Atrial natriuretic peptide concentrations in hypoxic secondary pulmonary hypertension: relation to haemodynamic and blood gas variables and response to supplemental oxygen

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ABSTRACT Plasma atrial natriuretic peptide concentrations, measured in samples drawn from the pulmonary artery, were raised in nine of 17 patients with hypoxic pulmonary hypertension but normal right atrial pressures at rest. No relationship was seen between atrial natriuretic peptide concentrations and mean pulmonary artery or right atrial pressure, or calculated pulmonary or systemic vascular resistance. Patients with the most severe hypoxaemia tended to have higher plasma atrial natriuretic peptide concentrations; three patients with no past history of oedema had concentrations more than twice the upper limit of normal. Treatment with supplementary oxygen for 30 minutes reduced pulmonary vascular resistance in all patients but had no significant effect on plasma atrial natriuretic peptide concentration. These findings suggest that atrial natriuretic peptide may be a factor in the control of sodium and water balance in hypoxic cor pulmonale, where the determinants of individual susceptibility to peripheral oedema are not well understood.

Introduction

Considerable variability exists in the development of peripheral oedema in the evolution of airflow obstruction, but its first appearance is of prognostic importance; 60% patients will not survive for more than five years.¹ The mechanism underlying the development of oedema remains uncertain. An increase in aldosterone secretion, resulting from activation of the renin-angiotensin-aldosterone cascade, may be important,^{2,3} though not all studies have found plasma aldosterone concentrations to be raised.⁴ There is little information about other factors known to control sodium and water balance. Atrial natriuretic peptide is a 28 amino acid formed by cleavage from its prohormone, cardiodilatin, in which form it is stored as electron dense granules in the atrial myocytes.⁵ It is released after perturbation of the atrial

wall with procedures such as volume loading,⁶ water immersion,⁷ or induced disorders of cardiac rhythm. The peptide has effects on the handling of sodium by the renal tubules⁸ and on systemic and pulmonary vascular tone,¹⁰ and it has a regulatory action on the renin-angiotensin-aldosterone cascade.¹¹

Studies in rats exposed to precisely controlled conditions of environmental hypoxia have shown plasma atrial natriuretic peptide concentrations to be increased and its release to be independent of associated pulmonary vascular and cardiac remodelling.¹² Raised plasma atrial natriuretic peptide concentrations were also reported in a group of patients with various lung diseases.¹³ Several patients in that study had primary disorders of the pulmonary vasculature or multisystem connective tissue diseases, and most had an arterial oxygen tension (P_{aO_2}) greater than 64 mm Hg at rest (1 mm Hg $\approx$ 0.13 kPa). In this study our objective was to measure plasma atrial natriuretic peptide concentrations in patients with severe hypoxaemia due to airflow obstruction, and to determine any correlation with haemodynamic and blood gas variables. A further aim was to assess the effects of supplementary oxygen.

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Methods

PATIENTS

We studied 17 patients with airflow obstruction and an arterial oxygen tension (P_{aO_2}) of <60 mm Hg (<8.0 kPa) when clinically stable. They were aged 54–74 (mean 62) years and had a forced expiratory volume in one second (FEV_1) of 0.38–0.90 (mean 0.68) l and a forced vital capacity of 0.61–2.80 (mean 1.80) l. All had irreversible airflow obstruction with an increase in FEV_1 of under 10% after inhaling a bronchodilator. P_{aO_2} was 39–58 (mean 49) mm Hg and P_{aCO_2} 37–66 (mean 51) mm Hg. Patients who had systemic hypertension or pulmonary hypertension due to other causes were excluded, as were those with disturbances of cardiac rhythm or overt disease of the left ventricle. All but three patients had a history of one or more episodes of peripheral oedema, though none had clinical signs of right heart failure at the time of the study. Individual values for blood gas and spirometric data are shown in table 1.

Patients gave written consent to the study, which was approved by the ethical committee of St Thomas's Hospital.

MEASUREMENTS

The usual medication was allowed until the day of the study, when patients fasted and lay quietly for at least two hours before measurements were made. A 7 French gauge thermodilution catheter was inserted into the pulmonary artery and 12 ml blood was taken into EDTA tubes on ice for assay of atrial natriuretic peptide. Right atrial and pulmonary artery pressures

were recorded and cardiac output was measured by the thermodilution method, 5% dextrose being used as the injectate; the mean of three measurements was used.

Pulmonary resistance and systemic vascular resistance were calculated by the use of standard equations.^{14 15} Arterial blood was taken from the radial artery with the patient breathing air for analysis of gas tensions. In 14 patients supplementary oxygen was given for 30 minutes, sufficient to raise the P_{aO_2} to 60 mm Hg or more in all patients. Haemodynamic measurements were repeated after 30 minutes and a further blood sample was taken from the pulmonary artery.

ATRIAL NATRIURETIC PEPTIDE ASSAY

Plasma was rapidly separated and stored at -20°C until assay. For assay of atrial natriuretic peptide we used a radioimmunoassay capable of detecting 1 fmol atrial natriuretic peptide immunoreactivity/tube with 95% confidence as previously described.¹⁶

STATISTICAL ANALYSIS

Linear regression analysis by the least square method was used to examine correlations between plasma atrial natriuretic peptide concentrations and blood gas and haemodynamic variables. Data on paired observations were compared by means of Student's *t* test, significance being assumed if $p < 0.05$.

Results

Mean pulmonary artery pressure ranged from 16 to 35 (mean 27, normal range <15 mm Hg) and pulmonary vascular resistance from 150 to 595 (mean 330, normal range <150) dyn s. cm^{-5} . Mean right atrial pressure, with reference to the sternal angle, ranged from -4 to 4 (mean 1, normal range <4) mm Hg (table 2).

Pulmonary artery plasma atrial natriuretic peptide concentrations ranged from 2 to 63 (mean 16) pmol/l and was raised in nine of 17 patients (normal range <10 pmol/l). The three patients with no history of peripheral oedema had raised atrial natriuretic peptide concentrations (table 2). There was a trend towards an inverse relation between P_{aO_2} and plasma atrial natriuretic peptide ($r = -0.48$, $p < 0.10$, $n = 17$; fig 1). No correlation was seen between plasma atrial natriuretic peptide and P_{aCO_2} ($r = 0.26$) or any of the other haemodynamic variables studied (right atrial pressure: $r = 0.3$; pulmonary artery pressure: $r = 0.16$; pulmonary vascular resistance: $r = 0.38$).

Supplementary oxygen increased the mean (SEM) P_{aO_2} from 48.6 (1.8) to 82.8 (4.1) mm Hg ($p < 0.001$), with a reduction in pulmonary vascular resistance from 358 (27) to 277 (27) dyn s. cm^{-5} ($p < 0.001$). There was, however, no significant change in plasma atrial natriuretic peptide concentrations (from 17 (4)

Table 1 Demographic, spirometric, and blood gas data on the 17 patients

Patient No	Age (y)	FEV_1 (l)	FVC (l)	P_{aO_2}	P_{aCO_2}
				(mm Hg)	
1	60	0.61	1.90	56.0	55.0
2	74	0.56	0.61	58.0	47.6
3	54	0.90	2.00	58.0	43.0
4	55	0.55	1.90	55.0	53.0
5	67	0.38	2.20	42.0	52.0
6	62	0.90	2.00	53.0	56.0
7	68	0.70	1.30	46.6	47.3
8	59	0.55	1.20	39.1	63.6
9	59	0.65	1.50	44.6	60.4
10	63	0.80	1.80	45.8	66.2
11	58	0.90	2.60	42.0	51.3
12	67	0.90	2.80	49.2	40.2
13	63	0.80	2.10	46.6	48.5
14	55	0.65	1.20	42.3	57.8
15	63	0.60	1.30	52.8	37.0
16	66	0.46	2.30	54.4	49.7
17	67	0.66	1.90	43.7	45.4
Mean	62	0.68	1.80	48.8	51.4
SD	5	0.16	0.56	6.2	7.9
SEM	1	0.04	0.13	1.5	1.9

Conversion: Traditional to SI units—Gas tensions: 1 mm Hg ≈ 0.13 kPa.

Table 2 Resting mean pulmonary artery pressure (PAP), cardiac output (CO), pulmonary vascular resistance (PVR), right atrial pressure (RA), and plasma atrial natriuretic peptide (ANP)

Patient No	PAP (mm Hg)	CO (l/min)	PVR (dyn s. cm ⁻⁵)	RA (mm Hg)	ANP (pmol/l)
1	23	5.9	248	1	13
2	30	4.9	343	-2	12
3	20	5.8	220	-1	2
4	35	4.3	595	-2	13
5*	30	4.4	509	2	63
6	32	5.7	306	0	6
7*	23	7.6	150	-2	42
8	26	5.0	304	4	28
9	32	4.7	532	0	16
10	29	7.9	263	-2	27
11*	32	8.2	274	4	19
12	16	5.9	244	0	10
13	32	6.7	408	0	6
14	24	6.9	224	0	3
15	21	6.0	273	-3	6
16	23	4.9	269	-4	9
17	29	5.2	453	-4	7
Mean	27	5.9	330	1.0	17
SEM	1.3	0.3	30	0.2	4

*Patients without a past history of oedema.

to 20 (5) pmol/l), although individual responses varied (fig 2).

Discussion

The finding of moderately raised pulmonary artery pressure with a normal or raised cardiac output (despite pronounced arterial oxygen desaturation) is characteristic of patients with pulmonary hypertension due to airflow obstruction,¹⁷ as is the response to supplementary inspired oxygen.¹⁸

We considered it important to study patients with normal right atrial pressures, as a raised pressure is a potent stimulus for release of atrial natriuretic peptide.¹⁹ We investigated only individuals whose hypoxaemia and pulmonary hypertension were secondary to airflow obstruction. Patients with primary pulmonary hypertension were not included for comparison because they have much higher pulmonary artery pressures, greater restriction of the pulmonary vascular bed, and a reduced cardiac output.²⁰ A preliminary report suggested that plasma atrial natriuretic peptide levels are increased in these patients in relation to the severity of the pulmonary hypertension.²¹ The inclusion of patients with primary pulmonary hypertension in other studies might explain why, in contrast to our findings, a relation was found between plasma atrial natriuretic peptide and pulmonary artery pressure and pulmonary vascular resistance.¹³

Individual values varied considerably, but most patients had atrial natriuretic peptide concentrations above those found in normal subjects after infusion of sufficient isotonic saline to give a right atrial pressure of 15 mm Hg, measured from the mid axillary line.¹⁶

The increase in atrial natriuretic peptide cannot therefore be accounted for by changes in right atrial pressure as this was normal in all subjects. The distending pressure across the atrial wall is determined by transatrial pressure—that is, right atrial minus intrathoracic pressure—and this may be increased in patients with airflow obstruction because of lower intrathoracic pressures even when right atrial pressure is normal. The present findings could also be explained by an increased potential for synthesis of atrial natriuretic peptide when the right atrium or right ventricle hypertrophies under conditions of hypoxia.

Fig 1 Relation between plasma atrial natriuretic peptide (ANP) and arterial oxygen tension (PaO₂) in 17 patients.

Fig 2 Response of 14 patients to 30 minutes' supplemental inspired oxygen: changes in arterial oxygen tension (P_{aO_2}), pulmonary vascular resistance (PVR), and plasma atrial natriuretic peptide (ANP).

This possibility is supported by the observation that atrial natriuretic peptide concentrations increase in rats with right ventricular hypertrophy produced by hypoxia¹² and in other models of cardiac hypertrophy.²²

We attempted to assess the stimulus for release of atrial natriuretic peptide by changing pulmonary haemodynamics acutely through supplementary inspired oxygen treatment. Atrial natriuretic peptide concentrations were not modified acutely by changes in P_{aO_2} or pulmonary vascular resistance, however, and this is consistent with the hypothesis that basal concentrations may be raised in patients with chronic hypoxia, in the absence of increased right atrial pressure. These results do not preclude an effect from more prolonged administration of oxygen, and this could be assessed in patients given long term oxygen treatment.

The substantially increased atrial natriuretic peptide concentrations in three patients with no history of peripheral oedema could have arisen by chance. The variable of diuretic treatments, which may disturb any relation between hypoxia and atrial natriuretic peptide concentrations, further complicates interpretation of our findings. The observation in these three patients raises the possibility that increased atrial natriuretic peptide concentrations may protect against fluid retention under conditions of hypoxia. More work is required to examine this relationship, perhaps by assessing the response to fluid loading. Interestingly, at high altitude the normal subjects with the lowest plasma atrial natriuretic peptide concentrations have the greatest symptom scores for mountain sickness.²³

The term right heart failure is unsatisfactory when applied to hypoxaemic patients, because cardiac output is usually normal or increased, as in the present study.¹⁷ This was emphasised in the Medical Research Council evaluation of long term oxygen treatment, where right ventricular hypertrophy was an inconsis-

tent feature at death in patients with severe airflow obstruction.²⁴ Volume overload in patients with chronic hypoxia and a normal cardiac output may be partly accounted for by individual variability in the factors determining water and sodium balance.

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