Gas Exchange after Pulmonary Thromboembolization in Dogs

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SUMMARY Gas exchange following experimental pulmonary thromboembolization was studied with an inert gas elimination technique in 17 dogs. Pulmonary arterial, systemic arterial, and expired gas concentrations of six gases infused intravenously were measured before embolization and 5, 10, 15, 30, 60, and 120 minutes after embolization. Distributions of ventilation-perfusion (VA/Q) ratios were derived from the measured concentrations. In all dogs, embolization caused an increase in blood flow and ventilation to VA/Q ratios less than 1. There were no lung units with VA/Q ratios between 10 and 100 before embolization, but, in two-thirds of the dogs, such regions developed after embolization. Ventilation to unperfused lung showed a transient increase of 2-6%. Radioisotope studies of lobes removed post-mortem indicated that thromboemboli rarely caused complete abolition of lobar blood flow. Pulmonary embolization did not cause arteriovenous shunts to appear. The hypoxemia caused by embolization could be accounted for by the changes in VA/Q distributions. Over the 2-hour period after embolization, lung function improved as the distributions partially returned toward the preembolization patterns.

Methods

Grouping of Dogs

The 19 mongrel dogs (20-30 kg) utilized in this study were divided into three groups. In 12 dogs (group A) thromboemboli were formed in a segment of inferior vena cava. In five subsequent dogs (group B) the thromboemboli were formed in polyethylene tubing and then released into the inferior vena cava. In two dogs (group C) no emboli were formed, but a cuff was inflated around the left pulmonary artery to accomplish complete obstruction of blood flow. The purpose of studying the latter group was to test the sensitivity of the inert gas elimination method in differentiating between unperfused and poorly perfused lung.

Preparation of Dogs

Each dog was anesthetized with intravenous sodium pentobarbital (30 mg/kg) and paralyzed with intravenous gallamine triethiodide (40 mg). Supplemental doses of both drugs were administered as needed to ensure adequate anesthesia and paralysis. The dogs were ventilated by a Harvard respirator at 9-12 breaths/minute at a constant tidal volume and rate via a cuffed endotracheal tube. Tidal volume was set to give an arterial Pco₂ of 30-40 mm Hg. An automatic sigh device produced a breath equal to 3 times the tidal volume every 15 minutes except for the first 15-minute period after the embolization. All measurements were made at least 5 minutes after a sigh. All dogs were studied in the supine position breathing room air.

Catheters were placed in (1) the femoral artery, (2) the main pulmonary artery or the right main pulmonary artery (flow-directed Swan-Ganz 7-gauge inserted under pressure monitoring), and (3) two different peripheral veins. One peripheral vein was used for infusion of the solution of gases and the other for injection of anesthetics and isotopes (see below). Cardiac output was calculated for each inert gas, using the Fick principle, and the results were averaged. The details of the inert gas method are presented elsewhere.

Femoral and pulmonary artery pressures were measured with calibrated Statham P23Db pressure transducers. Expired concentrations of O₂ and CO₂ were continuously monitored by a Perkin-Elmer or a Varian M3 mass spectrometer. These signals were recorded on a Brush recorder.

Thrombus Formation

Group A

In each of the 12 dogs in group A the vena cava was exposed through a midline laparotomy. A 7 to 9-cm...
segment of vena cava situated between the iliac and renal veins was prepared by isolating and ligating all veins entering the segment. A catheter was introduced into this segment via a femoral vein. One clamp was placed on the iliac vein which had not been catheterized and another clamp on the vena cava caudal to the renal veins, thus completing the isolation of the vena cava segment. The blood in this segment was withdrawn and discarded.

At this time a 30-ml sample of femoral artery blood was withdrawn into a plastic syringe containing 2-3 ml of tantalum powder. Tantalum was used to permit radiographic visualization of the emboli in the lungs. The blood and the tantalum were well mixed. Thrombus formation was induced with either 3-4 ml of defibrinated human plasma (nine dogs) or with 60 units of topical thrombin (three dogs). The mixture was agitated immediately for 10-15 seconds, and a sufficient amount of the mixture was injected into the isolated segment of vena cava to restore the segment to its original volume of approximately 12 ml. The blood remaining in the syringe was examined to determine whether clotting was taking place. After 30 minutes, the vena caval clot was released by removal of the clamps and, if necessary, by manual milking of the vena cava.

**Group B**

The only difference between the five dogs in this group and those of group A was in the preparation of the thrombus. In group B, the thrombus was formed with topical thrombin in a segment of polyethylene tubing (25 cm long, 0.9 cm in diameter) and released directly into the cannulated inferior vena cava previously exposed at laparotomy. This method produced clots more reproducibly than did either of the approaches used in the group A dogs.

**Group C**

After left thoracotomy, an inflatable rubber cuff was placed around the left pulmonary artery of each of two dogs. Under visual inspection, water was injected into a bulb at the end of a tubular extension from the cuff to determine the amount of water necessary to produce complete arterial occlusion. The cuff then was deflated and the bulb was buried subcutaneously outside the thorax. The dog was allowed 5 days to recover from the thoracotomy and then was prepared as described, except that laparotomy was not performed. The subcutaneous bulb was exposed, and the cuff was inflated with the amount of water necessary to produce complete arterial obstruction.

**Time Course of the Study**

**Sample Collections**

Table 1 is a summary of the time course of the experimental procedure. At each time of sample collection, systemic and pulmonary arterial blood and mixed expired gas were sampled simultaneously for gas chromatographic determination of the concentrations of the six infused gases. One set was taken prior to embolization, and six were taken at 5, 10, 15, 30, 60, and 120 minutes after embolization. At the above times, 3 ml of systemic and pulmonary arterial blood were collected for measurement of $P_{O_2}$, $P_{CO_2}$, and pH (Radiometer electrodes). Minute ventilation was recorded with a calibrated Wright respirometer during each of the six collection periods. At the beginning of the study, blood samples were drawn for determination of hematocrit, hemoglobin, and $P_{50}$.

**Radiographic Studies**

In two of the dogs from group A and in three of the dogs from group B, anterior-posterior and lateral chest x-rays were done before embolization and 3, 25, and 115 minutes after embolization in order to visualize the tantalum-impregnated emboli.

**Photoscans**

Pulmonary ventilation and perfusion scans were done on seven and eight dogs, respectively, from group A, and on both dogs in group C. The scans were obtained with an Anger camera with a parallel hole collimator. The ventilation was measured with $^{133}Xe$ by following the wash-in and wash-out of the radioactive gas. This measurement was followed by a perfusion scan with one of three isotopes: (1) $^{99m}Tc$-labeled microspheres injected before embolization or occlusion, (2) $^{111}In$-labeled microspheres injected 20 minutes after embolization, (3) $^{198}I$-labeled macro-aggregated albumin injected 125 minutes after embolization.

**Post-Mortem Studies**

The dogs were killed with intravenous potassium chloride 130 minutes after embolization or arterial occlusion.

**Table 1 Time Course of the Experimental Procedure**

<table>
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<tr>
<th>Minutes before embolization</th>
<th>Preparation of dog, insertion of catheters</th>
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<td>150</td>
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<td>$^{99m}Tc$ perfusion scan and $^{133}Xe$ ventilation scan</td>
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<td>10</td>
<td>Blood and gas collection</td>
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<td>Thrombus release</td>
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<th>Minutes after embolization</th>
<th>X-rays</th>
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<td>$^{111}In$ perfusion scan and $^{133}Xe$ ventilation scan</td>
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<td>$^{99m}Tc$ perfusion scan and $^{133}Xe$ ventilation scan</td>
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<td>120</td>
<td>Blood and gas collection</td>
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<td>125</td>
<td>$^{131}I$ perfusion scan and $^{133}Xe$ ventilation scan</td>
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<td>Sacrifice and excision of lungs</td>
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<td>X-ray of excised lung and dissection of pulmonary arteries</td>
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<td>180</td>
<td>Isotopic activity determination in each lobe</td>
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the lungs were removed from the thorax, and an anterior-posterior x-ray was performed. This film gave a record of the position of all the emboli that were found on subsequent dissection. Emboli were recorded as present or absent in four classes of arteries: (1) the main pulmonary artery, (2) the right and left pulmonary arteries, (3) the seven lobar arteries, and (4) the sublobar arteries of each lobe. After radiographic studies and gross dissection, the lungs of eight of the dogs were prepared for isotopic activity determination by separating the lobes into individual containers.

Isotopic Measurements of Distribution of Pulmonary Blood Flow

The activity of the isotopes in each lobe was determined using a lithium-drifted germanium [Ge(Li)] detector which provided a clear separation of the photo-peaks of Tc, In, and I. The amounts of Tc, In, and I injected were approximately 1.5, 0.5, and 0.5 mCi, respectively, with 75,000-225,000 particles in each injection of Tc and In.

Results

Distribution of Ventilation-Perfusion Ratios

Figures 1 and 2 illustrate two different patterns of the distributions of blood flow and ventilation that occurred following embolization. Each figure shows the results in one dog before (upper panels) and 15 minutes after embolization (lower panels). The left panels of each figure give the measured retentions and excretions plotted against blood-gas partition coefficient and connected by a smooth line. In addition, the retention solubility and excretion solubility relationships for a homogeneous lung with the same alveolar ventilation and cardiac output are given by the solid lines for comparison. On the right panels of Figures 1 and 2 are the recovered distributions of blood flow and ventilation. For the distributions shown, the closed and open circles represent blood flow and ventilation respectively for discrete VA/Q compartments. The points have been joined by smooth lines for clarity of presentation. The distributions shown are smooth distributions compatible with the inert gas data, and the limitations of this type of analysis have been discussed in detail elsewhere.14 Shunt is represented by a point over the compartment with a VA/Q ratio of zero with the corresponding percentage of the cardiac output written next to the point. In this method, shunt includes blood flow to unventilated units and to other units with a VA/Q ratio less than 0.005. Dead space, given as a percentage of the total ventilation, is shown in the upper righthand corner of each set of distributions. This value includes instrument and anatomic dead space plus ventilation to

![Figure 1](http://circres.ahajournals.org/)

**Figure 1** Measured retentions (ratio of mixed arterial to mixed venous partial pressures) and excretions (ratio of mixed expired to mixed venous partial pressures) and resulting distributions of blood flow and ventilation (right) for one dog before embolization (top panels) and 15 minutes after embolization (bottom panels).
lung units with a $V_{A}/Q$ ratio greater than 100. Note that this definition differs from the conventional physiological dead space which does include a contribution of the dead space-like effects of units with $V_{A}/Q$ ratios greater than about 1. In the upper lefthand corner are the arterial $P_{O_2}$ predicted by the distributions along with the simultaneously measured arterial $P_{O_2}$.

The preembolization distributions for both dogs in Figures 1 and 2 are unimodal and similar to those already described for supine, anesthetized, and mechanically ventilated dogs. There is no ventilation or blood flow to very high or very low $V_{A}/Q$ ratios. The shunts measured before embolization, 2.6% and 0.0% for the dogs of Figures 1 and 2, respectively, remained unchanged after embolization. In Figure 1, there was an increase in dead space after embolization, but there was no increase in dead space in the other case. As shown below, the mean dead space increase 15 minutes after embolization was small (less than 6%). This is consistent with the finding that the thromboemboli caused only partial occlusion of lobar arteries as determined by the isotope data (see below).

Following embolization of the dog of Figure 1, the most noticeable change was the leftward shift of the perfusion distribution to lung units with lower $V_{A}/Q$ ratios. The blood flow going to units with a $V_{A}/Q$ ratio less than 1, including shunt, increased from 39% of the total blood flow before embolization to 51% after embolization. The measured arterial $P_{O_2}$ fell from 91 to 80 mm Hg and there was a rise in dead space from 37% to 50%.

By contrast, in Figure 2, the most obvious change is the presence of units with $V_{A}/Q$ ratios greater than 10. Although the percentage of the ventilation going to units with a $V_{A}/Q$ ratio greater than 1, including dead space, actually decreased slightly (96% before to 92% after embolization), the percentage of the ventilation going to units with $V_{A}/Q$ ratios between 10 and 100 increased from 0% to 20%. This increase in ventilation to the higher $V_{A}/Q$ units is seen easily in Figure 2. Also, in Figure 2, as in Figure 1, there is an increase in both blood flow and ventilation to $V_{A}/Q$ units less than 1, including shunt (21-54% for blood flow and 5-8% for ventilation). These changes in perfusion and ventilation to $V_{A}/Q$ units less than 1 were accompanied by a fall in the measured arterial $P_{O_2}$ from 84 to 79 mm Hg.

Thus, the same qualitative insult, i.e., a pulmonary embolism, was found to lead to two different patterns of blood flow and ventilation distributions. In one type (Fig. 1), no lung units with $V_{A}/Q$ ratios between 10 and 100 developed while, in the other type (Fig. 2), the development of such units was marked. Both patterns show an increase in perfusion to units with a $V_{A}/Q$ ratio less than 1, which would cause arterial hypoxemia. In general, the postembolization distributions had features that were a combination of those seen in these two examples. In each of the 15 dogs in which comparisons were made, the...
Changes in lobar blood flow following pulmonary embolization in five dogs. There were 21 lobes with increases in relative flow (upper panel) and 14 lobes with decreases in relative flow (lower panel). Results at zero time are control measurements prior to embolization.

Changes in the Distribution of Pulmonary Blood Flow

By measuring the radioactivity of each lobe post-mortem, it was possible to quantitate the percentage of the pulmonary artery flow diverted away from or into each lobe by the emboli. The $^{99m}$Tc counts gave the lobar distribution of pulmonary artery flow before embolization. The $^{111}$In and the $^{131}$I gave the distribution of blood flow 15 minutes after embolization. There were five embolized dogs, 1 from group A and 4 from group B, in which all three isotopes were injected and subsequently counted post-mortem. Figure 3 gives the pre- and postembolization relative flows for all the lobes in these five dogs. Complete obstruction, as indicated by a relative flow of less than 0.2%, occurred in only one lobe in one of these dogs, and this was in a small lobe. The cardiac output did not change significantly after embolization. The figure also indicates that there was either no reperfusion or that small amounts of reperfusion (less than 9% absolute flow) occurred between 20 and 120 minutes after embolization.

Prediction of the Arterial $P_{O_2}$

With the recovered distribution of blood flow and ventilation plus the measured values of mixed venous $P_{O_2}$ and $P_{CO_2}$, minute ventilation, cardiac output, base excess, hemoglobin, hematocrit, and $P_{50}$, it was possible to calculate expected values for the arterial and expired $P_{O_2}$ and $P_{CO_2}$. This was done by computer as previously described. For the 17 dogs of groups A and B, 180 pairs of measured blood gases with the corresponding retentions and excretions were available, and Figure 4 compares the measured arterial $P_{O_2}$ and the predicted arterial $P_{O_2}$. Note that the line of best fit and the line of identity lie close to each other. We conclude from this comparison that the hypoxemia seen after pulmonary embolization in these dogs is, in general, completely explained by ventilation-perfusion inequality. It is possible, in the few cases in Figure 4 where the arterial $P_{O_2}$ was less than 50 mm Hg and the expected values greater than measured, that a small component of the hypoxemia was not due to ventilation-perfusion inequality but to diffusion impairment.

Time Course of the Gas Exchange Abnormalities

The changes in distributions occurring over the first 2 hours after embolization are illustrated for two dogs in Figures 5 and 7. Figure 5 shows the time course of one
dog from group A over 60 minutes. The preembozilization
distributions are relatively narrow with no ventilation or
blood flow to very high or very low V'A/Q ratios and no
shunt. Five minutes following embolization, both high
and low V'A/Q ratio units are evident, and there is marked
hypoxemia. No shunt developed, and the dead space
remained essentially unchanged. Over the ensuing 55
minutes, there was a progressive narrowing of the distri-
butions with movement of the mean and standard devia-
tion of the blood flow and ventilation distributions back
toward the preembozilization values. Figure 6 shows the
measured retentions and excretions which gave the distrib-
utions shown in Figure 5. As the distribution patterns
returned toward the control pattern, the measured arterial
P02 returned toward the preembozilization value. No shunt
occurred and there was essentially no change in dead
space. At 60 minutes postembozilation, the distributions
and the arterial P02 were indistinguishable from the
preembozilization values. The perfusion scan recorded 2
hours after embolization was abnormal but showed, in

**Figure 5** Sequence of blood flow and ventilation distribution changes following pulmonary embolization in one dog. Note that at 60 minutes after embolization the distributions and the arterial P02 are very close to the preembozilization measurements.

**Figure 6** The measured retentions and excretions which gave the distributions seen in Figure 5. As in Figures 1 and 2, the solid lines give the retention and excretion curves for a homogeneous lung with the same total alveolar ventilation and blood flow. The solid line is shown for comparison with the broken line which is fitted to the data. The excretion values at 5 minutes lie considerably to the right of the homogeneous curve and show a progressive return to control conditions. Corresponding changes are seen in the retentions.
comparison to the photoscan done 20 minutes after embolization, that some reperfusion of the embolized areas had occurred. The ventilation scans done 20 and 120 minutes after embolization were unchanged from the control scan. Post-mortem dissection showed that this dog had only a small amount of thrombus in the pulmonary arteries.

A dog from group B with the time course in Figure 7 was different in several respects from the dog of Figure 5. The preembolization distributions were also narrow. The small amount of blood flow to units with VA/Q ratios between 0.01 and 0.1 had little effect on the measured arterial Po2 (94 mm Hg) or the predicted arterial Po2 (87 mm Hg). The marked hypoxemia (arterial Po2 = 40 mm Hg) occurring 5-10 minutes after embolization was accompanied by significant amounts of ventilation and blood flow to lower and higher VA/Q units. Dead space also increased markedly from 31-66% of tidal volume. Over the ensuing 2 hours, there was a tendency for the distributions and the arterial Po2 to return toward preembolization measurements, but the measurements 120 minutes after embolization were still grossly abnormal. The dead space remained higher than the control value throughout the 2 hours. The shunt remained very small.

For the dog described in Figure 7, the lobar blood flow data from the radioactive indium injected 20 minutes postembolization showed a marked reduction in relative flow to both diaphragmatic lobes. The relative flow in the left diaphragmatic lobe fell from 35% to 10%, respectively, and the left cardiac lobe remained unperfused. The right diaphragmatic relative flows were 10% and 17%, respectively, and the left cardiac lobe remained unperfused. The autopsy revealed thrombus in the main pulmonary artery, the right and left pulmonary artery, and in all lobar arteries.

The patterns of the blood flow and ventilation distribution changes of the remaining embolized dogs fell between those illustrated in Figures 5 and 7. After the initial changes, there was a general tendency for the distributions to return toward the preembolization patterns. Figure 8 shows the mean changes in the first two moments of the distributions. Figure 9 depicts the means of (1) the ratio of pulmonary artery pressure and cardiac output, (2) the measured arterial Po2, and (3) the dead space (ventilation to unperfused lung). For these graphs and for the values of cardiac output and shunt, the data from groups A and B are combined. The ratio of pulmonary artery pressure to cardiac output rose sharply after embolization and did not return to control values over the observation period. Mean pulmonary artery pressure (± SEM) was 8.9 ± 0.6 mm Hg (control), rising to a maximum of 25.8 ± 2.2 mm Hg at 5 minutes and falling to 17.9 ± 1.0 mm Hg by 2 hours. It is of interest to note that in the dogs in which the distributions returned to normal (for example, Figure 5) there was no greater reversal of pulmonary hypertension than in the dogs in which the high VA/Q areas persisted (for example, Figure 7). The measured arterial Po2 fell from a mean of 84 mm Hg before embolization to a mean of 62 mm Hg immediately after embolization and return to a mean of 76 mm Hg after 2 hours.

Embolization caused no significant change in the cardiac output measured with the inert gases using the Fick principle (P > 0.05). The preembolization shunt was less than 2.6% (mean 0.7%) before embolization. In each
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•o

3.0
2.0
1.0

VENTILATION DIST.

PERFUSION DIST.

2.0
1.0

0 30 60 90 120

TIME AFTER EMBOLIZATION, min.

FIGURE 8 Changes in the log mean of the blood flow and ventilation distributions (top) and in the log standard deviation of the ventilation distributions (middle) and the blood flow distributions (bottom) following embolization. In the top panel the VA/Q ratio is given on a log scale. Points are the means (n = 13-17) ± 1 SEM.

The dead space was significantly elevated over the control values at 5, 15, and 30 minutes after embolization (P < 0.05). The mean dead space before embolization was 41.6%. At 5, 15, and 30 minutes after embolization, the mean was 47.4%, 44.8%, and 44.0%, respectively. We initially were surprised that, in general, embolization caused such small increases in the ventilation to unperfused lung.

Consequently, we prepared the two group C dogs to create a definite dead space increase. Occlusion of the left pulmonary artery in these two dogs caused an increase in dead space that persisted over 60 minutes. A total of 10 postocclusion measurements were obtained in the two dogs. In all 10 measurements, the dead space was increased over the control values. The mean increase (± SEM) in the dead space was 10.6 ± 1.3% of the tidal volume.

This increase in dead space was probably the net result of several factors. First, if the distribution of ventilation had remained unchanged, dead space would have increased by an amount equal to the original alveolar ventilation of the occluded lung. However, if all of the ventilation of the occluded lung had been diverted to the perfused lung with no change in tidal volume, the dead space would in fact have decreased (by the volume of the airways of the unperfused lung). If ventilation had been partially redistributed, as was probably the case, the change in dead space would have been between these extremes. Another factor probably reduced dead space (as measured by any gas exchange approach), namely, the effect of mixing of expired gas from the perfused and unperfused lungs in the common dead space.21

The post-mortem lobar isotope data demonstrated that inflation of the cuff produced complete occlusion of the left pulmonary artery. Blood flow to the left lung as a percent of total pulmonary artery flow before and after occlusion was 38.2% and 0.3% in one group C dog and 42.4% and 0.2% in the other. Likewise, perfusion photoscans done before and after occlusion in both dogs showed complete cessation of blood flow to the left lung.

The increase in ventilation to unperfused lung (10.6%) was far less than the amount of unperfused lung (40.3%). The smaller increase in ventilation to unperfused lung (3%) that accompanied thromboembolization could have occurred with a proportionately smaller amount of unper-
fused lung. However, the post-mortem isotope data indicated that embolization reduced but did not abolish lobar perfusion so that any increase in the amount of unperfused lung, if it did occur, would have had to have occurred within lobes.

The important finding upon complete pulmonary artery occlusion was that areas with ventilation-perfusion ratios between 10 and 100 did not develop, suggesting that the bronchial circulation is not responsible for the perfusion in areas of high VA/Q observed after thromboembolism, and that, with the inert gas approach, it is possible to differentiate between poorly perfused, well ventilated areas and ventilation to unperfused lung.

The effects of occlusion of the left pulmonary artery on the rest of the distribution patterns was relatively small. There was no significant change ($P > 0.05$) in the means of the blood flow and ventilation distributions, in their dispersions, or in cardiac output and shunt. Occlusion did cause a small (6.6 ± 0.8 mm Hg (± SEM)) but significant decrease in the measured arterial $P_{O_2}$. These findings taken together suggest that some redistribution of ventilation to the perfused lung occurred although this was not evident on the $^{133}$Xe ventilation scans.

### Autopsy, Photoscan, and Radiological Measurements of Embolization

In all dogs, the amount of thrombus in the lung was examined at autopsy. However, there was no clear correlation between the amount of thrombus seen and the physiological measurements. On gross examination, none of the lungs showed evidence of edema or infarction. There was evidence of partial reperfusion of the embolized areas in varying degrees in nine of 12 dogs on the basis of the combined photoscan and lobar flow data. The tantalum-impregnated emboli were clearly visible on anterior-posterior and lateral chest x-rays. In five dogs with x-rays taken before and 3, 25, and 115 minutes after embolization, no change in the size or position of the tantalum shadows was seen.

Only one of the 14 $^{133}$Xe ventilation scans done in seven dogs was different from the preembolization scan. Also, the two group C dogs whose perfusion scans revealed complete obstruction of blood flow showed no change in ventilation scans after occlusion. Thus, despite the demonstrated changes in the distribution of pulmonary blood flow, no shifts in ventilation patterns could be demonstrated with radioactive xenon.

### Discussion

**Blood Flow and Ventilation Distributions**

Normal humans and dogs have relatively narrow distributions of blood flow and ventilation centered on a VA/Q ratio of approximately 1. In each dog in this study, pulmonary embolization led to an increase in ventilation-perfusion inequality. A common feature of all the distributions recorded 15 minutes after embolization was an increase in blood flow to VA/Q units less than 1. The distributions determined 5 and 10 minutes after embolization were, in general, even more abnormal. This increased perfusion to lower VA/Q units (with little or no shunt) was responsible for the lowered arterial $P_{O_2}$ noted in our series.

The development of regions with VA/Q ratios between 10 and 100 was variable. Two-thirds of the dogs had such areas by 15 minutes postembolization. It is of interest to consider why this occurs in some dogs and not in others.

Figure 10 shows a two-compartment lung model in which one compartment initially received 83% of the ventilation and blood flow while the other receives 17%. By embolizing the smaller compartment sufficiently to divert 90% of its blood flow, its ventilation-perfusion ratio rises to 10 but the VA/Q ratio of the larger compartment is hardly changed (from 1 to 0.85). This results in little change in the arterial $P_{O_2}$. If, however, the larger compartment is embolized but only 50% of its blood flow is diverted, the resulting situation is very different. Now, 58% of the blood flow goes to a compartment with a VA/Q ratio of only 0.3 while the remaining compartment has a VA/Q ratio only slightly higher than initially (2 rather than 1). The net result is a substantially lower arterial $P_{O_2}$.

![Figure 10](image-url)
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P02, but without the appearance of a compartment with a ventilation-perfusion ratio higher than the upper limit of normal. Thus, the diversion of a large fraction of flow from a small lung compartment can lead to the appearance of high VA/Q units, while the diversion of a smaller fraction of blood flow from a large compartment can lead to the appearance of lower VA/Q units and more hypoxemia.

Although the above model gave hypothetical conditions under which areas of high VA/Q might develop, there was no relationship between a number of variables and the development of high VA/Q areas in the present study that might clarify the pathophysiology. Thus, some dogs developing areas of high VA/Q were only mildly hypoxemic and others were severely hypoxemic. There was equally poor correlation between the development of high VA/Q regions and the degree of pulmonary artery hypertension on the one hand and the appearance of the perfusion scan on the other. The lack of such correlations may well be due to the coexistence of the patterns of embolism, illustrated in Figure 10, and the different effects of these two patterns on gas exchange and pulmonary artery pressure.

Accuracy of Recovered Distributions

The present study has shown that, following pulmonary thromboembolism, the distribution of ventilation-perfusion ratios becomes bimodal in a large percentage of dogs and that the ventilation to unperfused lung increases only minimally. The accuracy of these observations has been examined since, as pointed out by Olszowka,22 a variety of distributions is compatible with a given set of retentions. We have shown that the physiological importance of such variability depends on the particular set of data analyzed and have developed a scheme for examining the limits on the set of compatible distributions in a given case.14

This method has been applied to three representative sets of retentions (Figure 5, 15 minutes postembolization; Figure 7, 15 minutes and 120 minutes postembolization). The results give the numerical probability estimate that in each case the distribution of ventilation is unimodal (rather than bimodal as shown). These estimates are 0%, 2%, and 8%, respectively. The calculation of maximum ventilation41 shows that, although some ventilation may be present in the intermodal area, this must be much less than in the regions of the two modes. Mean maximum dead space values (ventilation to unperfused lung or to regions with VA/Q > 100) were respectively 51.7%, 49.0%, and 39.9%, which were close to the values given by the smoothing technique (Figs. 5 and 7) of 53.8%, 46.3%, and 43.4%, respectively.

We therefore conclude that the representative distributions shown in this paper reflect the major features of the family of compatible distributions with a high degree of reliability, while the fine detail of the distributions is beyond resolution.

Causes of Hypoxemia

The relationship between the measured arterial P02 and the arterial P02 predicted from the distributions of blood flow is shown in Figure 4. The shunt measured before embolization was small and did not change significantly after embolization. The figure is evidence that, in general, all of the hypoxemia is caused by ventilation-perfusion inequality. If failure of alveolar-end-capillary diffusion equilibration were responsible in part for the observed hypoxemia, there would have been a systematic discrepancy between the measured arterial P02 and that predicted from the VA/Q distribution. The predicted arterial P02 would have exceeded the measured value because it is highly unlikely that inert gas exchange is diffusion limited.23 Since there was essentially no shunt, Figure 4 is consistent with the conclusion that ventilation-perfusion inequality is solely responsible for the hypoxemia in pulmonary thromboembolization in these dogs (except possibly for a minor contribution from diffusion impairment occurring in some dogs when the arterial P02 was less than 50 mm Hg).

Post-mortem examination failed to reveal evidence of pulmonary edema in any dog. This is consistent with the observation that the highest mean pulmonary artery pressure was 25.8 mm Hg (mean for all dogs). Other studies16,18 have shown that, at considerably higher pulmonary artery pressures associated with more severe embolism, pulmonary edema may develop. Under these conditions, additional factors may contribute to hypoxemia, such as perfusion of poorly ventilated or unventilated alveoli and failure of diffusion equilibration. Another factor important in the discussion of hypoxemia is that throughout these studies tidal volume and respiratory frequency were held constant. If the dog had been allowed to breathe spontaneously (increasing ventilation after embolism), the hypoxemia might have been less severe, but the extent and pattern of the ventilation-blood flow disturbance would presumably have been similar.

Relationship between Physiological Dead Space for CO2 and the Distribution of Ventilation

Prior to embolism, physiological dead space for CO2 averaged 43%. No areas of high VA/Q were seen in the distributions and ventilation to unperfused lung averaged 41.6%, agreeing well with the CO2 dead space. These results confirm that in normal dogs physiological dead space for CO2 reflects the volume of the conducting airways.

Following embolism, physiological dead space for CO2 rose considerably more than did ventilation to unperfused lung. For example, at 15 minutes after embolism, CO2 dead space averaged 57% but ventilation to unperfused lung rose to only 45%. Most dogs (10 of 15) developed areas of high ventilation-perfusion ratios, explaining the increase in CO2 dead space and the discrepancy between it and ventilation to unperfused lung. Thus, by using the inert gas approach, it is possible to identify the components of the physiological dead space quantitatively and thereby clarify the change produced by thromboembolism.

Time Course of the Gas Exchange Abnormalities

Embolization caused a decrease in the mean VA/Q ratio of the blood flow distribution and an increase in the mean VA/Q ratio of the ventilation distribution. Along
with this indication of increased ventilation-perfusion inequality, the standard deviations of both the blood flow and the ventilation distributions increased (Fig. 8). Both the means and the standard deviations of the distributions began to return toward the preembolization values 5-15 minutes after the embolization. In many dogs however, the distributions 2 hours after embolization were different from the preembolization distributions.

The ratio of the pulmonary artery pressure to the cardiac output rose sharply immediately after embolization and remained elevated. The major cause of the increase in pulmonary artery pressure is the mechanical obstruction of vessels, though an added stimulus from released vasoactive substances is also present. Levy et al. showed that the humorally induced vasoactive element was substantially reduced 30 minutes after embolization. The tendency of the distribution patterns to return toward preembolization patterns may reflect this decrease in the vasoactive component and to a slowly achieved rematching of blood flow and ventilation.

Varying degrees of reperfusion of embo1ized areas were found in nine of 12 dogs during the 2 hours after embolization. Moser et al. have shown that, by 3 hours after thromboembolization in dogs, the thrombi have undergone a mean dissolution of 50%. A similar dissolution process may explain the reperfusion seen in this study.

Any reperfusion of embo1ized areas would be expected to lessen ventilation-perfusion inequality. However, the large amounts of thrombus still present 2 hours postembolization and the persistence of pulmonary hypertension suggest that not all of the return toward normal distributions was caused by reperfusion. A ventilation shift to favor the rematching of ventilation and perfusion is also possible.

Multiple mechanical and anatomic approaches have suggested that airflow constriction does occur following obstruction of pulmonary artery flow. Generalized bronchoconstriction induced by the release of bronchoactive substances at the time of embolization has been described. Levy et al. suggested that generalized bronchoconstriction may initially prevent the maximal ventilation shift. During temporary unilateral pulmonary artery occlusion, several investigators have demonstrated a ventilation shift away from the occluded lung possibly mediated by local hypoxia. Others have not demonstrated such a shift. Levy and Simmons suggested that, following thromboembolization in dogs, a ventilation shift did occur. No ventilation shift was seen in this study using 133Xe, although intralobar ventilation shifts would probably not have been detected.

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 Experimental Basis for QRS and T Wave Potentials in the WPW Syndrome

The Relation of Epicardial to Body Surface Potential Distributions in the Intact Chimpanzee

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SUMMARY The Wolff-Parkinson-White (WPW) syndrome was experimentally mimicked by stimulating seven different ectopic (pre-excitation) sites in intact chimpanzees. The objective was to determine how to differentiate one ectopic site from another possible ectopic site close by. The approach used was to obtain a direct picture of total cardiac electrical activity in the form of epicardial potential distributions to understand the cardiac origin of the surface potentials throughout ventricular depolarization and repolarization. QRS-T wave body surface maps were interpreted by visually comparing them directly with the associated measured epicardial potential distributions and by quantitative comparison with those produced by adjacent ectopic sites. During early QRS (delta wave) all sites produced a body surface maximum within the same small area on the anterior chest; however, the position of the minimum was markedly different and was related spatially to the position of the ectopic site. The epicardial measurements showed that during early excitation there was a minimum of large magnitude at the ectopic site while the nearby maximum was of much lower magnitude. The body surface maxima and minima during QRS provided an easy way to distinguish between ectopic sites on one ventricle vs. the other, but between adjacent sites on the same ventricle there was frequently little change in the pattern of the QRS maximum and minimum. However, adjacent sites produced distinct changes in the distant low level potential areas. The combined analysis of QRS and T waves showed that subepicardial ectopic sites 2-3 cm apart produced detectable differences in the body surface distributions. Furthermore, the T wave patterns were as useful as or more useful than those during QRS for predicting the ectopic pre-excitation site. On the epicardium, the positions of the repolarization maximum and minimum were the same as those of the earliest and latest areas of ventricular excitation, a feature which resulted in a better indication of cardiac electrical events on the body surface during ST-T waves than during QRS.

This paper considers the use of epicardial and body surface potential distributions throughout ventricular activation and repolarization as a basis for interpreting electrocardiograms according to the site of ventricular pre-excitation in the "classic" Wolff-Parkinson-White (WPW) syndrome.1-2 Previous electrocardiogram (ECG) classifications have used QRS3-8 exclusively, with most analyses focused on early ventricular activation during the delta wave.7-8 The restriction to QRS has been a natural one, since the isochrone method,7 the current standard index of total heart electrical activity, has provided a way to depict epicardial activation sequences at surgery,3 and these sequences have been used to indicate which parts of the ventricle contribute to the deflections throughout QRS.

There are, however, several fundamental limitations imposed by this approach for classifying pre-excitation QRS and T waves on the basis of total heart electrical activity. First, the electrocardiogram and the cardiac activation sequence must be recorded at different times and under different conditions. The QRS often changes in patients with WPW,4 Therefore, unless the activation sequence is rigorously controlled during both recordings, the measured sequence at surgery may differ from the preoperative one. Second, the isochrone method provides no way to study the T wave.10 Indirect measurements of repolarization, e.g., refractory periods, apply only to a
Gas exchange after pulmonary thromboemobolization in dogs.
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