Pulmonary and bronchial circulatory responses to segmental lung injury

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Lakshminarayan, S., S. Bernard, N. L. Polissar, and R. W. Glenny. Pulmonary and bronchial circulatory responses to segmental lung injury. J. Appl. Physiol. 87(5): 1931–1936, 1999.—In regional lung injury, pulmonary blood flow decreases to the injured regions, and anastomotic bronchial blood flow and total bronchial blood flow increase. However, the pattern of redistribution of the two blood flows to the injured and noninjured areas is not known. In six anesthetized sheep, pulmonary and bronchial blood flows were measured with 15-μm fluorescent microspheres by using the reference flow method. Blood flows were measured in the control state and 1 h after instilling 1 ml/kg of 0.1 N hydrochloric acid into a dependent segment of the left lung. The lungs were then removed, dried, and cubed into ~2-cm cubes while spatial coordinates were noted. Blood flow to each piece was calculated. Mean pulmonary blood flow to the noninjured pieces went from 730 ± 246 ml/min (P = 0.22), whereas in the injured pieces the pulmonary blood flow decreased from 246 ± 143 to 56 ± 46 ml/min (P < 0.01). In contrast, bronchial blood flow to the injured pieces increased from 0.51 ± 0.1 to 1.43 ± 0.85 ml/min (P = 0.005). We measured the change in flow as it related to the distance from the center of the injured area. Pulmonary blood flow decreased most at the center of the injury, whereas bronchial blood flow doubled at the center of injury and decreased with the distance away from the injury. The absolute increase in bronchial blood flow was substantially less than the decrease in pulmonary blood flow in the injured pieces. We also partitioned the observed variation in pulmonary and bronchial blood flow into that attributable to structure and that due to lung injury and found that 48% of the variation in pulmonary blood flow could be attributed to structure, whereas in the bronchial circulation 70% was attributable to structure. The reasons for these differences are not known and may reflect the intrinsic properties of the systemic and pulmonary circulations.

sheep; microspheres; bronchial blood flow; acid aspiration; pulmonary blood flow

IN DIFFUSE LUNG INJURY such as acute respiratory distress syndrome, it has been shown that pulmonary vessels supplying injured areas are often occluded, possibly by hypoxic vasoconstriction, occlusion by perivascular cuffs of edema, or intraluminal thrombosis (7). In dogs, we found that anastomotic bronchial systemic-to-pulmonary blood flow increases acutely when an isolated left lower lobe is injured through either the vascular route or via the airways (9). Total bronchial blood flow also increases in sheep after smoke inhala-

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Pressure tracings from this catheter were recorded just before microsphere injection to confirm location of the catheter in the left ventricle. Immediately before injection of microspheres into the left ventricle, the placed umbilical tape was tied, and the left pulmonary artery was temporarily occluded for 3 min after completion of microsphere injection. This prevented microspheres that had passed through systemic arteriovenous communications from reaching the left lung via the pulmonary circulation. Reference blood samples were withdrawn from the femoral arteries to calculate bronchial blood flow to the left lung in milliliters per minute. Under fiber-optic bronchoscopic guidance, a dependent segment of the left lung was located, and the bronchoscope was wedged into the segment. Through an polyethylene catheter passed through the suction channel of the bronchoscope, 1 ml/kg of 0.1 N hydrochloric acid was instilled into the segment. One hour after hydrochloric acid administration, pulmonary and bronchial blood flows were remeasured by injecting microspheres of different fluorescent colors. The animals were then deeply anesthetized, heparinized, and exsanguinated; lungs were removed; and the pulmonary vasculature was flushed free of remaining blood with a solution of normal saline and 2% dextan. When the effluent from the lungs was clear, the lungs were removed from the chest and inflated to 30 cmH2O, suspended from the tracheal cannula, and air-dried at 30 cmH2O (total lung capacity) for 7 days. The lungs were then placed in a plywood box that was filled with polyurethane foam and sliced into 1.2-cm-thick sections in the transverse plane from cranial to caudal) for a total of ~25–30 slices. The left lung slices were diced into 2-cm3 cubes in a miter-box, and the x-, y-, and z-coordinates for each piece were noted. This allowed for three-dimensional reconstruction of the left lung (x: right to left, y: dorsal to ventral, and z: cranial to caudal) and the spatial location of each cube of lung tissue. Each lung piece was weighed, coded for presence or absence of airways, and coded for the presence or absence of injury based on visual inspection. Pieces weighing <10 mg were excluded from analysis, since the amount of fluorescence in them is small, and there is larger error in both the weight and the fluorescence measurements. The pieces were then soaked in 2-ethoxyethyl acetate to extract the fluorescence from the microspheres, which was measured by using a fluorimeter (LS-50B, Perkin Elmer).

Statistical methods. Blood flow was calculated for each piece by using the standard reference flow formula (12)

\[ Q_i = \frac{(F_i \cdot R_i)}{F_{ref}} \]  

where \( Q_i \) is blood flow to each piece \( i \) (ml/min), \( F_i \) is fluorescence from each piece, \( R_i \) is the rate of reference blood withdrawal (ml/min), and \( F_{ref} \) is the fluorescence from the reference blood sample. Blood flow \( Q_i \) was determined for each fluorescent color used to identify bronchial and pulmonary flows to each piece pre- and postinjury.

The percentage of total pulmonary and bronchial flows to injured or noninjured pieces was determined for pre- and postinjury conditions. We calculated relative pulmonary and bronchial blood flows to each piece separately for injured and noninjured pieces in pre- and postinjury conditions. Relative flow to a piece within a region is calculated by dividing the flow to each piece during one condition by the mean flow to all pieces in the region during that condition. The relative flow units allow a clearer analysis of redistribution of flow during the two conditions. Thus, in each piece from the injured region, four relative flow values were calculated for pulmonary and bronchial flows both before and after injury. Similarly, for each piece in the noninjured region, four values of relative flow were calculated.

Relative blood flow units remove any effect of changes in cardiac output, driving pressure, or total flow to a region and also allow distribution of blood flow within a region to be determined independently of total blood flow to the lung and to the region. This normalization is important to the analysis of redistribution of flow. For example, if flow increases to the injured region from pre- to postinjury, but postinjury flow is allocated to pieces in exactly the same proportion as before the injury (i.e., no redistribution is present within the region), then relative flow units for each piece remain unchanged, with no redistribution of flow within the region. Also, in this example, a regression slope calculated for relative flow vs. the distance from the center of injury would be unchanged from pre- to postinjury states. On the other hand, if absolute flow units were used, or if flow was normalized within the entire lung (but not within the region of interest), then the calculated flow per piece as well as any slopes would change from pre- to postinjury, even though the allocation of flow within the region did not change.

We also measured the trend in flow in relation to the distance from the center of injury, which was determined by visual inspection. The slope of relative flow vs. distance from the center of injury was calculated by using ordinary least squares regression. The slope is expressed as percent relative flow units per centimeter away from the center of injury. A slope value of 7.1%, for example, means that the change in flow per centimeter distance is 7.1% of the mean flow per piece to the region.

We used the coefficient of variation (CV) to characterize heterogeneity. Descriptive statistics include the mean and SD of physiological parameters, slopes, and CVs. Descriptive statistics pre- and postinjury are compared by using the paired t-test. This test is also used to compare descriptive statistics between injured and noninjured regions or between pulmonary and bronchial flow. We also calculated the impact of injury on flow distribution by partitioning the total variation of flow within a region into two components: 1) a “piece” effect, the unchanging relative flow that reaches each piece during both injured and noninjured states, and 2) the flow component that changes between injured and noninjured states, possibly because of a combination of injury, time variation, and measurement error. The calculations have been described previously (2).

The variance component caused by flow changes across states (injured and noninjured) \( (\sigma^2_{\text{change}}) \) was estimated by

\[ \sigma^2_{\text{change}} = \frac{\sum_{i=1}^{n} \sum_{j=1}^{n} (Y_{ij} - \overline{Y})^2}{(n - 1)m} \]  

where \( Y_{ij} \) is the observed relative flow for piece \( i \) in the injured state \( j \), \( \overline{Y} \) is the mean relative flow for piece \( i \) across the states considered, \( n \) is the number of states, and \( m \) is the number of pieces.

The variance component due to piece effect \( (\sigma^2_{\text{piece}}) \) was estimated by

\[ \sigma^2_{\text{piece}} = \frac{\sum_{i=1}^{m} \sum_{j=1}^{n} (Y_{ij} - \overline{Y})^2}{m} \]  

The grand mean across all pieces and states \( \overline{Y} \) has a value of 1.0 when flow is normalized to a mean for each state. This formula for the piece effect differs slightly from that used in
mixed-effects modeling. We did not subtract $\sigma^2_{\text{change}}/n$ from the $\sigma^2_{\text{piece}}$, a subtraction that was intended to correct for any purely random error. However, $\sigma^2_{\text{change}}$ incorporates both systematic variation within a piece over states and purely random error. Subtraction would lead to an underestimate of $\sigma^2_{\text{piece}}$.

With this method, measured flow variation across all pieces and conditions is partitioned into constant and changing components. These calculations determine the percent of flow variation caused by a fixed flow to each piece vs. the percent changes that arise from injury, time fluctuation, or random measurement error.

RESULTS

The total number of injured pieces from the left lung of six animals was $120 \pm 65$ (mean $\pm$ SD) (range 53–238). The mean number of noninjured pieces from the left lung was $518 \pm 192$ (range 331–842), resulting in a range from 6 to 36% of the left lung being injured. The injury caused a major redistribution of flow in the lung, within injured and noninjured regions alike.

Changes in pulmonary blood flow distribution were greater with injury than the bronchial flow. Mean pulmonary blood flow to noninjured pieces before injury was $727 \pm 246$ ml/min and postinjury it was $574 \pm 347$ ml/min ($P = 0.22$). In contrast, mean pulmonary blood flow to the injured pieces was $246 \pm 143$ ml/min, which decreased to $56 \pm 46$ ml/min after injury ($P = 0.01$).

Cardiac output fell in two animals after lung injury. Because cardiac output influences bronchial blood flow, we corrected for this by dividing bronchial blood flow by the cardiac output obtained just before we made the measurements of bronchial blood flow in the injured pieces. The bronchial blood flow to the injured region was $0.51 \pm 0.17$ ml·min$^{-1}$·l$^{-1}$ cardiac output, and it increased to $1.43 \pm 0.85$ ml·min$^{-1}$·l$^{-1}$ cardiac output ($P = 0.04$).

Cardiac output and allocation of flow. Pulmonary flow decreased by about one-third, and bronchial flow approximately doubled from pre- to postinjury (Table 1). The allocation of flow to injured and noninjured regions also changed substantially. Before injury, 26% of pulmonary flow was distributed to the region that was subsequently injured, whereas only 9% reached this region postinjury. This reallocation, combined with the overall decrease in total pulmonary flow to the lung, resulted effectively in a fivefold reduction in pulmonary flow to the injured region.

Bronchial blood flow had a very different redistribution pattern. Approximately one-fifth of the total bronchial flow was allocated to the injured region both before and after injury. This near-constant allocation combined with an increase in total bronchial flow to the lung tripled the mean bronchial flow to the injured region.

Redistribution of blood flow within injured and noninjured regions. The balance of results on flow is presented in relative flow units, calculated as described above. Before injury, bronchial and pulmonary flows showed a negative radial gradient; i.e., flow decreased in pieces farthest from the center of injury in both the injured and noninjured regions (Table 2). Whereas effects of injury varied across animals, the negative gradient for mean pulmonary flow either changed to a positive gradient in the injured region or became less steep in the noninjured region. This resulted in decreased pulmonary flow near the center of the injury, and this decrease was a statistically significant shift to the noninjured region. The bronchial blood flow showed a different redistribution pattern. In both injured and noninjured regions, the negative radial gradient of bronchial flow became steeper; i.e., flow to the center of the injury increased twofold after injury, causing a mean increase in the allocation of bronchial flow toward the center of the injury, although the change was not statistically significant.

Total lung heterogeneity as well as regional lung heterogeneity (injured and noninjured regions) increased substantially after injury for both bronchial and pulmonary blood flows. Mean pulmonary blood flow heterogeneity increased in the injured region from 59 to 134% ($P < 0.05$). The increase in the noninjured

| Table 1. Physiological parameters and flow, pre- and postinjury |
|-----------------|-----------------|-----------------|-------|
|                  | Preinjury       | Postinjury      | Value |
| Cardiac output, l/min | 3.61 ± 0.75    | 3.13 ± 1.24    | 0.3   |
| Total pulmonary blood flow, ml/min | 973 ± 201   | 630 ± 341      | 0.06  |
| Total bronchial blood flow, ml/min | 3.29 ± 1.95  | 6.39 ± 6.81    | 0.2   |
| Total no. pieces | 638 ± 160       |                |       |
| Injured region |
| Pulmonary blood flow, ml/min | 246 ± 143    | 56 ± 46        | 0.01  |
| Bronchial blood flow, ml/min | 0.51 ± 0.17  | 1.43 ± 0.85    | 0.04  |
| %Qbr               | 16 ± 13        | 22 ± 12        |       |
| %Qpulm             | 26 ± 14        | 9.0 ± 14       |       |
| %Pieces            | 20 ± 11        |                |       |
| No. pieces         | 120 ± 65       |                |       |
| Noninjured region |
| Pulmonary blood flow, ml/min | 727 ± 246    | 574 ± 347      | 0.2   |
| Bronchial blood flow, ml/min | 2.8 ± 2.0    | 5.1 ± 6.1      | 0.3   |
| %Qbr               | 84 ± 13        | 79 ± 9         |       |
| %Qpulm             | 74 ± 15        | 91 ± 10        |       |
| %Pieces            | 80 ± 11        |                |       |
| No. pieces         | 518 ± 192      |                |       |

Values are means ± SD; n = 6 sheep.

| Table 2. Radial gradients (slopes) of blood flow vs. distance from center of injury by region and type of flow |
|-----------------|-----------------|-----------------|-------|
|                  | Preinjury       | Postinjury      | Value |
| Pulmonary blood flow |
| Injured region   | -7.1 ± 15.6    | 11.6 ± 33.8     | -18.8 ± 30.9 | 0.2 |
| Noninjured region | -13.1 ± 6.9   | -2.6 ± 5.8      | -10.5 ± 7.6  | 0.02 |
| Bronchial blood flow |
| Injured region   | -5.2 ± 12.0    | -11.9 ± 11.7    | 6.8 ± 17.1   | 0.4  |
| Noninjured region | -4.4 ± 4.6    | -9.4 ± 5.0      | 5.0 ± 7.1    | 0.15 |

Values are means ± SD; n = 6 sheep.
region was not as large, a 23% difference (P < 0.05).
Mean bronchial blood flow heterogeneity also increased in the injured region from 70 to 86% (P = 0.07). Mean bronchial blood flow heterogeneity in the noninjured region increased 32% (P < 0.05). Total left lung heterogeneity increased 39% for the pulmonary circulation and 27% for the bronchial circulation (P < 0.05).

The large change in CVs from pre- to postinjury suggests substantial redistribution of both bronchial and pulmonary flows within regions, more clearly illustrated by partitioning the total flow variation. The total flow variation across all pieces and observation times can be partitioned into two components. One component is a "piece effect," which can be thought of as a fixed unchanging allocation of relative flow to each piece occurring both pre- and postinjury. The second component of variation results from flow changes caused by a combination of injury, random time variation, and methodological error. On average, 48% of relative pulmonary flow variation to the injured lung region was due to piece effect; the remaining 52% represents relative flow changes due to injury, time variation, and method error (Table 3). In the noninjured region, 67% of pulmonary flow variation was caused by piece effect, and 33% was due to changing allocation.

The bronchial flow also showed large components of variation due to change, although these were smaller than for pulmonary flow. The change components for the bronchial circulation were 30 and 23% in injured and noninjured regions, respectively (Table 3).

**DISCUSSION**

The present study shows that after acid-aspiration injury to a segment of the lung, pulmonary blood flow decreases while bronchial blood flow increases to the injured pieces. This reinforces previous observations that these two blood flows act differently and probably respond independently to injury (9, 13). This study also adds spatial information to this independence. We have shown that this decrease in pulmonary blood flow is greatest at the center of the injured area and that the fall becomes progressively less with distance from the injured area. In contrast, the increase in bronchial blood flow is greatest at the center of the injury and tends to fall off further away from the injury. The absolute increase in bronchial blood flow was considerably less than the absolute decrease in pulmonary blood flow in the injured pieces.

Stothert et al. (13) have shown that injury from smoke inhalation in sheep caused a 6-fold increase in systemic blood flow to the lower trachea and an 11- to 14-fold increase in the intrapulmonary central airways. They also observed an increased hyperemic response as airway diameter decreased from the trachea to 2-mm airways. In airways <2 mm, the hyperemic response diminished, suggesting regional differences in the reactivity in the bronchial circulation.

Stothert et al. (14) showed in a chronic sheep model that airway injury caused by aspiration of hydrochloric acid increased bronchial blood flow and that this increase could be attenuated by pretreatment with cyclooxygenase inhibitors. Inhibition of thromboxane synthetase did not have such a protective effect. The precise mechanism that causes pulmonary blood flow to decrease and bronchial blood flow to increase to an injured area is unknown. Mechanisms responsible for the fall in pulmonary blood flow after injury have been attributed to the release of vasoactive amines, intravascular thrombosis from white cell and platelet aggregations, and hypoxic pulmonary vasoconstriction (7). The bronchial circulation responds differently to hypoxia. Charan et al. (4) showed that anastomotic bronchial blood flow (that portion of the bronchial blood that drains into the pulmonary circulation) increased with systemic hypoxia. Warren and Powell (17) showed that acute alveolar hypoxia increased bronchopulmonary anastomotic flow in dogs. These investigators also observed cyclooxygenase inhibitors to block bronchial vasodilatation. Similarly, Wagner and Mitzner (16) showed in sheep that systemic hypoxemia (arterial PO2 30–45 Torr) decreased bronchovascular resistance. Although our animals were not hypoxemic (arterial PO2 >200 Torr), it is possible that alveolar hypoxia existed in the injured area.

Deffebach et al. (5) have shown in dogs that pretreatment with cyclooxygenase inhibitors attenuates the increased bronchial blood flow after both intravascular and airway injury. An interesting finding in our present study is that changes in pulmonary and bronchial blood flows diminished as one proceeded away from the central injury, even though several of the pieces away from the center of injury were visibly injured. This would suggest that vasoactive amines and other local stimuli in the center of the injured areas may affect the upstream vasculature and alter flow to the entire region. The precise underlying mechanism is unknown, but possibilities include 1) diffusion of vasoactive amines along bronchovascular bundles to the upstream flow regulating segments of the arteries, 2) neural reflexes, or 3) cell-to-cell communications.

Marshall et al. (10) reported that bronchial arterial hypoxemia attenuates hypoxic pulmonary vasoconstriction. Thus one role for an acute increase in bronchial blood flow to an injured area may be preservation or accentuation of the hypoxic pulmonary vasoconstriction that diverts pulmonary blood flow away from the

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**Table 3. Components of variation in pulmonary and bronchial blood flows in the injured and noninjured regions**

<table>
<thead>
<tr>
<th></th>
<th>&quot;Piece&quot;</th>
<th>&quot;Change&quot;</th>
<th>Total Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary blood flow</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injured region</td>
<td>47.9 ± 22.0</td>
<td>52.1 ± 21.9</td>
<td>100</td>
</tr>
<tr>
<td>Noninjured region</td>
<td>66.9 ± 8.9</td>
<td>33.1 ± 8.9</td>
<td>100</td>
</tr>
<tr>
<td>P value</td>
<td>0.14</td>
<td></td>
<td></td>
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<tr>
<td>Bronchial blood flow</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injured region</td>
<td>69.6 ± 7.2</td>
<td>30.4 ± 7.2</td>
<td>100</td>
</tr>
<tr>
<td>Noninjured region</td>
<td>77.3 ± 6.7</td>
<td>22.7 ± 6.7</td>
<td>100</td>
</tr>
<tr>
<td>P value</td>
<td>0.21</td>
<td></td>
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</tr>
</tbody>
</table>

Values are means ± SD. P values for pulmonary vs. bronchial: injured, P = 0.003; noninjured, P = 0.001.
injured area, thus minimizing low ventilation-to-
perfusion ratio regions in the injured area of lung. In
chronic inflammatory states, such as lung abscess or
bronchiectasis, angiogenesis and new vessel formation
develop in the bronchial circulation, but this regenera-
tive power does not exist in the pulmonary circulation.
The signal for angiogenesis is unknown, but an interest-
ing hypothesis is that, during the acute phase of injury,
dilation of the bronchial vasculature would provide oxy-
genated blood to the area of injury and, possibly,
also stimulate new vessel formation. Although intrava-
cular thrombosis occurs in the pulmonary circulation,
this does not seem to occur in the bronchial circulation,
as evidenced by an acute increase in bronchial blood
flow. The bronchial circulation may be somewhat pro-
tected from acid aspiration by its submucosal position
in the airway, whereas the pulmonary circulation may
not because of its thin alveolar capillary barrier.

The absolute rise in bronchial blood flow was substanci-
antly less than the fall of pulmonary blood flow. In
contrast to the pulmonary circulation, the bronchial
circulation normally plays a minor role in gas-exchange
function. Because the bronchial circulation transports
arterialized oxygenated blood to the lung, it partici-
pates little in oxygen uptake, but does excrete carbon
dioxide (15). The role of increased bronchial blood flow
in response to inflammation in the injured area, as well as
its beneficial effects in recovery, are unknown. A
small amount of oxygen-rich bronchial blood perfusing
an injured area may be sufficient to provide nutrients
and cells to overcome the injury or to prevent hyoxia
in cells of the injured area that may become necrotic
in the face of decreased ventilation and pulmonary perfu-
sion. Thus increased bronchial blood flow during injury
may serve a nutrient rather than a gas-exchange function.
Further studies are required to delineate the
precise mechanisms that underlie the bronchial blood
flow increases and the role they play in recovery from
lung injury.

Bronchial blood flow heterogeneity (CV) has not been
previously reported. Due to the branching nature of the
airways and their blood supply from the bronchial
circulation, one would expect bronchial blood flow to be
heterogeneous in the lung. Before injury, bronchial
blood flow heterogeneity was 81%. The increases in
heterogeneity of both pulmonary and bronchial blood
flow after segmental lung injury are a reflection of the
marked changes in blood flow to the lung after injury.
Bronchial blood flow increased in the injured region
while pulmonary blood flow decreased. Both changes
were not uniform in magnitude, since the CVs changed.
Interestingly, heterogeneity increased more in the re-

gions that lost flow (injured region for pulmonary flow
and noninjured region for bronchial). This may be due
to a heterogeneous lung injury or a nonhomogeneous
humoral response to the injury.

The variation in pulmonary or bronchial blood flow
between the many pieces in a lung, and between two
points in time (without a perturbation), could be due to
the structure of the vascular bed, to redistribution of
blood flow, temporal changes in blood flow, or method
artifact. Based on components of variation, our analy-
sis permits partition or quantification of the relative
contribution of the above-mentioned factors to the
variation in blood flow within an experiment that
includes a perturbation, in this case, aspiration injury
due to hydrochloric acid. Previous studies from our

database (2, 8) on the effect of increased gravitational
force or increased cardiac output due to exercise showed
that, in normal noninjured lungs, structure accounts
for ~70% of the blood-flow variation and thus is the
major determinant of pulmonary blood flow. In this
context, structure means a stable factor that remains
stable regardless of time or physiological perturbation.
Redistribution, temporal changes, and method error
accounted for <30% of the observed variation in pulmo-
nary blood flow. This is in contrast to what occurs in an
area of injured lung. Our present study shows that 48%
of total variation in pulmonary blood flow in an injured
lung could be attributed to “structure,” whereas the
remaining 52% were due to a combination of redistribu-
tion of blood flow, time, and method error. In contrast,
70% of the total variation in bronchial blood flow was
due to structure and 30% to redistribution, time, and
method noise in the injured regions. This may be due to
a greater structural integrity of the bronchial circula-
tion then that of the pulmonary circulation. The causes
underlying the behavior differences of the two circula-
tions are unknown. Possibilities include the magnitude
decrease of pulmonary blood flow and increase in
bronchial blood flow, the size (area) of the two circula-
tions, or sites and mechanisms of vascular regulation
for the two circulations. It is also not known what
changes would be observed if the route of injury was
intravascular or via the airway injury, and further
studies are warranted.

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