Thorax 1994;**49**:1251-1258

Contribution of multiple inert gas elimination technique to pulmonary medicine · 5

Series editor: R Rodriguez-Roisin

Ventilation-perfusion relationships in acute respiratory failure

C Mélot

The optimum approach to therapy in acute respiratory failure resulting either from the adult respiratory distress syndrome (ARDS) or from severe bacterial pneumonia remains a challenge for the clinician. Such therapy is essentially supportive until the basic lung injury resolves. Effective respiratory support should be provided, taking into account the physiopathological process underlying the altered pulmonary gas exchange. A precise knowledge of the mechanisms of arterial hypoxaemia is therefore essential.

As mentioned in a previous review in this series,[1] standard blood gases and derived indices of pulmonary gas exchange such as the venous admixture (Qva/Qt) and the physiological dead space (V_D/V_T) do not permit clear differentiation between shunt and units with low ventilation-perfusion ratios ($\dot{V}_A/\dot{Q}$), as well as between regions having little (high $\dot{V}_A/\dot{Q}$) or no perfusion ($\dot{V}_A/\dot{Q}$ of infinity – that is, anatomical dead space), as the cause of altered gas exchange. The multiple inert gas elimination technique (MIGET)[2,3] takes advantage, not only in recovering the distribution of $\dot{V}_A/\dot{Q}$ ratios, but in controlling all the other factors determining arterial blood gases including shunt, $\dot{V}_A/\dot{Q}$ mismatch, limitation of diffusion of oxygen, and extrapulmonary factors including ventilation, cardiac output, oxygen uptake, haemoglobin, acid-base status, P_{50}, and blood temperature.

However, the MIGET – if it has been a milestone in the comprehensive approach of the mechanisms of altered gas exchange in acute respiratory failure – remains to be interpreted cautiously when both distributions of ventilation and perfusion are altered simultaneously by a pathological process or by pharmacological and therapeutic interventions. The only way to separate alteration in one of these distributions from the other is to perform a simultaneous determination by an independent method, either that of the ventilation distribution or of the perfusion distribution.[4] Depending on the model used by the MIGET that constrains all alveoli to have 1 of 50 $\dot{V}_A/\dot{Q}$ values evenly spaced on a logarithmic scale, the ventilation distribution and the perfusion distribution are linked together. In order to illustrate the limitation due to the interdependence between these two distributions in the recovered $\dot{V}_A/\dot{Q}$ distribution by the MIGET, $\dot{V}_A/\dot{Q}$ isopleths are plotted on a ventilation versus perfusion diagram (fig 1). For a high $\dot{V}_A/\dot{Q}$ ratio the slope of the isopleth is steep and a considerable effect on distribution of $\dot{V}_A/\dot{Q}$ could arise either from subtle changes in blood flow[4] or from huge changes in ventilation. Conversely, for a low $\dot{V}_A/\dot{Q}$ the slope is shallow and a change in $\dot{V}_A/\dot{Q}$ distribution could result from an easily detectable drop in perfusion or equally from a subtle reduction in ventilation (fig 1). In addition, acetone used by the MIGET to explore high $\dot{V}_A/\dot{Q}$ areas and dead space is highly soluble in water and consequently easily lost in the conducting airways[5] or in the tubing of the ventilator in

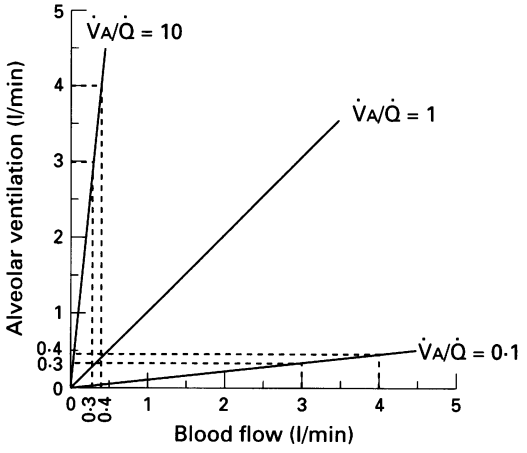

Figure 1 Alveolar ventilation ($\dot{V}_A$) versus blood flow ($\dot{Q}$) with $\dot{V}_A/\dot{Q}$ isopleths ($\dot{V}_A/\dot{Q}$ = 0.1, 1, and 10). $\dot{Q}$ and $\dot{V}_A$ are both arbitrarily fixed at 4 l/min. In a low $\dot{V}_A/\dot{Q}$ area (for example $\dot{V}_A/\dot{Q}$ = 0.1) the slope is flat and a change in $\dot{V}_A/\dot{Q}$ distribution could be the result of an easily measurable decrease in blood flow from 4 to 3 l/min (that is, 25% of cardiac output) or equally by a hardly detectable decrease in $\dot{V}_A$ from 0.4 to 0.3 l/min (that is, 2.5% of ventilation). Conversely, in a high $\dot{V}_A/\dot{Q}$ area (for example, $\dot{V}_A/\dot{Q}$ = 10) the slope is steep and a change in $\dot{V}_A/\dot{Q}$ distribution could be the result of an easily measurable decrease in alveolar ventilation from 4 to 3 l/min (that is, 25% of ventilation) or equally by a hardly detectable decrease in $\dot{Q}_T$ from 0.4 to 0.3 l/min (that is, 2.5% of cardiac ouput).

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patients undergoing mechanical ventilation. Changes in high $\dot{V}A/\dot{Q}$ areas must therefore be interpreted cautiously. Nevertheless, despite these limitations the MIGET is now considered as a classically reliable technique for the measurement of distribution of $\dot{V}A/\dot{Q}$ ratios at bedside in an intensive care setting.

Adult respiratory distress syndrome (ARDS)

Although ARDS has been recognised since the first description by Ashbaugh *et al*[6] in 1967 as a cause of acute respiratory failure characterised by hypoxaemia, the underlying aberrations in gas exchange and their alteration by positive end expiratory pressure (PEEP) or by pharmacological interventions has been poorly defined until studies using the MIGET.

MECHANISMS OF HYPOXAEMIA

The physiological hallmark of ARDS is severe hypoxaemia refractory to high concentrations of inspired oxygen. The pathological basis of the hypoxaemia has been shown to be alveolar flooding. The mechanisms of the hypoxaemia have been variously ascribed, before the MIGET studies, to right-to-left shunt,[7] $\dot{V}A/\dot{Q}$ inequality,[8] and impairment of diffusion.[9] Moreover, interpretations of altered blood gases in such patients is complicated by concomitant physiological stresses on gas exchange, such as changing cardiac output, anaemia, and acid-base disturbances.

The study by Dantzker *et al* in 1979,[10] subsequently confirmed by many others,[11-18] was a seminal paper that elucidated with the MIGET the mechanisms of arterial hypoxaemia in patients with ARDS. In 16 patients on mechanical ventilation, eight of whom had had no PEEP, all the patients had increased shunt – that is, perfusion to unventilated lung – from 18% to 68% of the cardiac output (fig 2A). Besides shunt, seven patients had low $\dot{V}A/\dot{Q}$ units (fig 2B). All these abnormal $\dot{V}A/\dot{Q}$ units received 48% of blood flow. The remaining 52% of blood flow perfused lung units with normal or increased $\dot{V}A/\dot{Q}$ ratios representing effective gas exchanging units. The presence of large intrapulmonary shunt explained the profound hypoxaemia of ARDS poorly responsive to high inspiratory concentrations of oxygen. The presence of a mode with low $\dot{V}A/\dot{Q}$ units in half of the patients explained the increase in venous admixture with decreasing inspired fractional concentration of oxygen (F_{IO_2}) documented previously by Lamy *et al* in 28 of 45 patients with ARDS.[19] The close agreement between measured arterial P_{O_2} and predicted arterial P_{O_2} seen in these patients argued against a failure of alveolar-end capillary equilibrium and ruled out any significant diffusion impairment in ARDS.

EFFECTS OF ALTERATION OF CARDIAC OUTPUT

Several studies, both in humans and in animal models, have shown that a change in cardiac output resulted in a parallel change in intrapulmonary shunt.[11 20-23] Several mechanisms have been proposed to explain the observed increase in shunt with the increase in cardiac output: (a) shortened transit time of the erythrocytes at a high cardiac output with incomplete equilibrium between alveolar P_{O_2} and end capillary P_{O_2} in these regions;[24] (b) an increased mixed venous P_{O_2} at a higher cardiac output with reduced hypoxic pulmonary vasoconstriction and a redistribution of blood flow preferentially to shunt areas;[20 25 26] (c) an increased amount of oedema in regions of lung injury at a higher cardiac output.[27]

The effect of changing cardiac output on intrapulmonary shunt was studied by Lynch *et al*[21] in a canine model of pulmonary oedema induced by oleic acid. Cardiac output was alternately depressed and augmented using either pharmacological agents or mechanical alteration to venous return. Changes in cardiac

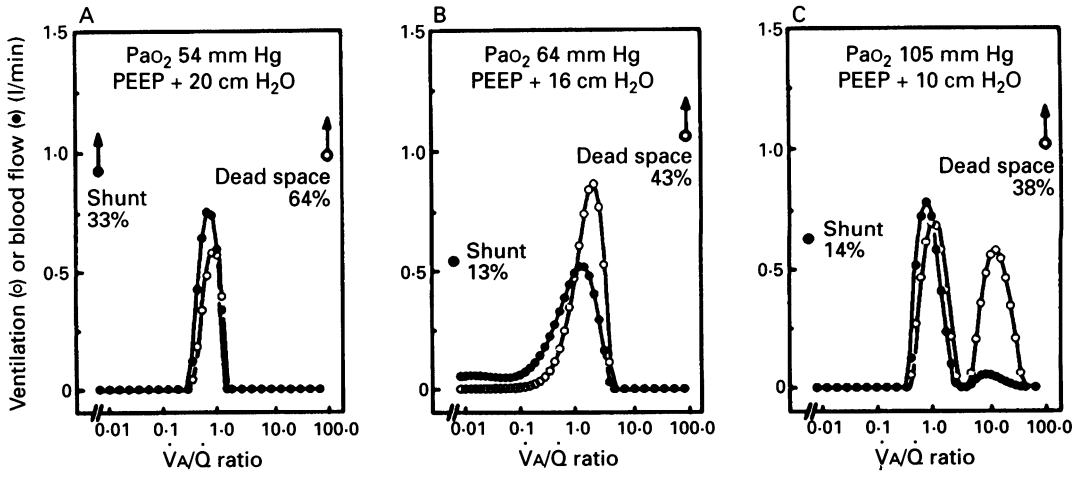

Figure 2 Three main patterns of $\dot{V}A/\dot{Q}$ distributions measured using the MIGET in patients with ARDS intubated and mechanically ventilated with PEEP. (A) A unimodal normal mode centred on $\dot{V}A/\dot{Q}$ = 1 with an increase in shunt and in dead space. (B) A low $\dot{V}A/\dot{Q}$ mode in addition to the normal mode with an increase in shunt and in dead space. (C) A normal $\dot{V}A/\dot{Q}$ mode with a high $\dot{V}A/\dot{Q}$ mode with an increase in shunt and in dead space. Pa_{O_2} = arterial P_{O_2}; PEEP = positive end expiratory pressure. Redrawn from references 13 and 14.

output were not associated with change in the shape of the $\dot{V}A/\dot{Q}$ distributions but there was a significant linear correlation between the level of cardiac output and the shunt fraction. The shunt fraction also varied directly with the mixed venous P_{O_2}. Breen *et al*,[27] comparing oxygen and inert gas exchange, concluded that incomplete alveolar-end capillary equilibrium for oxygen contributed very little to any increase in pulmonary shunt with cardiac output in an animal model of pulmonary oedema. They hypothesised that cardiac output increased shunt by increasing oedema or haematocrit in oedematous lung regions.[27]

As in animals with experimentally induced diffuse lung disease, alterations of cardiac output in patients with ARDS have been shown to cause similar adjustments for shunt. This has been demonstrated when cardiac output was varied by mechanical means with extracorporeal membrane oxygenation,[23] by blood volume expansion,[22] and by pharmacological agents.[22] The MIGET studies have shown that, when cardiac output is altered either by mechanical[11] or by pharmacological means,[13 16 17] the shape of the $\dot{V}A/\dot{Q}$ distributions did not change but shunt increased with cardiac output. Sandoval *et al*[25] suggested that the increase in shunt, measured by the Berggren method,[28] resulted from an increase in mixed venous P_{O_2} rather than an increase in cardiac output itself, suggesting an inhibition of hypoxic pulmonary vasoconstriction in unventilated lung regions.[29] On the contrary, studies using the MIGET provided evidence that intrapulmonary shunt increased with cardiac output even in the absence of changes in mixed venous P_{O_2} (table 1).[13 16]

Moreover, a recent animal study by Domino *et al*[30] using the MIGET in a lung lobe model of pulmonary oedema showed that hypoxic pulmonary vasoconstriction was attenuated in the injured lobe, tempering the role of hypoxic pulmonary vasoconstriction in the observed changes in shunt.

EFFECTS OF PEEP

The effects of PEEP on $\dot{V}A/\dot{Q}$ distribution mainly result from two mechanisms: the effects on shunt and the effects on physiological dead space.

Table 1 Effects of vasodilators and a vasoconstrictor on pulmonary vascular tone and gas exchange in patients with ARDS

	Pap	*QT*	*Pa_{O_2}*	*$P\bar{v}_{O_2}$*	*Shunt*	*MIGET studies (Reference no)*
Vasodilators:						
Diltiazem	↘	=	↘	=	↗	14
Sodium nitroprusside	↘	=	↘	=	↗	15
Ketanserin	↘	=	=	=	=	15
Nitroglycerin	↘	=	↘	=	↗	16
Prostaglandin E_1	↘	↗	↘	=	↗	16
	↘	↗	↘	=	↗	13
Prostacyclin (intravenous)	↘	↗	=	↗	↗	17
	↘	↗	↘	=	↗	52
Prostacyclin (aerosolised)	↘	=	↗	?	↘	53
Nitric oxide	↘	=	↗	=	↘	52
Vasoconstrictor:						
Almitrine	↗	=	↗	↗	↘	54

Pap = pulmonary artery mean pressure; QT = cardiac output; Pa_{O_2} = arterial P_{O_2}; $P\bar{v}_{O_2}$ = mixed venous P_{O_2}; shunt = inert gas shunt; ↗ = increased; ↘ = decreased; = = no change.

Effects on physiological dead space

The physiological VDVT calculated from the arterial and mixed expired partial pressures of carbon dioxide is raised in patients with ARDS.[19] Low levels of PEEP reduce the VDVT in these patients but higher levels consistently increase it.[31] Two mechanisms were demonstrated by studies using the MIGET: (a) increase in anatomical dead space by distension; (b) derecruitment of some lung units creating high $\dot{V}A/\dot{Q}$ or dead space units ($\dot{V}A/\dot{Q}$ of infinity).

The first study in which the MIGET was used to analyse the effect of PEEP on $\dot{V}A/\dot{Q}$ distributions was by Dueck *et al*[32] in dogs with normal or oedematous lungs. Increasing PEEP caused progressive depression of cardiac output associated with an increase in ventilation to both high $\dot{V}A/\dot{Q}$ and unperfused regions. However, at PEEP levels higher than 10 cm H_2O, retention of carbon dioxide developed except in the most severely affected dogs with highest shunt levels. In these there were fewer high $\dot{V}A/\dot{Q}$ areas and a further reduction in shunt resulted in a fall in arterial P_{CO_2}. Thus, the changes in arterial P_{CO_2} with increasing PEEP, which differ in moderately and severely affected animals, can be explained rationally with the use of the MIGET. Similarly, Hedenstierna *et al*[4] showed that, in the normal dog lung, PEEP caused a high $\dot{V}A/\dot{Q}$ mode with carbon dioxide retention. Moreover, these authors observed a redistribution of pulmonary blood flow with PEEP by measuring blood flow distribution using an isotopic technique. The study by Coffey *et al*[33] elucidated the effect of PEEP on physiological dead space in dogs with oleic acid-induced pulmonary oedema. Physiological dead space can be influenced by changes in anatomical dead space, $\dot{V}A/\dot{Q}$ heterogeneity, shunt, and the Haldane effect. Physiological dead space decreased with 5 and 10 cm H_2O PEEP but increased progressively at higher PEEP levels as reported earlier by Suter *et al*.[31] The decrease in physiological dead space at 5 or 10 cm H_2O PEEP was due to reductions in shunt and mid range $\dot{V}A/\dot{Q}$ heterogeneity. The increase in physiological dead space that occurred with higher PEEP levels was due to increased ventilation to high $\dot{V}A/\dot{Q}$ regions and a larger anatomical dead space. The Haldane effect magnified the shunt component of dead space (as the low oxygen saturation of shunted blood allows it to carry more carbon dioxide to the pulmonary vein, increasing the Pa_{CO_2}), but reduced the influence of mid range $\dot{V}A/\dot{Q}$ heterogeneity.[33]

Patients with ARDS have a large amount of ventilation distributed to unperfused or poorly perfused regions.[10-12 18] In a study by Ralph *et al*[18] arterial P_{CO_2} did not change during PEEP, except for a small increase at the highest PEEP levels. Although the inert gas dead space and ventilation to high $\dot{V}A/\dot{Q}$ regions did not show consistent changes, individual patients did show the appearance of a high $\dot{V}A/\dot{Q}$ mode with increasing PEEP (fig 2C),[10] a response similar to that observed in dogs with oleic acid lung injury.[32 33] In patients with ARDS a lesser reduction in blood flow by PEEP, due to thera-

peutic intervention attempting to maintain cardiac output, could be the reason for differences between clinical studies[10,12,18] and controlled animal studies.[32,33] Indeed, when cardiac output was kept constant during PEEP, a high $\dot{V}A/\dot{Q}$ mode did not develop and dead space increased only by 5%.[12]

Effects on intrapulmonary shunt

Most patients showed improvement in arterial Po_2 with PEEP which mainly resulted from a decrease in the intrapulmonary shunt.[10,18] At least two different mechanisms have been proposed to explain the reduction in shunt induced by PEEP: (a) alveolar re-expansion because of the increase in functional residual capacity (FRC) above closing volume,[34,35] and (b) decreased perfusion to unventilated lung areas due to a decrease in cardiac output with PEEP (vascular derecruitment).[11]

Dantzker *et al*[10] studied the effect of incremental increases in PEEP to 12 patients with ARDS on the $\dot{V}A/\dot{Q}$ distributions and showed that PEEP acts by reducing the proportion of shunt units that are converted in units with normal $\dot{V}A/\dot{Q}$ by an "on-off" phenomenon, indicating that PEEP allows the recruitment of non-functional gas exchanging units. As already discussed, a fall in cardiac output results in a parallel decrease in intrapulmonary shunt. Thus, it has been suggested that some of the change observed in the shunt when PEEP is applied may be a result of the drop in cardiac output.[11] However, Matamis *et al*[12] showed that maintenance of cardiac output by dopamine infusion during PEEP ventilation did not prevent the expected fall in shunt. The beneficial effect of PEEP on shunt at constant flow was explained by redistribution of blood flow from shunt units to normal units, resulting from alveolar re-expansion rather than reduction in cardiac output. These results highlight interpretations provided by the MIGET in such a complicated setting in which alterations of cardiac output by mechanical means were corrected by pharmacological agents.

EFFECTS OF BREATHING 100% OXYGEN

Another advantage of the MIGET is that it allows the investigator to study the effects of oxygen breathing on the distribution of $\dot{V}A/\dot{Q}$ ratios. It has been suggested that inhalation of oxygen increases the quantity of unventilated lung regions in normal subjects[36] and in patients with ARDS.[37] The $\dot{V}A/\dot{Q}$ measurements showed that, in acute respiratory failure, units with low $\dot{V}A/\dot{Q}$ ratios are converted into shunt.[37] The mechanism for this has been related to absorption atelectasis.[38] Another possible mechanism has been the inhibition of hypoxic pulmonary vasoconstriction in shunt units due to an increase in mixed venous Po_2.[29]

In patients with acute respiratory failure Lemaire *et al*[39] found no difference between intrapulmonary shunt measured by Berggren's method and that of the MIGET. The apparent stability of these alveoli with low $\dot{V}A/\dot{Q}$ during ventilation with oxygen makes it more likely that they represented fluid-filled alveoli whose volumes were sufficiently increased at the peak of inspiration to permit some gas transfer.[10,39] Another explanation could be that the large rise in alveolar Po_2 in the low $\dot{V}A/\dot{Q}$ units (less than about 0·1) causes a large increase in oxygen flow into the blood, and this might be sufficiently large to exceed the rate of delivery of inspired gas. Under these conditions such units could not eliminate gas and would appear as unventilated by the MIGET. More recently Santos *et al*[40] showed that, in patients with acute respiratory failure, ventilation with 100% oxygen for one hour increased shunt by 30%. More interestingly, they also showed that shunt remained elevated one hour after returning to the original FIo_2 (below 0·4). The amount of blood flow to low $\dot{V}A/\dot{Q}$ units did not vary during 100% oxygen, suggesting that increase in shunt was more from absorption atelectasis than from a release of hypoxic pulmonary vasoconstriction.

EFFECTS OF BODY POSITION, DIFFERENTIAL VENTILATION, AND SELECTIVE PEEP

The large intrapulmonary shunt found in patients with ARDS requires an increased FIo_2 and PEEP to minimise hypoxaemia. Both of these interventions are associated with well recognised complications (oxygen toxicity to the lung, barotrauma). Some studies showed that turning patients with ARDS from the supine to the prone position improved arterial oxygenation.[41,42] Langer *et al*[43] described 12 patients with acute respiratory failure in whom the prone position caused variable effects on gas exchange. Recently, Gattinoni *et al*[44] conducted a prospective study of the effect of a supine to prone change using computed tomographic (CT) scanning of the lungs, and also measured gas exchange in 10 patients with acute respiratory failure. Whilst changes in the location of CT scan densities were observed, the average density was not altered and no significant changes were noted in gas exchange. However, large improvements in arterial Po_2 and in intrapulmonary shunt were observed in two patients. Albert *et al*[45] investigated this phenomenon using the MIGET in an animal model with acute lung injury induced by oleic acid. They showed that the prone position selectively decreased intrapulmonary shunt and improved arterial Po_2. Thus, the prone position may be useful as an additional modality to improve arterial oxygenation in some patients with ARDS.

In ARDS the matching of ventilation and perfusion in each lung can be improved by applying differential ventilation with selective PEEP with the patient lying in a lateral position. The lowered FRC in patients with acute respiratory failure may compromise ventilation of dependent lung regions whilst the fractional perfusion to these regions is increased. PEEP cannot restore the balance between ventilation and perfusion to normal, but this can be satisfied further by delivering less gas to non-dependent and more to dependent lung re-

gions. In practice this can be accomplished by placing the patient in the lateral position, ventilating each lung separately in proportion to its perfusion (differential ventilation), and applying PEEP solely to the dependent lung to ensure the distribution of gas to the lower regions of that lung (selective PEEP). By this means an improved $\dot{V}A/\dot{Q}$ ratio within separately ventilated lungs can be obtained.[46–49] Interestingly, differential ventilation and selective PEEP have been used in patients with bilateral, diffuse lung damage.[46–49] MIGET studies are scarce in this setting but Klingstedt *et al*[50] showed that, in patients without acute lung disease, differential ventilation and selective PEEP in the lateral position improved $\dot{V}A/\dot{Q}$ matching with a more even overall $\dot{V}A/\dot{Q}$ distribution in both lungs and a decreased perfusion to shunt and low $\dot{V}A/\dot{Q}$ regions.

EFFECTS OF PHARMACOLOGICAL ALTERATION IN PULMONARY VASCULAR TONE (table 1)

The MIGET has been used in patients with ARDS where reduction of pulmonary vascular tone and pulmonary hypertension was obtained by pharmacological means. Diltiazem, a calcium channel blocking agent, reduced pulmonary vascular tone.[14] A reduction in pulmonary vascular tone was obtained without changing either the cardiac output or mixed venous P_{O_2}, with a deterioration in arterial oxygenation. The inert gas data showed a significant increase in intrapulmonary shunt. Similar results were reported with sodium nitroprusside[15] and nitroglycerine.[16] The MIGET measured an increase in blood flow to hypoxic units (with zero and low $\dot{V}A/\dot{Q}$ ratios), suggesting a change in gas exchange by inhibition of hypoxic pulmonary vasoconstriction.[51] Ketanserin (an antagonist of serotonin receptors), a pulmonary vasodilator devoid of any effect on hypoxic pulmonary vasoconstriction, reduced pulmonary artery pressure in patients with ARDS without deterioration in gas exchange.[15]

Prostaglandin E_1 (PGE_1), a potent short acting pulmonary vasodilating prostaglandin, caused gas exchange to deteriorate in patients with ARDS due to a combination of reduction in pulmonary vascular tone and increase in cardiac output, without changes in mixed venous P_{O_2}.[13,16] $\dot{V}A/\dot{Q}$ distributions showed an increase in intrapulmonary shunt and a large fall in arterial P_{O_2} in some patients (fig 3). To study the mechanism by which PGE_1 increased true shunt and allowed gas exchange to worsen the lung model used by the MIGET has been manipulated so that cardiac output remained constant to quantitate the effect of the reduction in pulmonary vascular tone.[13] Deleterious effects of PGE_1 on gas exchange mainly resulted from the reduction in pulmonary vascular tone (table 2) and was present with no change in mixed venous P_{O_2}. These results must be compared with those obtained with intravenous prostacyclin, a pulmonary vasodilating prostaglandin which caused worsening $\dot{V}A/\dot{Q}$ distribution in ARDS but not the arterial P_{O_2} when mixed venous P_{O_2} increased significantly.[17,52]

Improvement in gas exchange with reduction in pulmonary hypertension has recently been reported with aerosolised prostacyclin in three patients with severe ARDS.[53] The MIGET showed that the beneficial effect on gas exchange resulted from a redistribution of blood flow from shunt areas to regions of normal $\dot{V}A/\dot{Q}$ ratios due to selective pulmonary vasodilation in well ventilated areas with aerosolised prostacyclin.

Reyes *et al*[54] reported beneficial effects on gas exchange of transient perfusion of almitrine, a peripheral chemoreceptor agonist with direct vasoactive properties on pulmonary vessels. There was an improvement in $\dot{V}A/\dot{Q}$ distributions with a reduction in shunt and an improvement in arterial P_{O_2} and mixed venous P_{O_2} at the price of a slight increase in pulmonary hypertension. They suggested that almitrine could enhance hypoxic pulmonary vasoconstriction, diverting blood from shunt units to those with normal $\dot{V}A/\dot{Q}$ ratios.

An exciting further development has been the identification of nitric oxide as an endothelium derived relaxing factor[55] and the recognition

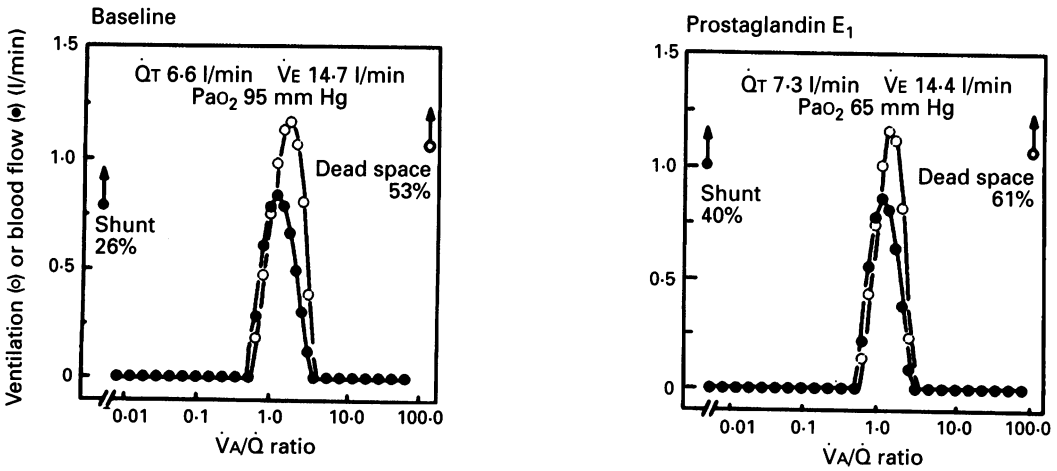

Figure 3 Effect of prostaglandin E_1 (PGE_1) 0.04 μg/kg/min on $\dot{V}A/\dot{Q}$ distribution measured using the MIGET in a patient with ARDS intubated and mechanically ventilated with PEEP + 10 cm H_2O. PGE_1 increased cardiac output from 6.6 l/min to 7.3 l/min and shunt from 26% to 40%. PaO_2 decreased from 95 mmHg to 65 mmHg. $\dot{Q}T$ = cardiac output, $\dot{V}E$ = minute ventilation; PaO_2 = arterial P_{O_2}. Redrawn from reference 13.

Table 2 Theoretical effect on predicted arterial P_{O_2}, calculated from the measured $\dot{V}_A/\dot{Q}$ distributions, of increased cardiac output ($\dot{Q}_T$) and reduced pulmonary vascular tone by PGE_1 in six patients with ARDS. Results are expressed as mean (SE)

		PGE_1	
	Baseline	*Unchanged $\dot{Q}_T$*	*Increased $\dot{Q}_T$*
Cardiac index ($\dot{Q}_T$) (l/min/m²)	3·23 (0·26)	3·23 (0.26)	3·86 (0·33)*
Pulmonary artery pressure (mmHg)	29 (2)	24 (2)*	24 (2)*
Predicted arterial P_{O_2} (mmHg)	97·2 (7·8)	77·8 (8·3)*	75·7 (7·6)*
Shunt (% of $\dot{Q}_T$)	20·8 (4·1)	28·4 (5·0)*	31·8 (5·4)*
Mixed venous P_{O_2} (mmHg)	36 (2)	38 (3)	38 (3)

* $p < 0.01$ from baseline value (calculated with data from reference 13).

of a potential role for this agent in matching ventilation and perfusion in acute lung injury. Investigation in vivo is difficult because nitric oxide is the most rapidly binding ligand of haemoglobin. Since nitric oxide is inactivated by haemoglobin, its vasorelaxant effects are restricted to the vascular smooth muscle underlying the endothelium. This problem can be overcome if nitric oxide is inhaled, thereby reaching directly the pulmonary arteriolar smooth muscles. Rossaint *et al* showed that inhalation of nitric oxide causes selective pulmonary vasodilation in ventilated lung regions and improves $\dot{V}_A/\dot{Q}$ distributions by diverting blood flow from shunt areas to those of normal $\dot{V}_A/\dot{Q}$ mode.[52] In patients with ARDS the MIGET provided a clear understanding of the mechanism of improved gas exchange and arterial P_{O_2}, and demonstrated the selective vasodilation induced by inhaled nitric oxide in ventilated areas with normal $\dot{V}_A/\dot{Q}$ ratios.

EFFECTS OF MIXED VENOUS P_{O_2} ON ARTERIAL OXYGENATION

As discussed above, the effect of the association between cardiac output and shunt on arterial oxygenation will depend on the effect that alterations in cardiac output have on mixed venous P_{O_2}. In some of the studies in patients with ARDS the expected increases in the mixed venous P_{O_2} with increasing cardiac output (or decreases with decreasing cardiac output) resulted in no change in arterial P_{O_2} as shunt varied (table 1).[17] However, mixed venous P_{O_2} often failed to behave as expected, sometimes remaining unchanged as cardiac output was altered and occasionally even decreasing as cardiac output increased. This was ascribed to a causal relationship between oxygen delivery ($\dot{D}_{O_2}$) and peripheral oxygen consumption ($\dot{V}_{O_2}$). Several studies have identified an abnormal relationship between $\dot{D}_{O_2}$ and $\dot{V}_{O_2}$ in patients with ARDS and sepsis.[56–61] At rest $\dot{V}_{O_2}$ is normally independent of $\dot{D}_{O_2}$ provided the latter is maintained above a critical level, but oxygen consumption becomes delivery dependent above this threshold in ARDS.[56–61] The mechanisms underlying this observation are poorly understood, but it has been interpreted as evidence of covert tissue hypoxia and has been associated with a high mortality.[58] An increased plasma lactate concentation, which may reflect an imbalance between metabolic requirements and $\dot{D}_{O_2}$, could be a useful marker of oxygen uptake supply dependency.[59 60 62] Under these circumstances changes in shunt induced by cardiac output would have significant effects on arterial oxygenation.

Severe pneumonia

Patients with pneumonia frequently have arterial hypoxaemia. Several factors including increased whole body oxygen uptake,[63] increased intrapulmonary oxygen uptake,[64] increased intrapulmonary shunt,[65] $\dot{V}_A/\dot{Q}$ mismatching,[65] increased postcapillary shunt (that is, increased bronchial blood flow),[63 66] and/or alveolar-end capillary oxygen diffusion limitation[66] have been implicated as potential mechanisms of arterial hypoxaemia. The role of these factors has been clarified by studies using the MIGET.

MECHANISMS OF HYPOXAEMIA

Wagner *et al*,[67] in a canine model of pneumococcal lobar pneumonia, showed that pure shunt was present during the first 48 hours of infection, whereas after two days the shunt resolved and perfusion was mainly distributed to alveoli with low $\dot{V}_A/\dot{Q}$ ratios.

The study by Lampron *et al*[68] demonstrated that the most common pattern of $\dot{V}_A/\dot{Q}$ mismatching in patients with bacterial pneumonia severe enough to require mechanical ventilation was a combination of intrapulmonary shunt and increased perfusion to units with low $\dot{V}_A/\dot{Q}$ ratios. The study by Gea *et al*[69] confirmed these results in patients mechanically ventilated and extended them to spontaneously breathing patients with less severe pneumonia. No differences between the predicted and measured arterial oxygen tension were observed in the MIGET studies, indicating no role for additional factors such as intrapulmonary oxygen consumption, oxygen diffusion limitation, or postcapillary shunt due to increased bronchial blood flow.

EFFECTS OF BREATHING 100% OXYGEN

Reports of the effects of 100% oxygen breathing on $\dot{V}_A/\dot{Q}$ relationships in patients with pneumonia are conflicting. It had been reported that shunt may remain unchanged or may even increase when the patient is breathing 100% oxygen. Since a substantial proportion of pulmonary blood flow is diverted to low $\dot{V}_A/\dot{Q}$ units, the development of absorption atelectasis is expected so that shunt should increase in these patients.

Lampron *et al*[68] were unable to find an increase in intrapulmonary shunt with the MIGET in patients with severe pneumonia during ventilation with 100% oxygen. Similar results were also reported by Gea *et al*[69] who showed a widening of the blood flow distribution, suggesting a reduction in hypoxic pulmonary vasoconstriction. However, neither study showed an increase in shunt despite the fact that mixed venous P_{O_2} increased, suggesting only minimal hypoxic pulmonary vasoconstriction in human bacterial pneumonia.

EFFECTS OF BODY POSITION

In 1981 Fishman[70] proposed the lateral position for patients with single lung injuries. Several investigators reported a better oxygenation in patients in the lateral position with the good lung dependent.[71-73] The likely mechanism of improved gas exchange may be better $\dot{V}_A/\dot{Q}$ matching; perfusion being gravity dependent is directed towards the good lung, while only a small fraction of pulmonary blood flow but a greater portion of tidal volume is distributed to the non-dependent lung. Gillespie *et al*[74] reported four patients with unilateral disease who improved their arterial oxygenation when the good lung was dependent. The MIGET has confirmed that positional changes cause reduction in shunt or in areas with low $\dot{V}A/\dot{Q}$ ratios or in both.[74]

Conclusions

The MIGET has made it possible to differentiate changes in the arterial Po_2 caused by alterations in the gas exchanging function of the lung from those due to changes in the mixed venous Po_2. It has also played a part in assessing the effects of alterations in cardiac output, pulmonary vascular tone, or both on arterial blood gas tensions in patients with acute respiratory failure.

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