CLINICAL SIGNIFICANCE OF PULMONARY FUNCTION TESTS

Alterations in Gas Exchange Following Pulmonary Thromboembolism*

David R. Dantzker, M.D., F.C.C.P., and James S. Bower, M.D., F.C.C.P.

Pulmonary thromboembolization typically results in alterations in gas exchange. Investigations of the pattern and magnitude of these alterations both in humans and experimental animals, however, have produced inconsistent results. We believe that this inconsistency is a result of a variety of problems involved in studying pulmonary thromboembolism. In patient studies, for instance, the time elapsed since embolization is difficult to determine and the presence or absence of associated cardiopulmonary disease has often been poorly documented. Even criteria for the diagnosis of pulmonary thromboembolism have varied from study to study. Results of studies of experimental animals, on the other hand, may vary depending upon the species studied, the specific experimental circumstances, and the size and composition of the embolized material.

In this review, we will attempt to summarize the currently available information concerning the mechanisms and magnitude of the gas exchange abnormalities resulting from pulmonary embolism. We will examine both pulmonary and extrapulmonary factors that alter gas exchange in patients with pulmonary thromboembolism and will evaluate the utility of arterial blood gas analysis in its differential diagnosis.

INTRAPULMONARY SHUNT

Right-to-left intrapulmonary shunts subsequent to pulmonary embolism have been demonstrated both in man and in experimental animals. Wilson et al studied 21 patients with angiographically-demonstrated pulmonary emboli while breathing room air and 100 percent oxygen. They found that intrapulmonary shunting accounted for most of the hypoxemia observed in their patients, and this shunting gradually diminished during the first month following embolization. The magnitude of the shunting did not correlate with the percentage of the pulmonary vascular bed embolized or with the mean pulmonary artery pressure.

Shunting has also been found to be responsible for the abnormal gas exchange seen in animals following microembolization with either glass or polystyrene beads or homologous blood clots. Figure 1 shows the distribution of ventilation and blood flow with respect to the ventilation-perfusion ratio in an anesthetized, ventilated dog. Prior to embolization, 93 percent of the cardiac output is distributed to lung units with VA/Q ratios of between 0.1 and 1.0, and there is a small amount of blood flow perfusing very low VA/Q units and shunt. Following the injection of 200-400 µm polystyrene beads in an amount sufficient to increase the pulmonary vascular resistance by 3 to 4 times, there is a dramatic increase in the shunt, a slight increase in blood flow to low VA/Q units, and the development of new lung units with very high VA/Q ratios.

Although the etiology of the intrapulmonary shunt following pulmonary thromboembolism has not been clearly established, several possible mechanisms have been suggested. Hemorrhagic atelectasis due to loss of surfactant, for instance, may result from embolic occlusion of the pulmonary vascular bed. Later dissolution or distal migration of embolic material may then lead to reperfusion of these atelectatic and unventilated lung units. Alternatively, it has been suggested that elevations of pulmonary artery pressure cause the opening of pre-existing pulmonary arterial-venous anastomoses. Although this hypothesis is supported by the direct relationship frequently observed between pulmonary artery pressure and degree of shunt, Cheney and colleagues were unable to demonstrate anatomic anastomoses with up to fourfold increases in pulmonary artery pressure. Finally, the existence of localized areas of post-embolic pulmonary edema causing intrapulmonary shunting have been postulated. Increased extravascular lung water can indeed be measured following microembolization of

*From the University of Michigan Medical Center, Department of Medicine, Division of Pulmonary Disease, Ann Arbor.
Reprint requests: Dr. Dantzker, Pulmonary Division, Box 055, University of Michigan Hospital, Ann Arbor 48109

CHEST, 81: 4, APRIL, 1982

ALTERATIONS IN GAS EXCHANGE FOLLOWING THROMBOEMBOLISM 495
the pulmonary vascular bed. Its presence may result either from release of humoral substances, leakage in the unobstructed vessels due to damage induced by increased stress on the endothelial cells, or fluid leakage from extraalveolar vessels.

Intracardiac right-to-left shunts may also develop in the presence of right ventricular failure and elevated right atrial pressure. This shunt occurs through the foramen ovale which remains patent in about 15 percent of normal individuals. A flap valve over the foramen prevents shunting when left atrial pressure exceeds right atrial pressure, but allows right-to-left flow when right atrial pressure exceeds that in the left atrium.

VENTilation-PERFUSION INequality

The development of ventilation-perfusion inequality has also been demonstrated to provide a major contribution to the deranged gas exchange seen following pulmonary embolization. Kafer, for instance, studied 21 patients who were felt to have pulmonary thromboembolism on the basis of perfusion lung scan abnormalities. He measured their PaO₂ while breathing room air and while breathing 100 percent oxygen and estimated the contribution of VA/Q inequality and shunt to each patient's hypoxemia. Although both played a role, VA/Q inequality was estimated to be the more important mechanism.

Ventilation-perfusion inequality has also been demonstrated following large, homologous pulmonary emboli in dogs. Figure 2 shows the ventilation-perfusion distribution obtained from a dog prior to embolization. The blood flow is confined to

![Diagram of ventilation-perfusion ratio](image_url)
a single narrow mode with neither high nor low $V_A/Q$ units and no shunt. Following embolization there are units which are overperfused and underventilated and units which are overventilated and underperfused. There is, however, no intrapulmonary shunt despite marked increases in pulmonary artery pressure. In addition, there is no increase in the dead space defined as the ventilation of totally unperfused lung units. This absence of an increase in dead space following significant embolization has been noted in other studies and suggests that complete occlusion of blood flow may be an uncommon occurrence.

It is of interest that in addition to the $V_A/Q$ pattern just discussed, a variety of other patterns of $V_A/Q$ inequality resulted from homologous clot embolization in dogs. Despite similar degrees of vascular obstruction as reflected by similar increases in pulmonary vascular resistance, some dogs develop only increased perfusion to low $V_A/Q$ units and others only increased perfusion to high $V_A/Q$ units. The development of such a wide range of patterns of $V_A/Q$ inequality following embolization can be explained by the manner in which the emboli lead to the redistribution of blood flow from embolized units to nonembolized units. Figure 3 shows that almost total occlusion of blood flow from a relatively small number of lung units would result in lung units with high $V_A/Q$ ratios and an increase in physiologic dead space, but no significant increase

**Figure 2.** The distribution of ventilation and blood flow in a dog before and after embolization with autologous clot. Following embolization, there is a marked increase in ventilation-perfusion inequality, but no increase in shunt or dead space. (Reproduced from Dantzker et al, Circ Res 1978; 42:92-103 by permission of the American Heart Association).

**Figure 3.** Two compartment lung model with ventilation and blood flow matched in the top panel. In the middle panel blood flow to the small compartment has been reduced by 90 percent and diverted to the large compartment. This will result in the development of a high $V_A/Q$ unit, but a minimal decrease in the $V_A/Q$ of the larger compartment (1 to 0.9). Thus, no significant hypoxemia would ensue. In the bottom panel, flow to the larger compartment has been decreased by 50 percent and diverted to the small compartment. This leads to 58 percent of the blood flow distributed to a lung unit with $V_A/Q$ of 0.3 and significant hypoxemia. In each case, the $P_{O_2}$ and $P_{CO_2}$ of the mixed venous blood are assumed to remain constant at 40 and 45 mm Hg respectively. (Reproduced from Dantzker et al, Circ Res 1978; 42:92-103 by permission of the American Heart Association.)
in low $V_{A}/Q$ units and thus not much hypoxemia. By contrast, only partial occlusion of a large portion of the pulmonary vascular bed would lead to the development of low $V_{A}/Q$ units and hypoxemia, but no significant increase in units with high $V_{A}/Q$ ratios.

It is likely that the pattern of $V_{A}/Q$ inequality that results from thromboemboli is related both to the size and distribution of the emboli. Young et al demonstrated in dogs that emboli less than 150 $\mu$m never led to the appearance of high $V_{A}/Q$ units while larger emboli always did. They argued that the smaller emboli were obstructing vessels within a functional gas exchange unit and that collateral perfusion prevented the development of high $V_{A}/Q$ units. The apparent tendency of emboli to accumulate in well-ventilated areas of lung may also serve to direct more of the cardiac output to lung units that already have low $V_{A}/Q$ ratios.

The distribution of blood flow and ventilation in the lung may also be affected by local alterations. Release of vasoactive substances at the site of embolization, for instance, may cause local bronchoconstriction and lung units with low $V_{A}/Q$ ratios. Hypoxic vasoconstriction, on the other hand, reduces perfusion to lung units with low $V_{A}/Q$ ratios, and hypocapnic bronchoconstriction reduces the ventilation of lung units with high $V_{A}/Q$ ratios. These conservative mechanisms may explain in part the finding in experimental animals of normalization of $V_{A}/Q$ inequality within hours of the embolic event and the clinical finding of relatively unimpaired gas exchange in some patients with proven pulmonary emboli.

**Decreased Mixed Venous Oxygen Content**

A final element in the pathogenesis of alterations in arterial blood gas tension seen following pulmonary thromboembolism is a decrease in the oxygen content of mixed venous blood. Figure 4 shows that in the presence of $V_{A}/Q$ inequality, arterial $O_2$ content falls as the mixed venous oxygen tension falls. In patients with pulmonary thromboembolism, the mixed venous $P_O_2$ may fall due to decreases in cardiac output or inability of cardiac output to keep pace with increased tissue oxygen demand.

Although very few measurements of mixed venous oxygen content have been made in patients following acute pulmonary embolism, cardiac output is usually in the normal range. Decreased cardiac indices have, however, been observed following acute embolization sufficient to cause hemodynamic instability. Further, patients with chronic, recurrent pulmonary embolization and pulmonary hypertension very frequently have a reduced cardiac output and a low mixed venous oxygen content. Among seven patients with thromboembolic pulmonary hypertension studied in our laboratory, five have had a mixed venous $P_O_2$ of less than 35 mm Hg.

The ventilation-perfusion distribution of a patient with chronic thromboembolic disease and pulmonary hypertension is shown in Figure 5. Despite widespread vascular occlusion, there is only minimal $V_{A}/Q$ inequality present along with a very small intrapulmonary shunt. The patient’s arterial $P_O_2$ was 60 mm Hg, and this degree of hypoxemia was out of proportion to what might have been expected on the basis of the $V_{A}/Q$ distribution alone. This discrepancy is explained by the amplifying effect of the patient’s mixed venous $P_O_2$ of 29 mm Hg on the arterial $P_O_2$. It can be calculated, in fact, that if this patient’s mixed venous $P_O_2$ was corrected to 40 mm Hg, his arterial $P_O_2$ would be 84 mm Hg.

**Arterial Blood Gas Abnormalities in Man**

Arterial hypoxemia is found in most patients who have experienced pulmonary thromboembolization. Figure 6 demonstrates the distribution of arterial partial pressure of oxygen ($P_{A}O_2$) during room air breathing in 54 previously reported patients without
underlying lung disease.\textsuperscript{1,18,20} All patients had their emboli demonstrated by pulmonary angiography and were studied within three weeks of the first symptoms suggesting pulmonary thromboembolism. Although many factors are likely to have contributed to the wide range of PaO\textsubscript{2} values observed, the size of the embolus seemed to have been of particular importance. Among those patients studied by McIntyre et al.\textsuperscript{19} for instance, a direct linear relationship was demonstrated between the percentage of the pulmonary vascular bed obstructed and the value of the patient's PaO\textsubscript{2}.

It is of interest that among the patients reviewed, the PaO\textsubscript{2} was often well maintained. The PaO\textsubscript{2} was 90 mm Hg or greater in 6 percent of the patients, and 14 percent had a PaO\textsubscript{2} $\geq$ 80 mm Hg. Among those with a PaO\textsubscript{2} $\geq$ 80 mm Hg, there were sufficient data to calculate an alveolar-arterial oxygen gradient in three of seven patients. In all three, the gradient was widened.

Severe hypoxemia resulting from pulmonary thromboembolism was also frequently observed. A PaO\textsubscript{2} $\leq$ 60 mm Hg was found in 26 percent of patients while a PaO\textsubscript{2} $\leq$ 50 was present in 14 percent. Among the seven patients with a PaO\textsubscript{2} $\leq$ 50 mm Hg, there were six who had angiographic evidence that more than 50 percent of their pulmonary vascular bed was obstructed. All of these patients had significant pulmonary hypertension and two died shortly after being studied.

Tachypnea accompanies pulmonary thromboembolism in 92 percent of cases, and it is frequently accompanied by arterial hypocarbia.\textsuperscript{17} Among 34 patients without previous cardiopulmonary disease reported by Wilson et al.\textsuperscript{1} and by Stanek et al.\textsuperscript{20} there were 27 with a PaCO\textsubscript{2} less than 38 mm Hg, 13 less than 32 mmHg, and 6 less than 26 mm Hg. The highest PaCO\textsubscript{2} observed was 44 mm Hg. Even in the presence of significant underlying lung disease, recent reports suggest that hyperventilation is a characteristic response to acute pulmonary vascular occlusion. Among three recently reported patients with chronic obstructive pulmonary disease and elevations of PaCO\textsubscript{2}, all had a fall of PaCO\textsubscript{2}.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{The distribution of ventilation and blood flow in a 35-year-old patient with recurrent pulmonary embolism and pulmonary hypertension. Despite a mean pulmonary artery pressure of 70 and extensive angiographically-documented pulmonary embolisation, the V\textsubscript{A}/Q distribution is relatively normal. (Reproduced from Dantzker and Bower, J Clin Invest 1979; 64:1050-55.)}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure6.png}
\caption{The arterial PaO\textsubscript{2} from 54 patients without previous cardiopulmonary disease and angiographically proven acute pulmonary embolism.\textsuperscript{1,19,20}}
\end{figure}
following the occurrence of acute thromboembolism.\textsuperscript{21}

The pH of the arterial blood is dependent upon a variety of factors. Acute embolization most characteristically results in hypocarbia and an acute respiratory alkalosis. Patients with chronic, recurrent embolization and pulmonary hypertension, on the other hand, frequently chronically hyperventilate and are found to have a chronic respiratory alkalosis.\textsuperscript{18} Rarely in patients suffering massive embolization with markedly diminished cardiac output a metabolic acidosis due to excess lactate production may be observed.

Although hypoxemia, hypocarbia, and acute respiratory alkalosis comprise the most characteristic pattern of arterial blood gas abnormalities following pulmonary embolization, these changes are neither sufficiently sensitive nor specific to be of substantial use in differential diagnosis. Certainly, the diagnosis of pulmonary embolism should not be excluded on the basis of finding $\text{PaO}_2 \geq 80$ mm Hg as has been suggested by others.\textsuperscript{22}

**Dead Space and Expired CO\textsubscript{2} Alterations in Man**

The Bohr dead space ($\text{Vd/Vt}$) as determined from measurement of the partial pressure of CO\textsubscript{2} in arterial and mixed expired gas represents the sum of the anatomic dead space and the alveolar dead space. Anatomic dead space is constituted primarily by the large conducting airways and is relatively fixed in size. The alveolar dead space is determined by ventilation to lung units with $V_A/Q$ ratios greater than the mean for that individual. In normal individuals, these units occur predominantly at the lung apices which are underperfused relative to the lung base. When tidal volume is increased, as during mild exercise, the ratio of anatomic dead space to tidal volume falls. In addition, exercise causes increased perfusion to the lung apices and a fall in alveolar dead space. The combination of these effects causes a fall in $\text{Vd/Vt}$ during mild exercise.

Several authors have suggested that an elevation of resting $\text{Vd/Vt}$ or a failure of $\text{Vd/Vt}$ to decrease during exercise is a sensitive indicator of the presence of obliterative pulmonary vascular disease. Nadel et al.\textsuperscript{23} for instance, studied eight patients with documented pulmonary vascular disease and found a resting elevation of $\text{Vd/Vt}$ in two patients and an increase of $\text{Vd/Vt}$ with exercise in all eight patients. Jones and Goodwin\textsuperscript{24} similarly found a very high incidence of abnormality at rest or during exercise in patients with obstruction of the pulmonary vascular beds. The increased $\text{Vd/Vt}$ at rest is postulated to be due to persistent ventilation of areas of lung not perfused due to vascular obstruc-

tion. The increase of $\text{Vd/Vt}$ with exercise has been suggested to occur due to a release of hypocarbic bronchoconstriction induced by hyperventilation and a resulting abnormal increase of ventilation to unperfused lung units.

Subsequent authors, however, have failed to document a uniformly increased resting $\text{Vd/Vt}$ or an increase in $\text{Vd/Vt}$ during exercise in patients with pulmonary vascular obstruction. Reidel et al.\textsuperscript{25} studied 25 patients with thromboemboli demonstrated by pulmonary angiography to obstruct more than 30 percent of the pulmonary vascular bed. They found an elevated $\text{Vd/Vt}$ in 57 percent of these patients. Among patients with lesser degrees of vascular obstruction, resting $\text{Vd/Vt}$ was elevated in 18 percent. Further, only 9 percent of all patients failed to have a fall in $\text{Vd/Vt}$ with exercise. Mohsenifar and colleagues\textsuperscript{26} studied 12 patients with obliterator pulmonary vascular disease and found $\text{Vd/Vt}$ at rest to be normal in all but one and increased during exercise in only one patient.\textsuperscript{27} These authors suggest that partial obstruction of precapillary pulmonary vascular bed allows increased flow to poorly perfused areas and, therefore, a normal fall in $\text{Vd/Vt}$ with exercise.

The arterial to end-expiratory CO\textsubscript{2} gradient reflects the same alterations in gas exchange measured by the Bohr dead space. It too has been suggested to be increased following pulmonary embolism because expired gas from unperfused lung units will dilute the CO\textsubscript{2} from the expired gas from normal lung units.\textsuperscript{28} The end-tidal CO\textsubscript{2} thus falls relative to the arterial value and falls outside the normal range of approximately 5 mm Hg. Like elevation of the Bohr dead space, however, this finding has not been found consistently in patients with thromboembolism and is present in a variety of other disorders.

**Summary**

There is a broad spectrum of gas exchange abnormalities that result from pulmonary thromboembolism. The severity and mechanism of these abnormalities are likely to depend upon the size and location of emboli, the presence or absence of pre-existing cardiopulmonary disease, and the time elapsed since embolization. Arterial blood gas alterations and changes in expired gas composition reflected in the Bohr dead space and arterial to end-tidal CO\textsubscript{2} gradient are neither sufficiently sensitive nor specific to be of great use in the differential diagnosis of pulmonary thromboembolism.

**References**