

Early effects of intravenous terbutaline on cardiopulmonary function in chronic obstructive bronchitis and pulmonary hypertension

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ABSTRACT Terbutaline sulphate (0.25 mg) was given intravenously to 10 recumbent patients with severe irreversible airflow obstruction and pulmonary hypertension who were undergoing right heart catheterisation. Alveolar ventilation index, cardiac index, and mean pulmonary artery pressure all rose significantly at 5 minutes and then fell by 35 minutes, although the first two remained higher than control levels. This was accompanied by a small but significant rise in arterial oxygen tension at 5 minutes. There were no significant changes in ventilation-perfusion relationships at either 5 or 35 minutes.

Beta-adrenergic-stimulating drugs are frequently given intravenously in the treatment of exacerbations of airflow obstruction resulting from both asthma and chronic bronchitis. These drugs may aggravate existing hypoxaemia in both asthma¹⁻³ and chronic bronchitis^{2,4-6} by adversely affecting ventilation-perfusion relationships. This is thought to be due to the combination of the increase in cardiac output produced by the β_1 activity of the drug and pulmonary and systemic vasodilatation produced by the β_2 activity,⁷⁻⁹ both effects resulting in an increase in intrapulmonary shunting and venous admixture. This may be partially offset in patients with reversible airflow obstruction by bronchodilatation and increased alveolar ventilation.¹⁻⁴ Patients with severe fixed airflow obstruction and pulmonary hypertension, however, may not respond in a similar way and may be at greater risk of developing further hypoxaemia after treatment.

Terbutaline is less likely to cause increased hypoxaemia because it is a relatively selective β_2 -adrenergic agonist,¹⁰⁻¹² having little β_1 effect on cardiac output and hence on the pulmonary circulation,¹³⁻¹⁶ although a reduction in arterial oxygen tension (P_{aO_2}) does occur in some patients when it is given by the parenteral routes.¹⁷⁻¹⁸

Stockley *et al*¹⁹ showed a small but significant increase in venous admixture in patients with chronic bronchitis and pulmonary hypertension 40 minutes after an intravenous dose of terbutaline, without a fall in arterial oxygen tension. The doses of terbutaline, however, were small. Using a larger intravenous dose, Teule *et al*¹⁷ found no significant change in venous admixture, but

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there was a slight fall in P_{aO_2} after 20 minutes in patients with chronic obstructive bronchitis but without clinical cor pulmonale. Peak serum concentrations of terbutaline, however, occur about five minutes after an intravenous bolus²⁰ and thus any effects on cardiopulmonary function should be maximal at this time and thereafter decline.

The purpose of the present study was to investigate the early cardiopulmonary changes occurring after an intravenous bolus of terbutaline in a group of patients with severe fixed airflow obstruction and pulmonary hypertension. In particular, we were interested in any adverse effect on ventilation-perfusion relationships and arterial oxygen tension.

Methods

Ten patients (table) with chronic obstructive bronchitis were studied; none had any significant improvement in airflow obstruction following inhaled bronchodilators. All were hypoxaemic at rest and had experienced at least one episode of cardiac failure with oedema. The patients were being assessed for long-term domiciliary oxygen treatment in accordance with the criteria for the Medical Research Council trial and were studied in a stable clinical state at least six weeks after any episode of cardiac failure or respiratory infection. Some were receiving digoxin and all were taking diuretics. Bronchodilator and oxygen treatment were discontinued at least 24 hours before investigation. All patients gave informed consent to the catheterisation as part of the protocol of the MRC trial. All were informed of the nature of the additional drug study and told that we wished to monitor the effect of terbutaline on the cardio-

Details of lung function in patients studied (values in parentheses are those predicted for the patients' age and height²⁴)

Patient	Age (y)	Body surface area (m ²)	FEV ₁ (l)	FEV ₁ /FVC (%)	RV (l)	RV/TLC (%)	TLCO (mmol/min ⁻¹ kPa ⁻¹)	PaO ₂ (mm Hg)	PaCO ₂ (mm Hg)
1	58	1.67	0.34 (3.09)	20 (70)	5.84 (2.33)	66 (29)	8.0 (9.2)	43.3	49.3
2	68	1.88	1.01 (2.78)	43 (66)	3.85 (2.34)	54 (31)	8.5 (7.9)	57.9	42.8
3	66	1.98	0.61 (2.92)	41 (67)	3.31 (2.52)	56 (30)	6.3 (8.9)	54.6	45.2
4	66	1.68	0.94 (1.89)	42 (75)	3.19 (1.75)	58 (43)	7.3 (6.8)	51.1	42.3
5	62	1.75	0.93 (3.18)	24 (69)	3.49 (2.56)	44 (30)	5.0 (9.6)	77.2	33.8
6	61	1.69	0.54 (2.74)	31 (69)	3.92 (2.20)	61 (29)	5.3 (8.2)	39.2	69.6
7	60	1.82	0.84 (2.63)	37 (69)	4.08 (2.07)	57 (29)	7.3 (7.8)	65.0	45.0
8	72	1.59	0.75 (2.40)	36 (65)	2.21 (2.38)	44 (32)	5.5 (7.5)	59.1	47.4
9	41	1.71	0.41 (3.55)	35 (77)	2.82 (1.99)	57 (26)	6.1 (10.1)	62.5	42.5
10	68	1.44	0.63 (2.24)	33 (66)	3.56 (2.10)	60 (31)	4.0 (6.9)	58.1	44.3
Mean ± SEM	62.2 8.6	1.72 0.15	0.70 0.20	34 2.27	3.62 0.96	55.7 7.0	6.3 1.4	56.8 3.42	46.2 2.9

Conversion: Traditional to SI units - Blood gases: 1 mm Hg = 0.133 kPa. FEV₁ = forced expiratory volume in one second; FVC = forced vital capacity; RV = residual volume; TLC = total lung capacity; TLCO = transfer factor; PaO₂ = arterial oxygen tension; PaCO₂ = arterial carbon dioxide tension.

respiratory system. No patient who was asked refused to participate.

Pulmonary function was measured by conventional techniques.¹⁹ All patients underwent right heart catheterisation and were studied supine and fasting. After 30 minutes' rest arterial gas tensions were measured; expired gases were collected, measured, and analysed for oxygen and carbon dioxide content; and heart rate and intravascular pressures were recorded.

After this, terbutaline (250 µg) was injected into the pulmonary artery over 30-45 seconds without the patients' knowledge and ventilatory measurements were repeated after 3½-6½ minutes, blood samples being taken at 5 minutes. All measurements were repeated 35 minutes after the drug had been given.

Cardiac output, pulmonary vascular resistance, and intravascular pressures were measured and calculated as previously described.¹⁹ Total systemic vascular resistance was taken as the mean brachial artery pressure divided by the cardiac output. Calculation of tidal volume (V_T), respiratory rate, and ventilation was made from the expiratory trace recorded on a Tissot spirometer. Physiological dead space (V_D) and the ratio with tidal volume (V_D/V_T) were calculated from the Bohr equation and the respiratory exchange ratio. Venous admixture (Q_S/Q_T) and the alveolar arterial oxygen difference (A-aDO₂) were calculated from the shunt equation, the ideal alveolar oxygen tension being obtained from the alveolar gas equation. Alveolar ventilation was calculated as the difference between overall and dead-space ventilation. All measurements have been corrected for body surface area and expressed as the cardiac and

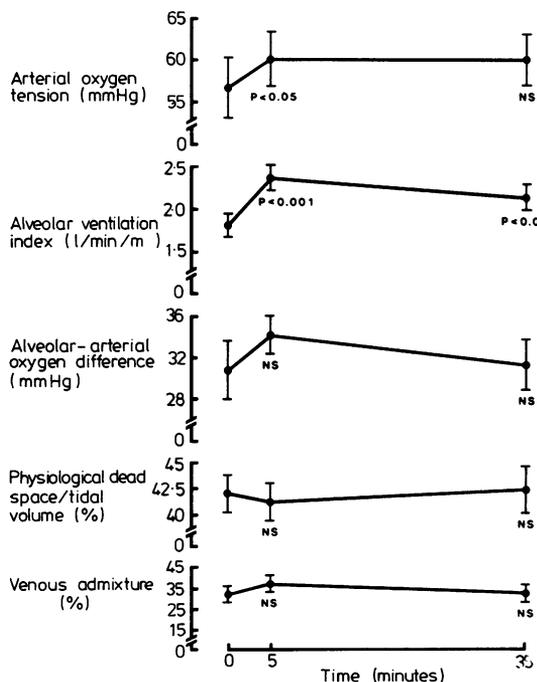


Fig 1 Effects of intravenous terbutaline on arterial oxygen tension, ventilation and ventilation-perfusion relationships in patients with chronic obstructive lung disease and cor pulmonale (conversion: traditional to SI units - 1 mm Hg = 0.133 kPa).

ventilatory index. The significance of any change observed was calculated using a paired Students' *t* test. Peak expiratory flow rate was recorded at the beginning and the end of each study to confirm that there was no change in airflow obstruction.

Results

The patients' characteristics and results of lung function testing are shown in the table. The injection of terbutaline caused no noticeable side effects in any of the patients studied.

Effects on arterial gas tensions, ventilation-perfusion relationships, and peak expiratory flow rates

The results are summarised in figure 1. P_{aO_2} rose slightly at 5 minutes from a mean of 56.8 (SE \pm 3.4) mm Hg to 60.3 (SE \pm 3.2) mm Hg (7.6 \pm 0.45 to 8.0 \pm 0.43 kPa), but by 35 minutes the change was no longer significant. This was accompanied by an increase in the alveolar ventilation index from a mean control level of 1.83 (SE \pm 0.14) litres/min/m² to 2.37 (SE \pm 0.15) l/min/m². This value subsequently fell to 2.14 (SE \pm 0.16) l/min/m² but was still higher than the control value. There were no changes in venous admixture, A-aDO₂, or V_D/V_T at either 5 or 35 minutes. P_{aCO_2} did not alter from a mean control value of 46.2 (SE \pm 2.9) mm Hg (6.2 \pm 0.4 kPa).

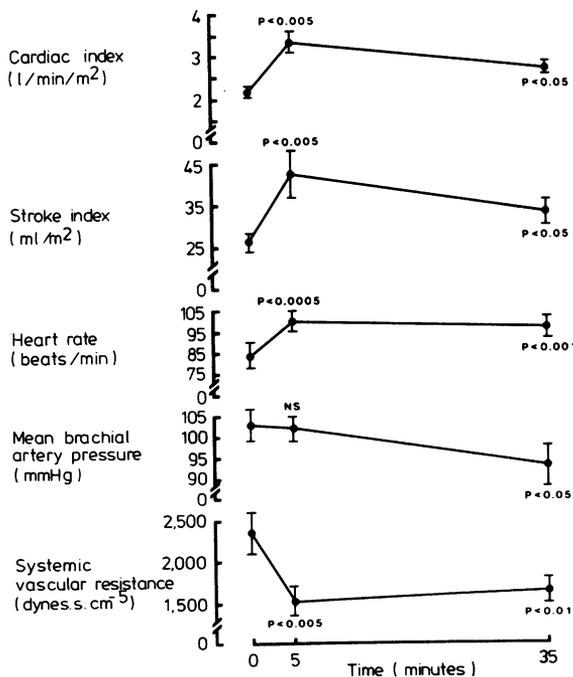


Fig 2 Systemic circulatory effects of intravenous terbutaline in patients with severe chronic obstructive lung disease and cor pulmonale (conversion: traditional to SI units - 1 mm Hg = 0.133 kPa).

Effects on systemic circulation

The results are summarised in figure 2. The cardiac index rose from a mean control level of 2.17 (SE \pm 0.15) l/min/m² to 3.36 (SE \pm 0.26) l/min/m² at 5 minutes, falling slightly at 35 minutes to 2.74 (SE \pm 0.16) l/min/m², still higher than the control values. This was accompanied by a rise in heart rate at 5 minutes from a mean control value of 84.4 (SE \pm 5.8) to 99.9 (SE \pm 5.2) beats/min, falling slightly to 97.8 (SE \pm 5.3) beats/min at 35 minutes. Similarly, the stroke index rose from a mean control level of 26.6 (SE \pm 2.1) to 42.5 (SE \pm 5.3) ml/m² at 5 minutes and remained raised at 35 minutes (33.3 \pm 3.2 ml/m²). Mean brachial artery pressures, 102.6 (SE \pm 3.8) mm Hg, did not alter significantly after 5 minutes but had fallen to 93.3 (SE \pm 4.8) mm Hg at 35 minutes. This was accompanied by a widening of the pulse pressure at 5 minutes, which returned to control levels at 35 minutes.

These changes were reflected in the calculated total systemic vascular resistance, which fell sharply at 5 minutes and rose slightly at 35 minutes, although remaining below the control values.

Effects on pulmonary circulation, oxygen uptake, and carbon dioxide production

Results are summarised in figure 3. The increase in car-

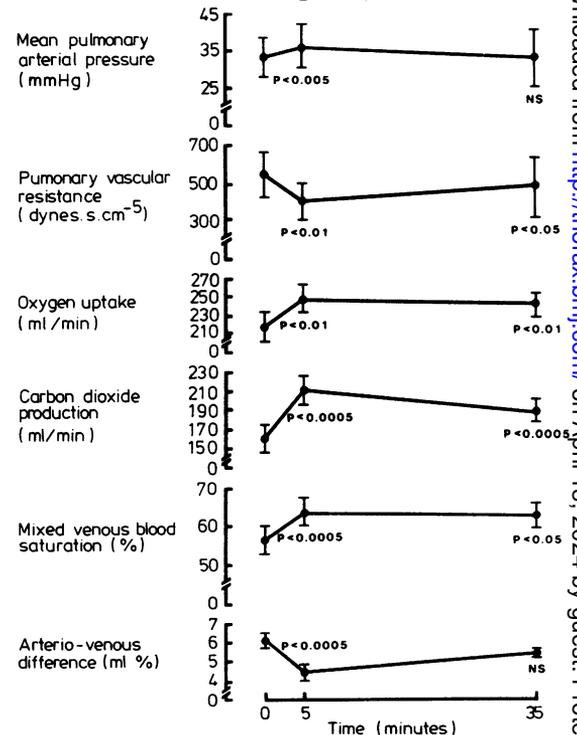


Fig 3 Effects of intravenous terbutaline on the pulmonary circulation of patients with chronic obstructive lung disease and cor pulmonale (conversion: traditional to SI units - 1 mm Hg = 0.133 kPa).

diac output and hence pulmonary blood flow was accompanied by a small rise in mean pulmonary artery pressure from a control level of 33.0 (SE \pm 5.6) mm Hg to 36.1 (SE \pm 6.1) mm Hg at 5 minutes, with a return to control levels at 35 minutes. There was no change in the mean pulmonary wedge pressure. These changes were reflected in a fall in the calculated pulmonary vascular resistance from a mean control level of 553 (SE \pm 117) dynes s cm⁻⁵ to 411 (SE \pm 96) dynes s cm⁻⁵ at 5 minutes and 477 (SE \pm 145) dynes s cm⁻⁵ at 35 minutes.

Oxygen uptake rose from 218.5 (SE \pm 14.7) ml/min to 247.6 (SE \pm 15.2) ml/min at 5 minutes and remained raised at 240.9 (SE \pm 11.7) ml/min at 35 minutes. Similarly, carbon dioxide production increased from a mean control level of 161.9 (SE \pm 11.8) ml/min to 210.8 (SE \pm 15.7) ml/min at 5 minutes, also remaining raised (186.2 (SE \pm 12.4) ml/min) at 35 minutes. This was accompanied by a fall in the arteriovenous oxygen difference from 6.0 (SE \pm 0.33) mm Hg (0.8 \pm 0.04 kPa) to 4.4 (SE \pm 0.43) mm Hg (0.6 \pm 0.06 kPa) at 5 minutes, with return to control levels at 35 minutes. Mixed venous blood saturation rose from a mean control level of 56.5 (SE \pm 3.1) mm Hg (7.5 \pm 0.4 kPa) to 63.6 (SE \pm 3.7) mm Hg (8.5 \pm 0.5 kPa) at 5 minutes and remained raised at 62.3 (SE \pm 2.77) mm Hg (8.3 \pm 0.37 kPa) at 35 minutes.

Discussion

Halmagyi and Cotes⁴ suggested that agents affecting cardiac output and pulmonary vascular resistance may give rise to increased venous admixture, thereby reducing arterial oxygen tension in patients with chronic airflow obstruction, particularly if pulmonary hypertension is present. Terbutaline is one such agent but as its action is largely selective and directed to β_2 receptors with a much less pronounced action on the heart¹⁰⁻¹⁶ it would be expected to have fewer adverse effects on ventilation-perfusion relationships. This assumption has been confirmed in both reversible^{9, 16} and irreversible airflow obstruction, with¹⁹ and without cor pulmonale.¹⁷ Nevertheless, in several studies a small and unpredictable fall in PaO₂ has been noted in some of the patients studied,^{9, 17, 18} although there are no studies relating to early cardiopulmonary changes when drug concentrations are at their highest.

In the present study no significant changes were noted in any of the indices of ventilation-perfusion inequality at either 5 minutes or 35 minutes after the drug was given, although the PaO₂ rose initially in all but one patient. The maximum rise observed was in patient 2, from 57.9 mm Hg (7.7 kPa) to 72.5 mm Hg (9.64 kPa). The only patient (No 5) in whom the PaO₂ fell had the highest resting PaO₂ - 77.0 mm Hg (10.24 kPa) - and least physiological impairment of lung function as well as the lowest resting venous admixture (12%) and mean pulmonary artery pressure (18 mm Hg). Although the

changes in PaO₂ after bronchodilator drugs may be unpredictable,²¹ in the present study the patients with the lowest resting PaO₂ and highest pulmonary vascular resistance all experienced a transient rise in PaO₂. This suggests that there is only a small risk of a dangerous fall in PaO₂ even in the most severely affected patients.

The rise in PaO₂ was unexpected but accompanied by an increase in alveolar ventilation. Possibly this reflects a direct action of terbutaline on chemoreceptors increasing ventilatory drive, as similar changes have been noted for salbutamol,²⁵ but further studies will be necessary to clarify this point. No changes were observed in PCO₂ despite the increase in alveolar ventilation. This may be explained by a rise in oxygen uptake and carbon dioxide production as a result of the increased ventilatory work, which may have partly offset the effect of increased ventilation on PaCO₂.

The increase in cardiac output, stroke volume, and heart rate at 5 minutes were expected and were associated with an appreciable fall in total systemic vascular resistance but no early change in mean brachial artery pressure. Later, at 35 minutes, the brachial artery pressure had fallen significantly and was accompanied by small reductions in both stroke index and cardiac index compared with the 5-minute value. The heart rate did not change from the 5-minute value but remained significantly raised. These early changes cannot be explained solely by a reflex response to systemic vasodilatation and hypotension, as has been suggested,^{19, 22} for two reasons. Firstly, no early fall in blood pressure was recorded and, secondly, all measurements were made in the supine position, where postural effects would be minimal.¹⁷ Nevertheless, the blood pressure did fall at 35 minutes in the presence of a lower cardiac output but a sustained increase in heart rate, which is more typical of a predominant β_2 effect. The β_1 effects of terbutaline are dose related however, and thus the early changes, when drug concentrations are highest, are probably due to a combination of the β_1 effect on the heart and β_2 peripheral vasodilatation. Later, as serum concentrations decline, the β_1 effect is less prominent than the sustained β_2 action. This would explain the sustained tachycardia at 35 minutes, which is probably due largely to a reflex response to systemic hypotension and systemic vasodilatation (β_2 effects).^{13, 14}

The mean pulmonary artery pressure rose transiently with cardiac output and pulmonary vascular resistance fell. By 35 minutes the pulmonary artery pressure had returned to resting levels, although the cardiac output remained raised and pulmonary vascular resistance reduced. This may reflect changes in pulmonary vascular capacitance in response to the increased cardiac output rather than a direct β_2 vasodilating effect of terbutaline on pulmonary resistance vessels,²³ although either or both mechanisms may be operating.

In summary, terbutaline sulphate in the dose used

had no major detrimental effects on gas exchange in the patients studied. The effects on the cardiovascular system were more noticeable at 5 minutes, when drug concentrations are likely to be at their highest, and suggest a combined β_1 and β_2 response. It is concluded that terbutaline in this dose can be given to such patients without worsening their gas exchange and that it may even produce a temporary improvement.

We would like to thank Miss J Downs for her typing and Mr BJ Milton for technical assistance.

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