

Effect of intravenous terbutaline on arterial blood gas tensions, ventilation, and pulmonary circulation in patients with chronic bronchitis and cor pulmonale

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Stockley, R. A., Finnegan, P., and Bishop, J. M. (1977). *Thorax*, 32, 601–605. **Effect of intravenous terbutaline on arterial blood gas tensions, ventilation, and pulmonary circulation in patients with chronic bronchitis and cor pulmonale.** Terbutaline sulphate was given intravenously to 10 patients with pulmonary vascular disease secondary to chronic hypoxia. The resting cardiac index increased after terbutaline in all the patients between 5 and 74% above the control level. The greatest change was seen in patients who had received the largest total dose. The rise in cardiac index was associated with a fall in pulmonary vascular resistance although mean pulmonary artery pressure remained unaltered. There was a significant increase in the venous admixture but this did not adversely affect the arterial oxygen tension.

The peak expiratory flow rate did not change significantly but there was an increase in ventilation from a mean value of 4.36 l/min/m² to 4.67 l/min/m².

The results show that terbutaline has little adverse effect on the pulmonary circulation or gas exchange in patients with irreversible airways disease who are in a stable state.

Terbutaline is a beta-adrenergic stimulating drug which acts mainly on β_2 receptors (Carlström, 1970). Its action, therefore, results in predominantly bronchodilatation and vasodilatation.

There are many studies of its bronchodilator activity in patients with reversible airways disease via the oral (Legge *et al.*, 1971), subcutaneous (Freedman, 1971; Arner, 1970), and inhaled route (Koch, 1972; Harris, 1973).

Systemic vasodilatation has been assessed by Carlström and Westling (1970) and Arner *et al.* (1970). Normal subjects showed a rise in cardiac output of up to 65% after the injection of 250 μ g terbutaline, greatest within the first five minutes but still present at least 60 minutes after the injection and associated with a fall in peripheral vascular resistance of up to 45%.

There are few studies of the circulatory effects of terbutaline in patients with lung disease. Harris (1973) found that cardiac output did not change when patients with reversible airways disease inhaled terbutaline.

Some patients with chronic airways obstruction develop pulmonary hypertension secondary to chronic hypoxaemia. If terbutaline causes vasodilatation in the pulmonary as well as the systemic circulation, it could benefit such patients by reducing the pulmonary vascular resistance and right ventricular work.

However, the effects of β -adrenergic agents on cardiopulmonary function in patients with chronic airways obstruction are complex. Halmagyi and Cotes (1959) suggested that agents affecting the pulmonary circulation may increase venous admixture, thereby reducing the systemic oxygen tension if given in such patients.

The present study was designed to investigate the possibility that terbutaline in therapeutic doses might cause beneficial pulmonary vasodilatation in patients with chronic airways obstruction and pulmonary hypertension. In addition, it was proposed to study the extent of any fall in arterial oxygen tension due to increased venous admixture effect.

Patients and methods

Ten patients with chronic bronchitis were studied, all of whom had severe airways obstruction (Table 1) and were hypoxaemic at rest (Table 2). All had suffered at least one episode of cardiac failure but none was studied sooner than six weeks after the episode when they were in a stable clinical state. All patients were receiving treatment with digoxin

and diuretics and underwent right heart catheterisation before entry into the Medical Research Council trial of long-term oxygen therapy. None of the patients received oxygen or bronchodilators in the 24 hours preceding the investigation. All gave informed consent to the procedure.

PULMONARY FUNCTION TESTS

Pulmonary function was measured on the day

Table 1 Details of patients studied

Patient	Age	Ht (m)	Wt (kg)	TLC (l)	RV (l)	FEV ₁ (l)	FEV ₁ /FVC (%)	DLco (mmol/min/kPa)
WN	64	1.67	81.5	5.38 (5.95)	3.28 (2.15)	0.67 (2.65)	32 (68)	3.0 (8.3)
GB	60	1.77	59.5	6.10 (6.90)	3.14 (2.35)	0.97 (3.12)	30 (69)	4.2 (9.3)
AT	69	1.68	54.0	7.17 (6.05)	4.23 (2.25)	0.89 (2.52)	44 (66)	4.9 (7.7)
JR	47	1.63	73.0	6.31 (5.60)	4.26 (1.75)	0.59 (3.02)	36 (74)	3.2 (8.7)
WJ	44	1.68	51.0	5.94 (6.00)	3.40 (1.80)	0.46 (3.30)	24 (75)	2.1 (9.4)
VS	59	1.65	62.0	5.30 (5.80)	1.75 (2.00)	0.53 (2.72)	25 (70)	2.4 (8.0)
FM	61	1.68	82.0	7.63 (6.10)	4.85 (2.10)	0.50 (2.76)	28 (69)	6.9 (8.0)
HB	49	1.66	75.5	5.02 (5.80)	2.15 (1.85)	0.69 (3.08)	38 (74)	2.3 (8.9)
HJ	49	1.80	55.5	8.35 (7.10)	4.43 (2.25)	0.80 (3.58)	25 (74)	2.2 (10.4)
LW	56	1.79	91.0	6.34 (7.00)	3.25 (2.35)	0.99 (3.32)	46 (71)	2.8 (9.8)

TLC = total lung capacity; RV = residual volume; FEV₁ = forced expired volume in one second; FVC = forced vital capacity; DLco = transfer factor for carbon monoxide. All volumes are corrected to BTPS. The patient's weight (Wt) and height (Ht) are shown and values in parentheses are those predicted for the patient's age and height (Cotes, 1975).

Table 2 Response to terbutaline

Patient	Dose of terbutaline (μg)	Heart rate (beats/min)	Cardiac index (l/min/m ²)	PAP (mmHg)	PWP (mmHg)	PVR (dyne/s/cm ⁵)	BAP (mmHg)	Ventilatory index (l/min/m ²)	PEFR (l/s)	PaO ₂ (mmHg)	PaCO ₂ (mmHg)	
WN	115	C	98	3.07	31	4	366	85	3.75	1.8	47.3	58.6
		T	(99)	(3.82)	(30)	(4)	(283)	(89)	(4.32)	(1.9)	(48.1)	(55.9)
GB	80	C	89	4.67	24	4	201	109	2.97	2.4	55.4	49.7
		T	(90)	(5.79)	(22)	(2)	(162)	(89)	(4.88)	(2.3)	(56.1)	(39.3)
AT	75	C	63	2.39	27	7	424	70	4.52	2.2	57.0	50.3
		T	(72)	(2.71)	(29)	(7)	(413)	(70)	(5.45)	(2.3)	(59.6)	(51.0)
JR	100	C	88	2.81	53	5	764	86	5.30	1.2	46.0	56.0
		T	(96)	(3.25)	(54)	(5)	(674)	(82)	(5.25)	(1.2)	(44.5)	(55.4)
WJ	70	C	114	2.53	61	6	1139	90	5.24	1.3	35.7	55.7
		T	(114)	(2.88)	(66)	(8)	(1056)	(85)	(4.68)	(1.3)	(39.4)	(49.3)
VS	85	C	93	4.67	27	8	193	135	6.40	1.6	71.0	37.5
		T	(99)	(4.89)	(30)	(5)	(242)	(125)	(5.97)	(1.3)	(70.0)	(39.0)
FM	115	C	78	4.23	25	10	148	99	3.07	1.5	50.7	50.5
		T	(87)	(5.18)	(28)	(10)	(145)	(93)	(3.11)	(1.6)	(47.7)	(51.2)
HB	250	C	81	3.47	42	7	440	86	2.77	2.2	48.0	40.1
		T	(90)	(6.05)	(38)	(6)	(231)	(86)	(3.35)	(2.2)	(45.5)	(47.3)
HJ	250	C	69	3.49	32	3	388	93	3.34	1.8	52.5	42.8
		T	(78)	(4.89)	(26)	(3)	(220)	(76)	(4.11)	(2.1)	(57.0)	(35.6)
LW	250	C	78	3.70	46	9	382	92	5.19	2.5	48.0	45.0
		T	(99)	(4.73)	(50)	(9)	(330)	(87)	(5.56)	(2.7)	(50.0)	(37.9)
Mean			85.1 (92.4)	3.50 (4.42)	36.8 (37.3)	6.3 (5.9)	445 (376)	94.5 (88.2)	4.36 (4.67)	1.8 (1.9)	51.2 (51.8)	48.6 (46.2)
SD			14.7 (11.9)	0.83 (1.19)	13.0 (14.5)	2.3 (2.6)	300 (284)	17.4 (14.6)	1.17 (0.95)	0.5 (0.5)	9.1 (8.9)	7.1 (7.6)

The total dose of terbutaline given is shown together with the resting heart rate, cardiac index, mean pulmonary artery pressure (PAP), mean pulmonary wedge pressure (PWP), mean brachial artery pressure (BAP), pulmonary vascular resistance (PVR), ventilatory index, peak expiratory flow rate (PEFR), and arterial oxygen and carbon dioxide tensions (PaO₂ and PaCO₂ respectively). C = control values and T = terbutaline values in parentheses. (Note conversion to SI units, 1 mm = 0.133 kPa and 1 dyne/s/cm⁵ = 10⁻¹ kPa l⁻¹ s⁻¹).

before cardiac catheterisation. Static lung volumes were measured by spirometry, forced expired volumes from the integrated output of a Fleisch pneumotachograph, and diffusing capacity for carbon monoxide using the single breath method. Total lung capacity was measured using the helium dilution method. The results are summarised in Table 1.

ARTERIAL BLOOD GAS TENSIONS

Arterial oxygen tension (P_{aO_2}) and carbon dioxide tension (P_{aCO_2}) were determined using polythene-covered Radiometer electrodes, calibrated with high and low gas tensions before each measurement. In measurements of tonometered blood, these electrodes gave 95% confidence limits of ± 0.52 kPa (P_{aO_2}) and ± 0.44 kPa (P_{aCO_2}). Venous admixture was estimated from the shunt equation using the calculated ideal alveolar oxygen tension.

CIRCULATORY STUDIES

Patients were studied supine in the fasting state. A No. 9 double-lumen Cournand catheter was passed into the pulmonary artery for simultaneous measurement of pulmonary artery pressure (PAP) and pulmonary wedge pressure (PWP). The zero reference point for intravascular pressures was 5 cm vertically below the manubriosternal angle. A Cournand needle was inserted into the brachial artery to measure pressure and for sampling arterial blood to measure gas tension and oxyhaemoglobin saturation. Cardiac output was measured by the direct Fick method. The patients breathed through a two-way valve for at least 5 minutes before any measurements were made. Expired gas was collected in a Tissot spirometer for 3 minutes and analysed by the Scholander method to determine oxygen uptake and carbon dioxide production. During the period of gas collection pulmonary vascular pressures were recorded and simultaneous samples of mixed venous and arterial blood were taken. Oxyhaemoglobin saturation was measured by a spectrophotometric method. The standard error of a single estimation of cardiac output in the supine position was 8.1%.

Pulmonary vascular resistance was calculated from the pressure gradient across the pulmonary vascular bed divided by pulmonary blood flow. All values for cardiac output and ventilation have been corrected for body surface area to give the cardiac and ventilatory index.

Thirty minutes before the measurement of resting cardiac output, peak expiratory flow rate (PEFR) was recorded as the best of three at-

tempts, using a Wright peak flow meter. After resting cardiac output had been determined, terbutaline was injected slowly into the pulmonary artery during one minute and the cardiac output was measured again after a further 40 minutes. When all other recordings had been completed the PEFR was measured again.

The significance of any change observed was determined using a paired Student *t* test.

DOSE OF TERBUTALINE

The first seven patients were given 1.4 $\mu\text{g}/\text{kg}$ terbutaline sulphate. In view of the small changes produced by this initial study, a further group of three patients were given a single bolus of 250 μg , which is the recommended therapeutic dose.

Results

The effects of terbutaline on individual patients are shown in Table 2. The PA mean pressure at rest was 24 mmHg or more in all patients. There was no significant change in PAP or PWP, in the group as a whole, after the injection of terbutaline ($P < 0.1$ and $P < 0.2$ respectively).

Cardiac output increased in all patients to a variable extent. In the group as a whole, terbutaline caused a significant increase ($P < 0.0025$) in cardiac index from a mean value of 3.50 l/min/m² to 4.42 l/min/m². The increase varied from 5 to 24% in the seven patients who received 1.4 $\mu\text{g}/\text{kg}$ terbutaline but was greater in the three patients who received the larger dose (27–74%).

The change in cardiac output was accompanied by a significant rise ($P < 0.0005$) in mean oxygen uptake from 253 ml/min STPD ($SD \pm 32.9$) to 284 ml/min ($SD \pm 48.8$). The arteriovenous oxygen difference was significantly reduced ($P < 0.0025$), after terbutaline, from a mean value of 42.8 ml/l STPD ($SD \pm 1.03$) to 38.5 ml/l ($SD \pm 1.05$).

The heart rate rose significantly ($P < 0.0025$) from 85.1 beats/min to 92.4 beats/min, and stroke index increased ($P < 0.0125$) from a mean value of 42.1 ml/m² ($SD \pm 10.9$) to 48.7 ml/m² ($SD \pm 14.5$). Pulmonary vascular resistance fell from a mean value of 445 dynes/s/cm⁵ to 376 dynes/s/cm⁵.

There was a small but significant increase of venous admixture effect after the injection of terbutaline ($P < 0.0125$). The average control value was 35.7% ($SD \pm 9.6$), rising to 38.9% ($SD \pm 10.9$) after administration of the terbutaline. At the same time mixed venous oxygen saturation rose ($P < 0.05$) from 55.9% ($SD \pm 11.0$) to 58.6% ($SD \pm 10.6$).

The P_{aO_2} did not change significantly ($P < 0.25$) from the mean control value of

51.2 mmHg. The greatest observed fall in PaO_2 for any patient was 3.0 mmHg (Table 2). There was a slight but insignificant fall in Paco_2 from a mean value of 48.6 mmHg to 46.2 mmHg.

The mean ventilatory index rose from 4.36 l/min/m² to 4.67 l/min/m² following terbutaline ($P < 0.05$). Similarly, the alveolar ventilatory index rose ($P < 0.05$) from 1.94 l/min/m² ($\text{SD} \pm 0.36$) to 2.27 l/min/m² ($\text{SD} \pm 0.47$).

There was a significant increase in carbon dioxide production ($P < 0.025$) following the infusion of terbutaline. The mean value for CO_2 production was 189 ml/min ($\text{SD} \pm 22.8$), rising to 209 ml/min ($\text{SD} \pm 35.4$) after the drug was administered.

Peak expiratory flow rate was unchanged, the mean control being 1.8 l/s and 1.9 l/s after the terbutaline ($P < 0.25$). There was a significant fall ($P < 0.025$) in mean brachial artery pressure from 94.5 mmHg to 88.2 mmHg.

Discussion

Carlström and Westling (1970) and Arner *et al.* (1970) demonstrated that terbutaline has a marked dose-related effect on the systemic circulation. The purpose of the present study was to assess the effect of terbutaline on the pulmonary circulation in a group of patients with bronchitis who had developed pulmonary vascular disease. In particular, it was considered possible that terbutaline might prove beneficial by reducing pulmonary vascular resistance. The first seven patients received 1.4 $\mu\text{g}/\text{kg}$ terbutaline, which results in a free serum level of 2 ng/ml after 30 minutes (Davies, 1972). This is a slightly lower concentration than the peak level of free drug observed one to three hours after a single oral dose of 5 mg (Nilsson *et al.*, 1972). In view of the small changes observed in these patients the remainder were given a larger total dose (250 μg).

After the injection of terbutaline the cardiac output increased, and this was greater in the patients who received 250 μg , confirming the results obtained by Arner *et al.* (1970) in normal subjects. This increase may be either the result of β_1 adrenergic stimulation by the drug, or a reflex response to systemic hypotension following the fall in systemic vascular resistance due to β_2 adrenergic stimulation (Gibson and Coltart, 1971).

In the initial study a small dose of terbutaline was used in an attempt to minimise the β_1 adrenergic effects. However, an increase in cardiac output occurred despite this low dose, and mean brachial artery pressure fell, suggesting a decrease in the peripheral vascular resistance. This, together

with the minimal effect of terbutaline on β_2 adrenergic receptors *in vitro* (Persson and Johnson, 1970), suggests that the increase in cardiac output was mainly secondary to its β_2 adrenergic activity.

Despite the increase in cardiac output pulmonary arterial pressure remained unaltered owing to a fall in PVR. The relation between pulmonary blood flow and vascular resistance in chronic bronchitis was studied by Harris *et al.* (1968), who demonstrated a 38% reduction in PVR when blood flow was doubled. This was considered to be the result of distension or recruitment of pulmonary vessels. It is, therefore, probable that the fall in PVR with terbutaline was mainly due to the increased cardiac output rather than to drug induced vasodilatation.

Previous work by Halmagyi and Cotes (1959) and Harris (1970) suggested that agents affecting the pulmonary circulation may adversely affect the ventilation to perfusion ratio, resulting in an increase in venous admixture. The present study demonstrated a small but significant increase in venous admixture following the injection of terbutaline. Despite this increase there was no alteration in PaO_2 , probably because of the associated rise in mixed venous oxygen saturation. Alveolar ventilation increased in proportion to the increased carbon dioxide production, arterial carbon dioxide tension remaining unaltered.

It is concluded that intravenous terbutaline in therapeutic doses has no major effect upon the pulmonary circulation in patients with chronic bronchitis. Although venous admixture was slightly increased there was no fall in arterial oxygen tension.

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