Pleurectomy in asbestos-related pleural disease

Table 3 Operative findings

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parietal pleural thickening</td>
<td>Diffuse</td>
<td>Diffuse</td>
<td>Diffuse</td>
<td>Multiple large plaques</td>
</tr>
<tr>
<td>Thickness of parietal pleura (mm)</td>
<td>7</td>
<td>5</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Visceral pleural thickening</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Adhesions between visceral and parietal pleura</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Operative findings to benign asbestos-related pleural disease are similar to those previously reported. This condition needs to be distinguished from the more common self-limited episodes of pleural pain which can be associated with benign asbestos-related pleural effusions. In the series reported by Robinson and Musk pain lasted for an average of 10 weeks (range 2–26 weeks). Several features supported an organic basis for our patients' pain. Firstly, pleural rubs in asbestos pleural disease are uncommon yet they were present in all patients on most reviews. Secondly, increased erythrocyte sedimentation rate and fever were noted. Thirdly, chest radiographs showed progressive changes. Lastly, thoracic nerve blocking procedures and thoracic epidural blocks relieved the pain.

Pleurectomy is therefore unlikely to be helpful for persistent pain due to benign asbestos-related pleural disease where there is a significant neuralgic component. However, patients without this component who have pleuritic pain which is chronic, debilitating, and not responding to conventional analgesia may respond to the procedure.


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Thorax 1995;50:183–185

Pulmonary vasorelaxant activity of atrial natriuretic peptide and brain natriuretic peptide in humans

Robert I Cargill, Brian J Lipworth

Abstract

**Background** - Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) exhibit in vitro pulmonary vasodilator activity, but little information is available regarding their effects in the human pulmonary vasculature. Their effects in the human pulmonary circulation and their ability to modulate the pulmonary pressor effects of angiotensin II have therefore been evaluated.

**Methods** - Eight healthy volunteers were studied on three separate occasions. Infusions of either ANP, BNP, or placebo were given for 60 minutes with a concomitant infusion of angiotensin II given for the final 30 minutes. Pulmonary haemodynamics were measured by pulsed wave Doppler echocardiography at baseline (T₀), before commencing angiotensin II (Tₗ₀), and at the end of the infusion period (Tₜ₀).

**Results** - Mean pulmonary artery pressure (MPAP) showed a fall with ANP and BNP infusion at Tₗ₀ compared with placebo. Although angiotensin II infusion had significant pulmonary pressor effects on all three study days, MPAP at Tₜ₀ was lower when ANP (18±3 (2±0) mm Hg) and BNP (16±1 (1±5) mm Hg) were given concomitantly compared with placebo (21±8 (1±6) mm Hg).

**Conclusions** - These findings indicate that both ANP and BNP exhibit pulmonary vasorelaxant activity in humans in terms of antagonism of the pulmonary pressor effects of angiotensin II. This would support the hypothesis that ANP and BNP act as circulating counter-regulatory hormones in states of pathological pulmonary vasoconstriction.

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Keywords: natriuretic peptides, pulmonary circulation, angiotensin II.

Although the systemic haemodynamic effects of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) in humans are well documented, relatively little is known regarding their effects in the human pulmonary vascular bed. Both ANP and BNP have been shown to exhibit in vitro pulmonary vasodilator activity, but little information is available regarding their effects in the human pulmonary vasculature.
relaxant activity in rats, and ANP infusion can reduce pulmonary vascular resistance in patients with cor pulmonale. In addition, the interplay between the natriuretic peptide system and the renin-angiotensin system which is important in terms of hormonal and systemic pressor effects has not been studied in the human pulmonary circulation.

We have therefore studied the effects of ANP and BNP on pulmonary vascular tone in humans and their interaction with angiotensin II in the pulmonary circulation.

Methods
SUBJECTS
Eight normal male volunteers of mean (SE) age 29.2 (2.8) years were studied on three occasions. Clinical history and examination, biochemical and haematological screening, 12 lead electrocardiogram and echocardiogram were all normal, and informed consent for the study protocol previously approved by the Tayside Committee for Medical Ethics was obtained.

STUDY PROTOCOL
On each study day intravenous cannulae for peptide infusion were inserted and subjects remained supine for the remainder of the study. After resting to reach steady state baseline haemodynamics (T₀) a 60 minute infusion of either human ANP (10 pmol/kg/min), human BNP (10 pmol/kg/min), or placebo (5% dextrose) was commenced. After 30 minutes (T₃₀) a concomitant infusion of human angiotensin II (6 ng/kg/min) was started and both infusions were continued for a further 30 minutes (T₆₀). Haemodynamic parameters were measured just before commencing each infusion (T₀ and T₃₀) and at the end of the total infusion period (T₆₀).

MEASUREMENTS
Mean arterial blood pressure (MAP) was measured by a semi-automatic sphygmomanometer. All other haemodynamic measurements were made non-invasively by pulsed wave Doppler echocardiography. Cardiac output (CO) was measured from aortic blood flow as previously described. Mean pulmonary arterial pressure (MPAP) was calculated from measurement of pulmonary acceleration time as described by Dibestani et al. Total pulmonary vascular resistance (PVR) was calculated as (MPAP/CO) x 80 dyne.s.cm⁻⁵. We have previously shown these methods to be highly reproducible with intraindividual variability (as CV%) for measurement of pulmonary acceleration time to be 1.7% and for aortic stroke distance 1.2%.

DATA ANALYSIS
A Statgraphics (STSC Software Publishing Group, Maryland, USA) computer software package was used to analyse the data with comparisons made by multifactorial analysis of variance and, where significant, Duncan’s multiple range testing with p<0.05 considered significant. Values are expressed in the text as mean (SE).

Results
PULMONARY HAEMODYNAMICS
MPAP and PVR were similar at T₀ on all three study days. At T₆₀, MPAP was significantly lower following infusion of ANP and BNP than with placebo (figure). PVR at T₆₀ was also significantly lower after ANP and BNP infusion than after placebo (figure). Angiotensin II had significant pulmonary pressor effects although MPAP at T₆₀ was significantly lower when ANP or BNP were infused compared with placebo (figure). Similarly, PVR at T₆₀ was significantly lower when ANP or BNP were given concomitantly compared with placebo (figure).

To obviate the effects of different baseline values at T₀, we calculated the change in MPAP induced by angiotensin II between T₆₀ and T₀. The ΔMPAP response was significantly attenuated by BNP (6.9 ± 1.0 mm Hg) but not by ANP (9.8 ± 1.6 mm Hg) compared with placebo (10.8 ± 1.1 mm Hg). Similarly, ΔPVR was significantly attenuated by BNP (125 ± 22 dyne.s.cm⁻⁵) in comparison with ANP (177 ± 22 dyne.s.cm⁻⁵) or placebo (208 ± 19 dyne.s.cm⁻⁵).

SYSTEMIC HAEMODYNAMICS
There were no significant changes in MAP or CO in response to ANP or BNP infusion.
Mean (SE) systemic haemodynamic responses

<table>
<thead>
<tr>
<th>Treatment</th>
<th>T₀</th>
<th>T₉₀</th>
<th>T₉₀-</th>
<th>T₉₀/Wt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>88±4 (2-9)</td>
<td>87±9 (1-7)</td>
<td>116±9 (3-4)*</td>
<td>5±0 (0-19)*</td>
</tr>
<tr>
<td>MAP</td>
<td>6±30 (0-19)</td>
<td>6±57 (0-31)</td>
<td>5±06 (0-19)*</td>
<td></td>
</tr>
<tr>
<td>CO</td>
<td>9±04 (2-1)</td>
<td>8±61 (2-9)</td>
<td>107±1 (2-6)*</td>
<td>5±25 (0-19)*</td>
</tr>
<tr>
<td>ANP</td>
<td>6±41 (0-19)</td>
<td>6±92 (0-40)</td>
<td>5±25 (0-19)*</td>
<td></td>
</tr>
<tr>
<td>BNP</td>
<td>8±66 (2-3)</td>
<td>8±39 (2-5)</td>
<td>104±0 (3-1)*</td>
<td>5±28 (0-34)*</td>
</tr>
<tr>
<td>CO</td>
<td>6±57 (0-38)</td>
<td>6±73 (0-38)</td>
<td>5±28 (0-34)*</td>
<td></td>
</tr>
</tbody>
</table>

MAP=mean arterial pressure (mm Hg); CO =cardiac output (L/min); ANP, BNP = atrial and brain natriuretic peptides.

* Significant differences between T₀ and T₉₀/T₉₀.
† Significant differences compared with placebo.

In response to angiotensin II CO was reduced equally on all three study days and, whilst MAP increased, levels at T₉₀ were significantly lower during ANP or BNP infusion compared with placebo (table).

**Discussion**

This study demonstrates for the first time that ANP and BNP possess in vivo pulmonary vasorelaxant activity in humans. These effects, in lowering basal pulmonary vascular tone (at T₀), are perhaps less important than the finding that ANP and BNP attenuated the pulmonary pressor effects of angiotensin II (at T₉₀). However, since MPAP was decreased by both ANP and BNP, a more representative measure of their antagonism of angiotensin II responses might be to compare changes between T₀ and T₉₀ which showed that BNP, but not ANP, significantly reduced the MPAP delta response to angiotensin II. ANP and BNP may therefore play an important part as counter-regulatory hormones in states where there is pathological pulmonary vasoconstriction, particularly where there is associated activation of the renin-angiotensin system.

The exact role of angiotensin II in the physiopathology of pulmonary hypertension and cor pulmonale is still unclear, although two findings would indicate that it has a key role in this process. Firstly, there is evidence from animal studies that angiotensin II can modulate the pulmonary vasoconstrictor response to hypoxia. Secondly, we have previously shown that the human pulmonary vascular bed is more sensitive to the systemic vasculature to the pressor effects of angiotensin II. Thus, the interaction of the natriuretic peptides and angiotensin II in the pulmonary circulation may be more marked than previously studied systemic haemodynamic effects.

Echocardiographic measurements of pulmonary haemodynamic changes in normal individuals are reproducible, accurate, and easily applied. Calculation of PVR does, however, exclude changes in pulmonary capillary wedge pressure and thus we may have overestimated the effects of angiotensin II on pulmonary vascular tone. It has, however, been shown that, for a 10 mm Hg increase in MAP induced by angiotensin II, the associated increase in pulmonary capillary wedge pressure is only 1-7 mm Hg. Thus, in this study the magnitude of the MPAP response to angiotensin II (10-8 mm Hg) would be greater than any calculated change in pulmonary capillary wedge pressure (4-9 mm Hg).

The finding that ANP and BNP have pulmonary vasorelaxant activity and are antagonists of angiotensin II raises some therapeutic possibilities, perhaps in patients with cor pulmonale where the renin-angiotensin system is activated. Increasing endogenous levels of ANP and BNP by endopeptidase 24-11 inhibitors may have pulmonary haemodynamic benefits or, alternatively, may suppress overactivity of the renin-angiotensin system by ACE inhibition. This latter strategy has produced conflicting results but, as was the case in congestive heart failure, the true benefit may not be apparent until chronic dosing studies are evaluated.

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