Gas exchange abnormalities in pulmonary vascular and cardiac disease

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Pulmonary vascular disease is generally defined as an anatomical narrowing of the pulmonary vasculature, especially the muscular arteries, either from lung disease or as a primary disease of the pulmonary vessels. In a broader sense it can also be defined as a change in the overall regional pulmonary vascular impedance stemming from anomalies in the lumen or the walls of pulmonary vessels. We will therefore review different clinical situations causing pulmonary vascular disease where gas exchange can be evaluated using the multiple inert gas elimination technique (MIGET). Pulmonary embolism (PE), unilateral pulmonary artery occlusion, and polycythemia are first discussed, with special reference to the effect of haemodilution. We then summarise the response to structural abnormalities in the pulmonary arteries in patients with primary pulmonary hypertension or cirrhosis of the liver. Cardiac failure occurring in these conditions tends to accentuate the disturbances in gas exchange as a result of the interplay between intrapulmonary and extrapulmonary factors which determine \( P_{aO_2} \) values. However, most primary cardiac diseases occur in patients with previously normal lungs. We therefore conclude with a separate discussion of the adaptation of pulmonary gas exchange processes to a change in cardiac output in the absence of any associated pulmonary abnormality.

Diseases with intravascular abnormalities

PULMONARY EMBOLISM

Consequences of heart-lung interactions

When clots lodge in one or more pulmonary arteries, the pathophysiological consequences will clearly depend on the duration and extent of the acute interruption of blood flow in the pulmonary vascular bed. The haemodynamic consequences are afforded by two principal factors: (1) the increase in pulmonary vascular resistance, and (2) the previous cardiovascular status of the patient. In patients without cardiovascular disease the thin walled right ventricle may fail under high workload and cardiac output (CO) may drop. In many other clinical situations, however, CO remains in the normal range or even rises. In the lung, apart from the continuation of the ventilation of non-perfused areas, embolism may lead to: (1) some degree of bronchoconstriction and atelectasis, with a concomitant redistribution of alveolar ventilation, and (2) enhanced pulmonary vasoreactivity, possibly due to hypoxaemia, release of humoral mediators by clot, or a distension reflex in the obstructed vessels. Moreover, in spontaneously breathing patients ventilatory drive increases. In many cases hypoxaemia is the only obvious manifestation of the complex interaction between the effects of embolism and the adaptive responses of the heart and lungs. The relative involvement of factors such as intrapulmonary shunt, ventilation-perfusion (VA/Q) inequalities, and diffusion limitation to oxygen in individual cases has only recently begun to be clarified. This is largely due to the use of the MIGET in patients with angiographically demonstrated pulmonary embolism. Although only a few studies have been carried out with the inert gas method, there is a parallel between the pattern of gas exchange abnormalities and the course of the disease.

Early phase:

(1) Ventilation-perfusion relationships in the non-embolised areas. In the acute phase of the disease — that is, the first 48 hours following the embolic episode — the acute shrinkage of the pulmonary vascular bed induces functional disorders in the alveoli of occluded areas as well as in the remaining ventilated and perfused lung. Pulmonary gas exchange ultimately depends on the combined effects of two main mechanisms: (1) mechanical redistribution of pulmonary blood flow away from obstructed vascular areas towards non-occluded vessels; and (2) redistribution of alveolar ventilation induced by bronchoconstriction or atelectasis in occluded areas. However, inert gas studies of spontaneously breathing patients have shown that there is no typical pattern of distribution of either ventilation or perfusion after acute pulmonary embolism (PE). In our most recent study we found that the pattern depends
largely on the cardiac output (CO). There was a significant inverse relationship between the blood flow perfusing ventilated areas (cardiac output minus blood flow perfusing true shunt) and the mean value of the ventilation-perfusion ratio (mean VA/Q ratio). This finding indicates that CO greatly outweighs other contributory factors (increased ventilation, redistribution of alveolar ventilation from embolised to non-embolised regions, pulmonary vasoreactivity) that might affect VA/Q ratios and their distribution. Thus the VA/Q pattern in PE seems to be mainly influenced by passive consequences of the vascular obstruction: (1) redistribution of blood flow, when CO is increased or preserved, results in overperfusion of non-embolised regions with a concomitant appearance of low VA/Q units (fig 1); (2) for a fixed obstruction blood flow through low VA/Q compartment falls or even stops in response to a drop in CO. Under these conditions, VA/Q ratios tend to be higher than those observed in normal subjects at rest (fig 2). However, the greater the vascular obstruction, the larger must be the fall in CO to avoid overperfusion and hence low VA/Q mode in non-obstructed areas.

(2) Dead space. Vascular obstruction creates zones where alveoli are ventilated but not perfused. Alveolar ventilation is wasted and these unperfused areas must therefore be added to the anatomical dead space. However, in PE the percentage of the total ventilation that effectively exchanges gas in the perfused areas falls with increased pulmonary vascular obstruction. The VA/Q ratio of these areas is theoretically infinite, but in practice in the MIGET it is defined as a VA/Q ratio of over 100. In some areas there may be incomplete vascular obstruction, which reduces perfusion, thereby increasing the VA/Q ratio. A significant proportion of the ventilation has now been measured in high VA/Q areas (VA/Q >10) in various inert gas studies. These studies showed that there was a good correlation between the mean pulmonary vascular obstruction quantified on angiography by the Miller index and total dead space ventilation. However, the mean inert dead space was always found to be less than the percentage of obstruction observed on the angiograms. These findings suggest that alveolar ventilation is redistributed from occluded to non-obstructed areas. This shift in ventilation from the embolised areas is probably triggered by hypocapnia in the alveolar gas in the non-perfused or underperfused areas.

(3) Intrapulmonary shunt. Shunt is also frequently observed in the same acute phase, although it may be produced by different mechanisms such as oedema, alveolar collapse, or opening of the foramen ovale. D’Alonzo et al were the first to study the functional effects of acute, massive pulmonary embolism using the MIGET. In one of the two patients investigated within 24 hours of the acute episode, 20% of the cardiac output was shunt, although the chest radiograph was normal. In our series, the mean fraction of shunt was low (5.5(5.4)%), although individual values of 10%, 15%, and 13% were recorded. Animal studies have clearly shown the existence of pulmonary oedema during experimental pulmonary embolism, but there is no direct evidence for fully developed pulmonary oedema in man. In our case reported a few years ago, pulmonary oedema was noted in the permeable zones on the chest radiographs, suggesting that it was due to ex-
cessive perfusion (overperfusion) and/or pressure in the remaining non-obstructed areas. An alternative mechanism of intrapulmonary shunting is atelectasis, due to a combination of bronchoconstriction or atelectasis in the obstructed areas. Although we did not detect any regional infiltrates on chest radiographs in our series, we suspected that treatment may have led to some degree of reperfusion in the embolised and atelectatic regions.

Late phase:
Huet et al. observed a moderate to severe amount of shunt (range 3–17% of CO) with radiographic evidence of atelectasis or alveolar filling in patients whose inert gas measurements were carried out two to 10 days after PE. However, these parenchymal alterations may have developed some time after the initial obstruction, and they may also have been a consequence of fibrinolytic therapy. Interestingly, we observed post-fibrinolytic reperfusion oedema in one patient with massive pulmonary embolism (fig 3). In the reperfused areas there was radiographic evidence of alveolar filling with oedema. The inert gas technique indicated that 24% of the blood flow was perfusing shunt. The gas exchange and radiographic abnormalities returned to normal within a few weeks. This observation suggests that reperfusion may lead to alveolar flooding, probably due to alterations in alveolar membrane permeability from the prolonged interruption of blood flow.

Determinants of hypoxaemia in the course of pulmonary embolism
In human studies the effects of acute embolism on overall gas exchange are not readily distinguishable from the effects of previous clots. Dantzker et al. studied abnormalities in gas exchange over the two hours following experimental embolisation in 18 anaesthetised, mechanically ventilated dogs. There was no change in CO2 mixed venous PO2 remained constant, and the hypoxaemia was explained in terms of a change in VA/Q distributions. Low VA/Q ratios were observed but shunt was absent. Hypoxaemia may be increased by either high CO (decreasing the overall VA/Q ratio) or low CO (decreasing the mixed venous oxygen partial pressure). This balancing effect of CO on both intrapulmonary and extrapulmonary gas exchange leads to hypoxaemia. This decrease in PaO2 may be enhanced in certain patients by some degree of shunt, possibly derived from the effects of a previous embolism.
In any event, diffusion limitation to oxygen appears to play a minor part. Consideration of the results of these experimental and clinical studies suggests the following explanation for the gas exchange abnormalities arising during PE; except in rare cases of acute oedema or reopening of the foramen ovale, true shunt does not appear to occur in the acute phase of PE. At this stage of the disease hypoxaemia depends mainly on the extent of the low VA/Q ratios and the drop in mixed venous PO2. In the subacute stage the ensuing shunt may become a supplementary cause of hypoxaemia even though the initial determinants are starting to regress as a result of reperfusion and cardiac output has returned to normal. In the absence of perfusion, alveolar dead space cannot participate in pulmonary gas exchange. If an embolus is, or becomes, partially occlusive, such an area is converted into a zone with high VA/Q ratios. As the percentage of blood flow to these areas is low, their influence on arterial oxygen levels is minimal.

Effect of oxygen therapy
We have recently demonstrated that breathing 40% oxygen during the acute phase of PE leads to further alterations in pulmonary gas exchange. The main effect was a significant decrease in cardiac output with a concomitant slight improvement in VA/Q relationships. Pulmonary vascular resistance did not change. We did not observe the expected effects of oxygen inhalation in these hypoxaemic patients. Although the effect of breathing 100% oxygen was not tested, the release of hypoxic pulmonary vasoconstriction by oxygen therapy might have been altered or masked by a pulmonary vasoconstrictor effect from a distension reflex and/or release of humoral mediators.

Effect of unilateral pulmonary artery occlusion
The diversity of the gas exchange abnormalities observed after pulmonary embolism prompted
us to examine the effect of experimental unilateral occlusion of the pulmonary artery. In 10 patients studied prior to operation for bronchial carcinoma, cardiac output remained constant following inflation of balloon occlusion of one of the main pulmonary arteries. Moreover, although there was a significant increase in ventilation of non-perfused areas, the alveolar dead space evaluated by the MIGET was always significantly lower than the expected value based on the assumption of a more than 40% vascular obstruction. Furthermore, the expected overperfusion in the contralateral lung did not lead to any VA/Q abnormalities. Mean VA/Q and blood flow distribution remained constant. We therefore concluded that ventilation is better and more efficiently redistributed after balloon occlusion than after embolism, although the mechanism still remains uncertain.

**Chronic Thromboembolic Pulmonary Hypertension**

Although most pulmonary emboli resolve, they continue to obstruct vessels to varying extents in a minority of patients. The thrombosed areas tend to become organised and endothelialised. Obstruction may develop after a single embolus or after recurrent emboli fail to resolve, and the end result in both situations is pulmonary hypertension. The original embolic event may not have been recognised, and patients may be erroneously diagnosed as having chronic lung disease or primary pulmonary hypertension.

The gas exchange impairment is characterised by a moderate VA/Q inequality with a hypoxaemic effect that is exacerbated by a low mixed venous Po2 (PvO2). Usually there is no intrapulmonary shunting, and an absence of zones of very low or very high VA/Q ratios. The dead space is increased. The lowered PvO2 from the cardiac impairment is a quantitatively significant determinant of the decreased PaO2 that is commonly observed in such patients. Moreover, the marked fall in PaO2 during exercise in these patients is also largely due to the influence of the fall in PvO2 on the abnormal lung units.

**Effect of Excessive Polycythaemia and Haemodilution**

Although haemodilution induces an increase in cardiac output, its effects on gas exchange are largely unknown. In a study performed in Andean natives with polycythaemia and gross hypoxaemia we observed increases in both cardiac output and ventilation after haemodilution. The abnormal basal VA/Q distribution pattern (mainly due to hypventilation) was improved a little, but PaO2 remained unchanged despite a significant increase in total ventilation. These paradoxical results were assumed to be due to the combined effect of an insufficient reduction in haemoglobin concentration and a high residual VA/Q mismatch. To our knowledge there are no reports in the literature on the effect of haemodilution in polycythaemic COPD patients at sea level. A study of this kind would not be easy to carry out on a large series of patients and, in any case, polycythaemia in hypoxaemic patients with COPD is now effectively prevented by oxygen therapy. Nevertheless, our data and simulations suggested that the reduction in haemoglobin concentration by haemodilution in polycythaemic patients at sea level (PvO2 = 150 mm Hg) led to a greater improvement in PaO2 for the same degree of VA/Q inequalities than that observed in our polycythaemic Andean natives.

**Diseases with Structural Abnormalities in Pulmonary Vessels**

**Primary Pulmonary Hypertension (PPh)**

In idiopathic pulmonary hypertension PaO2 may fall in the later stages of the disease, although VA/Q inequalities tend to be moderate. MIGET studies have now shed more light on the mechanisms underlying the disturbances in gas exchange stemming from these abnormalities of the vascular bed. In patients suffering from chronic obliterative pulmonary vascular disease Dantzker et al showed that much of the cardiac output was distributed to lung units with near normal VA/Q ratios, while only a small percentage (mean <10%) circulated through underventilated or unventilated areas (shunt). Administration of oxygen, isoproterenol, nitroprusside, or nifedipine worsened VA/Q relationships due to a reduction in pulmonary vascular tone and an increased blood flow in very low VA/Q units and/or shunt. This deleterious effect of pulmonary vasodilatation was not accompanied by a negative effect on arterial oxygenation as the vasodilators also increased cardiac output. The resultant increase in mixed venous oxygen content raised the end capillary arterial Po2 in low VA/Q units, thus preventing the decrease in arterial Po2 that would otherwise have occurred. These two studies indicated that most subjects with chronic obstruction of the pulmonary vascular beds have increased pulmonary vascular tone, which in turn contributes to the maintenance of ventilation-perfusion matching in the lungs. Any reduction in arterial Po2 was thus assumed to be mainly due to the low mixed venous Po2 caused by the greatly reduced cardiac output. An inert gas study performed during exercise in patients with chronic pulmonary hypertension corroborated the key role of the decreased PvO2 due to an inadequate cardiac output when workload increases without significant change in VA/Q inequalities.

**Liver Cirrhosis**

Although it is thought that there is some connection between primary pulmonary hypertension and portal hypertension secondary to hepatic cirrhosis, the gas exchange abnormalities observed in patients with liver cirrhosis appear to be related more to a decrease in pulmonary vascular tone.

Patients with liver cirrhosis are sometimes severely hypoxaemic. Decrease in oxygen tension would also lead to a reduction in haemoglobin concentration in the lungs. In patients in whom a decrease in carbon dioxide tension is not compensated for by increased ventilation, arterial pH may drop due to hypoxaemia. Chronic systemic hypoxaemia can give rise to adaptive changes in arterial and venous beds. Decrease in arterial pH resulting from hypoxaemia and/or hypocapnia can cause a decrease in arterial blood flow. The decrease in arterial blood flow may also be due to a decrease in the cardiac output. However, these decreases are not necessarily accompanied by a decrease in oxygen tension in the lung, since the venous oxygen tension depends on mixed venous oxygen content and oxygen delivery.
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A recent animal study has shown that substances metabolised by the liver are involved in the regulation of pulmonary vascular tone and reactivity. Normalisation of liver function should therefore tend to correct systemic and pulmonary vascular abnormalities and alterations in \( \text{VA/Q} \) distributions. Eriksson et al. evaluated intrapulmonary shunt and \( \text{VA/Q} \) relationships before and after liver transplantation in six patients. After transplantation the hyperkinetic circulatory syndrome disappeared, accompanied by a decrease in cardiac output and an increase in systemic and pulmonary vascular resistance. \( \text{PaO}_2 \) returned to normal in all patients, and both shunt and low \( \text{VA/Q} \) relationships were reduced (the sum of shunt and low \( \text{VA/Q} \) units fell from a mean of 11.8% preoperatively to 0.6% of \( \text{CO} \) postoperatively). These results added further support to the other studies that suggest a direct functional relationship between the respiratory and cardiovascular alterations in patients with liver disease.

Pulmonary gas exchange in cardiac disease

The salient physiological abnormality in pulmonary vascular disease from an acquired heart condition is pulmonary venous hypertension. Mitral stenosis and left ventricular failure of any aetiology are the main culprits. There are only a few reports of inert gas studies of the gas exchange abnormalities in such patients. Nevertheless, it would be logical to assume that any disturbances stem from the fall in cardiac output. In dogs with a baseline \( \text{VA/Q} \) distribution within normal limits, alterations in cardiac output were induced first by bleeding followed by reinfusion of blood. \( \text{Po}_2 \) was remarkably well maintained during haemorrhage, despite a 75% fall in cardiac output. The authors offered no convincing explanation for this phenomenon. After reinfusion cardiac output rose to above control values, but there was no evidence of appreciable shunt or perfusion to low \( \text{VA/Q} \) areas. \( \text{PaO}_2 \) remained in the normal range. Under these circumstances, the large change in oxygen transport did not lead to a large fall in \( \text{Po} \), as the interaction between \( \text{Po}_2 \) and \( \text{VA/Q} \) distribution effectively regulates the overall \( \text{PaO}_2 \) in the normal lung. In humans most of the reports deal with \( \text{VA/Q} \) relationships after cardiac surgery. The results are quite comparable to those observed in dogs, although the baseline distributions displayed some degree of \( \text{VA/Q} \) inequalities. We have reported a case of left ventricular failure in a patient with no clinical or radiological evidence of pulmonary oedema (personal communication). Right heart catheterisation detected post-capillary pulmonary hypertension with a decreased cardiac index: mean pulmonary artery, pulmonary capillary wedge and right atrial pressures were 36, 25, and 5 mm Hg, respectively. Pulmonary vascular resistance lay within the normal range. Inert gas measurements demonstrated a high \( \text{VA/Q} \) ratio distribution. The mean \( \text{VA/Q} \) values for both blood flow and ventilation were 2 and 2.7 respectively. This
pattern of distribution (fig 4) maintained a normal Pao2 (78 mm Hg) in the presence of a lowered Pvo2 due to the inadequate cardiac output and the impaired peripheral gas exchange. It is now established that the effect of a reduced Pvo2 on Pao2 can be offset by the great increase in V/AQ ratio resulting from the combined effect of increased ventilation and decreased cardiac output as it is currently observed in cardiogenic shock.

Conclusion
The results from MIGET studies on patients with different pulmonary vascular pathologies point to the key role of cardiac output on overall respiratory gas exchange. The cardiac output will be conditioned by both structural alterations in the pulmonary vascular bed and the changes in resistance induced by the disease. In vascular lung diseases the pattern of V/AQ ratio distributions and a low mixed venous Pvo2 are the two main factors underlying the impairment in gas exchange. In primary cardiac diseases the normal lung maintains Pao2 by efficient adjustment of the V/AQ distribution to the fall in cardiac output.

The authors thank Mrs Patricia Bordes for her secretarial assistance.

Contribution of multiple inert gas elimination technique to pulmonary medicine--4. Gas exchange abnormalities in pulmonary vascular and cardiac disease.

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Thorax 1994 49: 1169-1174
doi: 10.1136/thx.49.11.1169