

November 1980 her plasma urea concentration was 60.2 mmol/l (362 mg/100 ml) and she had peripheral gangrene in both feet. She died on 1 December.

Postmortem examination showed a laminated haematoma 12 cm in diameter around the left kidney, almost certainly due to the renal biopsy. Histologically there were classical Kimmelstiel-Wilson nodules and 60% hyalinised glomeruli in both kidneys, together with widespread arteriosclerosis. The anterior lobe of the pituitary gland showed old, extensive infarction.

Discussion

This patient had unequivocally diabetic hyperglycaemia only at the time of treatment of her loin carbuncle. No record of the retinal appearance was made then, but she had heavy proteinuria and a reduced creatinine clearance, almost certainly due to diabetic nephropathy. Quite possibly a long period of asymptomatic hyperglycaemia had preceded formation of the abscess. The return of normoglycaemia almost immediately postoperatively suggests, however, that such hyperglycaemia was probably mild, unless the pituitary infarction occurred at about the same time. The extent of infarction must have been incomplete physiologically, for despite low plasma growth hormone concentrations plasma cortisol concentrations were normal when measured seven months later. Pituitary infarction has been reported in 2% of diabetics coming to postmortem examination,³ and it was the regression of severe diabetic retinopathy in a diabetic who developed Sheehan's syndrome⁴ that led to the use of hypophysectomy as a treatment for this complication. Diabetic nephropathy was unaffected or worsened: the original patient died in renal failure.⁴ Our patient's retinopathy did not regress despite pituitary hypofunction, and renal function deteriorated relentlessly. Insulin requirements in

patients who had undergone hypophysectomy dropped to between one third and one quarter of their preoperative dosage,² illustrating the Houssay phenomenon¹; our case suggests that in non-insulin dependent diabetics glucose tolerance may return to normal, resembling the metabolic improvement seen in patients with acromegaly who receive treatment.

It is now widely accepted that the development of diabetic microvascular complications is proportional to the severity and the duration of hyperglycaemia, although patients presenting in renal failure with biopsy appearances of diabetic glomerulosclerosis and normal glucose tolerance have been reported.⁵ None of these patients had retinopathy, and no data on pituitary function were reported. Occult pituitary hypofunction may possibly be present in such cases, and this would explain the apparent paradox of severe diabetic microangiopathy in the presence of normal glucose tolerance at the time of presentation.

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Effects of pirbuterol and sodium nitroprusside on pulmonary haemodynamics in hypoxic cor pulmonale

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Abstract

The acute haemodynamic effects of oral pirbuterol (a beta-agonist) were contrasted with those of sodium nitroprusside, a vasodilator, in six patients with hypoxic chronic bronchitis and emphysema. Sodium nitroprusside (1-5 mg/kg intravenously) reduced mean pulmonary arterial pressure and total pulmonary vascular resistance significantly ($p < 0.01$) without change in cardiac output or right ventricular ejection fraction, measured by radionuclide ventriculography. Oral pirbuterol (22.5mg) produced a greater reduction in total pulmonary vascular resistance than sodium nitroprusside,

largely as a result of increasing cardiac output. Right ventricular ejection fraction also increased significantly after pirbuterol ($p < 0.01$). Pirbuterol in a lower dosage (15 mg by mouth) in six further patients with hypoxic chronic bronchitis and emphysema produced similar changes in total pulmonary vascular resistance and right ventricular ejection fraction. Nine of the patients who were studied acutely thereafter received pirbuterol 15 mg thrice daily for six weeks, which produced a significant fall in systolic pulmonary arterial pressure and a rise in right ventricular ejection fraction ($p < 0.01$), without a significant fall in arterial oxygen tension.

Pirbuterol acts as a vasodilator on the pulmonary circulation in these patients and may in addition improve right ventricular performance by an inotropic action.

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Introduction

The association between the arterial hypoxaemia of chronic lung diseases and the development of pulmonary hypertension is well known,¹⁻⁶ the hypoxaemia producing pulmonary vasoconstriction by a mechanism as yet unknown. Although the pro-

gression of pulmonary hypertension in patients with chronic bronchitis and emphysema is slow,⁷ it heralds the development of cor pulmonale, with a worsening of the prognosis.⁸ In these patients with hypoxic cor pulmonale any drug that reduces pulmonary artery pressure in the long term without further disturbing the ventilation-perfusion balance should improve the prognosis.

Pirbuterol is a beta sympathomimetic drug structurally similar to salbutamol. Although animal studies in vitro have shown its principal cardiovascular effect to be vasodilatation,⁹ in vivo animal experiments have also shown it to have a positive inotropic action.^{10,11} The distinction between these two actions is difficult to establish in man; several studies, however, have shown the beneficial effects of pirbuterol on the systemic circulation both acutely^{12,13} and chronically¹⁴ in ischaemic cardiac failure.

We compared the acute haemodynamic effects of oral pirbuterol with those of the vasodilator sodium nitroprusside in patients with hypoxic chronic bronchitis and emphysema with cor pulmonale. The chronic effects of oral pirbuterol were assessed after six weeks' treatment with the drug. We combined radionuclide ventriculography with pulmonary haemodynamic measurements to obtain a detailed assessment of the effects of pirbuterol on right ventricular performance.

Patients and methods

We studied 12 patients (six men, six women) aged 42-72 with severe irreversible airflow obstruction as a result of chronic bronchitis and emphysema¹⁵ (forced expiratory volume in one second 0.65 (SD 0.2), forced vital capacity 1.75 (0.59)l). All had hypoxaemia (arterial oxygen tension 7.28 (0.28) kPa (55 (2) mm Hg)), and most had hypercapnia (arterial carbon dioxide tension 6.65 (0.80) kPa (50 (6) mm Hg)) with a compensated respiratory acidosis (hydrogen ion concentration 42 (4) nmol (ng)/l). All had peripheral oedema, indicating that they had had cor pulmonale at some time in the past, but all were in a stable state at the time of study as defined by a stable body weight, stable forced expiratory volume in one second, and the absence of acute respiratory infection or peripheral oedema for three weeks before study. Arterial blood gas tensions were also stable for this period.

ACUTE STUDIES

All patients were receiving inhaled beta₂-sympathomimetics and ipratropium and also diuretics. One patient was receiving digoxin. To ensure a stable physical and haemodynamic state during the study no drugs were given on the morning of study, each patient's normal drug treatment being given on the preceding evening. The patients were studied while semisupine in bed in the afternoon after a light lunch; no premedication was given.

Haemodynamic measurements were made with the patient at rest; during infusion of sodium nitroprusside; and at intervals of 30 minutes for two hours after oral pirbuterol was given. Ten of the 12 patients received intravenous sodium nitroprusside in a dose of 1.5 mg/kg body weight, which reduced systemic arterial blood pressure by at least 10 mm Hg and mean pulmonary artery pressure by at least 5 mm Hg. When all of the haemodynamic variables had returned to control values pirbuterol was given by mouth in a dose of 22.5 mg (six patients) or 15 mg (six patients).

CHRONIC STUDIES

Nine of the 12 patients who were studied acutely also then received oral pirbuterol 15 mg three times a day in addition to their usual drugs for six weeks, at which time pulmonary artery pressure and right and left ventricular ejection fractions were measured. Three patients did not complete this study: two developed an arrhythmia possibly associated with pirbuterol, and one had an intercurrent infective exacerbation of bronchitis at the time at which the six week study was planned.

MEASUREMENTS

Arterial blood gas tensions when the patients breathed air were measured during the control period, 90 minutes after pirbuterol was given, and after six weeks' treatment. Ear oxygen saturation was measured continuously during the acute study with a Hewlett-Packard (47201A) ear oximeter. Heart rate was measured from the electrocardiograph, and systemic arterial blood pressure with a sphygmomanometer. Right atrial, right ventricular, and pulmonary artery pressures were measured with a Swan-Ganz flow directed triple lumen catheter. Measurements were averaged over five respiratory cycles. All intracardiac pressures were referenced to a point 5 cm below the sternal angle. Cardiac output was measured in triplicate by thermodilution. As left atrial pressure is not always easy to assess from pulmonary artery wedge pressure in these patients total pulmonary vascular resistance was calculated by the formula:

$$\text{Total pulmonary vascular resistance (kPa s/cm}^5\text{)} = \frac{\text{pulmonary artery pressure (mm Hg)}}{\text{cardiac output (l)}} \times 8$$

Right and left ventricular ejection fractions were measured by a modified gated equilibrium blood pool radionuclide technique.¹⁶ Briefly, after intravenous injection and equilibration in the blood pool of human serum albumin labelled with 750 MBq technetium-99m imaging is carried out in a 20° left anterior oblique position with a 10° caudal tilt. Left ventricular ejection fraction is calculated in the normal manner, but for the right ventricle separate regions of interest at end systole and end diastole must be identified. This is accomplished by a combination of inspection of the ventriculogram, an edge detection programme, and a Fourier based phase analysis. The method gives values close to those obtained with the "single pass" technique, with low inter observer and intra observer variation, and, moreover, allows multiple ventriculograms to be obtained under different physiological and pharmacological conditions.

End diastolic volumes were calculated from the following equations:

$$\begin{aligned} \text{Stroke volume} &= \frac{\text{cardiac output}}{\text{heart rate}} \\ \text{Ejection fraction} &= \frac{\text{end diastolic volume} - \text{end systolic volume}}{\text{end diastolic volume}} \\ &= \frac{\text{stroke volume}}{\text{end diastolic volume}} \end{aligned}$$

Twelve minute walking distance¹⁷ was measured in seven patients before and after six weeks of treatment with oral pirbuterol.

In 10 patients pirbuterol concentrations were assayed in venous plasma¹⁸ one and two hours after the drug was given. Values are expressed as means (SEM). Differences between means were compared with a paired *t* test or with analysis of variance when repeated measurements were made.

Results

ACUTE STUDY

The maximum effects of pirbuterol occurred 90 minutes after the drug was given, and therefore we quote only these results. In the six patients who received 22.5 mg pirbuterol neither sodium nitroprusside nor pirbuterol significantly changed ear oxygen saturation or arterial oxygen and carbon dioxide tensions (table I). Systemic arterial blood pressure fell with sodium nitroprusside but was unaltered by pirbuterol. Both drugs produced a small increase in heart rate of an average of five beats/min. Sodium nitroprusside also reduced pulmonary arterial pressure, by 23%, but had no significant effect on cardiac output, whereas pirbuterol reduced pulmonary artery pressure by 13% and increased cardiac output by 21% and stroke volume by 9%. Sodium nitroprusside and pirbuterol both reduced pulmonary vascular resistance, but this was more noticeable with pirbuterol (table 1). Both drugs reduced systemic vascular resistance by a similar amount. Left ventricular ejection fraction rose with both sodium nitroprusside and pirbuterol, but this increase was not significant after pirbuterol. The greater increase in left ventricular ejection fraction with sodium nitroprusside was associated with a reduction in left ventricular end diastolic volume. In contrast, sodium nitroprusside did not significantly change right ventricular ejection fraction, whereas this rose with pirbuterol.

In the six patients given 15 mg pirbuterol the effects on arterial blood gas tensions and haemodynamics were similar to those produced

TABLE I—Mean (SEM) haemodynamic variables and arterial blood gas tensions during infusion of sodium nitroprusside and 90 minutes after administration of oral pirbuterol 22.5 mg (n=6)

	Control	Sodium nitroprusside	90 mins after 22.5 mg oral pirbuterol
Heart rate (beats/min)	89 (4)	95 (5)*	95 (4)*
Arterial blood pressure (mm Hg):			
Systolic	126 (6)	99 (5)†	123 (5)
Diastolic	75 (4)	58 (2)†	72 (5)
Arterial blood gas tensions (kPa):			
Oxygen	7.0 (0.4)		6.6 (0.3)
Carbon dioxide	6.6 (0.2)		6.4 (0.3)
Oxygen saturation (%)	88 (1)	87 (2)	
Hydrogen ion concentration (nmol/l)	41 (2)		41 (2)
Pulmonary artery pressure (mm Hg):			
Systolic	48 (4)	35 (3)‡	40 (3)*
Diastolic	24 (2)	20 (2)†	23 (2)
Mean	31 (2)	24 (2)†	27 (2)
Cardiac output (l/min)	4.53 (0.26)	4.43 (0.18)	5.46 (0.24)†
Pulmonary vascular resistance (kPa s/cm ⁵)	55.6 (5.3)	43.7 (5.3)†	40.7 (4.9)†
Right ventricular ejection fraction	0.45 (0.02)	0.48 (0.03)	0.54 (0.03)†
Left ventricular ejection fraction	0.61 (0.05)	0.71 (0.05)*	0.67 (0.05)
Stroke volume (ml)	52 (4)	48 (4)	58 (3)*
Right ventricular end diastolic volume (ml)	114 (6)	100 (7)	112 (11)
Left ventricular end diastolic volume (ml)	87 (10)	79 (9)*	90 (9)

Significance of difference from control values: * p < 0.05, † p < 0.01, ‡ p < 0.001.

Conversion: SI to traditional units—Blood gas tensions: 1 kPa ≈ 7.5 mm Hg. Pulmonary vascular resistance: 1 kPa s/l ≈ 0.1 dyne s/cm⁵.

by the higher dose of the drug, although the changes in pulmonary artery pressure were no longer significant (table II). Two patients were not given intravenous sodium nitroprusside during the acute study; this did not alter the effects of oral pirbuterol given subsequently.

Plasma pirbuterol concentrations varied (table III), and we could not establish a significant relation between the concentrations and any of the haemodynamic variables. In the six patients given 22.5 mg pirbuterol the plasma pirbuterol concentrations achieved a therapeutic level, and in these six patients significant reductions in pulmonary artery pressure were achieved. Lower plasma pirbuterol concentrations occurred in the six patients given 15 mg pirbuterol, and in three patients (cases 7, 8, 11) with very low concentrations pulmonary artery pressure did not fall.

TABLE II—Mean (SEM) haemodynamic variables and arterial blood gas tensions during infusion of sodium nitroprusside and 90 minutes after administration of oral pirbuterol 15 mg (n=6)

	Control	Sodium nitroprusside	90 mins after 15 mg oral pirbuterol
Heart rate (beats/min)	86 (7)	97 (12)	97 (8)*
Arterial blood pressure (mm Hg):			
Systolic	122 (6)	101 (5)‡	122 (6)
Diastolic	74 (6)	58 (3)†	74 (3)
Arterial blood gas tensions (kPa):			
Oxygen	7.5 (0.2)		6.5 (0.4)
Carbon dioxide	6.7 (0.4)		6.2 (0.3)
Oxygen saturation (%)	86 (1)	85 (3)	84 (3)
Hydrogen ion concentration (nmol/l)	43 (1)		44 (1)
Pulmonary artery pressure (mm Hg):			
Systolic	46 (5)	37 (5)‡	48 (6)
Diastolic	22 (2)	18 (3)†	21 (2)
Mean	27 (3)	20 (3)†	28 (3)
Cardiac output (l/min)	4.34 (0.50)	4.59 (0.79)	5.66 (0.60)†
Pulmonary vascular resistance (kPa s/cm ⁵)	51.1 (3.6)	37.6 (8.5)	39.2 (2.3)†
Right ventricular ejection fraction	0.47 (0.04)	0.55 (0.08)	0.53 (0.04)*
Left ventricular ejection fraction	0.56 (0.02)	0.61 (0.03)†	0.59 (0.03)
Stroke volume (ml)	52 (7)	49 (7)	61 (8)*
Right ventricular end diastolic volume (ml)	117 (21)	91 (13)*	116 (14)
Left ventricular end diastolic volume (ml)	95 (14)	80 (13)	103 (13)

Significance of difference from control values: * p < 0.05, † p < 0.01, ‡ p < 0.001.

Conversion: SI to traditional units—Blood gas tensions: 1 kPa ≈ 7.5 mm Hg. Pulmonary vascular resistance: 1 kPa s/l ≈ 0.1 dyne s/cm⁵.

CHRONIC STUDY

In the nine patients who were treated with pirbuterol for six weeks systolic pulmonary artery pressure was reduced as compared with the control values and the right ventricular ejection fraction was increased, but there was no significant fall in arterial oxygen tension or significant increase in heart rate (table IV). Forced expiratory volume in one second, forced vital capacity, body weight, and 12 minute walking distance were also unchanged over this period.

TABLE III—Plasma pirbuterol concentrations in 10 patients 60 and 120 minutes after administration of the drug

Case No	Dose of pirbuterol (mg)	Plasma pirbuterol (g/l)	
		60 min	120 min
3	22.5	45.1	34.6
4	22.5	9.6	35.2
5	22.5	4.2	45.0
6	22.5	43.7	24.8
7	15	8.1	10.0
8	15	2.1	1.9
9	15	26.1	36.2
10	15	19.4	36.8
11	15	6.9	3.7
12	15	34.8	33.9

TABLE IV—Mean (SEM) haemodynamic variables and arterial blood gas tensions before and after six weeks' treatment with oral pirbuterol 15 mg thrice daily (n=9)

	Control	After six weeks' pirbuterol 15 mg thrice daily
Heart rate (beats/min)	86 (5)	92 (5)
Arterial blood pressure (mm Hg):		
Systolic	124 (5)	121 (5)
Diastolic	73 (4)	74 (3)
Arterial blood gas tensions (kPa):		
Oxygen	7.2 (0.3)	6.9 (0.2)
Carbon dioxide	6.8 (0.2)	7.2 (0.3)
Oxygen saturation (%)	86 (2)	84 (2)
Hydrogen ion concentration (nmol/l)	43 (1)	44 (1)
Pulmonary artery pressure (mm Hg):		
Systolic	43 (3)	35 (2)†
Mean	28 (2)	26 (2)
Right ventricular ejection fraction	0.45 (0.04)	0.52 (0.03)†
Left ventricular ejection fraction	0.60 (0.03)	0.61 (0.03)
Forced expiratory volume in 1 s (l)	0.58 (0.06)	0.60 (0.05)
Forced vital capacity (l)	1.66 (0.1)	1.66 (0.1)
12 minute walking distance (m)	424 (100)	439 (104)

Significance of difference from control values: * p < 0.05, † p < 0.01, ‡ p < 0.001.

Conversion: SI to traditional units—Blood gas tensions: 1 kPa ≈ 7.5 mm Hg.

Discussion

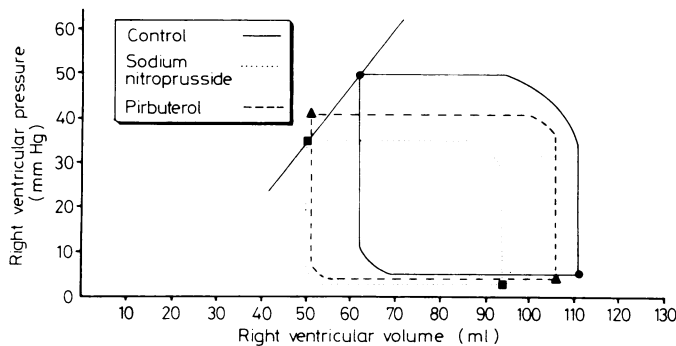
We showed that modest reduction in systolic pulmonary arterial pressure may be achieved with the beta agonist pirbuterol in patients with pulmonary hypertension as a result of severe hypoxic chronic bronchitis and emphysema. This effect was sustained after six weeks of oral treatment with pirbuterol. Moreover, cardiac output and right ventricular ejection fraction increased in all patients, with both 15 and 22.5 mg pirbuterol. Cardiac output rose principally as stroke volume increased. Pulmonary vascular resistance fell, this reduction being greater than with the vasodilator sodium nitroprusside. Pulmonary vasodilatation was induced by pirbuterol with no change in systemic blood pressure.

Pirbuterol increases cardiac output in patients with severe congestive cardiac failure,^{12-14 19} but these effects, as in our study, are not well correlated with plasma concentration.^{13 20} In our study the maximum effects of pirbuterol occurred at 90 minutes.

Debate continues over whether the mechanism of these haemodynamic effects of pirbuterol is inotropic or simply secondary to the vasodilator properties.^{12-14 19 20} In this study pulmonary artery pressure but no change in cardiac output, whereas pirbuterol produced a fall in pulmonary artery pressure and an increase in cardiac output. Arguably, sodium nitroprusside is not the ideal vasodilator to be contrasted with pirbuterol because of its combined arterial and venous effects. The comparison may, however, be valid as pirbuterol is also thought to have venodilator properties.²¹ Assessment of contractility in man is difficult. Ventricular ejection fractions and other variables of the ejection phase are influenced by alterations in the loading conditions of the ventricles, and in particular by changes in the afterload. Sagawa *et al* suggested that the relation of the end systolic pressure to the end systolic volume is not influenced by the loading conditions of the ventricle but is

sensitive to inotropic interventions.²² We drew idealised loops of right ventricular pressure and volume when the pressure changes were greatest for the six patients given 22.5 mg pirbuterol (figure). The pressure and volumes at end systole and end diastole were measured; others were not. Sodium nitroprusside displaces the end systolic pressure volume point downwards. If pirbuterol was acting only as a vasodilator the relation between the two variables would fall on the same line, but after pirbuterol this point is displaced leftwards, implying that pirbuterol has an additional inotropic action.

The beta agonist terbutaline usually has effects on pulmonary artery pressure, cardiac output, and pulmonary vascular resist-



Pressure volume loops from right ventricles in six patients with chronic bronchitis and emphysema during control conditions (●), during infusion of sodium nitroprusside (■), and after administration of pirbuterol 22.5 mg (▲). Points shown are mean end diastolic (on the right) and mean end systolic (on the left) pressure volume points.

ance similar to those of pirbuterol,²³ at least when given either intravenously²⁴ or subcutaneously,²⁵ but the effects of oral dosing are unknown.

As pirbuterol produced only modest reductions in pulmonary artery pressure, the fall in pulmonary vascular resistance was largely due to an increase in cardiac output, which occurred in all patients. However, no significant further fall in arterial oxygen saturation occurred in these patients as a result of the haemodynamic effects of pirbuterol. This is in contrast to results of previous studies in patients with acute bronchial asthma, in which both aminophylline²⁶ and non-selective adrenergic agents²⁷ reduced arterial oxygen saturation despite improving airway resistance. A recent study, however showed that the beta₂-agonist terbutaline when given intravenously did not change venous admixture or arterial oxygen tension in patients with chronic bronchitis and emphysema.

The reductions in pulmonary artery pressure produced by acute administration of pirbuterol were sustained after six weeks' oral treatment. Side effects of pirbuterol were few, but multiple ventricular ectopic beats occurred in one patient during the acute study after 22.5 mg pirbuterol, and atrial fibrillation occurred in another patient during the chronic study. Both had had frequent ventricular and supraventricular ectopic beats before starting the drug. Five further patients showed no increase in the number of ectopic beats during 24 hour ambulatory cardiac monitoring during the chronic study. We suggest, however, that pirbuterol is contraindicated in patients with frequent ectopic beats, as has been recommended by others.²⁹

These initial results in a group of severely disabled patients suggest that pirbuterol may be valuable in patients with the "blue and bloated" syndrome of chronic bronchitis and emphysema because it vasodilates the pulmonary circulation, so improving right ventricular performance and thus systemic oxygen delivery, and does not aggravate hypoxaemia. Whether these haemodynamic benefits, if produced by pirbuterol over the long term, will improve the grave outlook for such patients remains to be determined, as also does the role of pirbuterol given in addition to long term continuous oxygen treatment in such patients.^{30 31}

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