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# Neurohormonal Activation in Patients With Right Ventricular Failure From Pulmonary Hypertension: Relation to Hemodynamic Variables and Endothelin Levels

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***Objectives.*** **This study sought to determine whether neurohormonal activation occurs in isolated right heart failure.**

***Background.*** **Neurohormonal activation appears to parallel the severity of left heart failure, but little is known about its role in right heart failure.**

***Methods.*** **We evaluated neurohormonal activation and endothelin levels in 21 patients with primary pulmonary hypertension at the time of right heart catheterization.**

***Results.*** **Plasma norepinephrine levels correlated significantly with pulmonary artery pressure ($r = 0.66$, $p < 0.01$), cardiac index ($r = -0.56$, $p < 0.01$) and pulmonary vascular resistance ($r = 0.69$, $p < 0.001$). Atrial natriuretic peptide levels were higher in the pulmonary artery than the right atrium and femoral artery and correlated closely with pulmonary artery oxygen saturation ($r = -0.73$, $p < 0.0001$). Plasma renin levels were not elevated. Endothelin levels were increased and correlated with right atrial pressure ($r = 0.74$, $p < 0.0001$) and pulmonary artery oxygen saturation ($r = -0.070$, $p < 0.0004$).**

***Conclusions.*** **Neurohormonal activation occurs in patients with isolated right ventricular failure and inherently normal left ventricles and appears to be related to the overall severity of cardiopulmonary derangements. The elevation in endothelin levels is consistent with its release in response to pulmonary hypertension.**

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The left ventricle has traditionally been the focus of studies relating to neurohormonal activation in heart failure that can result from isolated left ventricular dysfunction or left ventricular dysfunction in combination with right ventricular dysfunction (1,2). It has never been possible to determine the relative contribution of each ventricle with respect to neurohormonal activation, although some recent studies (3) have placed greater emphasis on right ventricular function as a predictor of outcome in patients with left ventricular failure.

The present study was undertaken to determine whether neurohormonal activation occurs in patients with isolated right ventricular failure and intrinsically normal left ventricular function. We hypothesized that if neurohormonal activation was observed, it would lead to a better understanding of the physiologic signals for such activation. To that end, patients with primary pulmonary hypertension represent an ideal patient group to study.

We also investigated the role of endothelin production and release in patients with pulmonary hypertension and right ventricular failure. Endothelin levels have recently been observed to be elevated in patients with chronic left ventricular failure with secondary (4,5) and primary pulmonary hypertension (6). However, how endothelin relates to the hemodynamic state or to other neurohormones in primary pulmonary hypertension has not yet been clarified.

## Methods

**Study patients.** Twenty-one consecutive patients with primary pulmonary hypertension referred to the University of Illinois at Chicago were entered into the study (14 women, 7 men; mean [±SD] age 41 ± 13 years, range 15 to 58). All patients were evaluated by clinical history, physical examination, chest radiography, perfusion lung scanning, pulmonary function testing, echocardiography and right heart cardiac catheterization. Secondary causes of pulmonary hypertension were excluded on the basis of criteria used by the National Institutes of Health (NIH) registry on primary pulmonary hypertension (7). Normal left ventricular function was documented in every patient by echocardiography. All patients had a complete chemistry profile to exclude hepatic or renal dysfunction. The study protocol was approved by the University of Illinois Institutional Review Board before patient entry.

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**Hemodynamic studies.** All vasoactive medications were withheld for at least 48 h before the study. All patients underwent diagnostic right heart catheterization after an overnight fast. Right atrial, pulmonary artery and pulmonary capillary wedge pressures and cardiac output (in triplicate) were determined using a flow-directed thermodilution catheter advanced into the pulmonary artery through the femoral veins. Systemic arterial pressure was determined by means of a small cannula in the femoral artery. Pulmonary and systemic vascular resistance values were calculated according to standard formulas.

**Sample collection.** After collection of hemodynamic data, the patients were moved to a quiet room and allowed to rest in a supine position for 30 min. Blood samples were drawn simultaneously from the thermodilution catheter and the femoral cannula from three sites: pulmonary artery, right atrium and femoral artery. Blood samples for plasma norepinephrine were placed in prechilled (Amersham) collection tubes containing ethyleneglycoltetraacetic acid (EGTA) and glutathione, and blood samples for plasma renin activity, atrial natriuretic peptide and endothelin level determinations were placed in tubes containing ethylenediaminetetraacetic acid (EDTA) at room temperature. All samples, except plasma renin activity, were placed on ice immediately after collection and then centrifuged at 2,500 rpm for 12 min at 4°C. The plasma was then transferred to 12 × 75-mm polypropylene tubes and frozen upright at −70°C. Samples were shipped on dry ice to the University of Minnesota for analysis, within 15 days of collection. Plasma norepinephrine levels were measured by a radioenzymatic method (Catecholamine Assay Kit, Amersham), whereas plasma renin activity, atrial natriuretic peptide and endothelin levels were measured by radioimmunoassay. The endothelin assay had the following cross-reactivities: endothelin-1 100%; endothelin-2 91%; endothelin-3 0.05%; "big" endothelin 76%.

**Survival estimates.** To determine whether neurohormonal activation might be associated with prognosis, 1-, 2-, 3-, 4- and 5-year survival was computed for each patient on the basis of a formula derived from the data base of the NIH registry on primary pulmonary hypertension, which includes cardiac index, mean pulmonary artery pressure and mean right atrial pressure (8). This formula has been validated in two subsequent clinical studies (9,10).

**Statistical methods.** Mean values ± SD were computed for all hemodynamic variables. Because the distribution for neurohormonal measurements was highly skewed, nonparametric statistics were used to describe these data as median (25th to 75th percentile), and to perform statistical tests. Comparisons of neurohormonal and endothelin values from samples drawn from the right atrium, pulmonary artery and femoral artery sites were made using the Friedman test and the Wilcoxon signed-rank test. The neurohormonal and endothelin values obtained from the samples drawn from the pulmonary artery site were used for estimating the Spearman correlation coefficients with the measured hemodynamic data and various biochemical tests. One-way analysis of variance was used to test the differences between groups with respect to expected survival rates and levels of plasma norepinephrine; $p \leq 0.05$ was considered significant without adjustments for multiple comparisons.

**Table 1.** Baseline Hemodynamic Variables in 21 Patients With Primary Pulmonary Hypertension

| | Mean ± SD | Range |
|---|---|---|
| Heart rate (beats/min) | 86 ± 16 | 59–115 |
| Systemic arterial pressure (mm Hg) | 88 ± 13 | 56–120 |
| PA pressure (mm Hg) | 56 ± 15 | 26–80 |
| RA pressure (mm Hg) | 11 ± 7 | 3–30 |
| Pulmonary capillary wedge pressure (mm Hg) | 8 ± 3 | 3–15 |
| Cardiac index (liters/min per $m^2$) | 1.92 ± 0.54 | 1.19–3.28 |
| Systemic vascular resistance (U) | 24 ± 9 | 9–40 |
| Pulmonary vascular resistance (U) | 16 ± 8 | 2–33 |
| Systemic arterial oxygen saturation (%) | 88 ± 9 | 62–96 |
| PA oxygen saturation (%) | 52 ± 14 | 25–71 |

PA = pulmonary artery; RA = right atrial.

## Results

**Hemodynamic variables.** At catheterization, all 21 patients had hemodynamic variables characteristic of primary pulmonary hypertension (Table 1): Pulmonary artery pressure ranged from 26 to 80 mm Hg (mean 56 ± 15) and pulmonary vascular resistance from 2 to 33 U (mean 16 ± 8 U). These ranges reflected the broad spectrum of severity of primary pulmonary hypertension present in this group.

**Neurohormonal values.** Median values for plasma norepinephrine (441 pg/ml) and atrial natriuretic peptide (134 pg/ml) obtained from the pulmonary artery were increased in patients with primary pulmonary hypertension compared with previously established normal values from the same laboratory (Table 2). The median value for plasma renin activity was similar, but that for endothelin (12.5 pg/ml) was increased, in patients with primary pulmonary hypertension compared with previously established normal values.

Neurohormone and endothelin levels assayed from the right atrium, pulmonary artery and femoral artery sites were also compared (Table 2). Mean levels of atrial natriuretic peptide obtained from the pulmonary artery (278 pg/ml) were significantly higher ($p = 0.0004$) than samples from the right atrium (235 pg/ml) and tended to be higher than those from the femoral artery (239 pg/ml, $p = 0.06$). However, there were no significant differences in values of plasma norepinephrine, plasma renin activity, or endothelin obtained from the three sites. Correlations between neurohormone and endothelin levels and other variables consequently were made between the levels obtained from the pulmonary artery site.

Plasma norepinephrine levels correlated significantly with right atrial pressure ($r = 0.61$, $p < 0.01$), pulmonary artery pressure ($r = 0.66$, $p < 0.01$), cardiac index ($r = -0.56$, $p < 0.01$) and pulmonary artery oxygen saturation ($r = -0.55$, $p < 0.01$). However, the closest correlation was between plasma

**Table 2.** Neurohormonal and Endothelin Values Obtained From Pulmonary Artery, Right Atrium and Femoral Artery in 21 Patients With Primary Pulmonary Hypertension

| | Primary Pulmonary Hypertension | | Normal Values | |
|---|---|---|---|---|
| | PA Site | RA Site | FA Site | Peripheral Vein |
| PNE (pg/ml) | 441 (315–582) | 501 (365–555) | 443 (317–515) | 255 (201–340) |
| PRA (pg/ml per h) | 2.4 (1.2–3.4) | 3.0 (1.6–4.2) | 1.9 (1.3–3.9) | 3.1 (2.1–5.1) |
| ANP (pg/ml) | 134 (117–358) | 114 (56–332)* | 173 (98–353)† | 24 (12–32) |
| ET (pg/ml) | 12.5 (9.5–20.6) | 13 (9.5–19.4) | 11 (9.3–19.2) | 6.9 (6.2–8.2) |

*p = 0.004, †p = 0.06 versus pulmonary artery (PA) site. Data presented are median (interquartile range). ANP = atrial natriuretic peptide; ET = endothelin; FA = femoral artery; PNE = plasma norepinephrine; PRA = plasma renin activity; RA = right atrial.

norepinephrine levels and pulmonary vascular resistance ($r = 0.69$, $p < 0.001$) (Fig. 1). In contrast, atrial natriuretic peptide levels correlated most closely with pulmonary artery oxygen saturation ($r = -0.73$, $p < 0.0001$) (Fig. 2) and to a lesser extent with mean right atrial pressure ($r = 0.44$, $p = 0.05$).

Correlations were also found between endothelin levels and mean right atrial pressure ($r = 0.74$, $p < 0.0001$) and pulmonary artery oxygen saturation ($r = -0.70$, $p < 0.0004$) (Fig. 3). We also found a correlation between endothelin and atrial natriuretic peptide levels ($r = 0.54$, $p = 0.01$) and endothelin and plasma norepinephrine levels ($r = 0.49$, $p < 0.01$) but not between endothelin levels and pulmonary vascular resistance ($r = 0.25$, $p = NS$).

Previous studies of left heart failure (11) have shown a strong relation between plasma norepinephrine levels and patient survival. To test whether a similar relation could be found with right heart failure, the present patients were classified into three groups according to plasma norepinephrine values: <370 pg/ml (group 1), 370 to 500 pg/ml (group 2) and >500 pg/ml (group 3). These values were then used to calculate the estimated 5-year survival rate according to the NIH registry on primary pulmonary hypertension equation predicting survival for patients with primary pulmonary hypertension (Table 3, Fig. 4). The resulting predicted 5-year survival rates were significantly different: 44% for group 1, 31% for group 2 and 17% for group 3 ($p = 0.0009$).

## Discussion

Neurohormonal activation contributes to the development of symptoms related to chronic congestive heart failure (12). Because neurohormones correlate poorly with one another, it is likely that there are multiple mechanisms that cause neurohormonal activation. Neurohormonal activation can alter the loading conditions of the heart by increasing impedance and blood volume, thus causing further reductions in cardiac function (2). The precise physiologic signals that result in neurohormonal activation are not fully understood but may relate to left ventricular stroke volume and left atrial and ventricular filling pressures or the effect of cardiac dysfunction on the peripheral vasculature (2). It was recently demonstrated (3) that patients with biventricular dysfunction have a poorer prognosis than those with left ventricular dysfunction only, suggesting that right ventricular performance contributes to the prognosis of these patients. Whether this relates to neurohormonal activation has not been explored.

**Present study.** We studied neurohormonal activation in patients with primary pulmonary hypertension because such

**Figure 1.** Individual patient data (**circles**) show a strong positive correlation ($r = 0.76$, $p < 0.0001$) between plasma norepinephrine (PNE) levels and pulmonary vascular resistance (PVR). **Diagonal line**: $y = 0.01x + 9.05$.

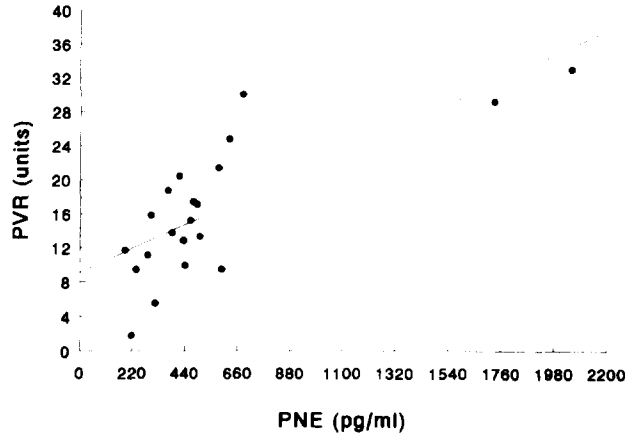
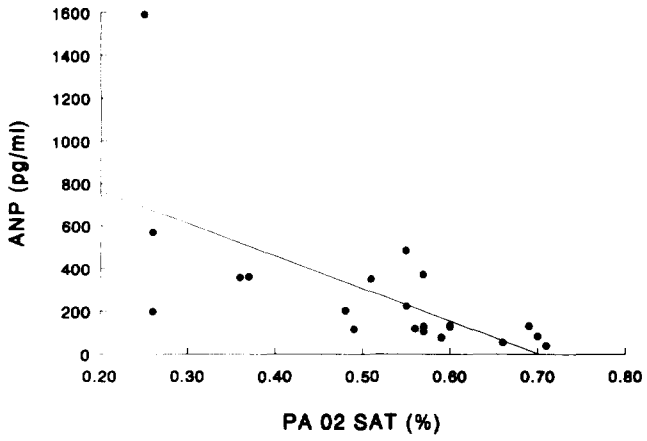



**Figure 2.** Atrial natriuretic peptide (ANP) levels and pulmonary artery oxygen saturation (PA $O_2$ SAT) show a strong negative correlation ($r = -0.65$, $p < 0.001$). Format as in Figure 1.



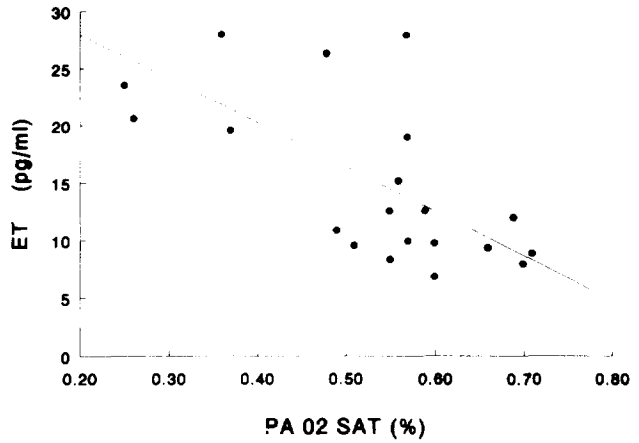



**Figure 3.** Endothelin (ET) levels and pulmonary artery oxygen saturation (PA $O_2$ SAT) show a strong negative correlation ($r = -0.71$, $p < 0.0003$). Format as in Figure 1.

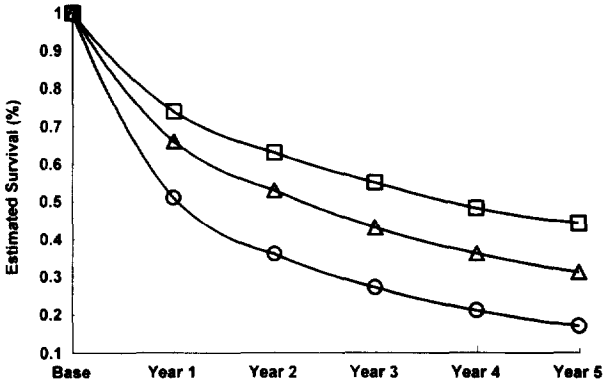



**Figure 4.** Estimated survival of patients according to plasma norepinephrine (PNE) levels: **squares** = <370 ng/ml; **triangles** = 370 to 500 ng/ml; **circles** = >500 ng/ml. Patients with the highest levels of plasma norepinephrine are projected to have the poorest prognosis.

patients have right ventricular dysfunction in the presence of normal left ventricular performance. The present study showed that neurohormonal activation occurs in patients with primary pulmonary hypertension and significantly relates to the severity of hemodynamic dysfunction. Furthermore, neurohormonal activation is strongly related to pulmonary arterial oxygen saturation, a physiologic manifestation of the severity of heart failure that has not been fully explored in studies of left heart failure. These findings suggest that the signals for neurohormonal activation are not solely confined to the left side of the heart and may relate more to the overall level and nature of cardiopulmonary abnormalities than any single physiologic disturbance.

Neurohormonal values were similar when sampled from the right atrium, pulmonary artery and femoral artery, with the exception of those for atrial natriuretic peptide, which was higher in the pulmonary artery. This finding is consistent with the observation of atrial natriuretic peptide release from the right atrium in these patients (13). The lack of plasma renin activity level elevation may be a function of the small number of patients with severe right ventricular failure and systemic venous congestion, but further investigation is warranted.

*Endothelin*, a product of endothelial cells, has been shown to have elevated levels in patients with congestive heart failure and secondary and primary pulmonary hypertension (4,5). Although endothelin has several biologic effects, one major activity appears to relate to vasoconstriction and the maintenance of blood pressure (14). Elevated endothelin levels in pulmonary hypertension has been suggested as indicating a role for endothelin in the pathophysiology or maintenance of pulmonary hypertension in several disease states (6).

It has been difficult to determine whether endothelin is related more to the cause or the effect of primary pulmonary hypertension. The elevation of endothelin levels seen in secondary forms of pulmonary hypertension suggests that it is a response to physiologic signals from the pulmonary vascular endothelium. However, the finding of elevated levels in the neonatal fawn hooded rat, an animal that develops spontaneous pulmonary hypertension, suggests that it may also be causative in pulmonary hypertensive states as well (15). The relation between endothelin and neurohormonal levels in the present study suggests that endothelin release is related to the cardiovascular physiologic state of the patient. The signals for endothelin production and release remain unclear, but the correlation of endothelin levels with pulmonary artery oxygen saturation, and not pulmonary vascular resistance, suggests that endothelin might not be directly involved in determining pulmonary vascular tone in primary pulmonary hypertension. Prostacyclin and thromboxane levels may also be related to neurohormonal activation in primary pulmonary hypertension, but these were not measured in the present study (16).

We explored the possibility that the level of neurohormonal activation in patients with primary pulmonary hypertension may be related to survival, as has been described in patients with chronic congestive heart failure (11). By classifying our

**Table 3.** Estimated Percent Survival (mean ± SD) Over 5 Years for 21 Patients With Primary Pulmonary Hypertension

| PNE Level (pg/ml) | 1 yr | 2 yr | 3 yr | 4 yr | 5 yr |
|---|---|---|---|---|---|
| <370 | 0.74 ± 0.12 | 0.63 ± 0.14 | 0.55 ± 0.16 | 0.48 ± 0.16 | 0.44 ± 0.15 |
| 370–500 | 0.66 ± 0.09 | 0.53 ± 0.11 | 0.43 ± 0.12 | 0.36 ± 0.12 | 0.31 ± 0.11 |
| >500 | 0.51 ± 0.16 | 0.36 ± 0.16 | 0.27 ± 0.14 | 0.21 ± 0.11 | 0.17 ± 0.10 |

PNE = plasma norepinephrine.

patients into three groups according to plasma norepinephrine levels, we were able to demonstrate different predicted survival rates, raising the possibility that neurohormonal activation may be a determining factor for survival in primary pulmonary hypertension as it is in congestive left heart failure.

**Study limitations.** Although we were able to study patients with a wide range of hemodynamic derangements, the relatively small number of patients limits our ability to define these relations with precision. In addition, the endothelin assay used detects several forms that may have diminished the specificity of the observations. Finally, although the equation developed to predict survival in patients with primary pulmonary hypertension has been validated in two subsequent studies, the prognostic value of plasma norepinephrine levels remains speculative and may be an indirect reflection of hemodynamic variables rather than an independent factor.

**Conclusions.** Patients with isolated right ventricular dysfunction from primary pulmonary hypertension and inherently normal left ventricles appear to have neurohormonal activation that relates to the severity of their hemodynamic derangement. This finding suggests that the signals for neurohormonal activation do originate from a specific chamber in the heart: rather, they are related to the physiologic state of the patient and the interplay of factors that determine cardiovascular performance. Neurohormonal activation may be a marker of prognosis in these patients and may provide another focus for the long-term treatment of primary pulmonary hypertension.

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