Mechanism of arterial hypoxemia following pulmonary thromboembolism in dogs

STEVEN E. LEVY AND DANIEL H. SIMMONS
Department of Medicine, University of California, Los Angeles, School of Medicine, Los Angeles 90024; and Cedars-Sinai Medical Research Institute, Los Angeles, California 90029

LEVY, STEVEN E., AND DANIEL H. SIMMONS. Mechanism of arterial hypoxemia following pulmonary thromboembolism in dogs. J. Appl. Physiol. 39(1): 41-46. 1975.—Mongrel dogs (29) were anesthetized, paralyzed, and ventilated at a constant minute volume. AaDo₂ breathing air and 100% O₂, venous admixture breathing air (Qva/Qt) and 100% O₂ (Qs/Qt), single-breath diffusing capacity for CO (DLco), and total pulmonary resistance (Rt) and pulmonary compliance (Cl) were measured before and after pulmonary embolization with autologus in vivo venous thrombi. Nine dogs were heparinized before embolization. In the 20 nonheparinized dogs AaDo₂ breathing air increased from 11 to 26 mmHg, Qva/Qt from 4 to 22%, and Qs/Qt from 5 to 8%. DLco decreased 24%, Rt increased 43%, and Cl fell 30%. In the nine heparinized dogs AaDo₂ breathing air increased from 8 to 13 mmHg and Qva/Qt from 3 to 8%; Qs/Qt did not change. DLco decreased 31%; Rt and Cl did not change significantly. The increase in Qva/Qt of 5% in the heparinized dogs was significantly less (P < 0.001) than the increase of 18% in the nonheparinized dogs. These findings suggest that arterial hypoxemia following thromboembolism is due to ventilation-perfusion inequality caused by changes in lung mechanics.

pulmonary thromboemboli; venous admixture; ventilation-perfusion; lung mechanics; diffusing capacity

ARTERIAL HYPOXEMIA is one consequence of embolization of the pulmonary circulation both in man and the experimental animal. Various mechanisms have been proposed to explain this alteration in pulmonary gas exchange, including a decrease in diffusing capacity due to a reduction in the surface area of the alveolar-capillary membrane (27), abnormally rapid passage of blood through a pulmonary capillary bed decreased in volume (2), ventilation-perfusion abnormalities (5, 13), atelectasis (8, 28), and right-to-left anatomical shunting (15). The purpose of this study was to define the mechanism or mechanisms responsible for the development of arterial hypoxemia in dogs following pulmonary embolization by autologous in vivo venous thrombi.

METHODS

Mongrel dogs weighing approximately 20 kg were anesthetized with pentobarbital sodium (30 mg/kg), intubated, paralyzed with succinylcholine given as a continuous infusion intravenously via an arm vein (10 mg/h), and ventilated at a constant frequency (10/min) and fixed tidal volume (16 ml/kg) throughout the experiment. Polyethylene catheters (PE-50) were placed in a femoral artery and the right ventricle to obtain arterial and mixed venous blood for measurement of pH, CO₂ tension, O₂ tension, and hemoglobin content. The pleural space was entered posteroilaterally through a lower intercostal space through a 1-cm skin incision using a blunt-ended clamp. A no. 10 Malecot catheter was then introduced into the pleural space and sutured in place leaving a 10-ml pneumothorax. The volume of the pneumothorax was confirmed prior to each measurement of intrapleural pressure. Aortic arch temperature was recorded with a thermistor probe passed via the remaining femoral artery to the arch of the aorta. Blood gas values were corrected to aortic arch temperature which has been shown to be equivalent to pulmonary capillary temperature (7) using the factor of Rosenthal for pH (20), and the factors of Bradley, Stupfel, and Severinghaus for O₂ and CO₂ tensions (3). Autologous in vivo thrombi were formed in isolated jugular and femoral venous segments using the method of Wessler (25). The thrombi formed were approximately 5 mm in diameter and 4-5 cm lung. The dog was then placed in the prone position.

Twenty-nine dogs were studied. One group of 20 dogs was embolized without prior heparinization, and a second group of nine dogs was anticoagulated after thrombus formation with 5,000 units of heparin given intravenously 30 min prior to the release of thrombi.

Physiologic measurements were carried out as follows in both groups. Simultaneous collections of expired gas, arterial blood, and venous blood from the right ventricle were made before and after embolization during ventilation with ambient air, and after breathing 100% oxygen for 10 min. An end-tidal gas sample was collected over several breaths during the last minute of 100% oxygen breathing through a needle placed through the side wall of the endotracheal tube. Diffusing capacity for carbon monoxide (DLco) was measured in duplicate by a modification of the single-breath technique of Ogilvie et al. (16) before and after embolization and prior to breathing 100% oxygen. Total pulmonary resistance (Rt) and pulmonary compliance (Cl) were measured continuously before, during, and after embolization by the loop method with electrical subtraction as described by Mead and Whittenberger (14). Transpulmonary pressure was measured with a Statham (PM5 ± 0.3 psid) differential transducer cou-
connected to the intrapleural catheter and the endotracheal tube. Airflow was measured with a Fleisch no. 1 pneumotachograph and a Statham (PM97 ± 0.05 psid) differential transducer. Tidal volume was obtained by electronic integration of the flow signal. The loops were recorded using an oscilloscopic recorder (Electronics for Medicine, model DR-8). The resistance of the pneumotachograph and endotracheal tube were subtracted from the measured total pulmonary resistance. No attempt was made to reverse postembolic changes by hyperinflation of the lungs. After completion of the postembolic physiologic measurements the first group of 20 dogs which had not been anticoagulated before embolization was given 5,000 units of heparin intravenously. Then, five of the first group of 20 dogs and 5 of the second group of 9 dogs heparinized previously were infused intravenously with 10 μCi of ¹³¹I-labeled macroaggregated albumin to determine the relative distribution of pulmonary blood flow with respect to weight of the lung segments that were still perfused (24). To separate lung segments that were still perfused from those that were totally nonperfused 20 ml of 50% India Ink were infused through the right ventricular catheter one minute prior to sacrifice. As expected there is no perfusion to non-carbon-stained segments (12), and non-carbon-stained segments, i.e., nonperfused segments, are found only when emboli are present in the segment (13). The perfused lung segments tend to be deeply carbon stained because of continuing recirculation of the India Ink, and for this reason the degree of carbon staining of the perfused lung segments cannot be used to determine the relative distribution of pulmonary blood flow to these segments. All 29 dogs were killed by infusing 20 ml of saturated potassium chloride through the right ventricular catheter. The heart and lungs were then removed. The lungs from the 19 dogs that were not infused with ¹³¹I-labeled macroaggregated albumin were dissected noting the presence and location of the emboli. The lungs from the 10 dogs that were infused with ¹³¹I-labeled macroaggregated albumin were rapidly frozen in liquid nitrogen and dissected into carbon-stained and non-carbon-stained lung segments. The weight and radioactivity, i.e., relative pulmonary blood flow, of each of the carbon-stained perfused lung segments from each dog was determined, the latter using a liquid scintillation counter. The weight and radioactivity of each of the carbon-stained perfused lung segments was expressed as a fraction of the weight or total radioactivity, respectively, of the perfused lung segments was expressed as a fraction of the total weight or total radioactivity, respectively, of the carbon-stained perfused lung segments from each dog. The weight and radioactivity of non-carbon-stained lung segments was not determined.

Calculations. Standard formulas were used to calculate O₂ consumption, CO₂ production, respiratory exchange ratio, "ideal" alveolar O₂ tension (Pₐₒ₂), (19), and the alveolar-arterial oxygen gradient (AaDo₂) breathing ambient air and 100% O₂.

The fraction of total pulmonary arterial blood flow functioning as venous admixture (Qva/Qt) was calculated using the standard shunt equation

\[ Q_{va}/Qt = Cc'_{O₂} - Cao_{O₂}Ce/uo - CV_{O₂} \] (1)

where \( Q_{va}/Qt \) = venous admixture as a fraction of total pulmonary blood flow; \( Cc'_{O₂} \) = end-capillary O₂ content, ml/100 ml, \( Cao_{O₂} \) = arterial O₂ content, ml/100 ml, and \( CV_{O₂} \) = mixed venous O₂ content, ml/100 ml.

In calculating \( Q_{va}/Qt \) the end-capillary O₂ content (Cc'ₒ₂) was determined as follows

\[ Cc'_{O₂} (ml O₂/100 ml) = Hb (g/100 ml) \times 1.34 \times 100 \times Sc_{O₂} (\%) + Pc'_{O₂} (mmHg) \times 0.003 \times 100 \times (mmHg) \] (2)

The end-capillary O₂ saturation (Sc'ₒ₂) was determined from the O₂ dissociation curve for dog blood (1), assuming the end-capillary O₂ tension (Pc'ₒ₂) to be equivalent to the "ideal" alveolar O₂ tension (Pₐₒ₂) when breathing ambient air, or the measured alveolar or end-tidal O₂ tension when breathing 100% O₂. The pH of the end-capillary blood was assumed to be the same as the arterial pH. The arterial and mixed venous oxygen contents were determined in a similar manner using the arterial and mixed venous O₂ tensions, pH, and hemoglobin, respectively.

Venous admixture (Qva/Qt) measured during ambient air breathing includes the shuntlike effect of areas of lung having decreased diffusion capacity, areas of lung having an inequality of ventilation with respect to perfusion such that the ventilation-perfusion ratio is reduced, and areas of lung which function as a true right-to-left shunt, i.e., areas of atelectasis and pulmonary arteriovenous communications. Venous admixture measured during 100% oxygen breathing, denoted hereinafter as (Qs/Qt), includes venous admixture due only to areas of lung that function as a true right-to-left shunt.

Mean values for the physiologic parameters before and after embolization were determined. To determine the physiologic effects of embolization the mean change in each physiologic parameter following embolization was also determined and the Student t-test was used to determine if the mean change was significantly different from zero, i.e., that embolization was associated with a significant change.

RESULTS

The effects of pulmonary embolization on pulmonary gas exchange and lung mechanics in the 20 nonheparinized and 9 heparinized dogs are summarized in Table 1. A fall in arterial oxygen tension (Pₐₒ₂) occurred after embolization in all 29 dogs from a mean of 94 to a mean of 68 mmHg in the nonheparinized dogs, and from 95 to 77 mmHg in the heparinized dogs. The fall in Pₐₒ₂ in both groups of dogs was in part due to the experimental design, since ventilation was maintained at the same fixed minute volume both before and after embolization. With cessation of gas exchange in embolized areas of lung, alveolar dead space increased. Therefore, effective alveolar ventilation decreased and mean arterial CO₂ tension (Pₐₑₚₐ₆) increased from 37 to 44 mmHg, causing the mean "ideal" Pₐₒ₂ to fall from 105 to 94 mmHg in the nonheparinized dogs. In the heparinized dogs the mean Pₐₑₚₐ₆ rose to a comparable degree from 38 to 45 mmHg, and the mean Pₐₒ₂ fell from 103 to 90 mmHg. In neither group was the fall in Pₐₒ₂ sufficient to account for the fall in Pₐₒ₂, i.e., the AaDo₂ increased.
The changes in the AaDo 2 breathing air and venous admixture (Qva/Qt) following embolization are of more significance with respect to the efficiency of pulmonary gas exchange and the development of arterial hypoxemia. In 19 of the 20 nonheparinized dogs there was an increase in the AaDo 2 breathing air, and in one there was no change; for all 20 dogs the mean AaDo 2 breathing air increased from 3 to only 5 mmHg, which was not a statistically significant change. Mean Qva/Qt in the nonheparinized dogs increased from 4 to 22 % after embolization, while in the heparinized dogs the mean Qva/Qt increased from 3 to only 8 %. The increase in Qva/Qt in both groups was significant (nonheparinized dogs, P < 0.001; heparinized dogs, P < 0.05).

However, the increase in Qva/Qt in the nonheparinized dogs of 18 % was significantly greater than the increase of 5 % in the heparinized dogs (P < 0.001). Mean Qs/Qt increased significantly (P < 0.05) in the nonheparinized dogs from 5 % of total pulmonary arterial blood flow to 8 % following embolization. In the heparinized dogs the mean Qs/Qt of 3 % did not change following embolization. Before embolization Qva/Qt was equivalent to Qs/Qt in both the nonheparinized and heparinized dogs. However, after embolization the mean Qva/Qt was significantly greater than the mean Qs/Qt in both groups, 22 and 8 % in the nonheparinized dogs (P < 0.001), and 8 and 3 % in the heparinized dogs (P < 0.05).

In the nonheparinized dogs DlCO decreased in five of six dogs, the mean decreasing from 21 to 16 ml/min per mmHg (−24 %). In the heparinized dogs DlCO decreased in all five dogs in which it was measured, from a mean of 76 to 18 ml/min per mmHg (−71 %). The decrease was significant in both groups (P < 0.05).

A change in lung mechanics occurred in all of the nonheparinized dogs in whom measurements were made. Mean RL increased from 3 to 4.3 cmH$_2$O/l per s (43 %) and mean CL fell from 83 to 58 ml/cmH$_2$O (−30 %). These changes were statistically significant (RL, P < 0.01; CL, P < 0.001).

The relationship between percent pulmonary blood flow (as determined by % radioactivity) and percent weight of carbon-stained, perfused lung segments following embolization is shown in Fig. 1 for the nonheparinized dogs, and in Fig. 2 for the heparinized dogs. The standard error of the estimate for percent segmental pulmonary blood flow with respect to percent segmental weight was 5.7 % in the nonheparinized dogs, and 5.9 % in the heparinized dogs, a difference that was not significant. In normal non-embolized dogs regional pulmonary blood flow is distributed uniformly with respect to lung weight at a segmental level, the standard error of the estimate for flow with respect to weight being 1.1 % (12). The significantly greater variability of flow with respect to lung weight in the embolized dogs suggests that there is an abnormal distribution of regional pulmonary blood flow after embolization, with both over perfusion and under perfusion of perfused lung segments.

**DISCUSSION**

There are four possible mechanisms that could explain the increase in venous admixture (Qva/Qt) that occurred in the nonheparinized dogs following embolization: 1) an arterial increase, as described by West (26) who used a computer model of the lung to demonstrate that the calculated Qva/Qt as an index of ventilation-perfusion ratio inequality in the lung is altered by a change in overall ventilation or pulmonary blood flow to the model lung in the absence of any change in the distribution of ventilation or perfusion; 2) diffusion impairment, due to a reduction in diffusion surface (27), thickening of the membrane second-
have been a decrease rather than an increase (17).

In West's model, calculated \( \dot{Q}_{va}/\dot{Q}_t \) increased when minute ventilation of the model lung was decreased or when pulmonary blood flow was increased. This explanation is unlikely since minute ventilation was fixed, and if there were a change in cardiac output (i.e., pulmonary blood flow) following embolization, it would probably have been a decrease rather than an increase (17).

A reduction in diffusing capacity can cause an increase in the alveolar arterial oxygen difference AaDo2 and functionally have a venous admixture effect during breathing of ambient air. Diffusing capacity for carbon monoxide fell significantly after embolization in this study, and this finding raises two questions. First, what was the mechanism of the decrease? Second, and more relevant, was the fall in diffusing capacity sufficient to cause the observed increase in the AaDo2 and thereby the increased venous admixture effect? With respect to the first question, the most likely mechanism for the decrease in diffusing capacity for carbon monoxide was a decrease in diffusion surface and pulmonary capillary blood volume in the embolized nonperfused lung segments resulting from the fall in pulmonary vascular distending pressure distal to the site of vascular obstruction (4). Interstitial edema can be excluded as a cause of the decrease in diffusing capacity, since it was not found on careful morphologic examination including light and electron microscopy in a previous study (13). Pulmonary transit time could decrease after embolization if cardiac output was unchanged and had to pass through a smaller number of patent pulmonary vessels. However, with embolization cardiac output frequently falls and this would tend to increase transit time (17).

Another possible cause for the decrease in diffusing capacity following embolization is the development of inequalities in the distribution of alveolar ventilation and perfusion, i.e., a V/Q inequality. As described subsequently there is evidence that a V/Q abnormality does develop following embolization, presumably as a consequence of the observed changes in lung mechanics. Heparinization prior to the release of the thromboemboli prevented the change in lung mechanics, and presumably modified the V/Q abnormality. If the change in diffusing capacity following embolization in the nonheparinized dogs was due to this mechanism, there should have been less of a fall following embolization in the heparinized dogs. Inasmuch as the diffusing capacity fell to a comparable degree as the diffusing capacity fell to a comparable degree in the heparinized dogs, it seems unlikely that the V/Q abnormality, presumed to occur following embolization, had any effect on the diffusing capacity.

Regardless of the mechanism responsible for the fall in diffusing capacity, the more relevant question is whether or not it could have been responsible for the increase in AaDo2 and \( \dot{Q}_{va}/\dot{Q}_t \). It has been predicted on a theoretical basis and confirmed experimentally that diffusion capacity for carbon monoxide must fall to less than 50% of normal in man before limiting O2 transport during exercise, whether due to a decrease in surface area from loss of capillaries or an increase in membrane thickness (11). On the basis of the theoretical analysis by Shepherd (21), the diffusing capacity would have to fall to approximately 10% of normal in man before the AaDo2 would increase at rest. While these facts were ascertained for man, it is likely that they also hold true for the dog, the difference being the absolute levels at which decreased diffusing capacity causes an increase in the AaDo2. It seems unlikely that the observed fall in diffusing capacity of 24% in the nonheparinized dogs could account for the increased AaDo2 following embolization, and, therefore, any of the increase in \( \dot{Q}_{va}/\dot{Q}_t \).

Another type of diffusion impairment must also be considered, namely that due to unequal distribution of diffusing capacity with respect to capillary perfusion (9, 10, 18). Piper et al. (18) proposed this concept when they were...
unable to account for the observed AaDo₂ in normal anesthetized dogs on the basis of right-to-left shunting and ventilation-perfusion ratio inequality. Theoretical considerations indicated that the AaDo₂ was always larger when diffusing capacity was unequally distributed with respect to capillary perfusion than when it was equally distributed, even though the total measured diffusing capacity was normal in both instances. Hyde et al. (9, 10), using a stable oxygen isotope, ¹⁸O, found the single-breath oxygen diffusing capacity in man to be significantly less than that predicted on the basis of the measured single-breath carbon monoxide diffusing capacity, and calculated that the single-breath diffusing capacity for carbon monoxide would be minimally affected by uneven distribution of diffusing capacity to capillary perfusion, while the single-breath oxygen diffusing capacity would be significantly reduced. They concluded that uneven distribution of diffusing capacity with respect to capillary perfusion within each gas exchange unit was the best explanation for their findings. This is an attractive hypothesis with regard to the development of arterial hypoxemia following pulmonary embolization and could be implicated even though the single-breath diffusing capacity for carbon monoxide did not fall dramatically. It is quite likely that differences in regional capillary blood flow would exist following embolization as a consequence of varying degrees of pulmonary vascular obstruction caused by the emboli. The macro-aggregated albumin perfusion studies demonstrated that there was an abnormal distribution of regional pulmonary blood flow in perfused lung segments following embolization, with overperfusion of some lung segments, as well as underperfusion of others. Unless there were proportional changes in the diffusion surface area and capillary blood volume in the areas with increased flow, the diffusion/capillary perfusion ratio (D/Q) would decrease. However, it is unlikely that this could have been the primary mechanism responsible for the increase in Qva/Qt in the nonheparinized dogs for the following reason: Qva/Qt increased from 4 to 22 % in the nonheparinized dogs and only from 3 to 8 % in the heparinized dogs, while the abnormal distribution of pulmonary blood flow following embolization, which presumably would be responsible for the development of the D/Q abnormality, was unaffected by heparinization. However, it might be argued that the increase in Qva/Qt of 5 % in the heparinized dogs could have been due to a D/Q abnormality. In this event only 5 of the 18 % increase in Qva/Qt, approximately one-third, that occurred in the nonheparinized dogs could have been attributed to a D/Q abnormality. While this explanation cannot be excluded, as no direct measurement of D/Q distribution was made, there is another more likely explanation for the increase in Qva/Qt that occurred in the heparinized dogs, which will be discussed subsequently.

Right-to-left shunting can also be excluded as the primary mechanism for the increase in Qva/Qt in the nonheparinized dogs since the increase in Qs/Qt of 3 % could only account for a small fraction, approximately one-sixth, of the 18 % increase in Qva/Qt. Thus, by exclusion, the primary mechanism responsible for the increase in Qva/Qt in the nonheparinized dogs must have been ventilation-perfusion (V/Q) inequality, with development of areas of lung having low V/Q ratios. This mechanism would account for at least 10 of the 18 % increase in Qva/Qt, approximately one-half in the nonheparinized dogs.

The most likely mechanism for the V/Q abnormality would be regional changes in lung mechanics resulting from constriction of the smooth muscle in the conducting airways (bronchoconstriction), or constriction of the smooth muscle of peripheral airways, the respiratory bronchioles, and alveolar ducts (pneumoconstriction) (6), resulting in increased “stiffness” of the alveolar ducts, decreased regional lung distension, and decreased alveolar ventilation with a decrease in V/Q ratio if perfusion persisted. Total pulmonary resistance (Rₚ) increased and pulmonary compliance (Cₚ) fell following embolization confirming previous studies using in vivo thrombemboli (23) and barium sulfate pulmonary embolism (8). The change in Rₚ is probably due to bronchoconstriction, and the change in Cₚ to pneumoconstriction. The changes after thromboembolization are probably mediated by serotonin released by platelets that have aggregated on the surface of the thrombi as they pass through the venous circulation and right heart into the pulmonary arteries (22). If the changes in lung mechanics observed in our study were not uniform, then a V/Q abnormality should develop with bronchoconstricted, pneumoconstricted areas being under-ventilated with respect to their perfusion, i.e., decreased V/Q ratio. Furthermore, if the changes were severe enough it is possible that airway or air space closure could occur with resultant atelectasis. This could then account for the slightly increased right-to-left shunt that was observed in the nonheparinized dogs following embolization. Wilson et al. (28) found that right-to-left shunting following pulmonary embolism in the human could account for the observed arterial hypoxemia, and that it could be decreased significantly by positive-pressure breathing. They interpreted this as evidence for atelectasis as the cause of the right-to-left shunting. Caldini (5), in a study of experimental thromboembolism in dogs, found a similar response to positive end-expiratory pressure breathing and interpreted the increased Qva/Qt as being secondary to perfusion of poorly or nonventilated alveoli rather than the opening of arteriovenous shunts, since increased expiratory pressure would not be likely to close arteriovenous communications within a lung.

It is also possible that the abnormal distribution of pulmonary blood flow following embolization in our study contributed to the V/Q abnormality with overperfused lung segments having a low V/Q ratio. Heparin when given prior to embolization has been shown to prevent the mechanical changes due to autologous in vivo thromboemboli (23) and if the observed mechanical changes in the present study were responsible for the development of the V/Q abnormality and right-to-left shunt and thus the increase in Qva/Qt and arterial hypoxemia, heparin should prevent or modify the change in Qva/Qt. Heparin was in fact found to prevent significant changes in Rₚ and Cₚ, and to significantly modify the development of arterial hypoxemia when given prior to embolization. However, the increase in Qva/Qt was...
not completely prevented following embolization, and there are two possible explanations. First, as discussed previously, there may have been a D/Q abnormality that was unaffected by heparin. Second, even though significant changes in measured lung mechanics were prevented by heparin, this does not exclude the possibility that there were changes in the size of small airways or changes in the distensibility of individual gas exchange units that would not be measurable but could alter the distribution of ventilation in a sufficient number of gas exchange units to cause an increase in \( Q_{\text{va}}/Q_t \) of 5%. This latter explanation seems more likely than a D/Q abnormality as the mechanism for the increase in \( Q_{\text{va}}/Q_t \) in the heparinized dogs.

Thus, the findings in this study are consistent with the following hypothesis. Consequent to pulmonary embolization with in vivo thromboemboli in dogs, diffuse but nonuniform bronchoconstriction and pulmonary vasoconstriction occurs due to serotonin release by platelets which have aggregated on the surface of the thrombus. The areas of lung with the greatest mechanical change become poorly ventilated, or nonventilated, and without a proportional change in perfusion, the \( V/Q \) ratio of these areas decreases, leading to increased venous admixture, a widened AaDo\(_2\) difference, and arterial hypoxemia.

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REFERENCES