Atrial natriuretic peptide in primary pulmonary hypertension

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ABSTRACT: Plasma levels of atrial natriuretic peptide (ANP) were determined during cardiac catheterization in nine patients with primary pulmonary hypertension (PPH) and the effect of prostacyclin infusion via a right heart catheter studied. The role of hypoxia on the release of ANP was investigated in a control group of six normal subjects who underwent an acute hypoxic challenge. Patients showed the typical haemodynamic changes of primary pulmonary hypertension with elevation of mean pulmonary artery pressure, 71.3 (13.8) mmHg, and low cardiac index, 1.9 (0.5) l·min⁻¹·m⁻². Plasma ANP was also elevated; mean pulmonary artery plasma ANP was 96.3 (77.6) pmol·l⁻¹ in PPH patients compared with mean venous plasma ANP of 8.9 (5.6) pmol·l⁻¹ in normal subjects. Prostacyclin infusion in PPH patients and hypoxic challenge in normal subjects did not significantly alter plasma ANP levels. The elevated levels of ANP in PPH are due to the altered haemodynamics secondary to increased pulmonary vascular resistance and may be responsible for the lack of peripheral oedema seen in this condition.


Infusion studies have established that ANP can produce a natriuresis and diuresis within the physiological range of plasma levels (14, 15). The lack of oedema seen in primary pulmonary hypertension could be due to elevation of plasma ANP levels in this condition. We report the ANP levels in PPH patients in relation to their haemodynamic disturbance and levels of hypoxia. In addition we have assessed the effect of hypoxia on ANP levels in a control group of normal volunteers.

Patients and methods

The study was approved by the local Ethical Committee. The patients were undergoing diagnostic right heart catheterization and each also received an intravenous infusion of prostacyclin (16) to assess the degree of vasoconstriction contributing to their clinical state. Nine patients aged 32–59 yrs were studied, all had severe primary pulmonary hypertension, details of clinical state and drug treatment are given in table 1. All drugs were withheld for 8 h and patients were sedated with diazepam. Subjects were studied in the supine position. A triple lumen catheter was inserted through the internal jugular and positioned in the pulmonary artery by fluoroscopic screening. Mean right atrial pressure (RAP) and mean pulmonary artery pressure (PAP) were recorded with Roche pressure transducers using the sternal angle as a reference point. Pulmonary arterial blood samples were taken for estimation of blood gas tension and oxygen saturation. Cardiac output was measured by the thermodilution technique using 5%
dextrose as the vehicle and taking the mean of three measurements (Edwards 9025A cardiac computer, Edwards Laboratories Inc., Puerto Rico). Arterial blood gas measurements were taken from an indwelling arterial cannula in the radial artery from which mean systemic arterial pressure (SAP) was recorded.

After baseline assessment of haemodynamic variables and plasma ANP subjects received an infusion of prostacyclin via the right heart catheter. Prostacyclin (0.5 mg epoprostenol, Wellcome Foundation, in 50 ml of glycine buffer) was made up in 200 ml 0.9% NaCl solution and the initial infusion rate was 133 ng·min⁻¹. Dosage was adjusted at 10 min increments until a 20% fall in systemic arterial pressure was observed. The subject was then maintained on this infusion rate and repeat sampling for plasma ANP was undertaken.

To determine whether hypoxia was contributing to the release of ANP in our patients we studied a control group of 6 healthy male subjects, aged 26–57 yrs, who underwent an hypoxic challenge. Subjects were connected to a rebreathing circuit consisting of an Ohio spirometer which enabled continuous monitoring of ventilatory rate and a soda lime scrubber to regulate inspired carbon dioxide. End-tidal carbon dioxide was monitored at the expiratory mouthpiece. Inspired oxygen content of the gas mixture measured at the inspiratory limb of the circuit and adjusted by the admission of room air into the circuit. Plasma ANP was determined from venous samples obtained from an indwelling cannula and arterial oxygen saturation was measured by ear pulse oximetry.

After 10 min rest, subjects rebreathed 6 l of air for 20 min and baseline estimations of plasma ANP and oxygen saturation were obtained. Hypoxia was then induced by replacing 4 l of air with an equal volume of nitrogen in order to obtain an estimated oxygen saturation of 75–80%. Plasma for determination of ANP was obtained at the end of 20 min hypoxia and following a recovery period of 10 min.

Blood for estimation of plasma ANP was collected into chilled EDTA tubes, centrifuged and stored at -20°C for subsequent assay. ANP was extracted using a Seepak C18 column using 60% acetonitrile followed by radioimmunoassay as described in detail previously [14]. The 95% confidence limits of detection of the assay were 2.5 pmol·l⁻¹. Linear regression analysis using the least squares model was performed to determine any correlation between plasma ANP and haemodynamic variables. The effect of treatment was assessed on paired data using the Wilcoxon signed rank test and significance was assumed at a level of p<0.05.

Results

Pulmonary artery pressure was elevated in all patients. Mean baseline pulmonary artery pressure (systolic arterial pressure; PAP: right atrial pressure; PVR: pulmonary vascular resistance; SaO2: arterial oxygen saturation; T: thiazide; D: digoxin; N: nifedipine; C: captopril; F: frusemide.

Table 1. – Drug treatment and haemodynamic variables in patients with pulmonary hypertension undergoing right heart catheterization

<table>
<thead>
<tr>
<th>Subject</th>
<th>CI 1/min·m⁻²</th>
<th>Mean SAP mmHg</th>
<th>Mean PAP mmHg</th>
<th>Mean RAP mmHg</th>
<th>PVR mmHg·m⁻²</th>
<th>SaO2 %</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>1</td>
<td>1.7</td>
<td>77.0</td>
<td>53.0</td>
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<td>T</td>
</tr>
<tr>
<td>2</td>
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<td>76.0</td>
<td>70.0</td>
<td>10.0</td>
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<td>63.0</td>
<td>T</td>
</tr>
<tr>
<td>3</td>
<td>1.8</td>
<td>95.0</td>
<td>60.0</td>
<td>7.0</td>
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<td>94.0</td>
<td>79.0</td>
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<tr>
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<tr>
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</tr>
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</table>

CI: cardiac index; SAP: systemic arterial pressure; PAP: right atrial pressure; PVR: pulmonary vascular resistance; SaO2: arterial oxygen saturation; T: thiazide; D: digoxin; N: nifedipine; C: captopril; F: frusemide.
ANP pmol/l⁻¹

300

200

100

0

RA PA ART

Rest

PGI₂

Fig. 1. - Individual values and mean plasma ANP measured from right atrium (RA), pulmonary artery (PA) and a systemic artery (ART) in subjects undergoing right heart catheterization with trial of prostacyclin. ANP: atrial natriuretic peptide; PGI₂: prostacyclin.

ANP pmol/l⁻¹

20

10

0

Baseline Hypoxia Normoxia

Fig. 2. - Effect of acute hypoxic challenge on plasma ANP in six normal subjects. ANP: atrial natriuretic peptide.

In the normal subjects mean plasma ANP was 8.9 (5.6) pmol/l⁻¹ at rest but was not significantly changed during acute hypoxia 3.8 (3.1) pmol/l⁻¹. Following 10 min normoxia plasma ANP had returned 6.8 (5.9) pmol/l⁻¹ (fig. 2).

Discussion

In primary pulmonary hypertension, despite considerable reduction in cardiac output, oedema formation is a late feature whereas in cor pulmonale oedema occurs relatively early in the disease process when cardiac output is normal or even raised [13]. In patients with primary pulmonary hypertension prostacyclin causes relaxation of vascular smooth muscle and a fall in pulmonary vascular resistance with an increase in cardiac index [16]. In this study prostacyclin infusion did not affect ANP levels, presumably because no significant change in right atrial or pulmonary artery pressures occurred despite a fall in pulmonary vascular resistance.

The release of ANP has been shown to be dependent on right atrial filling pressure [17]. It is probable, however, that mean right atrial pressure does not accurately reflect the dynamic stretch to the atrial myocardium during the cardiac cycle in vivo, particularly in primary pulmonary hypertension where marked tricuspid regurgitation is common. If dynamic atrial stretch were important in ANP release this would explain the greater elevation of ANP than would be expected from the mean right atrial pressure measurements seen both in our study of primary pulmonary hypertension and in those of ADWOT et al. [18] and BURGHUBER et al. [19] who found a correlation between pulmonary artery pressure and plasma ANP in subjects with a wide range of pulmonary vascular resistance. Our study population had an homogeneous increase in pulmonary vascular resistance and correlation between ANP values and intracardiac pressure was poor. WINTER et al. [20] has found a similarly poor correlation in subjects with hypoxic secondary pulmonary hypertension where both pulmonary artery pressures and plasma ANP levels were lower than those found in the present study.

We were unable to demonstrate any increase in ANP levels during acute hypoxia in normal subjects, and indeed our study showed a large if nonsignificant trend for a fall in plasma ANP. Similar results have been obtained in animal models of hypoxia [10] and it seems unlikely that the degree of hypoxia experienced by our patients caused a significant contribution to the high levels of ANP observed. ANP relaxes pulmonary artery smooth muscle by an endothelium independent mechanism [21] and this effect is greater than that seen in comparable renal artery segments. It is possible that elevation of circulating ANP to levels seen in PPH may significantly influence pulmonary vascular resistance although concentrations of ANP required to produce pulmonary vasorelaxation in vivo are greater than those observed in this study. We have previously shown that the potent natriuretic and diuretic effects of ANP occur at plasma levels within the range found in this study [13] and it is probable that the elevation of ANP seen in primary pulmonary hypertension will increase the renal excretion of salt and water. Oedema formation occurs late in primary pulmonary hypertension when cardiac output is considerably reduced. In the kidney the action of ANP has been shown to be crucially dependent on renal perfusion pressure [22] and the lack of effect of high circulating levels of ANP in preventing the retention of salt and water late in the disease may be due to a fall in renal blood flow secondary to low output cardiac failure. With the natriuretic and diuretic actions of ANP limited by poor renal perfusion elevated levels of ANP may actually promote oedema formation by displacing fluid from the plasma to the interstitial compartment [23]. In early pulmonary hypertension oedema formation may be limited by elevated plasma levels of ANP secondary to dynamic atrial stretch.
References


**Natriuresis in Primary Pulmonary Hypertension**
