with a certain and variable amount draining from Thebesian veins directly into the RV cavity. Despite these uncertainties, these observations are of potential importance to our understanding of both the pathophysiology of the PAH and have potential therapeutic interventions.
Acknowledgements

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References


<table>
<thead>
<tr>
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<th>Normals (n = 15)</th>
<th>PAH (n = 15)</th>
<th>CHF (n = 15)</th>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>55 ± 12</td>
<td>54 ± 12</td>
<td>53 ± 12</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>6/9</td>
<td>6/9</td>
<td>5/10</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.87 ± 0.9</td>
<td>1.84 ± 0.8</td>
<td>1.82 ± 0.8</td>
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<td>HR (bpm)</td>
<td>70 ± 8</td>
<td>80 ± 13</td>
<td>87 ± 16*</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>107 ± 18</td>
<td>96 ± 15</td>
<td>85 ± 11*†</td>
</tr>
<tr>
<td>mRAP (mmHg)</td>
<td>5 ± 4</td>
<td>9 ± 5*</td>
<td>10 ± 6*</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>18 ± 7</td>
<td>51 ± 11*</td>
<td>37 ± 14*†</td>
</tr>
<tr>
<td>mPCWP (mmHg)</td>
<td>10 ± 5</td>
<td>7 ± 5</td>
<td>21 ± 14*†</td>
</tr>
<tr>
<td>PVR (WU)</td>
<td>1.4 ± 0.8</td>
<td>11.8 ± 5.8*</td>
<td>5.3 ± 5.2*†</td>
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<tr>
<td>CI (L/min/m²)</td>
<td>2.8 ± 0.4</td>
<td>2.3 ± 0.5*</td>
<td>2.0 ± 0.8*†</td>
</tr>
<tr>
<td>NEart (pmol/ml)</td>
<td>1.4 ± 1.0</td>
<td>3.0 ± 2.0*</td>
<td>2.9 ± 1.7*</td>
</tr>
<tr>
<td>NEcs (pmol/ml)</td>
<td>1.9 ± 1.1</td>
<td>5.1 ± 3.0*</td>
<td>4.6 ± 2.1*</td>
</tr>
<tr>
<td>NE ext ratio (%)</td>
<td>71 ± 12</td>
<td>54 ± 10*</td>
<td>59 ± 11*</td>
</tr>
<tr>
<td>CTCG of NE (pmol/ml)</td>
<td>1.5 ± 0.9</td>
<td>3.6 ± 2.2*</td>
<td>3.3 ± 1.4*</td>
</tr>
<tr>
<td>TBNESP (pmol/min)</td>
<td>2464 ± 1476</td>
<td>9812 ± 6033*</td>
<td>4660 ± 1856*†</td>
</tr>
</tbody>
</table>

BSA, body surface area; HR, heart rate; MAP, mean arterial pressure; RAP, mean right atrial pressure; PAP, mean pulmonary artery pressure; WU, wood units; PCWP, mean pulmonary wedge pressure; PVR, pulmonary vascular resistance; CO, cardiac output; NEart, norepinephrine arterial concentration; NEcs, norepinephrine coronary sinus concentration; CTCG of NE, corrected transcardiac gradient of norepinephrine

Data are mean ± SD; * P < 0.05 versus normals; † P < 0.05 versus PAH
### Table 2. The Effect of Inhaled NO

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Inhaled NO (40 ppm)</th>
<th>Recontrol</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>78 ± 12</td>
<td>76 ± 12</td>
<td>78 ± 9</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>96 ± 13</td>
<td>97 ± 11</td>
<td>98 ± 14</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>10 ± 3</td>
<td>9 ± 4</td>
<td>8 ± 3</td>
</tr>
<tr>
<td>PAP (mmHg)</td>
<td>48 ± 11</td>
<td>43 ± 14*</td>
<td>48 ± 11</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>9 ± 4</td>
<td>9 ± 4</td>
<td>9 ± 5</td>
</tr>
<tr>
<td>PVR (WU)</td>
<td>10.6 ± 6.0</td>
<td>8.8 ± 6.2*</td>
<td>10.6 ± 5.1</td>
</tr>
<tr>
<td>PA O₂ sat (%)</td>
<td>64 ± 6</td>
<td>69 ± 9</td>
<td>64 ± 5</td>
</tr>
<tr>
<td>Art O₂ sat (%)</td>
<td>94 ± 3</td>
<td>96 ± 4</td>
<td>94 ± 3</td>
</tr>
<tr>
<td>CS O₂ sat (%)</td>
<td>31 ± 4</td>
<td>32 ± 7</td>
<td>30 ± 5</td>
</tr>
<tr>
<td>CI (L/min)</td>
<td>2.2 ± 0.5</td>
<td>2.5 ± 0.7*</td>
<td>2.2 ± 0.5</td>
</tr>
<tr>
<td>NE art (pmol/ml)</td>
<td>2.7 ± 1.4</td>
<td>2.6 ± 1.3</td>
<td>2.7 ± 1.3</td>
</tr>
<tr>
<td>NE cs (pmol/ml)</td>
<td>4.5 ± 2.0</td>
<td>4.5 ± 2.5</td>
<td>4.6 ± 2.1</td>
</tr>
<tr>
<td>NE ext ratio (%)</td>
<td>52 ± 9</td>
<td>50 ± 20</td>
<td>45 ± 17</td>
</tr>
<tr>
<td>CTCG of NE (pmol/ml)</td>
<td>3.2 ± 1.5</td>
<td>3.1 ± 2.0</td>
<td>2.9 ± 1.4</td>
</tr>
</tbody>
</table>

PA, pulmonary artery; Art, arterial; CS, coronary sinus, sat, saturation; other abbreviations as for Table 1. Data are mean ± SD; * P < 0.05 versus control (n = 10)