

Ventilation-perfusion mismatching in acute severe asthma: effects of salbutamol and 100% oxygen

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ABSTRACT Ventilation-perfusion (\dot{V}_A/\dot{Q}) relationships and gas exchange were studied by the multiple inert gas technique in 19 patients admitted to hospital with acute severe asthma (FEV₁ 41% predicted) before and during the administration of intravenous salbutamol, inhaled salbutamol, or 100% oxygen. Eight patients received a continuous intravenous infusion of salbutamol (4 $\mu\text{g}/\text{min}$, total dose 360 μg) and were studied before treatment, after 60 and 90 minutes of treatment, and one hour after treatment had been discontinued. Six patients had measurements before and 15 minutes after inhaling 300 μg salbutamol from a metered dose inhaler on two occasions (total dose 600 μg) and one hour after the last dose. Measurements were also made in five patients before and while they breathed 100% oxygen for 20 minutes. At baseline (fractional inspired oxygen (FiO₂) 21%) all patients showed a broad unimodal (n = 10) or bimodal (n = 9) distribution of blood flow with respect to \dot{V}_A/\dot{Q} . A mean of 10.5% of the blood flow was associated with low \dot{V}_A/\dot{Q} units without any appreciable shunt. One of the best descriptors of \dot{V}_A/\dot{Q} inequality, the second moment of the perfusion distribution on a log scale (log SD \dot{Q}), was moderately high with a mean of 1.18 (SEM 0.08) (normal < 0.6). Measures of \dot{V}_A/\dot{Q} inequality correlated poorly with spirometric findings. After salbutamol the increase in airflow rates was similar regardless of the route of administration. Intravenous salbutamol, however, caused a significant increase in heart rate, cardiac output, and oxygen consumption ($\dot{V}O_2$); in addition, both perfusion to low \dot{V}_A/\dot{Q} areas and log SD \dot{Q} increased significantly. Inhaled salbutamol caused only minor changes in heart rate, cardiac output, $\dot{V}O_2$, and \dot{V}_A/\dot{Q} inequality. Arterial oxygen tension (PaO₂) remained unchanged during salbutamol administration, irrespective of the route of administration. During 100% oxygen breathing there was a significant increase in log SD \dot{Q} (from 1.11 to 1.44). It is concluded that patients with acute severe asthma show considerable \dot{V}_A/\dot{Q} inequality with a high level of pulmonary vascular reactivity. Despite similar bronchodilator effects from inhaled and intravenous salbutamol, \dot{V}_A/\dot{Q} relationships worsened only during intravenous infusion. PaO₂ remained unchanged, however, because the change in \dot{V}_A/\dot{Q} relationships was associated with an increase in metabolic rate and cardiac output.

Introduction

Gas exchange abnormalities, particularly hypoxaemia, are well known accompaniments of exacerbations of asthma, the degree of hypoxaemia showing a poor correlation with indices of severity of airflow obstruction.¹ Several studies have indirectly recog-

nised ventilation-perfusion (\dot{V}_A/\dot{Q}) mismatching as the fundamental mechanism underlying abnormal gas exchange in asthma.²⁻⁵ More direct evidence has come from quantitative measurements of \dot{V}_A/\dot{Q} relationships since the introduction of the multiple inert gas elimination technique.⁶⁻¹¹ Bronchodilators, though improving airflow rates in asthma, have been found to alter pulmonary gas exchange.¹² Thus the administration of salbutamol has occasionally been reported to decrease arterial oxygen tension (PaO₂) despite its beneficial effect on bronchoconstriction.¹³ Various

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results have been reported on the effects of beta agonists. Wagner *et al*⁶ observed a transient deterioration in PaO_2 and \dot{V}_A/\dot{Q} relationships in symptomless adults with asthma after giving inhaled isoprenaline. In a subsequent study by the same authors,¹⁴ inhaled metaproterenol administered after antigen challenge caused a rapid restoration of \dot{V}_A/\dot{Q} distribution to normal in all but one patient. Young *et al*⁷ also observed an improvement in both PaO_2 and \dot{V}_A/\dot{Q} relationships after salbutamol in patients with exercise induced asthma. A similar degree of improvement has been observed in children¹⁵ and in experimental canine "asthma."^{16,17}

The purpose of the present study was, firstly, to evaluate the effects on \dot{V}_A/\dot{Q} distribution of a beta₂ selective agonist, salbutamol, administered by two different routes in patients with acute severe asthma, and to examine the relation of any change to spirometric, haemodynamic, and gas exchange data; and, secondly, to assess whether hypoxic pulmonary vasoconstriction is present by determining the effects of 100% oxygen breathing on \dot{V}_A/\dot{Q} mismatching.

Methods

SUBJECTS

Nineteen non-smoking subjects with asthma (17 women and two men) were included in the study. They were aged 21–66 years (mean 42 (SEM 3) years). All had been admitted via the emergency room because of an attack of severe asthma as defined clinically by Clark.¹⁸ They were studied within a few days (mean 2 days) of admission. At the time of study all patients had symptoms, predominantly shortness of breath and wheezing; the mean FEV_1 was 41% of predicted.¹⁹ The patients had no history of other pulmonary diseases and only those without clinical or functional evidence of chronic airflow obstruction were eligible for the study. None of the subjects had consolidation or atelectasis on the chest radiograph. The study was approved by the hospital clinic investigation committee and oral consent was obtained from all the participants.

SPIROMETRY AND VENTILATORY MEASUREMENTS

Triplicate measurements of forced expiratory volume in one second (FEV_1), forced vital capacity (FVC; Vitalograph, Buckingham), and peak expiratory flow (PEF; Wright peak flow meter, Wright, Harlow) were made according to American Thoracic Society recommendations. As inert gas data were collected (see below), minute ventilation (\dot{V}_E) and respiratory rate were measured minute by minute through a previously calibrated Wright spirometer.

OXYGEN AND CARBON DIOXIDE MEASUREMENTS (ARTERIAL AND EXPIRED)

PaO_2 , carbon dioxide tension (PaCO_2), and pH were measured in duplicate with blood gas electrodes (IL-1302, Instrumentation Laboratories, Milan) from blood sampled through a catheter inserted in the radial or brachial artery, after the adequacy of local circulation had been ensured. The alveolar-arterial oxygen tension difference (A-a-PO_2) was calculated by using the alveolar air equation:

$$\text{PAO}_2 = \text{PIO}_2 - (\text{PaCO}_2/\text{R}) + (\text{PaCO}_2 \times \text{FIO}_2(1-\text{R})/\text{R}$$

where PAO_2 = alveolar oxygen tension, PIO_2 (inspired oxygen tension) = $\text{FIO}_2 (\text{P}_B - \text{P}_{\text{H}_2\text{O}})$, and R (the respiratory exchange ratio) was calculated from \dot{V}_E and the mixed expired oxygen and carbon dioxide concentrations. The ratio of physiological dead space (VD) to tidal volume (VD/VT) was calculated according to the Bohr equation, $\text{VD}/\text{VT} = (\text{PaCO}_2 - \text{PECO}_2)/\text{PaCO}_2$, where PECO_2 is mixed expired PCO_2 . Mixed expired gas samples for measurements of oxygen consumption (\dot{V}_{O_2}) and carbon dioxide production (\dot{V}_{CO_2}) were collected at the end of a flow through mixing chamber, and fractional concentrations of oxygen (FEO_2) and carbon dioxide (FECO_2) were measured by a paramagnetic oxygen analyser and infrared capnograph respectively (E Jaeger, Würzburg, West Germany) or by mass spectrometer (Medishield, Multi-gas MS2, Ohmeda-British Oxygen Company).

HAEMODYNAMIC MEASUREMENTS

Systemic arterial pressure and heart rate were continuously recorded through a four channel recorder (HP-7754 B). Cardiac output (\dot{Q}_T) was measured in duplicate (in triplicate if the two first tracings differed by more than 10%) by the indicator-dilution method. A 5 mg bolus of indocyanine green dye was injected into a catheter in the superior vena cava or right atrium and blood was sampled from a cannula in a peripheral artery. Dye concentration was measured in arterial blood by a densitometer attached to a DC-410 cuvette transducer (Waters Instruments Inc, Rochester, Minnesota); blood was reinfused after measurements were completed. Cardiac output curve tracings were recorded on a single channel cardiac output recorder (CO-IOR) and \dot{Q}_T was calculated from the area under each curve.^{20,21}

VENTILATION-PERFUSION RELATIONSHIPS

Ventilation-perfusion relationships were determined by the multiple inert gas elimination technique of Wagner *et al*.²² Briefly, a mixture of six inert gases with widely different solubilities (sulphur hexafluoride, ethane, cyclopropane, halothane, ether, and acetone) dissolved in saline was infused at 3–5 ml/min through a peripheral vein until a steady state condition had been reached. This was identified by monitoring end tidal

PCO₂, respiratory frequency, tidal volume, heart rate, and systemic arterial pressures. Duplicate samples of arterial blood and mixed expired gas were taken and the concentrations of inert gases measured in both samples with a modified gas chromatograph (HP 5880 A).^{23,24} Retention and excretion of each inert gas require mixed venous partial pressures of inert gas to be calculated from arterial and expired gases; this was accomplished by using the Fick principle. Results of \dot{V}_A/\dot{Q} dispersion indices are the means of duplicate measurements.

Theophylline blood levels were measured by fluorescence polarised immunoassay at the start of the study.

STUDY DESIGN

Before the study began, the usual doses of xanthine derivatives were withheld for at least 12 hours and of beta₂ adrenergic agents for at least eight hours.²⁵ Only intravenous methylprednisolone (240 mg/day) was continued. Patients were always studied at the same time of day (between 1000 and 1300 hours). Measurements were performed at the bedside with the patient in a semirecumbent position at 45° breathing room air through a low resistance valve (Hans Rudolph, Kansas City). Patients were studied on the first day they were able to accept the mouthpiece. All patients were studied before, during, and after the administration of salbutamol. In eight patients (group 1) given a continuous intravenous infusion of salbutamol (4 µg/min) spirometric, haemodynamic, and conventional and inert gas exchange was measured 60 and 90 minutes after the beginning of the infusion and 60 minutes after the drug had been discontinued. In a

further six patients (group 2) the same measurements were made 15 minutes after inhalation of 300 µg salbutamol from a metered dose inhaler (three puffs) on two occasions and 60 minutes after administration of the last three puffs. The same observer held the cannister and each manoeuvre was carried out in the same manner in all patients. In five additional patients (group 3) measurements were made before and during 100% oxygen breathing (20 minutes' duration). Each set of measurements was made in the following sequence: (1) heart rate and intravascular pressures, (2) simultaneous arterial blood and mixed expired gas sampling for respiratory and inert gas determinations, (3) cardiac output, (4) spirometry.

ANALYSIS

Unless otherwise stated, results are expressed as means with standard error of the mean in parentheses. Differences between baseline values of each group were analysed by one way analysis of variance. Comparisons of data obtained after intravenous and inhaled salbutamol were made by two way analysis of variance and Scheffé test. Wilcoxon's signed rank test for paired observations was used for the five patients of group 3.

Results

BASELINE DATA FOR ALL PATIENTS

Individual data for all 19 patients are presented in tables 1 and 2. All patients showed substantial airflow obstruction as shown by a moderate to severe reduction in FEV₁ and PEF. Baseline theophylline concentrations for the 14 patients given salbutamol were all

Table 1 Baseline data (mean (SEM) values) of the 19 patients

Hospital days*	Age (y)	Weight (kg)	Height (cm)	FVC (l)	FEV ₁ (l)†	PEF (l min ⁻¹)	\dot{V}_E (l min ⁻¹)
INTRAVENOUS SALBUTAMOL							
2 (1)	46 (3)	64 (3)	156 (1)	1.55 (0.17)	1.01 (0.13) [39 (4)]	171 (18)	7.8 (0.5)
INHALED SALBUTAMOL							
2 (0)	39 (8)	61 (4)	156 (2)	1.76 (0.19)	1.06 (0.12) [39 (4)]	150 (13)	9.0 (0.9)
100% OXYGEN							
1 (0)	40 (8)	62 (7)	157 (2)	2.52 (1.7)	1.34 (0.25) [46 (7)]	192 (38)	8.8 (0.8)
Total (n = 19)							
2 (0)	42 (3)	63 (2)	156 (0.8)	1.87 (0.17)	1.11 (0.09) [41 (3)]	170 (13)	8.5 (0.4)

*Interval between admission and day of study.

†Values in square brackets are percentages of predicted values.

Conversion: 1 mm Hg \approx 0.133 kPa.

FVC—forced vital capacity; FEV₁—forced expiratory volume in one second; PEF—peak expiratory flow; \dot{V}_E —minute ventilation; HR—heart rate; QT—cardiac output; MSAP—mean systemic arterial pressure; Pao₂—arterial oxygen tension; Paco₂—arterial carbon dioxide tension; A-aPo₂—alveolar-arterial oxygen gradient; Vo₂—oxygen consumption; Vco₂—carbon dioxide production.

below the therapeutic range (mean (SD) 1.9 (0.5) (range 0–4.9) mg/l). Mean heart rate and mean systemic arterial pressure were within the normal range (table 1). \dot{Q}_T was slightly increased (6.08 (0.27) l/min, cardiac index 3.77 (0.18) l min⁻¹/m²). Mean \dot{V}_E was 8.5 (0.4) l/min and \dot{V}_{O_2} 258 (16) ml/min. Mean P_{aO_2} was low at 70.7 (2.9) mm Hg* and less than 75 mm Hg in all but three patients. Mean P_{aCO_2} was slightly reduced at 35.1 (0.9) mm Hg and was above 40 mm Hg in only one patient. The mean alveolar-arterial P_{O_2} difference ($A-aP_{O_2}$) was increased at 35.6 (3) mm Hg. The mean physiological dead space (Bohr) was also slightly increased at 37.5% (2%).

The \dot{V}_A/\dot{Q} distributions were characterised by either a broadly unimodal ($n = 10$) or a bimodal ($n = 9$) blood flow distribution with a substantial amount of perfusion associated with low \dot{V}_A/\dot{Q} units (11% (3%) with $\dot{V}_A/\dot{Q} < 0.1$, excluding shunt). There were large individual differences in the amount of perfusion of low \dot{V}_A/\dot{Q} areas (range 0–38%). High \dot{V}_A/\dot{Q} areas ($\dot{V}_A/\dot{Q} > 10$, excluding inert dead space—that is, areas with $\dot{V}_A/\dot{Q} > 100$) were not seen. Indices of dispersion of blood flow (log SD \dot{Q}) and ventilation (log SDV) were increased (1.18 (0.08) and 0.77 (0.03) respectively, normal range 0.3–0.6).¹⁰ These variables, which represent the second moment of pulmonary blood flow and alveolar ventilation distribution respectively, are measured on a natural log scale. There was no correlation between FEV₁ % predicted or absolute values of FEV₁ and log SD \dot{Q} ($r = -0.28$ and -0.30), indicating a lack of relationship between the degree of airflow obstruction and \dot{V}_A/\dot{Q} distribution. In contrast, P_{aO_2} and $A-aP_{O_2}$ values correlated closely with

log SDQ ($r = -0.84$ and $r = 0.83$). Examining each variable in table 1 by one way analysis variance showed no significant differences between the three groups.

EFFECTS OF INTRAVENOUS SALBUTAMOL: GROUP 1 (tables 3 and 4)

Airflow and haemodynamic measurements Individual data are presented in table 3. After 60 minutes of salbutamol infusion there was a substantial and significant increase in airflow (44% increase in FEV₁ from 1.01 to 1.42 l, $p < 0.005$). This effect was sustained at 90 minutes. There was a slight tendency for values to have returned towards initial values when measured 60 minutes after salbutamol had been discontinued. There was a similar improvement in PEF ($p < 0.01$). Heart rate had increased by 35% ($p < 0.005$) and cardiac output by 49% ($p < 0.005$) 60 minutes after the start of the infusion, and values were similar at 90 minutes. There was again a trend for values to return toward baseline after the infusion had been discontinued. Minor changes in mean systemic arterial pressure and ventilatory measurements were not statistically significant.

Blood gas tensions and \dot{V}_{O_2} P_{aO_2} was unchanged 60 and 90 minutes after the start of the salbutamol infusion and one hour after salbutamol had been withdrawn. P_{aCO_2} had fallen slightly at 60 and 90 minutes ($p < 0.05$), but was similar to baseline values after salbutamol had been stopped. The $A-aP_{O_2}$ did not change significantly at any time during the study. Oxygen consumption increased during the salbutamol infusion by 22% ($p < 0.01$).

\dot{V}_A/\dot{Q} distribution (fig 1) All patients had substantial

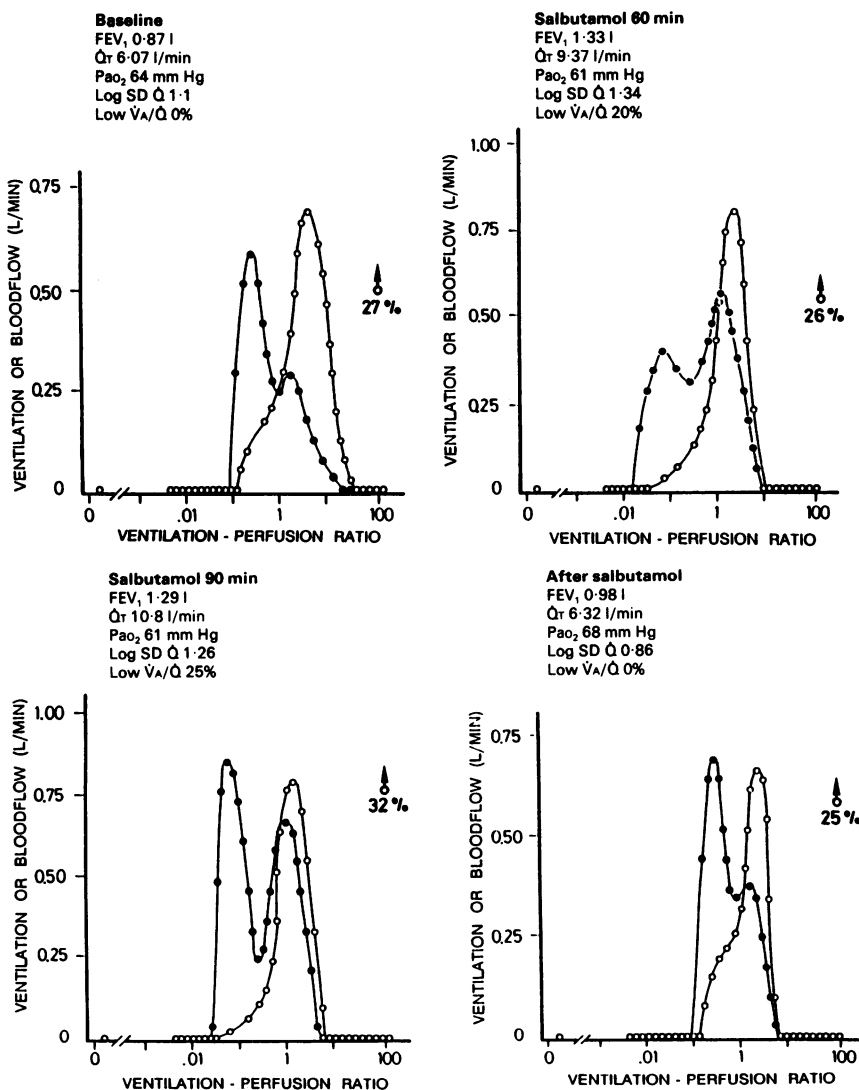
*1 mm Hg \approx 0.133 kPa.

HR (min ⁻¹)	\dot{Q}_T (l min ⁻¹)	MSAP (mm Hg)	P_{aO_2} (mm Hg)	P_{aCO_2} (mm Hg)	$A-aP_{O_2}$ (mm Hg)	\dot{V}_{O_2}	V_{CO_2}
						(ml/min)	
INTRAVENOUS SALBUTAMOL							
89 (3)	5.79 (0.27)	81 (5)	69.9 (4.2)	35.5 (1.2)	35.7 (4.9)	228 (19)	174 (11)
INHALED SALBUTAMOL							
92 (5)	5.97 (0.71)	100 (7)	66.5 (2.7)	33.0 (1.3)	42.1 (2.8)	294 (35)	210 (19)
100% OXYGEN							
86 (7)	6.68 (0.43)	84 (6)	77.0 (8.1)	36.9 (2.2)	27.4 (6.5)	256 (21)	224 (19)
Total (n = 19)							
89.1 (3)	6.08 (0.27)	88 (4)	70.7 (2.9)	35.1 (0.9)	35.6 (3)	258 (16)	200 (10)

Table 2 Baseline \dot{V}_A/\dot{Q} (mean (SD) values) data for the 19 patients

Shunt (%)	% \dot{Q}_T to low \dot{V}_A/\dot{Q} areas	Mean \dot{Q}	Log SD \dot{Q}^*	% \dot{V}_A to $\dot{V}_A/\dot{Q} > 100$	Mean \dot{V}	Log SD \dot{V}^*
INTRAVENOUS SALBUTAMOL						
0.4 (0.2)	7.5 (3.5)	0.60 (0.04)	1.07 (0.13)	25.2 (2.8)	1.56 (0.22)	0.77 (0.05)
INHALED SALBUTAMOL						
1.1 (1.0)	13.7 (5.3)	0.66 (0.14)	1.40 (0.09)	21.6 (3.6)	1.97 (0.21)	0.81 (0.06)
100% OXYGEN						
0.8 (0.7)	11.6 (5.4)	0.51 (0.10)	1.11 (0.17)	37.1 (8.2)	1.16 (0.19)	0.72 (0.06)
Total (n = 19)						
0.8 (0.4)	10.5 (2.6)	0.60 (0.05)	1.18 (0.08)	27.2 (2.9)	1.58 (0.14)	0.77 (0.03)

*Normal range 0.3-0.6.

 \dot{Q}_T —cardiac output; \dot{V}_A/\dot{Q} —ventilation-perfusion.

baseline \dot{V}_A/\dot{Q} inequality, and this clearly worsened during intravenous salbutamol administration. Log SDQ had increased from 1.07 to 1.29 at 60 minutes ($p < 0.02$) and to 1.33 at 90 minutes ($p < 0.02$), returning to baseline after the drug had been discontinued. Blood flow associated with areas of low \dot{V}_A/\dot{Q} doubled during the infusion ($p < 0.05$). Indices of the dispersion of ventilation distribution did not change.

EFFECTS OF INHALED SALBUTAMOL: GROUP 2 (tables 3 and 4)

Airflow and haemodynamic measurements Inhaled salbutamol caused FEV₁ to increase (by 43% after 300 μg salbutamol and by 56% after 600 μg ; $p < 0.01$); one hour after the last dose of salbutamol airflow remained increased ($p < 0.01$). These changes were not significantly different from those observed during the salbutamol infusion. Similar changes were evident with PEF ($p < 0.01$). In contrast to the intravenous study, there were no significant changes in heart rate, cardiac output, or mean systemic arterial pressures.

Blood gas tensions and $\dot{V}O_2$ PaO₂, PaCO₂, A-aPO₂, and $\dot{V}O_2$ values remained unchanged throughout the study. **\dot{V}_A/\dot{Q} distribution** \dot{V}_A/\dot{Q} inequality remained unchanged throughout the study as assessed by log SD Q and percentage of cardiac output to low \dot{V}_A/\dot{Q} units. At the end of the study ventilation distribution (log SD V) had improved significantly (by 19% from baseline, $p < 0.05$, table 4).

EFFECTS OF 100% OXYGEN (table 5, fig 2)

Mean airflow and haemodynamic measurements did not differ in the five patients between breathing room air and breathing 100% oxygen. PaO₂ and A-aPO₂ increased considerably (see table 5); mean PaCO₂ increased by 2 mm Hg. There was no significant shunt

while subjects were breathing 100% oxygen. Inert dead space showed a small but significant decrement. Dispersion indices of both blood flow (log SD Q) and ventilation (log SD V) increased significantly in all patients (from 1.11 to 1.44 and from 0.72 to 0.90), reflecting greater \dot{V}_A/\dot{Q} mismatching. There was an associated increase in blood flow to lung units with a low \dot{V}_A/\dot{Q} ratio (from 11.6% to 23.5% of cardiac output), which failed to reach significance ($p = 0.079$), probably because of the small number of patients and the high variability in this group. Patients who had more low \dot{V}_A/\dot{Q} areas in the initial study had the greatest change in \dot{V}_A/\dot{Q} mismatching in response to 100% oxygen.

Discussion

The multiple inert gas elimination technique estimates the degree of \dot{V}_A/\dot{Q} mismatching and provides a frequency distribution of lung units to allow the shape of this distribution to be determined. The log SD Q and log SD V are widely used overall descriptors of the amount of mismatch. These variables will provide a quantitative estimate of mismatching only when the \dot{V}_A/\dot{Q} distribution is unimodal and showing a logarithmically normal distribution. With other distributions it should be regarded as an index of abnormality only. In many patients with lung disease the most striking finding is the widening of the dispersion with or without the appearance of a true shunt (zero \dot{V}_A/\dot{Q}); in other disease states, however, bimodal or even trimodal \dot{V}_A/\dot{Q} distributions have been recovered. Although the existence and magnitude of such modes can generally be well defined, there are occasions when the inert gas elimination technique is limited to distinguishing unimodal from bimodal distributions unless linear programming is used.

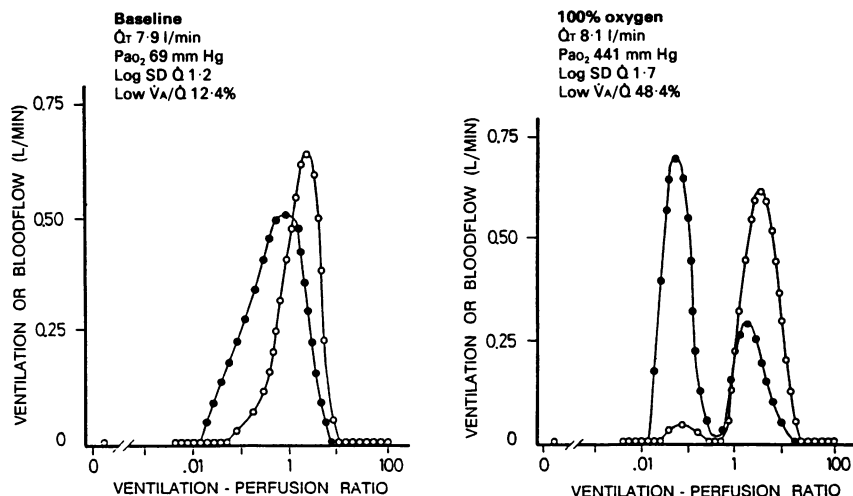


Fig 2 Broad and unimodal perfusion distribution in Patient 15 whilst breathing air—baseline, on left.

During the breathing of 100% oxygen (right) there is worsening of the \dot{V}_A/\dot{Q} distribution with a bimodal perfusion distribution and a considerable increase (48%) in perfusion associated with low \dot{V}_A/\dot{Q} areas. ○—○ Perfusion; ●—● ventilation.

Table 3 Changes in spirometric, haemodynamic, and conventional measurements of gas exchange during and after salbutamol administration

	Intravenous salbutamol							
	Baseline		60 min		90 min		After	
Spirometric data:								
\dot{V}_E (l min ⁻¹)	7.84	(0.5)	9.36	(0.8)	9.16	(0.7)	8.24	(0.7)
FEV ₁ (l)	1.01	(0.13)	1.42	(0.19)*	1.40	(0.16)*	1.25	(0.15)
FVC (l)	1.55	(0.17)	2.10	(0.21)*	2.07	(0.21)*	1.87	(0.19)
PEF (l min ⁻¹)	171	(18)	242	(34)*	245	(31)*	213	(28)
Haemodynamic data								
Heart rate (beats/min)	89	(3)	120	(3)*	116	(3)*	97	(3)
Cardiac output (l min ⁻¹)	5.8	(0.3)	8.6	(0.5)*	8.7	(0.5)*	6.4	(0.3)
Systemic arterial pressure (mm Hg)								
Systolic	120	(8.6)	116	(8.9)	110	(7.9)	116	(7.7)
Diastolic	64	(3.3)	59	(4.9)	57	(5.6)	64	(5.1)
Mean	81	(5.4)	74	(4.5)	72	(4.9)	77	(5.5)
Blood gas tensions								
Pao ₂	69.9	(4.2)	69.6	(4.7)	68.9	(5.2)	74.9	(5.7)
Paco ₂	35.5	(1.2)	33.8	(1.2)*	33.8	(1.2)*	34.2	(1.2)
A-aPO ₂	35.7	(5.0)	38.2	(5.8)	38.9	(5.4)	32.4	(6.6)
Other								
\dot{V}_{O_2} (ml min ⁻¹)	228	(20)	279	(30)*	269	(30)*	229	(23)
\dot{V}_{CO_2} (ml min ⁻¹)	174	(11)	192	(9)	180	(7)	171	(7)

*Significantly different from baseline ($p < 0.05$).

Conversion: 1 mm Hg \approx 0.133 kPa.

Abbreviations as in table 1.

\dot{V}_A/\dot{Q} DISTRIBUTION IN ACUTE SEVERE ASTHMA

In our study all 19 patients with acute severe asthma showed greater \dot{V}_A/\dot{Q} inequality than did young normal subjects. In each case blood flow dispersion ($\log SD \dot{Q}$) exceeded the 95% upper limit of normal. Shunt was minimal (0.8%) and ventilation dispersion ($\log SD \dot{V}$) only slightly increased above normal. These measurements show that a substantial amount of perfusion is associated with areas of lung with a low \dot{V}_A/\dot{Q} ratio. These measures of \dot{V}_A/\dot{Q} mismatching were accompanied by moderate to severe hypoxaemia in all but the four patients who had the lowest values of $\log SD \dot{Q}$.

Similar findings have been reported in adults with asthma. In six symptom free asthmatic subjects

Wagner *et al*⁶ found considerable \dot{V}_A/\dot{Q} inequality, characterised by a bimodal blood flow distribution, in which about 20% of the cardiac output was distributed to areas with a \dot{V}_A/\dot{Q} ratio lower than 0.1. Their six patients, however, also showed near normal values of FEV₁ and Pao₂. In contrast, Young *et al*,⁷ studying subjects with mild to moderate asthma under resting conditions, found unimodal blood flow distributions only. The different patterns of \dot{V}_A/\dot{Q} inequality in the two studies may be due to selection of patients, the different clinical conditions in which they were studied, the degree of airway obstruction, and previous drug treatment with bronchodilators.

Recently Wagner *et al*¹⁰ have shown that \dot{V}_A/\dot{Q} mismatch is present in most asthmatic patients with

Table 4 Changes in \dot{V}_A/\dot{Q} distributions (mean (SEM) values) after intravenous and inhaled salbutamol

	Intravenous salbutamol				Inhaled salbutamol			
	Baseline	60 min	90 min	After	Baseline	15 min	30 min	After
BLOOD FLOW DISTRIBUTION								
Shunt (%)	0.42 (0.20)	0.42 (0.23)	0.77 (0.71)	0.02 (0.03)	1.2 (1.02)	1.1 (0.89)	1.4 (1.37)	1.9 (1.52)
% Qr to low \dot{V}_A/\dot{Q}	7.5 (3.52)	14.6 (3.68)	17.7 (3.78)*	8.7 (3.46)	13.7 (5.3)	12.4 (2.9)	15.6 (4.4)	13.3 (2.8)
Mean \dot{Q}	0.60 (0.04)	0.44 (0.04)*	0.40 (0.03)*	0.56 (0.03)	0.66 (0.14)	0.74 (0.17)	0.61 (0.15)	0.71 (0.16)
Log SD \dot{Q}	1.07 (0.13)	1.29 (0.15)*	1.33 (0.14)*	1.10 (0.17)	1.40 (0.09)	1.42 (0.09)	1.46 (0.08)	1.32 (0.06)
VENTILATION DISTRIBUTION								
Mean \dot{V}	1.56 (0.22)	1.23 (0.15)	1.15 (0.14)	1.28 (0.16)	1.97 (0.21)	2.06 (0.31)	1.76 (0.25)	1.61 (0.25)
Log SD \dot{V}	0.77 (0.05)	0.72 (0.05)	0.70 (0.03)	0.67 (0.06)	0.81 (0.06)	0.75 (0.07)	0.76 (0.07)	0.66 (0.07)*

*Significantly different from baseline ($p < 0.05$).

Abbreviations as in table 2.

Inhaled salbutamol

Baseline	15 min	30 min	After
9.02 (0.9)	9.88 (1.6)	9.18 (1.2)	8.98 (1.1)
1.06 (0.12)	1.52 (0.2)*	1.65 (0.2)*	1.61 (0.17)*
1.76 (0.19)	2.43 (0.36)*	2.53 (0.3)*	2.52 (0.3)*
150 (13)	225 (25)*	249 (27)*	230 (23)*
92 (5)	92 (4)	95 (5)	91 (4)
6.0 (0.7)	6.3 (0.5)	6.2 (0.6)	5.8 (0.5)
138 (7)	139 (11)	133 (6.1)	135 (6.2)
73 (7)	69 (7)	64 (5.4)	67 (5.4)
100 (7)	95 (8)	89 (5.9)	92 (5.7)
66.5 (2.7)	68.0 (2.6)	68.1 (4.1)	72.0 (3.7)
33.0 (1.3)	32.0 (1.3)	31.9 (1.7)	31.5 (1.2)
42.1 (2.8)	41.8 (1.8)	42.2 (3.8)	38.9 (3.5)
294 (35)	258 (28)	258 (28)	249 (27)
210 (19)	215 (16)	206 (11)	205 (13)

stable chronic disease who have symptoms, and that this is due to the presence of low \dot{V}_A/\dot{Q} areas. Similarly, Roca *et al*¹¹ have shown severe \dot{V}_A/\dot{Q} mismatching in acute severe asthma in serial measurements made on patients in hospital. In contrast to Young *et al*,⁷ we saw a good correlation between arterial P_{O_2} and $A-aP_{O_2}$ and the dispersion index of blood flow, $\log SD \dot{Q}$.

Table 5 Haemodynamic, ventilatory, and conventional and inert gas data (mean (SEM) values) for five patients at baseline and while breathing 100% oxygen

	Baseline ($F_{IO_2} = 0.21$)	100% oxygen
FVC (l)	2.52 (0.45)	2.57 (0.49)
FEV ₁ (l)	1.34 (0.25)	1.22 (0.25)
PEF (l min ⁻¹)	193 (38)	182 (35)
\dot{V}_E (l min ⁻¹)	8.8 (0.8)	8.8 (0.7)
\dot{Q}_T (l min ⁻¹)	6.68 (0.43)	6.44 (0.5)
P_{aO_2} (mm Hg)	77 (8.1)	487 (40)*
P_{aCO_2} (mm Hg)	36.8 (2.2)	39.8 (2.5)*
$A-aP_{O_2}$ (mm Hg)	27.4 (6.5)	179.6 (36.5)*
\dot{V}_{O_2} (ml min ⁻¹)	256 (21)	
\dot{V}_{CO_2} (ml min ⁻¹)	224 (19)	
Shunt (%)	0.8 (0.7)	2.1 (1.9)
% \dot{Q}_T to low \dot{V}_A/\dot{Q}	11.6 (5.4)	23.5 (10.2)
Mean \dot{Q}	0.51 (0.10)	0.43 (0.13)
Log SD \dot{Q}	1.11 (0.17)	1.44 (0.15)*
% \dot{V}_A to $\dot{V}_A/\dot{Q} > 100$	37.1 (8.2)	33.8 (8.8)*
Mean \dot{V}	1.16 (0.19)	1.84 (0.42)*
Log SD \dot{V}	0.72 (0.06)	0.90 (0.12)*

*Significantly different from $F_{IO_2} = 0.21$ ($p < 0.05$, Wilcoxon's test).
Abbreviations as in tables 1 and 2.
Conversion: 1 mm Hg \approx 0.133 kPa.

 \dot{V}_A/\dot{Q} DISTRIBUTION AFTER SALBUTAMOL

Since the first description by Halmagyi and Cotes¹² of a fall in arterial oxygen saturation after aminophylline, many reports have shown a similar fall with different bronchodilating drugs.²⁶⁻²⁸ The fact that bronchodilating agents may affect gas exchange adversely in asthmatic patients despite its beneficial effect on bronchoconstriction has raised an interesting debate. Because non-specific beta agonists, such as isoprenaline, were thought to reduce P_{aO_2} through their beta₁ cardiovascular effects, it was suggested that more specific beta₂ agents, such as salbutamol, would not affect P_{aO_2} because they had less cardiovascular effect. On the other hand, the lack of an increase in cardiac output with a beta₂ selective drug would tend to maintain or worsen hypoxaemia if the drugs caused a deterioration in \dot{V}_A/\dot{Q} relationships.

Salbutamol, one of the most effective and selective beta₂ bronchodilators, also has some beta₁ activity, although not to the same extent as isoproterenol. Salbutamol is known to partially inhibit hypoxic pulmonary vasoconstriction, at least in dogs,²⁹ and hence, like other vasodilators, could cause a reduction in arterial P_{O_2} .³⁰⁻³² Previous studies of the effects of bronchodilators on \dot{V}_A/\dot{Q} inequality have reported different results. Wagner *et al*⁶ observed a transient deterioration both in \dot{V}_A/\dot{Q} matching and in P_{aO_2} despite a return to normal in maximal expiratory flow rates after inhalation of isoproterenol. In our study intravenous salbutamol caused further \dot{V}_A/\dot{Q} mis-

matching, a substantial increase in cardiac output, and an increase in oxygen consumption, the net effect of which was that P_{aO_2} was unaltered. In contrast, with inhaled salbutamol \dot{V}_A/\dot{Q} distribution was unchanged, and there were no changes in cardiac output, oxygen consumption, or P_{aO_2} . The differences in the effects on \dot{V}_A/\dot{Q} distributions of salbutamol when administered by the two different routes can be explained by the prominent cardiac and metabolic effects that occur with the higher plasma concentrations of salbutamol achieved with intravenous administration. There are insufficient data in our study to determine whether the increase in $\log SD \dot{Q}$ is due to an increase in cardiac output or is an additional vasodilator effect. In conclusion, both forms of administration of salbutamol improved airflow rates, and P_{aO_2} and $\log SD \dot{Q}$ were similar to initial values after either form of administration after discontinuation of intravenous treatment. These results are therefore consistent with the belief that \dot{V}_A/\dot{Q} mismatching in asthma is related to abnormal functioning of peripheral airways while airflow rates are essentially reflecting more central airways obstruction—hence the dissociation between spirometric measurements and gas exchange.¹¹ During the intravenous administration of salbutamol the remarkable finding was the considerable worsening of \dot{V}_A/\dot{Q} inequality, contrasting with the lack of \dot{V}_A/\dot{Q} changes with inhaled salbutamol.

CLINICAL IMPLICATIONS

From this study some clinical conclusions may be drawn. Firstly, the two routes of salbutamol administration have the same beneficial effect in relieving bronchial obstruction. Secondly, inhalation of salbutamol seems to be the better therapeutic approach because of the lack of deleterious effects on \dot{V}_A/\dot{Q} relationships. Although neither form of administration led to any substantial change in P_{aO_2} , when cardiac disease blunts the compensating rise in cardiac output intravenous salbutamol could probably aggravate pre-existing hypoxaemia, whereas with the inhaled route this would not be likely to occur. In addition, the lack of increase in oxygen consumption with inhaled salbutamol (which would allow $P\bar{v}O_2$ to increase, other things being equal) would tend also to offset any further decrease in P_{aO_2} .

RESPONSE TO 100% OXYGEN

Wagner *et al*⁶ found no change in \dot{V}_A/\dot{Q} relationships in four symptom free patients with asthma when they were breathing 100% oxygen. In contrast, a group of patients with symptoms studied by Corte and Young⁹ showed a deterioration in \dot{V}_A/\dot{Q} relationships when breathing 100% oxygen and in a few patients a small shunt appeared. In the present study, it seems clear that hypoxic pulmonary vasoconstriction had a major

role in determining ventilation-perfusion matching, as \dot{V}_A/\dot{Q} inequality worsened considerably after administration of 100% oxygen. Patients with symptoms probably have more hypoxic vasoconstriction than symptom free patients. We have shown similar results in patients with severe asthma requiring mechanical ventilation³³ and in those with chronic severe asthma.³⁴

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