Spatial pattern of ventilation-perfusion mismatch following acute pulmonary thromboembolism in pigs

John Y. C. Tsang, Wayne J. E. Lamm, Ian R. Starr, and Michael P. Hlastala. Spatial pattern of ventilation-perfusion mismatch following acute pulmonary thromboembolism in pigs. J Appl Physiol 98: 1862–1868, 2005. First published December 10, 2004; doi:10.1152/japplphysiol.01018.2004.—We studied the spatial distribution of the abnormal ventilation-perfusion (V\text{A}/Q\text{˙}) units in a porcine model of acute pulmonary thromboembolism (APTE), using the fluorescent microsphere (FMS) technique. Four piglets (~22 kg) were anesthetized and ventilated with room air in the prone position. Each received ~20 g of preformed blood clots at time t = 0 min via a large-bore central venous catheter, until the mean pulmonary arterial pressure reached 2.5 times baseline. The distributions of regional V\text{A} and blood flow (Q\text{˙}) at five time points (t = −30, −5, 30, 60, 120 min) were mapped by FMS of 10 distinct colors, i.e., aerosolization of 1-μm FMS for labeling V\text{A} and intravenous injection of 15-μm FMS for labeling Q\text{˙}. Our results showed that, at t = 30 min following APTE, mean V\text{A}/Q\text{˙} (V\text{A}/Q\text{˙} = 2.48 ± 1.12) and V\text{A}/Q\text{˙} heterogeneity (log SD V\text{A}/Q\text{˙} = 1.76 ± 0.23) were significantly increased. There were also significant increases in physiological dead space (11.2 ± 12.7% at 60 min), but the shunt fraction (V\text{A}/Q\text{˙} = 0) remained minimal. Cluster analyses showed that the low V\text{A}/Q\text{˙} units were mainly seen in the least embolized regions, whereas the high V\text{A}/Q\text{˙} units and dead space were found in the peripheral subpleural regions distal to the clots. At 60 and 120 min, there were modest recoveries in the hemodynamics and gas exchange toward baseline. Redistribution pattern was mostly seen in regional Q\text{˙}, whereas V\text{A} remained relatively unchanged. We concluded that the hypoxemia seen after APTE could be explained by the mechanical diversion of Q to the less embolized regions because of the vascular obstruction by clots elsewhere. These low V\text{A}/Q\text{˙} units created by high flow, rather than low V\text{A}, accounted for most of the resultant hypoxemia.

The mechanism of hypoxemia in acute pulmonary thromboembolism (APTE) remains poorly understood. The data from the urokinase trial showed that there was a wide variation of arterial oxygen tensions (P\text{A}O\text{₂}) among patients presented with this life-threatening illness (20). Patients’ chest X-rays are often unremarkable except for some minor atelectasis or small pleural effusion. In fact, when there is a substantial discrepancy between the degree of hypoxemia and radiological findings, acute pulmonary embolism becomes the first diagnosis to be ruled out. Further confusing the issues, previous studies on APTE using multiple inert-gas elimination technique (MIGET) reported conflicting results, with some showing significant shunts (8), whereas the others showed almost none (9).

The lack of bronchospasm in clinical examination and minimal consolidation on chest X-rays among patients with APTE did not suggest low alveolar ventilation (V\text{A}) as a major cause of hypoxemia. Recent investigation using multiple-breath helium washout technique by Tsang et al. (23) reported that ventilation heterogeneity did not change significantly following acute pulmonary beal embolization. On the other hand, many studies on acute pulmonary embolism showed significant redistribution of regional blood flow (Q) in the lung. Burton et al. (7), using a perfusion scan, reported that Q in the lung was substantially increased in the less embolized regions, whereas the heavily embolized areas received significantly lower Q. Tsang et al. (24) confirmed similar results using radioactive microspheres. Furthermore, Malik and van der Zee (17) also found that there was more fibrin deposition in the nonembolized regions of the lung, presumably because of the increased Q in these areas after acute embolic injury. Investigators over the past few decades proposed that there were some vasoactive or bronchospastic mediators released after APTE, such as histamine (27), serotonin (11, 15), platelet-activating factor (5, 6), prostaglandins (27, 21), endothelin-1 (16), or cytokines (26), etc., which could explain the pulmonary hypertension and possibly the disturbances in regional ventilation-perfusion (V\text{A}/ Q) matching. However, most of these reports were based on pharmacological studies using different antagonists to provide indirect evidence, but their casual relationships have not been well established. Furthermore, these data were mostly focused on pulmonary hemodynamics rather than gas exchange.

The recently developed technique using aerosolized and injected fluorescent microspheres (FMS) allowed the simultaneous measurement of regional V\text{A} and Q in the small regions (2 cm³) of the lung (3). Using appropriate data recording methods and computer software, a three-dimensional (3D) model of an experimental lung with various V\text{A}/Q could be reconstructed (1, 13). These results were more informative than those from the MIGET studies because of the additional anatomical correlations. An earlier report by Altemeier et al. (3) pioneered the study of V\text{A}/Q mismatch at 30 min after acute pulmonary bead embolization but did not report its spatial distributions.

The purpose of our investigation was to study the pattern of regional V\text{A} and Q after APTE in an animal model mimicking a clinical situation. We proposed to use aerosolized and injected FMS to serially mark the regional V\text{A} and Q following

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APTE for 2 h and correlate these data in physiological and anatomical terms, such as central vs. peripheral regions and clot locations, etc. Hopefully, we could also elucidate the mechanism of hypoxemia and resolve some of the conflicting issues in the past.

METHODS

Surgical preparations and physiological measurements. The experimental protocol was approved by the University of Washington Animal Care Committee.

Four piglets (22 ± 3 kg) were premedicated with ketamine (20 mg/kg im) and xylazine (2 mg/kg im). They were maintained under general anesthetic for the entire experiment using intravenous pentothal, initially set at 100 mg/h, but the dose was titrated as needed. These animals were ventilated with room air in the supine posture while the tracheostomy and vascular line insertions were completed.

One femoral arterial line and two femoral venous lines were inserted for the purposes of monitoring systemic blood pressure (BP), fluid infusion, and FMS injection, respectively. A Swan Ganz catheter (Edwards Laboratory) was inserted in the right external jugular vein for the measurement of pulmonary arterial pressure (Ppa), wedge pressure, and cardiac output (Qr), while a large-bore catheter was inserted in the left external jugular vein for the rapid infusion of preformed blood clots (see below). Generally, these animals received normal saline at 100 ml/h during the experiments. They were kept warm using a warming blanket so that the body temperature was maintained at ~38°C. No heparin was used.

After the insertion of the femoral arterial line, 80 ml of blood were withdrawn and mixed with 2,500 units of Thrombostat at 21°C so that clots were allowed to form and fibrinized over the next 2 h. They were suspended in normal saline in a large-bore syringe before injection at the appropriate time into the left external jugular vein.

On completion of the surgical procedures, the animals were placed in the prone posture and received suctioning of at least three consecutive breaths to remove residual atelectasis. Their mandatory control ventilatory settings were adjusted according to the arterial blood-gas analysis (so that PaO2, arterial PO2, was maintained at ~2 Torr, positive end-expiratory pressure was 0 cmH2O, respiratory rate was 18 to 20 breaths/min, and oxygen was at 21% or room air.

The time for the induction of APTE was defined as time 0 min. Approximately 12–16 pieces of preformed fibrinized clots (~20 g in total or ~1.5 g per piece) would be suspended in normal saline in a large-bore syringe and injected into the left external jugular vein over the next 10–15 min, until Ppa was 2.5 times the baseline value. On completion, there were no further injections of clots. On some occasions, ~200 ml of normal saline were given to restore BP.

Later, at time = 30, 60, and 120 min, FMS aerosolization and injection were similarly done following the physiological measurements and blood sampling, using microspheres of different colors each time. Stacking of breaths would be done consistently before data collection to minimize atelectasis. At time = 90 min, physiological measurements and blood sampling were also done, but no FMS were administered.

Postmortem lung preparations. At the end of the experiment, the animal was placed on a mesh sheet with intravenous pentothal, heparinized with 5,000 units, and exsanguinated. The lungs were extracted after gentle saline flush and inflated to no more than 25 cmH2O. The lobes were glued into their resting anatomical position and blown dry with warm air through the lungs for 72 h. Small puncture holes were made to allow good airflow through the lungs during the drying process.

After the thorough drying of the harvested lungs, they were sliced and diced into ~2-cm3-sized samples, with each sample carefully assigned a 3D coordinate according to a preestablished grid pattern. Approximately 950 pieces were analyzed per animal. For each lung sample, its spatial location, weight, amount of airway tissue, and the presence or absence of blood clots in arteries >1 mm were recorded. Furthermore, the fluorescent intensities of all 10 FMS embedded in each sample, which marked the regional Va and Q at five different time points (i.e., time = ~30, ~50, 30, 60, and 120 min), were measured. The details of the method have been given previously. Briefly, the fluorescent signal, or concentration of each color, was determined by measuring the fluorescence per piece in a spectrometer following 4 days of soaking in 2 ml of organic solvent (Cellosolve, Sigma-Aldrich, St. Louis, MO). Overlaps from adjacent colors were then corrected using a matrix inversion method (12).

Data analyses. After determining the regional Va and Q of each lung piece, the V/Q ratio could be readily calculated. By solving the mass balance equation, the corresponding regional PaCO2 could also be estimated (1). The composite V/Q and regional PaCO2 in each cluster were also plotted against time to examine their patterns of changes before and after APTE and their impact on overall gas exchange.

Finally, the PaCO2 measured directly by arterial blood gas could be compared with the PaCO2 estimated by the FMS data, obtained after knowing all of the regional V/Q. This comparison would serve also as quality control of experimental technique.

Table 1. Physiological parameters

<table>
<thead>
<tr>
<th>Table 1. Physiological parameters</th>
<th>Control 1 (~30 min)</th>
<th>Control 2 (~5 min)</th>
<th>30 min</th>
<th>60 min</th>
<th>90 min</th>
<th>120 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Ppa, cmH2O</td>
<td>1.7 ± 0.2† 2 Torr</td>
<td>2.7 ± 0.3† 3 Torr</td>
<td>2.7 ± 0.3† 3 Torr</td>
<td>2.3 ± 0.3 2.4 ± 0.3 2.2 ± 0.2 2 Torr</td>
<td>1.7 ± 0.2† 2 Torr</td>
<td></td>
</tr>
<tr>
<td>Mean BP, mmHg</td>
<td>96 ± 6.7</td>
<td>97.5 ± 5.4</td>
<td>110.5 ± 10.5 110.1 ± 15.0</td>
<td>106.8 ± 17.2 105.2 ± 16.9</td>
<td>104.9 ± 16.9 105.2 ± 16.9</td>
<td></td>
</tr>
<tr>
<td>Mean Qr, l/min</td>
<td>2.9 ± 0.23</td>
<td>2.6 ± 0.23</td>
<td>2.7 ± 0.3† 3 Torr</td>
<td>2.3 ± 0.3 2.4 ± 0.3 2.2 ± 0.2 2 Torr</td>
<td>1.7 ± 0.2† 2 Torr</td>
<td></td>
</tr>
<tr>
<td>Mean PVR, cmH2O/min−1</td>
<td>6.3 ± 1.8</td>
<td>7.9 ± 3.1† 4 Torr</td>
<td>16.5 ± 3.2 16.9 ± 2.7</td>
<td>15.0 ± 1.7 15.5 ± 0.8</td>
<td>16.9 ± 3.2 16.9 ± 2.7 15.0 ± 1.7 15.5 ± 0.8</td>
<td></td>
</tr>
<tr>
<td>Mean PaO2, Torr</td>
<td>108 ± 8.5</td>
<td>110 ± 8.5</td>
<td>65 ± 13§ 77 ± 10</td>
<td>84 ± 10 85 ± 7</td>
<td>65 ± 13§ 77 ± 10 84 ± 10 85 ± 7</td>
<td></td>
</tr>
<tr>
<td>Mean PaCO2, Torr</td>
<td>37 ± 3*</td>
<td>36 ± 2*</td>
<td>53 ± 8 51 ± 5</td>
<td>49 ± 5 49 ± 6</td>
<td>53 ± 8 51 ± 5 49 ± 5 49 ± 6</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD. Ppa, pulmonary arterial pressure; BP, blood pressure; Qr, cardiac output; PVR, pulmonary vascular resistance; PaO2, arterial PO2; PaCO2, arterial PCO2. Statistical significance based on repeated-measure ANOVA and Fisher’s paired least significant difference post hoc test: *P < 0.05 vs. 30, 60, 90, and 120 min; †P < 0.05 vs. controls, 60, 90, and 120 min; §P < 0.05 vs. 60, 90, and 120 min.

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The weight-normalized relative \( V_A \) (WNRVA) and weight-normalized relative \( Q \) (WNQR) of each lung sample were calculated in order that these lung samples could be compared with each other at the same time point and at different time points, when total \( V_A \) and \( Q \) (or total physiological dead space) were somewhat different. The steps are summarized as follows.

After the regional \( V_A \) and \( Q \) of each lung sample were obtained from the FMS data at a given time, they were first normalized to the weight of the sample. Because large airway and vasculature add to the piece weight, pieces designated as containing >20% large airways/vessels were omitted from the following weight normalization, which, on average, was 8.7 \pm 4.2% (SD) of the original lung pieces. At each time point when FMS were used, e.g., time = −30, −5, 30, 60, and 120 min, the mean weight-normalized \( V_A \) or \( Q \) of the lung samples was calculated by summing up the individual weight normalized \( V_A \) or \( Q \) at that time point, respectively, and dividing that sum by the total number of samples of the lung in that experiment. The lung samples could then be expressed as WNRVA and WNQR, relative to that mean for \( V_A \) and \( Q \), respectively, represented as 1 or 100%.

Afterward, lung samples were subject to metacluster analysis, according to the magnitude of WNQR after APTE. All pieces from all lungs were assigned by k-means clustering to the best matching pattern using statistical software (JMP, SAS Institute, Cary, NC). Briefly, three patterns of WNQR were found, i.e., decreased after APTE (\emph{cluster 1}), relatively unchanged after APTE (\emph{cluster 2}), and increased after APTE (\emph{cluster 3}). With these grouped data, the WNRVA and WNQR of each of these clusters before and after APTE through the entire experiment could be plotted against time and their changes examined.

The spatial locations of all of the lung pieces in the same cluster, labeled by the same color, were presented in a 3D lung model, again using the JMP software (SAS Institute). The positions of the thromboemboli seen within arteries (\( \geq 1 \) mm diameter) were also marked.

Thus the anatomical correlation of these three clusters could be visualized, particularly in terms of their relationship to the clots.

All data are expressed as means \( \pm \) SD, unless indicated otherwise. To assess the reproducibility of the FMS technique, linear regression analysis was done for the two control runs before APTE, for both regional \( V_A \) and regional \( Q \) in the same piece of lung. Repeated-measures ANOVA and Fisher’s paired least significant difference post hoc test were performed to detect difference in values over time. \( P \) was set at 0.05 as the level of significance.

### RESULTS

#### Physiological data.
Table 1 shows that, after APTE at time = 0 min, there were significant pulmonary hypertension and increases in pulmonary vascular resistance, whereas the \( Qr \) slightly decreased. \( P_{O2} \) from blood-gas data decreased abruptly but gradually recovered over time. \( P_{CO2} \) increased following APTE, whereas the total \( V_A \) remained fixed during the experiment.

#### Reproducibility of the FMS technique.
The linear regression coefficient \( (R^2) \) for \( V_A \) and \( Q \) between control run 1 (time = −30 min) and control run 2 (time = −5 min) were 0.90 ± 0.07 and 0.86 ± 0.06, respectively. They showed that, under control condition before APTE, there was good reproducibility of regional markings by FMS. Thus the subsequent changes in \( V_A \) or \( Q \) were mostly due to the induced pathophysiological changes.

Further reliability of the FMS technique is the comparison of the measured \( P_{O2} \) vs. that calculated for the FMS data using the mass balance equation. The linear regression coefficient \( (R^2) \) was 0.912 with a slope of 0.81 and an intercept of 15.6.

#### \( V_A/Q \) analyses.
Table 2 shows the data on \( V_A/Q \) heterogeneity. The \( V_A/Q \) in each region of the embolized lung were calculated directly from the FMS data and plotted in histograms at different times for each of the experiments. Mean \( V_A/Q \) was calculated from the main peak \( (V_A/Q \geq 100) \), whereas log SD \( V_A/Q \) represented the standard deviation or the heterogeneity of this main peak. Both increased significantly following APTE, mainly due to the creation of higher \( V_A/Q \) units. This would be the result of either increased regional \( V_A \) or decreased \( Q \). Note that both mean \( V_A/Q \) and log SD \( V_A/Q \) gradually improved over time.

Shunt, defined as \( V_A/Q < 0.01 \), was essentially 0% in all of the measurements. However, there was significantly increased physiological dead space, defined as \( V_A/Q > 100 \). Dead space reached its maximal value at 60 min after APTE but decreased by 120 min.

#### Cluster analyses.
Using cluster analyses, three subpopulations of lung pieces were identified according to the pattern of WNQR after APTE (Fig. 3), namely, those that decreased over

![Graph](https://via.placeholder.com/150)

\( y = 15.6 + 0.81x \)  \( R^2 = 0.912 \)

Fig. 1. Data from all 4 animal shows good matching between the measured arterial \( P_{O2} \) and \( P_{O2} \) calculated by the mass balance equation from the fluorescent microsphere (FMS) data. The line of regression (solid) and line of identity (dotted) are also shown.

### Table 2. Gas-exchange parameters

<table>
<thead>
<tr>
<th>Time</th>
<th>Control 1 (−30 min)</th>
<th>Control 2 (−5 min)</th>
<th>30 min</th>
<th>60 min</th>
<th>120 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ( V_A/Q )</td>
<td>1.02 ± 0.09</td>
<td>1.08 ± 0.13</td>
<td>2.48 ± 1.12*</td>
<td>1.70 ± 0.42</td>
<td>2.19 ± 0.83*</td>
</tr>
<tr>
<td>Log SD ( V_A/Q )</td>
<td>0.50 ± 0.16</td>
<td>0.40 ± 0.09</td>
<td>1.76 ± 0.23†</td>
<td>1.42 ± 0.26†</td>
<td>1.39 ± 0.21†</td>
</tr>
<tr>
<td>%Shunt</td>
<td>0±0</td>
<td>0±0</td>
<td>0±0</td>
<td>0±0</td>
<td>0±0</td>
</tr>
<tr>
<td>%Dead space</td>
<td>0±0</td>
<td>0±0</td>
<td>6.2±5.2*</td>
<td>11.2±12.7*</td>
<td>4.3±2.8*</td>
</tr>
</tbody>
</table>

Values are means ± SD. Acute pulmonary thromboembolism is at time = 0. Mean and log SD \( V_A/Q \) range from 0.01 to 100; %shunt, \( V_A/Q < 0.01 \); %dead space, \( V_A/Q > 100 \). Statistical significance based on repeated-measures ANOVA and Fisher’s paired least significant difference post hoc test: * \( P < 0.05 \) vs. controls 1 and 2; † \( P < 0.05 \) vs. all others.
time (cluster 1), remained unchanged over time (cluster 2), and increased over time (cluster 3).

Table 3 shows the number of pieces in each cluster in all of the experiments. Note that cluster 1 represented the most samples, and cluster 3 represented the fewest, and that this pattern is seen across all four animals.

Figure 3 shows the plot of WNRQ from these three preidentified clusters against time. They represent three distinct populations. On the other hand, WNRVA remained robust and changed proportionally less than WNRQ in the corresponding cluster (Fig. 4). Therefore, the increased number of high V̇A/Q̇ units following APTE (Table 2) was created mostly by reduced regional Q̇, rather than increased V̇A.

Table 3. Cluster distribution among all animals

<table>
<thead>
<tr>
<th>Animal</th>
<th>Cluster 1</th>
<th>Cluster 2</th>
<th>Cluster 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>321</td>
<td>230</td>
<td>127</td>
</tr>
<tr>
<td>B</td>
<td>624</td>
<td>186</td>
<td>151</td>
</tr>
<tr>
<td>C</td>
<td>495</td>
<td>275</td>
<td>224</td>
</tr>
<tr>
<td>D</td>
<td>466</td>
<td>228</td>
<td>126</td>
</tr>
<tr>
<td>Mean</td>
<td>477</td>
<td>230</td>
<td>157</td>
</tr>
<tr>
<td>±SD</td>
<td>124</td>
<td>36</td>
<td>46</td>
</tr>
</tbody>
</table>

When plotting regional V̇A/Q̇ vs. time (Fig. 5), low V̇A/Q̇ units were created following APTE in cluster 3, mainly due to increased regional Q̇, even though simultaneous WNRVA was also higher. High V̇A/Q̇ units were created in cluster 1. There was some recovery at 120 min. Cluster 2 remained relatively constant throughout the experiment in both WNRVA and WNRQ.

The regional PaO2 was plotted against time for all three clusters in Fig. 6. Due to the very low WNRQ in cluster 1, their V̇A/Q̇ units behaved effectively as dead space, and the corresponding regional PaO2 was the highest. The V̇A/Q̇ units of cluster 2 remained relatively constant, as both WNRVA and WNRQ changed little. The high V̇A/Q̇ at 30 min was due to just a few pieces that had very low Q̇ at that time point, which skews the mean upward, as indicated by the large SD value. Thus the corresponding PaO2 stayed near the preembolized, i.e., the control, level. Finally, due to the severalfold increases in WNRQ in cluster 3, V̇A/Q̇ and regional PaO2 decreased significantly in the first 60 min after APTE, despite a modest increase in WNRVA at the same time. This cluster 3 had the lowest PaO2, and was likely to be an important contributor to the observed arterial hypoxemia.

DISCUSSION

The experimental model used in the present study mimicked closely the clinical setting of APTE, using blood clots instead
of glass or polystyrene beads as embolic materials. These clots were delivered to the lung directly through the central vein and could be readily seen postmortem, obstructing major pulmonary vessels. Because these preformed clots were allowed to mature and fibrinize for 2 h in vitro, they were more resistant to the naturally occurring fibrinolytic process in the experimental animals. Patients who developed APTE often had blood clots from the deep veins in the legs, which might also have thrombosed in the preceding hours (4).

Table 1 shows the physiological changes after APTE, further confirming the validity of our experimental model. After APTE, there were significant increases in Ppa and pulmonary vascular resistance and decreases in PaO₂. Note that there was gradual recovery toward baseline in all of these parameters. Because the total V̇A was kept essentially constant during the experiment, the increase of PâCO₂ after APTE was mostly due to the creation of new high V̇A/Q̇ units and physiological dead space (Table 2). We do not think that the hemodynamic recovery was due to dissolution of the blood clots, as many of these high V̇A/Q̇ units persisted (Table 2 and Fig. 5) and PâCO₂ remained high.

Figure 2 and Table 2 show that there were significant increases in mean V̇A/Q̇, log SD V̇A/Q̇, and physiological dead space after APTE, while the shunt fraction remained low.

These results showed that the increases in V̇A/Q̇ heterogeneity after APTE were due to the creation of high V̇A/Q̇ units but also some lower V̇A/Q̇ units as well, although they were not as low as zero, which then would be considered as shunts.

Our data also showed that there was significant redistribution of WNRQ̇ after APTE (Fig. 3), with much reduced flow distal to the emboli and in the peripheral parts of the lung (cluster 1 in Fig. 7). The most likely explanation of this observation was the mechanical obstruction by the clots, which could impede any forward flow. Ischemia in these subpleural areas might cause pleuritic chest pain among patients with APTE and potentially pulmonary infarcts, especially when the left atrial pressure was elevated. Because of the reduced WNRQ̇ to these regions, they effectively behaved as high V̇A/Q̇ units and physiological dead space in terms of gas exchange. As it was mentioned, their creation resulted in higher mean V̇A/Q̇, log SD V̇A/Q̇ (Table 2), and PâCO₂ (Table 1). Following APTE, their regional PaO₂ was also the highest among the three clusters (Fig. 6).

In contrast, looking at cluster 3 in Fig. 3, there were areas in the lung in which WNRQ̇ was significantly increased, resulting in the creation of lower V̇A/Q̇ units (Fig. 5). They constituted ~18% of the lung regions, with V̇A/Q̇ about ≤0.5. Figure 7 showed that these regions were mostly located in the least embolized regions of the lung, and their corresponding regional PaO₂ was the lowest (Fig. 6). Regional pulmonary Q̇ blocked by embolic obstruction must be acutely diverted and increased to the more readily recruitable areas. Such abrupt changes in regional Q̇ might well account for the sudden overall hypoxemia seen after APTE (Table 1). Note that, after 30 min (Fig. 3), cluster 3 showed a gradual decrease in
WNRQ, resulting in the gradual recovery of the corresponding $V_d/Q$ units (Fig. 5) and $P_aO_2$ (Fig. 6) toward the preembolized condition. Thus the ongoing mechanical redistribution of regional $Q$ in the lung following APTE had a continuous impact in the determination of gas exchange.

Cluster 2, identified in our data analyses, had relatively little physiological effects because their WNRQ, WNRV, $V_d/Q$ ratio, and regional $P_aO_2$ stayed comparable during the experiment. It constituted $\sim 27\%$ of the lung regions, and these regions were spatially located mainly in the intermediary areas between clusters 1 and 3.

We also reported that the changes in WNRV in Fig. 4 were quite modest compared with those in WNRQ. These data were consistent with our results in Table 2, which showed that there was essentially no shunt, in which $V_d$ was zero. The relatively steady state of WNRV was consistent with an earlier study using multiple-breath helium washout technique, which showed that there was no significant increases in $V_d$ heterogeneity following pulmonary bead embolization (23). Clinically, there is rarely any consolidation in chest X-ray from patients with APTE, which would suggest reduced regional $V_d$ except for some minor atelectasis. In the previous studies of pulmonary embolism, the amount of lung water reported was generally not sufficient to cause significant hypoxemia due to significant pulmonary edema (22).

On the other hand, Burton et al. (7) showed that there was significant diversion of $Q$ from the embolized regions using nuclear scans of the patients with APTE. Tsang et al. (24) quantified regional $Q$ in the lung in relation to the embolic load by polystrene beads and found an inverse relationship. In another study, we reported that, following acute pulmonary bead embolism in an animal model, when $Q_r$ was restored to the preembolized level by either fluid or vasopressors, gas exchange remained poor even though the increased $Q$ was now diverted to the least embolized and presumably normal regions (25). The corresponding MIGET data showed consistently high $V_d/Q$ heterogeneity, regardless of the methods of resuscitation. Presumably, this observation was due to the creation of high and low $V_d/Q$ regions as pulmonary $Q$ was increased and diverted. Altemeier et al. (3), using the FMS technique, recently reported that these redistributions of regional pulmonary $Q$ might contribute to the hypoxemia after acute pulmonary bead embolization, but the anatomical correlations were not explored.

Kontos et al. (15a) showed that acute depression of $P_aO_2$ <40 Torr in patients was consistently associated with increased $Q_r$, whereas those with less hypoxemia had less striking increases in cardiac indexes (10). They reasoned that hypoxemia was the reason for the hyperdynamic state, due to sympathetic discharge or increase in venous return because of venoconstriction. Another way to explain these results would be that the increased $Q_r$ had caused more hypoxemia because more regions of high flow were created as a result of the higher total pulmonary $Q$. Thus more low $V_d/Q$ regions were created as total $Q$ or $Q_r$ increased, leading to more hypoxemia.

McIntyre and Sasahara (18a) reported that the degree of hypoxemia after APTE could be correlated with the extent of pulmonary vascular obstruction in a linear relationship ($r = 0.65$). One interpretation would be to suggest that, when the embolic load was increased, there would be more diversion of $Q$ to the least embolized regions, resulting in the creation of more, low $V_d/Q$ regions and hypoxemia. Furthermore, they also showed that, following APTE, previously healthy patients could not generate a Ppa beyond 40 mmHg due to the lesser muscularity in the right ventricle. However, if a pulmonary vasculature was healthy and recruitable on increased demand from higher flow, its cross-sectional area could be increased accordingly and the Ppa would not increase beyond a certain physiological point. This would be in contrast to other patients having APTE who had preexisting chronic obstructive lung disease or mitral valve disease. Their pulmonary circulation would be far more limited for recruitment, and, therefore, their ability to cope with increased regional flow in the lung would be more compromised. Interestingly, McIntyre (18) reported that patients with a previous history of chronic obstructive lung disease or mitral valve disease had a much higher Ppa and lower $Q_r$ after suffering from APTE. Admittedly, these patients with chronic pulmonary hypertension might also have more powerful right ventricles due to the chronic increase in afterload.

Therefore, these earlier reports, which showed that, following APTE, patients became more hypoxic when 1) $Q_r$ was high or when 2) the embolic load caused more vascular obstruction, were consistent with our conclusions that diversion of increased flow to the less embolized regions could result in the creation of low $V_d/Q$ regions and affect adversely the gas exchange.

Using the MIGET method, Dantzker and Bower (9) demonstrated the time sequence of $V_d$ and $Q$ in the lung following embolization. At the early stage, there were bimodal distribution of $V_d/Q$, increases in its heterogeneity, and creation of high $V_d/Q$ units. But after 60 min, these distributions were close to preembolization pattern. These results were consistent with our findings that there was dynamic redistribution of regional $Q$ in the lung after APTE. Because there were different ways to redistribute pulmonary $Q$, depending on the embolic size and location, the MIGET patterns might well be variable from experiment to experiment. Most of them showed varying increases in high $V_d/Q$ units, but the shunt fraction remained low at $<5\%$, which were our current findings. Furthermore, these changes were clearly dynamic over time. This might be one of the reasons that there was such a wide range of $P_aO_2$ among patients suffering from APTE. There were, however, rare exceptions that showed large shunts in experimental dogs that had massive pulmonary embolism (30). It was possible that the amount of $Q$ diversion in those unusual circumstances was extremely severe.

We speculated that, in the clinical setting, small subsegmental pulmonary emboli found incidentally in spiral computed tomography scan might be clinically insignificant, in the absence of deep vein thrombosis or other ongoing threats of further embolization. These small emboli would likely cause insignificant redistribution of $Q$ and areas of low $V_d/Q$, which would not lead to hemodynamic instability or further hypoxemia. Empirical treatment with anticoagulation is not without risks. Furthermore, the relative importance of mediators in affecting the pathophysiology of APTE needs to be reevaluated as new data come into light and old data are reexamined.

In summary, we conclude that the changes in $V_d/Q$ after APTE are mainly due to a dynamic redistribution of regional $Q$ in the lung and, to a lesser extent, a redistribution of $V_d$. The lower $V_d/Q$ regions created by higher flow were found in the
less embolized regions, presumably due to vascular recruitment since the local resistance was the lowest. They contributed the most to the acute hypoxemia after APTE, but the subsequent equilibration in the pulmonary vasculature resulted in some recovery toward the preembolized level. On the other hand, high $V_A/Q_\dot{V}$ regions, created by reduced flow, were found distal to the emboli and in the periphery of the lung, presumably due to vascular obstruction by the clots. They were in the subpleural and more peripheral areas and behaved physiologically like dead space. Because minute ventilation was constant, they contributed to the increase in $P_{aCO_2}$. The worsening of $V_A/Q_\dot{V}$ heterogeneity in the lung following APTE was mainly due to changes in $Q$ rather than $V_A$.

GRANTS

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