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.

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 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 arterial pressure as described by Dubestiani et al. Total pulmonary vascular resistance (PVR) was calculated as (MPAP/CO) × 80 dynes.s.cm⁻³. We have previously shown these methods to be highly reproducible with intra-individual 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 T30 MPAP was significantly lower following infusion of ANP and BNP than with placebo (figure). PVR at T30 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 T30 and T60. 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) dynes.s.cm⁻³) in comparison with ANP (177 (22) dynes.s.cm⁻³) or placebo (208 (19) dynes.s.cm⁻³).

SYSTEMIC HAEMODYNAMICS

There were no significant changes in MAP or CO in response to ANP or BNP infusion
Pulmonary vasorelaxant activity of ANP and BNP

<table>
<thead>
<tr>
<th></th>
<th>T₀</th>
<th>T₅₀</th>
<th>T₉₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo MAP</td>
<td>88.4 (-2.9)</td>
<td>87.9 (1.7)</td>
<td>116.9 (3.4)*</td>
</tr>
<tr>
<td>Placebo CO</td>
<td>6.30 (0.19)</td>
<td>6.57 (0.31)</td>
<td>5.06 (0.19)*</td>
</tr>
<tr>
<td>ANP MAP</td>
<td>90.4 (2.1)</td>
<td>86.1 (2.9)</td>
<td>107.1 (2.6)**</td>
</tr>
<tr>
<td>ANP CO</td>
<td>6.41 (0.19)</td>
<td>6.92 (0.40)</td>
<td>5.25 (0.19)*</td>
</tr>
<tr>
<td>BNP MAP</td>
<td>88.6 (2.3)</td>
<td>83.9 (2.5)</td>
<td>104.0 (3.1)**</td>
</tr>
<tr>
<td>BNP CO</td>
<td>6.57 (0.38)</td>
<td>6.73 (0.35)</td>
<td>5.28 (0.34)**</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 T₉₀/₅₀.
** Significant differences compared with placebo.

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

Discussion

This study demonstrates for the first time that both 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 pathophysiology 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 than 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.

ECHO Doppler 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.10 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.11 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 results12 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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