Atrial natriuretic peptide in stable and decompensated chronic obstructive pulmonary disease

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Abstract

Background—Plasma levels of atrial natriuretic peptide (ANP) are elevated in patients with chronic obstructive pulmonary disease (COPD) and may have a role in preventing oedema formation in these patients.

Methods—Plasma ANP levels were measured in 60 patients with COPD and these measurements were related to pulmonary haemodynamics, response to treatment during exacerbations, and clinical patterns of the stable disease.

Results—Plasma ANP levels did not correlate significantly with right atrial or pulmonary arterial pressures but did correlate significantly with both the right ventricular end diastolic volume and right ventricular wall volume measured by magnetic resonance imaging. Oxygen (2 l/min by nasal prongs for 30 minutes) did not change the mean pulmonary arterial pressure or the level of plasma ANP. In 20 patients with an acute exacerbation of COPD plasma ANP levels were higher in those with oedema (302 (185) pg/ml) than in those without oedema (87 (43) pg/ml). Oxygen given for one hour had no effect on plasma levels of ANP. However, plasma ANP levels fell over the first three days during treatment in those with oedema, the fall correlating with the change in body weight. In a further 20 stable patients with hypoxic COPD, those with hypercapnia and previous episodes of oedema had higher levels of plasma ANP (120 (50) pg/ml) than normocapnic patients with no previous oedema (54 (15) pg/ml).

Conclusions—The level of ANP is high in the plasma of patients with COPD, particularly during exacerbations in those with oedema. The association of a high plasma ANP level and volume overload is shown by the fall in ANP levels with treatment of the oedema, and the correlation between levels of ANP and right ventricular end diastolic or wall volumes.

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The traditional view of the development of peripheral oedema in patients with chronic obstructive pulmonary disease (COPD) sug-

gests that chronic hypoxia is responsible for pulmonary vasoconstriction which eventually leads to irreversible pulmonary hypertension, increased right ventricular work, and right ventricular failure.^{1,2} This sequence of events has been challenged recently.³ The right ventricular performance is relatively well preserved in patients with COPD, even in the face of pulmonary hypertension.^{4,5} Moreover, the decline in right ventricular function in patients with COPD presenting with oedema may not be as a direct result of an augmented right ventricular afterload.^{5,6} Furthermore, not all patients with COPD and pulmonary hypertension develop oedema, suggesting decompensated cor pulmonale during exacerbations of their condition. Several authors have suggested that abnormalities in salt and water balance underlie the clinical syndrome of oedema in patients with hypoxic COPD.⁷⁻¹⁰

Since de Bold *et al*¹¹ showed that human cardiocytes in both atria produce and store a potent natriuretic peptide—atrial natriuretic peptide (ANP)—this substance has been extensively studied in patients with congestive cardiac failure. In these patients plasma ANP levels correlate variably with the pulmonary arterial or right atrial pressures.¹²⁻¹⁵ The general view, however, is that atrial stretch is the major stimulus to the release of ANP.^{12,16,17}

The role of ANP in the development of the clinical syndrome of cor pulmonale is unknown. Recent reports of measurement of ANP levels in patients with various chronic lung diseases including COPD have shown that these patients have higher levels of plasma ANP than normal subjects.¹⁷⁻¹⁹ Preliminary studies also suggest that levels of ANP are even higher in those with decompensated cor pulmonale. Plasma ANP levels correlate weakly with pulmonary arterial pressure and right atrial pressures in some studies¹⁷⁻²⁰ but not in others,²¹ and are not influenced by short term supplemental oxygen.²¹

The aim of this study was to extend these observations on ANP to a larger group of patients with COPD. In particular we wished to correlate plasma ANP levels, not only with pulmonary haemodynamics, but also with right ventricular dimensions, the effects of treatment during acute exacerbations of COPD, and with the clinical patterns of the stable disease.

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Methods

STUDY POPULATION

Sixty patients with COPD were studied and formed three separate groups. Twenty patients were studied when clinically stable (table 1) at least 6 weeks after their last exacerbation of COPD. In these patients measurements of pulmonary haemodynamics were made as part of their assessment for domiciliary oxygen therapy. A further 20 patients were studied on admission to hospital with an acute exacerbation of COPD (table 1). The remaining 20 patients with COPD presented at the outpatient clinic when clinically stable and were divided into two clinical patterns: so called "blue bloaters" ($\text{PaO}_2 < 8.0 \text{ kPa}$, $\text{PaCO}_2 > 6.0 \text{ kPa}$, past history of peripheral oedema) and "pink puffers" ($\text{PaO}_2 \geq 8.0 \text{ kPa}$, $\text{PaCO}_2 \leq 6.0 \text{ kPa}$, no past history of peripheral oedema) (table 2) on the basis of their blood gas values and clinical findings.

HAEMODYNAMIC STUDY

Each patient was studied semisupine, resting at an angle of 45° . An arterial line was inserted into the non-dominant brachial or radial artery under local anaesthetic (2% lignocaine) to sample arterial blood. A Swan-Ganz thermodilution pulmonary arterial catheter (Edwards Laboratories, Santa Anna, California) was passed from a right antecubital vein to the pulmonary artery under local anaesthetic and coupled to a pressure transducer attached to a haemodynamic cart (Hewlett Packard Model No 78339A).

Table 1 Mean (SD) characteristics of patients with COPD studied when stable or during an acute exacerbation.

	Stable	Acute
n	20	20
Age (years)	67 (6)	70 (7)
FEV ₁ (l)	0.7 (0.2)	0.6 (0.2)
FVC (l)	1.7 (0.4)	1.1 (0.5)
PaO ₂ (kPa)	6.8 (0.8)	6.7 (0.9)
PaCO ₂ (kPa)	6.5 (0.9)	6.7 (1.7)
H ⁺ (nmol/l)	41 (0.9)	44 (1.8)

FEV₁—forced expiratory volume in one second; FVC—forced vital capacity; PaO₂, PaCO₂—partial pressures of oxygen and carbon dioxide; H⁺—hydrogen ion concentration.

Table 2 Mean (SD) characteristics of patients with stable COPD studied at presentation at the outpatient clinic.

	"Blue bloaters"	"Pink puffers"	p
n	11	9	
Age (years)	60 (8)	70.5 (5)	NS
FEV ₁ (l)	0.6 (0.3)	0.9 (0.2)	<0.02
FVC (l)	1.9 (0.6)	2.2 (0.8)	NS
PaO ₂ (kPa)	6.9 (1.0)	9.2 (0.7)	<0.001
PaCO ₂ (kPa)	7.2 (1.0)	5.7 (0.3)	<0.01
H ⁺ (nmol/l)	41 (2.5)	40 (3.4)	NS
ANP (pg/ml)	120(50)	54 (15)	<0.01

FEV₁—forced expiratory volume in one second; FVC—forced vital capacity; PaO₂, PaCO₂—partial pressures of oxygen and carbon dioxide; H⁺—hydrogen ion concentration; ANP—atrial natriuretic peptide.

Intracardiac pressures were measured by averaging over three respiratory cycles and were zero referenced to a point five cm below the sternal angle. Mean values were obtained by electrical integration. Cardiac output was determined by the thermodilution technique. The mean of at least three values which varied by less than 10% was used in the analysis. Heart rate was recorded continuously by an ECG monitor.

Radionuclide technique

Right ventricular ejection fraction (RVEF) was measured by gated radionuclide ventriculography following a peripheral venous injection of 750 MBq technetium-99m labelled human serum albumin.⁴ The normal value of RVEF in our laboratory is > 0.40 .^{4,22} Measurements were made at the end of the cardiac catheterisation when the patients breathed air.

Magnetic resonance imaging (MRI)

An MRI scan of the thorax was carried out 2–5 days after the right heart catheterisation in eight patients. A cardiac gating technique was used to acquire data at end systole and end diastole as previously described.^{23,24} Multiple images were obtained from the cardiac apex up to, but excluding, the right ventricular outflow tract in a plane orthogonal to the interventricular septum using 16 mm slice thickness. The right ventricular "free" wall volume (RVWV) and chamber volume were calculated by measuring the area from irregular regions of interest drawn around these structures in each image. Summation of the product of each area and the slice thickness was used to obtain the volume. Each image was analysed by an operator (LT) who was unaware of the clinical or haemodynamic data. Right ventricular end diastolic chamber volumes (RVEDV) could only be assessed in six of the eight patients. Details of the technique and its reproducibility have been published previously.²³ As previously described, the right ventricular end diastolic volume excludes the outflow tract which improves the reproducibility of the measurement but underestimates the true absolute value of the ventricular volume.²³

PLASMA ANP

Ten ml samples of blood were removed and placed into EDTA tubes to measure plasma levels of ANP. Plasma was rapidly separated, stored at -70°C , and measured in batches within two months by a specific radioimmunoassay.^{25,26} ANP antibody was raised in the rabbit by conjugation of synthetic ANP 1–28 with bovine thyroglobulin using carbodiimide as the coupling agent.²⁵ Iodine-125 labelled ANP was purchased from Amersham International Laboratories. ANP was extracted from plasma using Sep-PaK C-18 cartridges (Waters Associates, UK) and eluted with a mixture of ethanol, water, and acetic acid. The lower limit of detection for the assay was 10 pg/ml. The level of ANP was measured by a specific and sensitive radio-

immunoassay technique, using ¹²⁵I-ANP (1–28). The normal mean (SD) plasma level of ANP in our laboratory in patients undergoing cardiac catheterisation is 45 (15) pg/ml.²⁷

STATISTICAL METHODS

Comparison between mean values was made using the Wilcoxon rank test. Correlation coefficients were calculated from standard equations.

PROTOCOLS

Haemodynamic study

In the haemodynamic study ANP was measured in samples of blood from the right atrium, pulmonary artery, peripheral vein, and peripheral artery, both when the patients breathed room air and when hypoxaemia was corrected by breathing oxygen given at a flow rate of 2–3 l/min by nasal prongs for 30 minutes to achieve a Pao₂ ≥ 8.0 kPa.

Serial measurements of ANP levels during acute exacerbations of COPD

Patients presenting to our hospital with an acute exacerbation of COPD had samples of venous blood withdrawn on admission while breathing room air and again after breathing oxygen for one hour (2 l/min via nasal prongs). On each of the subsequent two days ANP levels were again measured while the patient breathed oxygen. Each sample was taken in the morning. If diuretic therapy was prescribed this was administered after the blood sample for ANP measurement was withdrawn. Since all samples were taken in the morning, no diuretics were given for at least 12 hours before the withdrawal of the blood samples. None of the patients were given respiratory stimulants, catecholamine infusions nor haemodynamically active drugs other than β₂ agonists. Oxygen, diuretics, nebulised β₂ agonists, and antibiotics where appropriate were thus the only drugs which were administered. Sodium intake was not controlled although no salt was added to the normal ward diet. Blood was also sampled six weeks after the exacerbation at a time when the patients were clinically stable.

ANP levels in relation to clinical patterns of COPD

A further 20 samples of blood were taken for ANP measurement from patients with COPD who were clinically stable at least six weeks after their last exacerbation of COPD. These patients were categorised clinically depending on the presence or absence of hypercapnia and past history of peripheral oedema (see above).

Results

HAEMODYNAMIC STUDY

All 20 patients who underwent right heart catheterisation had severe airflow limitation, were hypoxaemic, and the majority also had hypercapnia (table 1). However, they had a wide range of mean pulmonary arterial pressures (mean 27; range 16–45 mm Hg). Plasma ANP levels were not significantly dif-

Table 3 Effect of oxygen (2 l/min, nasal prongs) on plasma ANP levels in peripheral or central blood in 20 patients with stable COPD. Values are mean (range)

	Air	Oxygen
Pao ₂ (kPa)	6.8 (4.5–8.3)	10.7 (7.5–12.0)**
Paco ₂ (kPa)	6.5 (5.3–8.3)	6.7 (5.9–8.5)
PPA (mm Hg)	27 (16–45)	25 (14–41)
HR (b/min)	83 (64–114)	80 (61–108)
PRA (mm Hg)	2.5 (0–7)	–
PCW (mm Hg)	4.5 (1–10)	4.0 (0–9)
CO (l/min)	5.1 (3.3–7.6)	5.0 (2.9–7.9)
PVR (dyn s cm ⁻⁵)	290 (218–947)	273 (141–670)
ANPRA (pg/ml)	156 (33–294)	178 (45–418)
ANPPA (pg/ml)	146 (23–288)	137 (57–283)
ANPBA (pg/ml)	143 (32–272)	137 (51–303)

PRA—mean right atrial pressure; PPA—mean pulmonary arterial pressure; HR—heart rate; PCW—pulmonary capillary wedge pressure; CO—cardiac output; PVR—pulmonary vascular resistance; ANPRA—ANP in right atrium; ANPPA—ANP in pulmonary artery; ANPBA—ANP in brachial artery. **p < 0.01.

ferent when measured in the right atrium, pulmonary artery, or peripheral arterial blood (table 3). Oxygen given for 30 minutes (2–3 l/min via nasal prongs) did not change either the mean pulmonary arterial pressure nor the level of plasma ANP, but did correct the hypoxaemia (Pao₂ > 8.0 kPa) in all but one patient (table 3). No significant correlation was found between the level of plasma ANP and any of the pulmonary haemodynamic variables or the blood gas values (r = 0.1–0.4, p > 0.05). In eight patients who had an MRI scan within 3–5 days (RVWV 38 (11) ml, RVEDV 40 (17) ml), however, significant correlations were found between the right ventricular dimensions—that is, RVWV (r = 0.84, n = 8, p < 0.01, fig 1) and RVEDV (r = 0.81, n = 6, p < 0.05, fig 2)—and the plasma ANP level measured in peripheral blood. The mean (SD) RVEF measured by radionuclide ventriculography in these patients (n = 10) was 0.36 (0.10). There was no significant correlation between RVEF and plasma ANP level (r = –0.45, p > 0.05).

SERIAL MEASUREMENTS OF ANP IN PATIENTS WITH ACUTE EXACERBATIONS OF COPD

Twenty patients presenting with an acute exacerbation of COPD who required hospital admission were divided into two groups: 10 who presented on admission with peripheral

Figure 1 Relationship between plasma ANP level and right ventricular wall volume (RVWV) in eight patients with chronic obstructive pulmonary disease (r = 0.84, p < 0.01).

Figure 2 Relationship between plasma ANP level and right ventricular end diastolic volume (RVEDV) in six patients with chronic obstructive pulmonary disease ($r = 0.81$, $p < 0.05$).

oedema and 10 who presented without. There was no difference in the level of PaO_2 on admission (measured when breathing air) in those with oedema (5.6 (1.2) kPa) and those without (6.1 (0.5) kPa). However, those with oedema were more hypercapnic (PaCO_2 7.2 (1.3) kPa) and acidotic (H^+ ion 47(5) nmol/l) than those without oedema (PaCO_2 6.1 (2.3) kPa; H^+ ion 44 (3) nmol/l; $p < 0.05$). The FEV_1 measured at the time of discharge was also similar in both groups (patients with oedema, 0.57 (0.17) l; patients without oedema, 0.69 (0.30) l; $p > 0.05$). Patients without oedema had a statistically lower level of plasma ANP on admission both when breathing air and oxygen (2 l/min for one hour) (87(43) pg/ml on air; 96(21) pg/ml on oxygen) compared with those presenting with oedema (302(185) pg/ml on air; 281 (199) pg/ml on oxygen; $p < 0.01$). Oxygen (2 l/min for one hour) increased the PaO_2 in patients with and without oedema to 7.6 (1.8) kPa and 8.5(1.7) kPa respectively ($p < 0.05$), and the PaCO_2 to 7.5 (1.9) kPa and 6.4(1.2) kPa ($p < 0.05$), but did not change the level of plasma ANP for the group as a whole (ANP on air 205 (96) pg/ml; ANP on oxygen 194(103) pg/ml, $p > 0.05$) nor when those with or without oedema were analysed separately.

Plasma ANP levels during the second and third day after admission did not change significantly in the group as a whole nor when the values in those with and without oedema

Figure 3 Serial measurements of plasma ANP levels in patients with (hatched bars) and without (closed bars) oedema during an exacerbation of chronic obstructive pulmonary disease on day 1, when breathing air or oxygen (2–3 l/min for one hour), and on days 2 and 3, and 6 weeks later when clinically stable when breathing oxygen. ** $p < 0.01$, * $p < 0.05$ comparing patients with and without oedema; † $p < 0.05$ comparing measurements on day 1 and at six weeks.

were analysed separately (fig 3). There was, however, a significant fall in ANP while breathing oxygen on day 2 (168 (132) pg/ml) and day 3 (158 (11) pg/ml) compared with the values on admission (256 (181) pg/ml, $p < 0.05$) for the whole group. The mean plasma ANP level was still significantly higher on day 3 in those with oedema (232 (46) pg/ml) than in those without oedema (88 (17) pg/ml, $p < 0.05$). Six weeks after the acute exacerbation, when the patients were clinically stable, the level of ANP in the plasma was unchanged in those who presented without oedema (87 (16) pg/ml) compared with the level on admission (87 (43) pg/ml, $p > 0.05$) but had fallen further in those who presented with oedema (118 (47) pg/ml; $p < 0.05$) (fig 3). In the patients who had peripheral oedema at the time of admission the fall in body weight correlated with the fall in the level of plasma ANP ($r = 0.85$; $p = 0.002$) (fig 4).

ANP IN THE DIFFERENT CLINICAL PATTERNS OF COPD

Patients who were defined as having the “blue and bloated” syndrome of COPD had a lower FEV_1 , were more hypoxaemic, and were hypercapnic compared with those considered to be “pink puffers” (table 2).

Figure 4 Correlation between the changes in plasma ANP level and body weight over the first three days during exacerbations of chronic obstructive pulmonary disease in 10 patients ($r = 0.85$, $p = 0.002$).

Figure 5 Plasma ANP level in patients with the “blue and bloated” (BB) ($n = 11$) or “pink and puffing” (PP) ($n = 9$) patterns of chronic obstructive pulmonary disease. Individual and mean values are shown. The mean value for BB is significantly greater than that for PP (** $p < 0.01$).

The level of plasma ANP measured in those with the "blue and bloated" type of COPD was higher than in those with the "pink and puffing" type (table 2) although there was clearly some overlap between the groups (fig 5).

Discussion

ANP is an important humoral regulator of salt and water balance and of arterial pressure.¹⁴ When given to healthy subjects it causes natriuresis, vasodilation, and can also suppress the activity of the renin-angiotensin-aldosterone system,^{18,19} actions which would be beneficial in cor pulmonale.

Plasma ANP levels are elevated in patients with primary or secondary pulmonary hypertension^{16,21,28,29} and correlate with both the mean pulmonary arterial (PPA) and right atrial pressures in some studies^{17,20} but not in others.²¹ These conflicting data may arise because of the small number of patients studied and the narrow range of haemodynamic variables. Plasma ANP levels rise in response to the increase in PPA during exercise,²⁸ presumably because of an increase in right atrial pressure and atrial distension. However, in a group of patients with primary pulmonary hypertension with raised PPA levels (mean PPA 74(13) mm Hg) plasma ANP levels were elevated in all but one patient despite normal right atrial pressures.²⁹

Our study helps to resolve these conflicting data in a larger group of patients with a wide range of pulmonary arterial pressures. In this group we found no significant correlation between pulmonary arterial or right atrial pressure and simultaneously sampled plasma ANP levels. Furthermore, the levels of plasma ANP in patients with hypoxic COPD were similar in central venous and peripheral arterial blood, whereas others have found higher levels of ANP in central than in peripheral blood.¹⁷ Since atrial stretch is thought to be the major stimulus to the release of ANP it is not surprising that central venous pressure measurements, which are a poor reflection of atrial stretch, do not correlate well with the levels of ANP. Surprisingly, in previous studies the correlation between plasma ANP levels and right atrial pressure was present even when the atrial pressure remained within the normal range,¹⁷ although this relationship was not confirmed in other studies.²¹

Although we were not able to make direct measurements of atrial chamber size, we found a significant relationship between right ventricular end diastolic chamber volume and right ventricular wall volume, measured by MRI, and plasma ANP levels. We presume that an increase in right ventricular volume would also be associated with an increased atrial volume and presumably atrial stretch.³⁰ The correlation between ANP levels and right ventricular wall volume is interesting since in animal studies hypoxia is associated with both increased right ventricular mass and, in addition, an increase in messenger RNA expression for ANP in the right ventricular wall.³¹

These data confirm the presence of

elevated levels of plasma ANP in 60 patients with COPD. Although plasma ANP levels were higher in patients with an exacerbation of COPD than in normal subjects, very high levels (>120 pg/ml) occurred only in those with oedema. This finding did not relate to the severity of the disease. Previous studies suggest that, during an exacerbation of COPD, pulmonary arterial pressure rises³² which presumably would cause release of ANP as a result of increased atrial stretch.

An increase in central blood volume secondary to activation of the renin-angiotensin-aldosterone system and consequent salt and water retention³³ could also increase atrial stretch and ANP release. High levels of ANP should have a protective role in the development of oedema in patients with COPD and hypoxia due to its beneficial haemodynamic effects and the inhibitory effects of ANP on the renin-angiotensin system.³⁴ Furthermore, the release of ANP remains responsive to physiological manipulations in patients with COPD.³⁵ However, why sodium and water retention still occurs in patients with hypoxic COPD and oedema in the face of very high levels of plasma ANP remains unclear. Several explanations are possible such as a blunted renal response to ANP³⁶ or the possibility that the suppressive effect of ANP on the renin-angiotensin axis is outweighed by the stimulatory effect of inadequate renal perfusion³⁷ on the renin-angiotensin system.³⁸

Since the level of hypoxaemia was not different in patients with exacerbations of COPD with and without oedema, both groups would presumably have pulmonary hypertension at least acutely.³² However, the degree of hypercapnia and acidosis was higher in those with oedema, as noted in a previous study,³⁹ and may have contributed to a further increase in pulmonary arterial pressure, stimulation of the renin-angiotensin system, reduction of effective renal plasma flow, and thus the filtered sodium load.⁴⁰ The fall in plasma ANP levels with treatment in patients with oedema is likely to be due to a combination of factors including the improvement in blood gas values, a fall in pulmonary arterial hypertension,³² and reduction in central venous pressure consequent on a diuresis. Support for this latter mechanism comes from the relationship between the fall in body weight and the fall in ANP levels in these patients.

The pathogenesis of the oedema in cor pulmonale remains unknown.⁶ The adaptive mechanisms which occur in response to chronic pulmonary hypertension, such as an increase in right ventricular end diastolic volume,¹ may also produce a chronic elevation of ANP levels. This hypothesis is supported by the presence of elevated ANP levels in those patients who had hypercapnia and a past history of peripheral oedema compared with those who were normocapnic and had never had oedema. An increased level of ANP consequent upon the higher levels of pulmonary arterial pressure in the "blue bloaters" may be one of the reasons why oedema does not always develop in patients with COPD and

pulmonary hypertension, even during exacerbations.^{5,32}

Our data show that oxygen given acutely to hypoxic patients, whether in a stable state or during an exacerbation, has no effect on ANP levels. These findings confirm those of other workers in studies of patients with stable COPD.²¹ Furthermore, short term discontinuation of oxygen does not appear to affect the levels of ANP in patients with hypoxic COPD treated with long term oxygen therapy.²⁷ The effect of long term oxygen therapy on plasma ANP levels has not been studied, although oxygen given over six days to hypoxic patients with COPD did not alter the level of ANP in the plasma.²⁸

The results of this study suggest that the complex interactions between pulmonary haemodynamics, blood gas values, the renin-angiotensin system, and ANP in patients with exacerbations of COPD with and without oedema are worthy of further study, since they may lead to more logical treatment of patients with exacerbations of COPD and oedema.

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- 1 Fishman AP. State of art: chronic cor pulmonale. *Am Rev Respir Dis* 1976;114:775-94.
- 2 McFadden ER, Braunwald E. Cor pulmonale and pulmonary thromboembolism. In: Braunwald E, ed. *Heart disease, a text book of cardiovascular medicine*. Philadelphia: Saunders, 1988:1597-617.
- 3 Wilkinson M, Langhorne CA, Heath D, Barer GR, Howard P. A pathophysiological of 10 cases of hypoxic cor pulmonale. *Q J Med* 1988;66:65-87.
- 4 MacNee W, Xue QF, Hannan WJ, Flenley DC, Adie CJ, Muir AL. Assessment by radionuclide angiography of right and left ventricular function in chronic bronchitis and emphysema. *Thorax* 1983;38:494-500.
- 5 MacNee W, Wathen CG, Flenley DC, Muir AL. Right ventricular function in patients with stable and decompensated pulmonary heart disease: the effects of controlled oxygen therapy. *Am Rev Respir Dis* 1988;137:1289-95.
- 6 Richens JM, Howard P. Oedema in cor pulmonale. *Clin Sci* 1982;62:255-9.
- 7 Campbell RHA, Brand HL, Cox JR, Howard P. Body weight and body water in chronic cor pulmonale. *Clin Sci* 1975;49:323-35.
- 8 Farber MO, Weinberger MH, Robertson GL, Fineberg NS. The effects of angiotensin-converting enzyme inhibition on sodium handling in patients with advanced chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1987;134:820-6.
- 9 Reihman DM, Farber MO, Weinberger MH, Henry DP, Fineberg NS, Dowdeswell IR, et al. Effects of hypoxaemia on sodium and water excretion in chronic obstructive lung disease. *Am J Med* 1985;78:87-94.
- 10 Mannix ET, Dowdeswell I, Carlone S, Palange P, Arouoff GR, Farber MO. The effects of oxygen on sodium excretion in hypoxaemic patients with chronic obstructive lung disease. *Chest* 1990;27:840-4.
- 11 de Bold AJ, Borenstein HB, Veress AT, Sonnenberg H. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. *Life Sci* 1981;28:89-94.
- 12 Raine AEG, Erne P, Burgisser E, Muller F, Bolli P, Burkart F, et al. Atrial natriuretic peptide and atrial pressure in patients with congestive heart failure. *N Engl J Med* 1986;315:533-7.
- 13 Yamaji T, Ishibashi M, Takaku F. Atrial natriuretic factor in human blood. *J Clin Invest* 1985;76:1705-9.
- 14 Espiner EA, Richards AM. Atrial natriuretic peptide. An important factor in sodium and blood pressure regulation. *Lancet* 1989;ii:707-10.
- 15 Hartler E, Weissel M, Stummvoll HK, Woloszczuk W, Punzengruber CH, Ludvik B. Atrial natriuretic peptide concentrations in blood from right atrium in patients with severe right-heart failure. *Lancet* 1985;ii:93-4.
- 16 Lang RE, Tolken H, Ganten D, Luft FC, Ruskoaho H, Unger T. Atrial natriuretic factor—a circulating hormone stimulating by volume loading. *Nature* 1985;314:264-6.
- 17 Burghuber OC, Harter E, Punzengruber Ch, Weissel M, Woloszczuk W. Human atrial natriuretic peptide secretion in precapillary pulmonary hypertension. Clinical study in patients with COPD and interstitial fibrosis. *Chest* 1988;92:31-7.
- 18 Richards AM, Tonolo G, Polonia J, Montorsi P. Contrasting plasma atrial natriuretic factor concentrations during comparable natriuresis with infusions of atrial natriuretic factor and saline in normal man. *Clin Sci* 1988;75:455-62.
- 19 Richards AM, Ikram H, Yandle TG, Nicholls MG, Webster MW, Espiner EA. Renal, haemodynamic, and hormonal effects of human alpha atrial natriuretic peptide in healthy volunteers. *Lancet* 1985;ii:545-8.
- 20 Adnot S, Chabrier PE, Andrivet P, Viostat I, Piquet J, Brun-Buisson C, et al. Atrial natriuretic peptide concentrations and pulmonary haemodynamics in patients with pulmonary artery hypertension. *Am Rev Respir Dis* 1987;136:951-6.
- 21 Winter RJD, Davidson AC, Treacher D, Rudd RM, Anderson JV, Meleanger L, et al. Atrial natriuretic peptide concentrations in hypoxic secondary pulmonary hypertension: relation to haemodynamic and blood gas variables and response to supplemental oxygen. *Thorax* 1989;44:58-62.
- 22 Xue QF, MacNee W, Flenley DC, Hannan WJ, Adie CJ, Muir AL. Can right ventricular performance be assessed by gated equilibrium ventriculography. *Thorax* 1983;38:486-93.
- 23 Smith MA, Ridgway JP, Brydon JWE, Been M, Douglas RM, Kean DM, et al. ECG-gated T1 images of the heart. *Phys Med Biol* 1986;31:771-8.
- 24 Turnbull LW, Ridgway JF, Biernacki W, McRitchie H, Muir AL, Best JJK, et al. Measurement of right ventricular dimensions in chronic obstructive pulmonary disease using magnetic resonance imaging. *Thorax* 1990;45:597-601.
- 25 Harter E, Woloszczuk W, Stummvoll HK. Radioimmunoassay of atrial natriuretic peptides in human plasma. *Clin Chem* 1986;32/33:441-5.
- 26 Freestone S, MacDonald TM, Jeffrey RF, Brown JE, Lee MR. The renal effects of atrial natriuretic peptide in man are not attenuated by (+) sulpiride. *Br J Pharmacol* 1989;27:13-8.
- 27 Brown JE, Lee MR, Boon NA. Effect of cardiac tamponade on atrial natriuretic peptide concentrations: influence of stretch and pressure. *Clin Sci* 1990;79:377-80.
- 28 Watanabe H, Furui H, Yamaki K, Suzuki K, Takagi K, Sasamoto M, et al. Plasma atrial natriuretic polypeptide in chronic respiratory disease. *Am Rev Respir Dis* 1987;135 (Suppl):A145.
- 29 Morice A, Pepke-Zaba J, Davies L, Brown M, Higgenbottom T. Plasma levels of atrial natriuretic peptide in primary pulmonary hypertension. *Thorax* 1987;42:720.
- 30 Au J, Brown JE, Lee MR, Boon NA. Effect of cardiac tamponade on atrial natriuretic peptide concentrations: influence of stretch and pressure. *Clin Sci* 1990;79:377-80.
- 31 Raffestin B, Adnot S, Mercadier JJ, Levame M, Duc P, Braquet P, et al. Synthesis and secretion of atrial natriuretic factor during chronic hypoxia: a study in the conscious instrumented rat. *Clin Sci* 1990;78:597-603.
- 32 Abrahams AS, Cole RV, Green ID, Headworth-Whitty RB, Clerk SW, Bishop JM. Factors contributing to the reversible pulmonary hypertension in patients with acute respiratory failure studied by serial observations during recovery. *Circ Res* 1969;26:51-60.
- 33 Colice GL, Farber M, Rose CE, Raff H, Ramirez G. Fluid balance in acute and chronic lung disease. *Am Rev Respir Dis* 1988;134:1052-3.
- 34 Adnot S, Andrivet P, Chabrier PE, Piquet J, Plas P, Blaquet P, et al. Atrial natriuretic factor in chronic obstructive lung disease with pulmonary hypertension. Physiological correlates and response to peptide infusion. *J Clin Invest* 1989;83:986-93.
- 35 Carlone S, Palange P, Mannix ET, Farber MO, Aronoff GR, Brier M, et al. Atrial natriuretic peptide renin aldosterone in obstructive lung disease and heart failure. *Am J Med Sci* 1989;298:243-8.
- 36 Laragh JH, Cody RJ, Covit AB, Atlas SA. The renin system and atrial natriuretic hormone in congestive heart failure. *Acta Med Scand* 1986;707:45-53.
- 37 Farber MO, Weinberger MH, Robertson GL, Fineberg NS, Manfred IF. Abnormalities of sodium and H₂O handling in chronic obstructive lung disease. *Arch Intern Med* 1982;142:1326-30.
- 38 Shenker Y, Sider RS, Ostafin EA, Grekin RJ. Plasma levels of immunoreactive atrial natriuretic factor in healthy subjects and patients with oedema. *J Clin Invest* 1985;76:1684-7.
- 39 Farber MO, Bright TP, Strawbridge RA, Robertson GL, Manfredi F. Impaired water handling in chronic obstructive lung disease. *J Lab Clin Med* 1975;85:41-9.
- 40 Weitzenblum F, Santegean A, Ehrhart M, Memmoser M, Hirsh CH, Roegel E. Long-term course of pulmonary arterial pressure in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1984;130:993-8.