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

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Running Head: \( \dot{V}_A/\dot{Q} \) mismatch after pulmonary embolism

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ABSTRACT

We studied the spatial distribution of the abnormal $\dot{V}_A/\dot{Q}$ units in a porcine model of acute pulmonary thromboembolism (APTE), using the fluorescent microsphere (FMS) technique. Four piglets (~22 Kg) were anaesthetized and ventilated with room air in the prone position. Each received about 20 grams pre-formed blood clots at time = 0 minutes via a large bore central venous catheter, until the mean pulmonary artery pressure reached 2.5 times baseline. The distributions of regional ventilation ($\dot{V}_A$) and blood flow ($\dot{Q}$) at five time points (t = -30, -5, 30, 60, 120 min) were mapped by FMS of 10 distinct colors, i.e. aerosolization of 1 $\mu$m FMS for labelling ventilation and intravenous injection of 15 $\mu$m FMS for labelling perfusion. Our results showed that at time = 30 minutes following APTE, mean $\dot{V}_A/\dot{Q}$ ($\dot{V}_A/\dot{Q} = 2.48 \pm 1.12$) and $\dot{V}_A/\dot{Q}$ heterogeneity (Log SD $\dot{V}_A/\dot{Q} = 1.76 \pm 0.23$) were significantly increased. There were also significant increases in physiological dead space (11.2 ± 12.7 % at 60 min) but the shunt fraction ($\dot{V}_A/\dot{Q} = 0$) remained minimal. Cluster analyses showed that the low $\dot{V}_A/\dot{Q}$ units were mainly seen in the least embolized regions, whereas the high $\dot{V}_A/\dot{Q}$ units and dead space were found in the peripheral subpleural regions distal to the clots. At 60 and 120 minutes, there were modest recoveries in the hemodynamics and gas exchange towards baseline. Redistribution pattern was mostly seen in regional $\dot{Q}$ while $\dot{V}_A$ remained relatively unchanged. We concluded that the hypoxemia seen after APTE could be explained by the mechanical diversion of blood flow to the less embolized regions because of the vascular obstruction by clots elsewhere. These low $\dot{V}_A/\dot{Q}$ units created by high flow, rather than low ventilation, accounted for most of the resultant hypoxemia.
Key words: Acute pulmonary embolism
Cluster analyses
Fluorescent microspheres
Gas exchange
Hypoxemia
Regional blood flow
Regional ventilation
INTRODUCTION

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 tension (PaO₂) 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), while the others showing 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 (\(\dot{V}_a\)) as a major cause of hypoxemia. Recent investigation using multiple breath helium washout technique by Tsang et al reported that ventilation heterogeneity did not change significantly following acute pulmonary bead embolization (23). On the other hand, many studies on acute pulmonary embolism showed significant redistribution of regional blood flow (\(\dot{Q}\)) in the lung. Burton et al, using a perfusion scan, reported that blood flow in the lung was substantially increased in the less embolized regions while the heavily embolized areas received significantly lower blood flow (7). Tsang et al confirmed similar results using radioactive microspheres (24). Furthermore, Malik and his associates also found that there was more fibrin deposition in the non-embolized regions of the lung,
presumably because of the increased blood flow in these areas after acute embolic injury (17). 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 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 ventilation and perfusion in the small regions (2 cm³) of the lung (3). Using appropriate data recording methods and computer software, a three dimensional (3-D) model of an experimental lung with various $\dot{V}_A/\dot{Q}$ could be reconstructed (13, 1). These results were more informative than those from the MIGET studies because of the additional anatomical correlations. An earlier report by Altemeier et al pioneered the study of $\dot{V}_A/\dot{Q}$ mismatch at 30 minutes after acute pulmonary bead embolization but did not report its spatial distributions (3).

The purpose of our investigation was to study the pattern of regional ventilation and blood flow after acute pulmonary thromboembolism in an animal model mimicking a clinical situation. We proposed to use aerosolized and injected FMS to serially mark the regional ventilation and perfusion following APTE for two hours 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

1. Surgical preparations and physiological measurements: The experimental protocol was approved by the University Washington Animal Care Committee. Four piglets (22 ± 3 Kg) were pre-medicated with ketamine 20 mg/Kg i.m. and xylazine 2 mg/Kg i.m. They were maintained under general anaesthetic for the entire experiment using intravenous pentothal, initially set at 100 mg/hour 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 of systemic blood pressure (BP), fluid infusion and FMS injection respectively. A Swan Ganz catheter (Edwards Laboratory, CA) was inserted in the right external jugular vein for the measurement of pulmonary arterial pressure (Ppa), wedge pressure, and cardiac output (Qt), while a large bore catheter was inserted in the left external jugular vein for the rapid infusion of pre-formed blood clots (see below). Generally, these animals received normal saline at 100 ml/hr during the experiments. They were kept warm using a warming blanket so that the body temperature was maintained at about 38°C. No heparin was used.

After the insertion of the femoral arterial line, 80 ml of blood was withdrawn and mixed with 2500 units of Thrombostat® at 21°C, so that clots were allowed to form and fibrinized over the next two hours. They were suspended in normal saline in a large bore syringe prior to injection at the appropriate time into the left external jugular vein. Upon completion of the surgical procedures, the animals were placed in the prone posture and received stacking of at least three consecutive breaths to remove residual atelectasis.
Their mandatory control ventilatory settings were adjusted according to the arterial blood gas results, such that PaCO₂ was approximately 35 ± 2 mmHg, PEEP = 0 cm water, rate = 18 to 20/min and oxygen at 21% or room air. Once they were set, there was no further adjustment of the settings for the remaining part of the experiment. At each of the subsequent data collection time points, hemodynamic parameters, such as BP, Ppa, wedge pressure, heart rate, \( \dot{Q}_t \) were measured, along with hemoglobin, arterial and venous blood gases, Fowler dead space (MacLab at 100mm/sec), tidal volume, airway pressure and respiratory rate.

The time for the induction of acute pulmonary thromboembolism (APTE) was defined as time = 0 minutes and all the events prior to and following that point would be recorded in relation to that time. In order to establish reproducibility of the aerosolized and injectable FMS, which marked the ventilation and perfusion in the lung respectively, there were two control runs at 30 minutes and 5 minutes prior to the induction of APTE (or time = -30 and –5 minutes). In each experiment, ten different FMS obtained from Molecular Probes (Eugene, OR) of distinct colors were chosen and used in random orders, five for aerosolization and five for injection. The details of the FMS techniques had been well described (2, 12).

After performing the two control runs and recording all the physiological measurements, the animals would receive acute pulmonary thromboembolism at time = 0 minutes. Approximately 12 to 16 pieces of pre-formed fibrinized clots (about 20 grams in total or about 1.5 gm 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 to 15 minutes, until Ppa was 2.5 times the baseline value. Upon completion, there were no further
injections of clots. On some occasions, about 200 ml of normal saline was given to restore BP.

Later, at time = 30, 60, and 120 minutes, 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 prior to data collection to minimize atelectasis. At time = 90 minutes, physiological measurements and blood sampling were also done but no FMS were administered.

2. Post mortem lung preparations: At the end of the experiment, the animal was deeply anaesthetized with intravenous pentothal, heparinized with 5000 U and exsanguinated. The lungs were extracted after gentle saline flush and inflated to no more than 25 cm of water. The lobes were glued into their resting anatomical position and blown dry with warm air through the lungs for 72 hours. Small puncture holes were made to allow good air-flow through the lungs during the drying process.

After the thorough drying of the harvested lungs, they were sliced and diced into approximately 2 cm³ size samples, with each sample carefully assigned a 3-D coordinate according to a pre-established grid pattern. Approximately 950 pieces were analysed 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 ten FMS embedded in each sample, which marked the regional ventilation and perfusion at 5 different time points (i.e. time = -30, -5, 30, 60 and 120 minutes), 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 florescence per piece in a spectrometer following four days of soaking in 2 ml of organic solvent (Cellosolve, Sigma-Aldrich, MO). Overlaps from adjacent colors were then corrected using a matrix inversion method (4, 28).

3. Data analyses: After determining the regional $\dot{V}_A$ and $\dot{Q}$ of each lung piece, the $\dot{V}_A/\dot{Q}$ ratio could be readily calculated. By solving the mass balance equation, the corresponding regional PaO$_2$ could also be estimated (1). The composite $\dot{V}_A/\dot{Q}$ and regional PaO$_2$ in each cluster were also plotted against time in order to examine their patterns of changes before and after APTE and their impact on overall gas exchange.

Finally, the PaO$_2$ measured directly by arterial blood gas, could be compared with the PaO$_2$ estimated by the FMS data, obtained after knowing all the regional $\dot{V}_A/\dot{Q}$. This comparison would serve also as quality control of experimental technique.

The weight normalized relative ventilation (WNR $\dot{V}_A$) and weight normalized relative perfusion (WNR $\dot{Q}$) of each lung sample, were calculated in order that these lung samples could be compared to each other at the same time point and at different time points, when total ventilation and cardiac output (or total pulmonary blood flow) were somewhat different. The steps are summarized as follows:

After obtaining the regional $\dot{V}_A$ and $\dot{Q}$ of each lung sample from the FMS data at a given time, they were first normalized to the weight of the sample. Since large airway and vasculature add to the piece weight, pieces designated as containing more than 20% large airways/vessels were omitted from the following weight normalizaton 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 minutes, the mean weight normalized $\dot{V}_A$ or $\dot{Q}$ of the lung samples was calculated by summing up the individual weight
normalized $\dot{V}_A$ or $\dot{Q}$ 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 WNR $\dot{V}_A$ and WNR $\dot{Q}$, relative to that mean for $\dot{V}_A$ and $\dot{Q}$ respectively, represented as 1 or 100%.

Afterwards, lung samples were subject to metacluster analyse according to the magnitude of WNR $\dot{Q}$ 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 WNR $\dot{Q}$ were found, i.e. decreased after APTE (Cluster 1), relatively unchanged after APTE (Cluster 2) and increased after APTE (Cluster 3). With these grouped data, the WNR $\dot{V}_A$ and WNR $\dot{Q}$ 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 the lung pieces in the same cluster, labelled by the same color, were presented in a 3-D lung model, again using the JMP software (SAS Institute, Cary, NC). The positions of the thromboemboli seen within arteries (≥ 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 were expressed as mean ± standard deviation unless indicated otherwise. In order to assess the reproducibility of the FMS technique, linear regression analysis was done for the two control runs prior to APTE, for both regional ventilation and regional perfusion in the same piece of lung. Repeated Measure ANOVA and Fisher's PLSD post hoc test were performed to detect difference in values over time. P was set at 0.05 as the level of significance.
RESULTS:

1. Physiological data

Table 1 showed that after APTE at time = 0 minutes, there were significant pulmonary hypertension and increases in pulmonary vascular resistance (PVR), while the cardiac output slightly decreased. Arterial PaO$_2$ from blood gas data decreased abruptly but gradually recovered over time. Arterial PaCO$_2$ increased following APTE, while the total ventilation remained fixed during the experiment.

2. Reproducibility of the FMS technique

The linear regression coefficients ($R^2$) for $\dot{V}_A$ and $\dot{Q}$ between control run #1 (time = -30 mins) and control run #2 (time=-5 mins) were $0.90 \pm 0.07$ and $0.86 \pm 0.06$, respectively. They showed that under control condition prior to APTE, there was good reproducibility of regional markings by FMS. Thus the subsequent changes in $\dot{V}_A$ or $\dot{Q}$ were mostly due to the induced pathophysiological changes.

Further reliability of the FMS technique is the comparison of the measured arterial PaO$_2$ versus that calculated for the FMS data using the mass balance equation (Figure 1). The linear regression coefficient ($R^2$) was 0.912 with a slope of 0.81 and an intercept of 15.6.

3. $V_A/Q$ analyses

Table 2 showed the data on $\dot{V}_A/\dot{Q}$ heterogeneity. The $\dot{V}_A/\dot{Q}$ 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 (Figure 2). Mean $\dot{V}_A/\dot{Q}$ was calculated from the main peak ($\dot{V}_A/\dot{Q}$ from 0.01 to 100), while log SD $\dot{V}_A/\dot{Q}$ represented the standard
deviation or the heterogeneity of this main peak. Both increased significantly following APTE, mainly due to the creation of higher $\dot{V}_A/\dot{Q}$ units. Presumably this could be the result of either increased regional $\dot{V}_A$ or decreased $\dot{Q}$. Note that both mean $\dot{V}_A/\dot{Q}$ and log SD $\dot{V}_A/\dot{Q}$ gradually improved over time.

Shunt, defined as $\dot{V}_A/\dot{Q} < 0.01$, was essentially 0% in all the measurements. However, there was significantly increased physiological dead space, defined as $\dot{V}_A/\dot{Q} > 100$. Dead space reached its maximal value at 60 minutes after APTE but decreased by 120 minutes.

4. Cluster analyses

Using cluster analyses, three sub-populations of lung pieces were identified according to the pattern of weight normalized relative flow (WNR $\dot{Q}$) after APTE (Figure 3), namely, those that decreased over time (Cluster 1), remaining unchanged over time (Cluster 2) and increased over time (Cluster 3).

Table 3 showed the number of pieces in each cluster in all 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 showed the plot of WNR $\dot{Q}$ from these three pre-identified clusters against time. They represent three distinct populations. On the other hand, WNR $\dot{V}_A$ remained robust and changed proportionally less than WNR $\dot{Q}$ in the corresponding cluster (Figure 4). Therefore, the increased number of high $\dot{V}_A/\dot{Q}$ units following APTE (Table 2) was created mostly by reduced regional flow, rather than increased $\dot{V}_A$.

When plotting regional $\dot{V}_A/\dot{Q}$ vs. time (Figure 5), low $\dot{V}_A/\dot{Q}$ units were created following APTE in Cluster 3, mainly due to increased regional flow, even though
simultaneous WNR $\dot{V}_A$ was also lower. High $\dot{V}_A/\dot{Q}$ units were created in Cluster 1. There was some recovery at 120 minutes. Cluster 2 remained relatively constant throughout the experiment in both WNR $\dot{V}_A$ and WNR $\dot{Q}$.

The regional PaO$_2$ was plotted against time for all three clusters in Figure 6. Due to the very low WNR $\dot{Q}$ in Cluster 1, their $\dot{V}_A/\dot{Q}$ units behaved effectively as dead space and the corresponding regional PaO$_2$ was the highest. The $\dot{V}_A/\dot{Q}$ units of Cluster 2 remained relatively constant, as both WNR $\dot{V}_A$ and WNR $\dot{Q}$ changed little. The high $\dot{V}_A/\dot{Q}$ at 30 min was due to just a few pieces that had very low $\dot{Q}$ at that time point which skews the mean upwards as indicated by the large SD value. Thus the corresponding PaO$_2$ stayed near the pre-embolized, i.e. the control level. Finally, due to the several fold increases in WNR $\dot{Q}$ in Cluster 3, $\dot{V}_A/\dot{Q}$ and regional PaO$_2$ decreased significantly in the first 60 minutes after APTE, in spite of a modest increase in WNR $\dot{V}_A$ at the same time. This Cluster 3 had the lowest PaO$_2$ and was likely to be an important contributor to the observed arterial hypoxemia.

Figure 7 showed the anatomical locations of the thromboemboli and the three sub-populations of the lung pieces in all four experiments. The high $\dot{V}_A/\dot{Q}$ units (Cluster 1, red) were mainly located in the peripheral regions, distal to the embolized sites. The low $\dot{V}_A/\dot{Q}$ units (Cluster 3, green) were mainly located in the less embolized regions, where blood flow was more readily redistributed. The mid-range $\dot{V}_A/\dot{Q}$ units (Cluster 2, blue) were found dispersed spatially in the intermediary areas, closer to the central hilar regions.
DISCUSSION:

The experimental model used in the present study mimicked closely the clinical setting of acute pulmonary thromboembolism, 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 post mortem, obstructing major pulmonary vessels. Because these pre-formed clots were allowed to mature and fibrinize for two hours in vitro, they were more resistant to the naturally occurring fibrinolytic process in the experimental animals. Patients who developed acute pulmonary thromboembolism often had blood clots from the deep veins in the legs, which might also have thrombosed in the preceding hours (22).

Table 1 showed the physiological changes after APTE, further confirming the validity of our experimental model. After APTE, there were significant increases in Ppa, PVR and decreases in PaO₂. Note that there was gradual recovery towards baseline in all these parameters. Because the total ventilation was kept essentially constant during the experiment, the increase of PaCO₂ after APTE was mostly due to the creation of new high $\dot{V}_A/\dot{Q}$ units and physiological dead space (Table 2). We do not think the hemodynamic recovery was due to dissolution of the blood clots as many of these high $\dot{V}_A/\dot{Q}$ units persisted (Table 2 and Figure 5) and PaCO₂ remained high.

Figure 2 and Table 2 showed that there were significant increases in mean $\dot{V}_A/\dot{Q}$, log SD $\dot{V}_A/\dot{Q}$ and physiological dead space after APTE, while the shunt fraction remained low. These results showed the increases in $\dot{V}_A/\dot{Q}$ heterogeneity after APTE was due to the creation of high $\dot{V}_A/\dot{Q}$ units but also some lower $\dot{V}_A/\dot{Q}$ units as well, though they were not as low as zero, which then would be considered as shunts.
Our data also showed that there was significant re-distribution of weight
normalized relative flow after APTE (Figure 3), with much reduced flow distal to the
emboli and in the peripheral parts of the lung (Cluster 1 in Figure 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 (25). Because of the reduced WNR $\dot{Q}$ to these regions,
they effectively behaved as high $\dot{V}_{A}/\dot{Q}$ units and physiological dead space in terms of gas
exchange. As it was mentioned, their creation resulted in higher mean $\dot{V}_{A}/\dot{Q}$, log SD
$\dot{V}_{A}/\dot{Q}$ (Table 2) and PaCO$_2$ (Table 1). Following APTE, their regional PaO$_2$ was also the
highest among the three clusters (Figure 6).

In contrast, looking at Cluster 3 in Figure 3, there were areas in the lung in which
WNR $\dot{Q}$ was significantly increased, resulting in the creation of lower $\dot{V}_{A}/\dot{Q}$ units (Figure 5). They constituted about 18% of the lung regions, with $\dot{V}_{A}/\dot{Q}$ about 0.5 or less. Figure 7
showed that these regions were mostly located in the least embolized regions of the lung
and their corresponding regional PaO$_2$ was the lowest (Figure 6). Regional pulmonary
blood flow blocked by embolic obstruction must be acutely diverted and increased to the
more readily recruitable areas. Such abrupt changes in regional blood flow might well
account for the sudden overall hypoxemia seen after APTE (Table 1). Note that after 30
minutes (Figure 3), Cluster 3 showed a gradual decrease in WNR $\dot{Q}$, resulting in the
gradual recovery of the corresponding $\dot{V}_{A}/\dot{Q}$ units (Figure 5) and PaO$_2$ (Figure 6)
towards the pre-embolized condition. Thus the ongoing mechanical re-distribution of
regional blood flow 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 WNR $\dot{Q}$, WNR $\dot{V}_A$, $\dot{V}_A/\dot{Q}$ ratio, and regional PaO$_2$ stayed comparable
during the experiment. It constituted about 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 weight normalized relative ventilation in
Figure 4 were quite modest compared to those in WNR $\dot{Q}$. These data were consistent
with our results in Table 2, which showed that there was essentially no shunt, in which
$\dot{V}_A$ was zero. The relatively steady state of WNR $\dot{V}_A$ was consistent with an earlier study
using multiple breath helium washout technique, which showed that there was no
significant increases in ventilation 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 ventilation 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 (19).

On the other hand, Burton et al showed that there was significant diversion of
blood flow from the embolized regions using nuclear scans of the patients with APTE
(7). Tsang et al quantified regional blood flow in the lung in relation to the embolic load
by polystrene beads and found an inverse relationship (24). In another study, we reported
that following acute pulmonary bead embolism in an animal model, when cardiac output
was restored to the pre-embolized level by either fluid or vasopressors, gas exchange
remained poor even though the increased blood flow was now diverted to the least embolized and presumably normal regions (26). The corresponding MIGET data showed consistently high $\dot{V}_A/\dot{Q}$ heterogeneity regardless of the methods of resuscitation.

Presumably this observation was due to the creation of high and low $\dot{V}_A/\dot{Q}$ regions as pulmonary blood flow was increased and diverted. Altemeier et al, using the FMS technique, recently reported that these redistributions of regional pulmonary blood flow might contribute to the hypoxemia after acute pulmonary bead embolization but the anatomical correlations were not explored (3).

Kontos et al showed that acute depression of PaO$_2$ below 40 mmHg in patients with APTE were consistently associated with increased cardiac output, while those with less hypoxemia had less striking increases in cardiac indices (10). They reasoned that hypoxemia was the reason for the hyperdynamic state, due to sympathetic discharge or increased in venous return because of venoconstriction. Another way to explain these results would be that the increased cardiac output had caused more hypoxemia because more regions of high flow were created as a result of the higher total pulmonary blood flow. Thus, more low $\dot{V}_A/\dot{Q}$ regions were created as total $\dot{Q}$ or cardiac output increased, leading to more hypoxemia.

Sasahara et al reported that the degree of hypoxemia after APTE could be correlated with the extent of pulmonary vascular obstruction in a linear relationship ($r = 0.65$) (14). One interpretation would be to suggest that when the embolic load was increased, there would be more diversion of blood flow to the least embolized regions, resulting in the creation of more, low $\dot{V}_A/\dot{Q}$ regions and hypoxemia. Furthermore, they also showed that following APTE, previously healthy patients could not generate a
pulmonary arterial pressure beyond 40 mm Hg due to the lesser musculature in the right ventricle. However, if a pulmonary vasculature was healthy and recruitable upon increased demand from higher flow, its cross sectional area could be increased accordingly and the pulmonary arterial pressure would not increase beyond a certain physiological point. This would be in contrast with other patients having APTE, who had pre-existing chronic obstructive lung disease (COPD) or mitral valve disease (MVD). 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 et al reported that patients with previous history of COPD or MVD had a much higher pulmonary arterial pressure and lower cardiac output after suffering from APTE (18). 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 (i) cardiac output was high or when (ii) the embolic load caused more vascular obstruction, were compatible with our conclusions that diversion of increased flow to the less embolized regions could result in the creation of low $\dot{V}_A/\dot{Q}$ regions and affect adversely the gas exchange.

Using the MIGET method, Dantzker et al demonstrated the time sequence of ventilation and blood flow in the lung following embolization (9). At the early stage, there were bimodal distribution of $\dot{V}_A/\dot{Q}$, increases in its heterogeneity and creation of high $\dot{V}_A/\dot{Q}$ units. But after 60 minutes, these distributions were close to pre-embolization pattern. These results were consistent with our findings that there was dynamic
redistribution of regional blood flow in the lung after APTE. Because there were different
ways to redistribute pulmonary blood flow, 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 $\dot{V}_A/\dot{Q}$ 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 PaO$_2$
among patients suffering from APTE. There were, however, rare exceptions which
showed large shunts in experimental dogs that had massive pulmonary embolism (30). It
was possible that the amount of blood flow diversion in those unusual circumstances was
extremely severe.

We speculated that in the clinical setting, small sub-segmental pulmonary emboli
found incidentally in spiral CT 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 blood flow and areas of low
$\dot{V}_A/\dot{Q}$, 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 re-evaluated as new
data come into light and old data are re-examined.

In summary, we conclude that the changes in $\dot{V}_A/\dot{Q}$ after APTE are mainly due to
a dynamic redistribution of regional blood flow in the lung and to a lesser extent, a
redistribution of ventilation. The lower $\dot{V}_A/\dot{Q}$ 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 towards the pre-embolized level. On the other hand, high $\dot{V}_A/\dot{Q}$ 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. Since minute ventilation was constant, they contributed to the increased in PaCO$_2$. The worsening of $\dot{V}_A/\dot{Q}$ heterogeneity in the lung following APTE was mainly due to changes in blood flow rather than ventilation.
ACKNOWLEDGEMENT

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Table 1. Physiological parameters

<table>
<thead>
<tr>
<th></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>
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</thead>
<tbody>
<tr>
<td>mean $P_{pa}$ (cm H$_2$O)</td>
<td>$25.3\pm4.1$ *1</td>
<td>$26.8\pm7.6$ *1</td>
<td>$56.2\pm2.2$ *2</td>
<td>$46.0\pm5.5$</td>
<td>$42.9\pm3.4$</td>
<td>$41.9 \pm 2.5$</td>
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<td>mean MBP (mm Hg)</td>
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<td>$97.5\pm5.4$</td>
<td>$110.5\pm10.5$</td>
<td>$110.1\pm15.0$</td>
<td>$106.8\pm17.2$</td>
<td>$105.2\pm16.9$</td>
</tr>
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<td>$2.9\pm0.2$ *3</td>
<td>$2.6\pm0.2$ *3</td>
<td>$2.7\pm0.3$ *3</td>
<td>$2.3\pm0.3$</td>
<td>$2.4\pm0.3$</td>
<td>$2.2\pm0.2$</td>
</tr>
<tr>
<td>mean PVR (cm H$_2$O x mm Hg x min$^{-1}$)</td>
<td>$6.3\pm1.8$ *1</td>
<td>$7.9\pm3.1$ *1</td>
<td>$16.5\pm3.2$</td>
<td>$16.9\pm2.7$</td>
<td>$15.0\pm1.7$</td>
<td>$15.5\pm0.8$</td>
</tr>
<tr>
<td>mean PaO$_2$ (Torr)</td>
<td>$108\pm4$ *1</td>
<td>$110\pm8$ *1</td>
<td>$65\pm13$ *2</td>
<td>$77\pm10$</td>
<td>$84\pm10$</td>
<td>$85\pm7$</td>
</tr>
<tr>
<td>mean PaCO$_2$ (Torr)</td>
<td>$37\pm3$ *1</td>
<td>$36\pm2$ *1</td>
<td>$53\pm8$</td>
<td>$51\pm5$</td>
<td>$49\pm5$</td>
<td>$49\pm6$</td>
</tr>
</tbody>
</table>

Values are mean ± SD. Statistical significance based on Repeated Measure ANOVA and Fisher's PLSD post hoc test. *1, p < 0.05 vs. 30, 60, 90, 120 min; *2, p < 0.05 vs. Controls, 60, 90, 120 min; *3, p < 0.05 vs. 60, 90, 120 min.
Table 2. Gas Exchange Parameters

<table>
<thead>
<tr>
<th></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 $\dot{V}_A/Q$</td>
<td>1.02±0.09</td>
<td>1.08±0.13</td>
<td>2.48±1.12 *1</td>
<td>1.70±0.42</td>
<td>2.19±0.83 *1</td>
</tr>
<tr>
<td>log SD $\dot{V}_A/Q$</td>
<td>0.50±0.16</td>
<td>0.40±0.09</td>
<td>1.76±0.23 *2</td>
<td>1.42±0.26 *1</td>
<td>1.39±0.21 *1</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 *1</td>
<td>11.2±12.7 *1</td>
<td>4.3±2.8 *1</td>
</tr>
</tbody>
</table>

APTE at time = 0; $^\#$, $\dot{V}_A/Q$ ranges from 0.01 to 100; $^\dagger$, $\dot{V}_A/Q < 0.01$; $^\oplus$, $\dot{V}_A/Q > 100$. Values are mean ± SD. Statistical significance based on Repeated Measure ANOVA and Fisher's PLSD post hoc test. *1, p < 0.05 vs. Control 1 & 2; *2, p < 0.05 vs. all others.
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>

Figure Legends

Figure 1. Data from all four animals shows good matching between the measured arterial PO2 and PO2 calculated by the mass balance equation from the fluorescent microsphere data. The line of regression (solid) and line of identity (dashed) are also shown.

Figure 2. Frequency polygons of ventilation or blood flow vs. \( \dot{V}_A/\dot{Q} \) for one representative animal.

Figure 3. Mean ± SE weight normalized relative perfusion over time for each cluster is calculated from the means of the four animals (metaclustering).

Figure 4. Mean ± SE weight normalized relative ventilation over time for each cluster is calculated from the means of the four animals (metaclustering).

Figure 5. Mean ± SE Ventilation / Perfusion ratio over time for each cluster is calculated from the means of the four animals (metaclustering).

Figure 6. Mean ± SE regional PaO2 over time for each cluster is calculated from the means of the four animals (metaclustering).

Figure 7. Lungs from all four animals (A-D) are shown. Lung pieces are color coded by cluster shown in previous figures. Yellow symbols represent pieces that contained large clots in the pulmonary arteries.
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REFERENCES


