Pulmonary and bronchial circulations: contributions to heat and water exchange in isolated lungs

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Serikov, V. B., and N. W. Fleming. Pulmonary and bronchial circulations: contributions to heat and water exchange in isolated lungs. J Appl Physiol 91: 1977–1985, 2001.—The relative contribution of the pulmonary and bronchial circulatory systems to heat and water exchange in normal lungs was evaluated in 20 isolated, in situ perfused dog lungs and in four patients undergoing elective cardiopulmonary bypass. In isolated dog lungs, if the pulmonary artery was perfused at a nominal flow rate (0.5 l/min), bronchial artery perfusion (up to 70 ml/min) did not significantly affect the expired gas temperature. When the lungs were not perfused through either system, 8 min of ventilation with cool, dry gas decreased the temperature of the expired gas by 6.2 ± 1.4°C. Selective perfusion of bronchial arteries at 68 ± 10 mmHg resulted in a mean flow rate of 28 ± 16 ml/min and increased the average temperature of the expired gas by 0.6°C. An increase in the rate of bronchial arterial perfusion to 55 ± 14 ml/min increased the average temperature of the expired gas by 1.3°C. The time constant for equilibration of tritiated water between the perfusate and the lung parenchyma was 130 ± 33 min for pulmonary arterial perfusion and 35 ± 13 min for combined bronchial and pulmonary perfusion, which indicated that filtration of water from high-pressure bronchial vessels facilitated water exchange in the lung interstitium. The rate of tracer equilibration was similar between the perfusate and gas in both variants of perfusion, but the ratios of tracer gas to perfusate were different (0.42 ± 0.06 for pulmonary, 0.98 ± 0.07 for combined), which indicates that bronchial vessels contribute mainly to the hydration of the bronchial mucosa. In humans, the bronchial blood flow was capable of maintaining heat supply after the initiation of cardiopulmonary bypass. Before bypass, when both pulmonary and bronchial blood flow were present, the mean time constant of the temperature decay after a switch to ventilation with cool, dry gas was 35 ± 12 s. The average temperature difference between the blood and expired gas was 2.4 ± 0.50°C. After 5 min of dry gas ventilation, the temperature difference between the expired gas and initial blood temperature decreased an average of 3.6 ± 0.6°C (P < 0.05). The time constant of temperature decay increased to 56 ± 14 s (P < 0.05). We conclude that bronchial perfusion has a less important role in the temperature balance of the respiratory tract compared with pulmonary arterial perfusion because heat flux is “flow limited” but is important in providing water for hydration of the mucosal surface and interstitial compartments of peribronchial tissues.

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HEAT AND WATER EXCHANGE within the respiratory tract determines the temperature of the bronchial mucosa and the osmolarity and viscosity of the mucosal fluids. Inadequate heat exchange during hyperventilation may decrease mucosal temperature and lead to bronchoconstriction (8, 14). Increases in the osmolarity of the mucosal fluids may contribute to the failure of respiratory defense mechanisms in patients with cystic fibrosis or inflammation (9, 23). The heat and water that are transferred to condition the ambient air come from the walls of the bronchial tree and are replenished by the blood flow to the bronchial tissues (18, 24, 32). Previously, it was believed that the conditioning of inspired air occurred primarily in the upper airways and that the bronchial blood supply adequately provided the heat and water for this process. However, controlled studies have shown that conditioning of the inspired air actually occurs along nearly the entire length of the bronchial tree, up to the 10th or 12th generation, and unconditioned air may penetrate deep into the peripheral airways (16, 19, 20). Solway et al. (30) have shown a prominent role of the pulmonary circulatory system as a heat source to the lung. Although the bronchial blood flow is directed largely to the primary sites of heat exchange, the observed cooling of the pulmonary arterial blood, the esophagus, and the development of bronchospasm in hyperventilated patients suggests that the reserves of this system are limited (8, 9, 30). The role of the bronchial circulatory system as a source of extravascular fluid in acute lung injury has been evaluated previously by us (3, 29) and others (1, 7, 35). Other studies have demonstrated a substantial contribution of the bronchial circulation to transvascular fluid exchange and the development of both pulmonary edema and bronchial wall edema (22). The rate of water distribution from the two vascular systems into the lung interstitium, the rate of water transfer into the mucosal tissues, and its subsequent rate of evaporation into the exhaled gas have not been previously studied.

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We hypothesized that the pulmonary heat and water exchange with respired gas is “flow limited” in the walls of bronchial tree by the hemodynamics of bronchial circulation. The goal of this study was to determine the relative contributions of the two systems of lung circulation, pulmonary and bronchial, to the processes of heat and water exchange with inspired air. The first aim was to determine the relative contribution of both circulatory systems to heat exchange during normal ventilation using isolated, perfused canine lungs. However, in dogs, the bronchial tree is the primary heat-exchange system. Thus the relative role of the bronchial circulation in heat exchange may be different from that in humans. Therefore, we also performed comparative studies in human lungs during elective cardiopulmonary bypass. The second aim was to determine the rate of equilibration of tritiated water (THO) between the circulation and the respired air and the rate of humidification of the inspired air during selective perfusion of the two vascular systems, by using isolated canine lungs.

METHODS

Specific Protocols

1) To investigate the relative contributions of pulmonary and bronchial perfusion to lung heat exchange, we performed selective perfusion of the lung circulatory systems in isolated, perfused lungs from beagles (9–11 kg). In seven preparations, we perfused only the pulmonary arteries, and the pulmonary blood flow was varied between 0.1 and 2 l/min. In these experiments, the bronchial arteries and veins were ligated so that bronchial blood flow was zero. In five additional preparations, both the pulmonary artery and the thoracic aorta were perfused simultaneously, or only the bronchial arteries were perfused, as described in detail previously (11). To provide two different rates of bronchial perfusion, the perfusion pressure was set at either 50–60 or 90–100 mmHg. Perfusion lasted for 15–20 min because perfusate was not recovered and was partially lost to the body via anastomoses in the mediastinum. Total flow through the isolated portion of aorta varied from 25–40 (at low pressure) to 80–120 (at high pressure) ml/min. Concurrent recordings of tracheal airway temperature changes were compared.

2) To investigate the contribution of pulmonary and bronchial vessels to water exchange with the respired gas, the same modes of perfusion were used. Isolated lung preparations from eight mongrel dogs (12–16 kg) were used for these studies. In four preparations, only the pulmonary artery was perfused with no bronchial blood flow. In the remaining four preparations, the pulmonary and bronchial arteries were perfused simultaneously. Perfusion of the bronchial arteries utilized a second roller pump, connected to the same perfusate reservoir.

3) To investigate the role of the two arterial systems in heat exchange in humans, we measured the temperature changes in the expired gas in the tracheas of intubated patients (n = 4) undergoing cardiopulmonary bypass. Measurements were done before bypass (both pulmonary and bronchial blood flow present) and immediately after the onset of bypass (only bronchial blood flow).

General Methodologies, Animal Studies

Isolated, perfused lungs. After institutional Animal Care and Use Committee approval, in situ isolated, perfused, ventilated lungs were prepared as previously described (11, 27) and as illustrated in Fig. 1. Dogs were anesthetized with a bolus of pentobarbital sodium (30 mg/kg) followed by a maintenance infusion titrated to hemodynamic and reflex responses. Auffed endotracheal tube (7.5–8.0 mm ID) was placed, heparin (1,000 U/kg) was administered, and the dogs were then exsanguinated via a carotid arterial catheter. A median sternotomy was performed, and the pulmonary artery and left atrium were cannulated with large-bore plastic catheters. Ligatures were placed around the superior and inferior venae cavae, and brachiocephalic and left subclavian arteries, as well as the descending thoracic aorta. In addition, the intercostal arteries and veins from the third through the ninth intercostal spaces were isolated and ligated bilaterally.

The bronchoesophageal arteries remained patent in experiments in which both pulmonary and lung vessels were perfused. In dogs, the majority of systemic blood supply to the lungs is via the bronchoesophageal arterial system, which has a variable anatomical location (4). Perfusion of the entire thoracic aorta ensures perfusion of bronchial arteries independent of their exact location (3, 11). Venous blood from the bronchial arteries is drained predominantly into the pulmonary veins (18), but direction of this anastomotic flow depends on the driving pressure. During perfusion of only pulmonary vessels, retrograde perfusion of bronchial vessels was prevented by clamping the arterial and venous cannulas of the bronchial perfusion system. For the same reason, in lungs in which only the pulmonary arterial vessels were perfused, the bronchoesophageal artery and systemic veins at the lung hilum were carefully ligated to prevent the loss of perfusate into the systemic vessels.

The pulmonary arterial and left atrial catheters were connected to an extracorporeal perfusion circuit. Thermocouples were placed inside the pulmonary artery and left atrium. Pulmonary arterial and left atrial pressures were measured by calibrated transducers (Statham P23, Medex, Hilliard, OH), zeroed at the level of left atrium and continuously displayed on a physiological monitor (HP78353B, Hewlett-Packard Medical, Palo Alto, CA). The lungs were perfused with a 1:1 mixture of autologous blood and dextran 70 by use of a precalibrated roller pump (Sarns model 3500, 3M Health Care, St. Paul, MN). Perfusion rates varied from 0 to 2 l/min with pulmonary arterial pressure maintained between 10 and 30 mmHg and left atrial pressure between 0 and 8 mmHg. Blood temperature was maintained at 38°C by using a heat-exchange unit (American Electromedics, Amherst, NY) positioned between the perfusion pump and the pulmonary artery.

A tracheostomy tube (7 mm ID) was placed with the distal tip 3 cm above the carina. The lungs were ventilated with a mixture of 5% CO2-95% O2 by use of a constant-volume pump (model 613, Harvard Apparatus, Holliston, MA) at tidal volume of 0.18 liters and a frequency of 12 min−1. The inspiratory-to-expiratory ratio was 1:1, and the peak inspiratory pressure was 21 ± 3 cmH2O with positive end-expiratory pressure of 6–8 cmH2O. The inspired gas was delivered either directly from the respirator (cool, dry) or through a humidifier (model SCT 3000, Marquest Medical Products, Englewood, CO) (heated, humidified) by using a three-way stopcock. The expired gas returned first to a plastic mixing chamber (volume 0.75 liter) and then to the ventilator. Sampling tubes for the measurements of humidity were attached.
to both the cross connector (inspiratory and expiratory gas) and the mixing chamber (expiratory gas). Gas temperature was measured by a thermocouple fixed in the middle of the tracheostomy tube, 1 cm from the distal tip. Ventilatory parameters [pressure, flow rates, tidal volumes, frequency, and minute ventilation (ATPS)] were measured by using a Korr RSS 100 pneumotachometer system (Korr Medical Technologies, Salt Lake City, UT). The portions of the ventilation circuit adjacent to the animal were placed inside a plastic bag that was continuously filled with warm air (42°C) (Bair Huggar model 500/OR, Augustine Medical, Eden Prairie, MN), and the entire preparation was covered with water-filled heating blankets maintained at 38°C.

In five animals, in addition to perfusion via the pulmonary artery, selective perfusion of the bronchial arteries through the isolated portion of the thoracic aorta (11) was performed. A catheter (1 cm OD, 10 cm length) was placed in the descending thoracic aorta, and a second catheter (4 mm OD) was inserted into the hemiazygous vein to allow drainage of the perfusate from the bronchial veins. The aortic catheter was connected via a heat exchanger to a 2.5-l reservoir containing a mixture of normal saline and dextran 70 (1:1). The perfusate was pressurized (80–120 mmHg) and preheated to 38°C before infusion to ensure a constant temperature throughout the 10- to 15-min infusion period.

Temperature and humidity measurements. Data from the thermocouples were conditioned by use of a custom-built multichannel amplifier and were captured by a computerized data acquisition system (model SCXI-1200, National Instruments, Austin, TX). Data were then logged to disk by using a laptop computer (model T1860CS, Toshiba American Information Services, Irvine, CA) running LabView software (Version 3.1.1, National Instruments) with custom routines for real-time displays. The humidity measurements utilized a specially constructed, rapid-response humidity probe as previously described (12). Briefly, nitrocellulose tubing (0.15-mm diameter) that allowed unrestricted transfer and evaporation of water from its surface was placed in the center of the Plexiglas body of the sensor (0.5 mm ID). A thermocouple (0.001 in.) was positioned inside the tubing, and the thermocouple wire served as a support for the tubing. Both sides of the tubing were then connected to water reservoirs of ~1 ml such that a free flow of water was allowed through the tubing. Continuous gas flow through the body of the sensor of 100 ml/min was maintained by using a calibrated pump. The linear velocity of the gas through the sensor was 3.25 m/s. The temperature of the gas entering the sensor was measured by a thermocouple located in front of the wet tubing. The body of the sensor was maintained at 40°C by a custom-built, temperature-controlled heater. The response time of the sensor was <100 ms. Humidity was calculated from the values of peak temperature recorded by the dry and wet thermocouples of a humidity probe in the mixing chamber (12). The sensor was calibrated for both dynamic response (100 ms) and steady-state values of humidity at 40°C by using a humidity generator and calibration system (models C-1 and D-2, respectively, General Eastern Instruments, Woburn, MA) in an environmental chamber (model 3528, Lab-Line Instruments, Melrose Park, IL). Calibration of the sensor was performed after each experiment. At a steady state, the overall thermal conductance was calculated as the ratio of total heat loss to the difference between the blood temperature and the temperature of the expired gas (15, 28). Total heat loss was calculated as the sum of dry gas enthalpy, the water vapor enthalpy, and the heat of water evaporation (24).

Distribution of THO. THO (10 μCi) was introduced into the perfusate reservoir and rapidly mixed. The changes in the specific activity of THO as a function of time were measured in both the expired gas (condensate) and the perfusate. Sam-
pulmonary and bronchial arterial perfusion

Selected hemodynamic parameters and temperatures of expired gas during selective or simultaneous

cheal tube. Patients were ventilated by use of a servo venti-

T-connector that was placed just proximal to the endotra-

Products). The second port of this stopcock was attached to a

proximal to a humidifier (model SCT 3000, Marquest Medical

three-way stopcock was placed in the respiratory circuit

temperature of the inspired and expired gas was recorded at

probe was positioned 2–3 cm above the distal end. The

endotracheal tube was suctioned for mucus, and a sterile thermocouple

preparation for cardiopulmonary bypass. The endotracheal

arterial and venous return cannulas were placed in

arterial catheters were placed. A sternotomy was performed,

from four patients (three men and one woman), age 66–78,

search Committee, written, informed consent was obtained

beta-counter.

of THO was measured by using PRO-POP scintillation cock-

vapor was condensed and then collected. The specific activity

and the condensate was collected and weighed. To measure

surface. The collecting tubing was exchanged every 15 min,

pulmonary artery were recorded and compared with

arterial pressure was 25

and the perfusate tempera-

the pulmonary artery was maintained at 0.5

bronchial arteries in isolated dog lungs, the flow in the

pausal and bronchial arteries during the dual perfusion of the pulmonary and bronchial vessels is shown in Fig. 2. When the pulmonary artery was perfused at a nominal flow rate (0.5 l/min), bronchial artery perfusion (0–70 ml/min) did not sig-

change in the rate of bron-

ventilated for 5–6 min with dry gas without changing the
tidal volume or respiratory rate. The temperature changes in the pulmonary artery were recorded and compared with prebypass values.

Statistical Analysis

All data are expressed as means ± SE. Data were com-

pared by ANOVA, either unpaired or paired Student’s t-test,

RESULTS

Selective Perfusion of the Circulatory Systems

During the dual perfusion of the pulmonary and bronchial arteries in isolated dog lungs, the flow in the pulmonary artery was maintained at 0.5 ± 0.05 l/min, the arterial pressure was 25 ± 3 mmHg, left atrial pressure was 0–4 mmHg, and the perfusate tempera-
ture was 37°C. A typical result demonstrating the
effects of selective perfusion of the pulmonary or bron-
chial vessels is shown in Fig. 2. When the pulmonary

parameter and temperatures of expired gas during selective or simultaneous pulmonary and bronchial arterial perfusion

Table 1. Selected hemodynamic parameters and temperatures of expired gas during selective or simultaneous pulmonary and bronchial arterial perfusion

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0</th>
<th>0</th>
<th>0</th>
<th>0.5</th>
<th>0.5</th>
<th>0.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA flow, l/min</td>
<td>0</td>
<td>28 ± 16</td>
<td>55 ± 14</td>
<td>0</td>
<td>34 ± 15</td>
<td>64 ± 16</td>
</tr>
<tr>
<td>BA flow, ml/min</td>
<td>0</td>
<td>68 ± 10</td>
<td>105 ± 22</td>
<td>0</td>
<td>76 ± 10</td>
<td>106 ± 21</td>
</tr>
<tr>
<td>PA pressure, mmHg</td>
<td>6.2 ± 1.4</td>
<td>5.6 ± 1.8</td>
<td>4.3 ± 1.0</td>
<td>2.3 ± 0.04*</td>
<td>2.2 ± 0.07*</td>
<td>2.42 ± 0.08*</td>
</tr>
<tr>
<td>Temperature difference between blood and gas, °C</td>
<td>6.2 ± 1.4</td>
<td>5.6 ± 1.8</td>
<td>4.3 ± 1.0</td>
<td>2.3 ± 0.04*</td>
<td>2.2 ± 0.07*</td>
<td>2.42 ± 0.08*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 5 lungs. PA, pulmonary arterial; BA, bronchial arterial. *P < 0.05 vs. the corresponding group without pulmonary perfusion.
surface, the temperature in ideal conditions should equilibrate to the temperature of the “wet bulb” thermometer, which will be 6–8°C under these conditions. However, because the heat flux with evaporation from the lungs is rather small (5–10 W), the lung mass is 200–300 g, and there are additional structures in the mediastinum and chest wall through which heat exchange occurs, this process would take 70–90 min to reach equilibrium. Also, in the absence of blood flow, mucous surfaces will dry, evaporation will stop first in the large bronchi, then in the distal bronchi, and the rate of cooling will change. We observed these phenomena in our experiments in many instances and, according to our experience, drying of the airways becomes quite evident after 8–10 min of dry gas ventilation without perfusion. For this reason, we used a time interval of 8 min to assess the temperature changes. In addition, the overall estimated thermal conductivity of the lung as a function of pulmonary blood flow with or without bronchial perfusion was calculated. Figure 3 shows the linear relationship between these two variables. Changes in bronchial perfusion were associated with small changes in the lung thermal conductivity, and in the presence of the pulmonary blood flow the influence of bronchial blood flow on the temperature of the expired gas was minimal.

In the surgical patient studies, the mean cardiac output before initiation of cardiopulmonary bypass was 5.43 ± 1.56 l/min. Minute ventilation was 6.17 ± 1.18 l/min with an average tidal volume of 0.64 ± 0.1 l (0.009 l/kg) and a rate of 8.3 ± 1.5 min⁻¹. Blood temperature was 36.8 ± 0.3°C, and the mean time constant of the temperature decay after a switch to ventilation with cool, dry gas was 35 ± 12 s. The average temperature difference between the blood and expired gas was 2.4 ± 0.5°C. After the initiation of bypass (average bypass flow 5.45 ± 0.6 l/min), the blood flow to the lungs was limited to the bronchial circulation. The temperature in the pulmonary artery changed after the onset of bypass (decreased in 1 patient, increased in 3, maximal amplitude of change 0.7°C) and we corrected the instant temperature of the expired gas to the instant changes in the temperature of the blood in the pulmonary artery by subtracting or adding the respective changes. Patients were first ventilated with warm, humidified gas. After initiation of bypass, they were switched to cool, dry gas ventilation for 15 min. The changes in the rate of temperature decline before and after bypass are summarized in Fig. 4. During the 5 min of dry gas ventilation, the temperature difference between the expired gas and initial blood temperature decreased an average of 3.8 ± 0.06°C (P < 0.05). The time constant of temperature decay increased to 56 ± 14 s (P < 0.05).

**Dynamics of Water Distribution in Normal Lungs**

The rate of equilibration of THO between perfusate, lung tissue, and expired gas was evaluated in isolated, perfused dog lungs. All preparations were ventilated at a rate of 12 min⁻¹ and a tidal volume of 20 ml/kg body wt. Perfusion via the pulmonary artery was adjusted to produce a mean pulmonary arterial pressure of 23 ± 6 mmHg, left atrial pressure was 0–4 mmHg, and the perfusate flow was 0.65 ± 0.05 l/min. Temperature was maintained at 37°C. Perfusion of the aortic segment with bronchial arteries was at a rate of 60 ml/min, resulting in an arterial pressure of 92 ± 9 mmHg. Measurements of the total water content in the expired gas

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**Fig. 3.** Estimated overall thermal conductivity of the lung as a function of pulmonary blood flow (n = 7, ○) or bronchial blood flow (n = 5, squares). □, perfusion of bronchial vessels without pulmonary perfusion; ■, perfusion of bronchial vessels simultaneously with pulmonary perfusion. *P < 0.05 compared with initial blood flow by paired t-test, +P < 0.05 for the difference between groups by unpaired t-test.

**Fig. 4.** Relative peak temperature of expired gas (Tgas) related to blood temperature (Tblood) during ventilation with dry gas in intubated patients before bypass (○) and during bypass (●). *P < 0.05 between groups by paired t-test, n = 4.
gas showed that it was near saturation for 37°C (0.042 ± 0.03 g/l) during perfusion of both the pulmonary system alone and the pulmonary and bronchial systems combined, without any difference between the groups. The dynamics of THO equilibration are summarized in Table 2 for pulmonary perfusion and in Table 3 for pulmonary and bronchial arterial perfusion. For the pulmonary arterial perfusion alone, the time constant of equilibration (blood-tissue) was 130 ± 33 min. For bronchial and pulmonary perfusion combined, it was 35 ± 23 min (P < 0.05). The perfusate volume was 790 ± 65 ml for pulmonary perfusion alone and 830 ± 75 ml for pulmonary and bronchial perfusion combined. Postmortem total lung mass (with blood in the small vessels) was 235 ± 23 g for the group of pulmonary perfusion alone and 260 ± 35 g for the group of pulmonary and bronchial perfusion combined. In the group with dual perfusion of bronchial and pulmonary vessels, THO appeared in expired gas at the same rate (time constant 34 ± 11 min) as during perfusion of pulmonary arteries alone (time constant 31 ± 13 min). The ratio of instant values of THO activity in exhaled gas to perfusate was significantly higher during pulmonary and bronchial perfusion (0.98 ± 0.07, P < 0.05) than during pulmonary perfusion alone (0.42 ± 0.06, P < 0.05). In the case of combined pulmonary and bronchial perfusion, equilibration between the perfusate and the exhaled gas occurred within 1 h.

**DISCUSSION**

If the inspired gas temperature and humidity change, expired gas temperature will shift to a new equilibrium due to the cooling of bronchial tree. Changes in the time constant of temperature decay after a switch from ventilation with heated, humidified gas to cool, dry gas can be related to changes in the pulmonary blood supply (25, 26). However, the lung has two separate circulatory systems, pulmonary arterial and bronchial arterial. These two systems generally supply different structures and have different functions, but they also have numerous anastomoses (34). The studies reported here demonstrate that, in the presence of normal pulmonary arterial blood flow, perfusion of the bronchial arteries does not significantly affect expired gas temperature measured at the level of the trachea (Fig. 2). This is consistent with the previous findings of Solway et al. (30), who performed similar measurements in the more distal airways of anesthetized dogs after selective occlusions of the pulmonary or bronchial circulation. In this study, hyperventilation using 18–28 l/min dry, room temperature or −10°C gas was used to provide the heat challenge to the lungs. The temperature measurements were done deep in the bronchial tree, at the level of the segmental or subsegmental bronchi (4–5 mm diameter in dogs) with the proximal airways excluded. For our studies, we used normal ventilation with dry gas at room temperature and measured the expired gas temperature at the level of the trachea, because it depends on the temperature of the bronchial mucosa (16) and includes the contributions of both the segmental and lobar bronchi in the heat-exchange evaluations. Furthermore, because the breathing pattern affects both the site and mechanism of heat exchange in the bronchial tree (16, 19, 20), the ventilatory parameters were kept constant.

Heat is transferred from the blood in the arteries, capillaries, and veins of the lungs to the bronchial mucosa by lateral conduction through the tissues (28, 30, 32). Despite the optimal location of the bronchial circulation for heat exchange, it is such a small fraction of the total pulmonary circulation in normal lungs that it can be effective in heating the airway only during a low thermal burden. These experimental protocols allowed us to demonstrate that in the absence of pulmonary arterial blood flow the bronchial arterial blood flow did provide a measurable heat flux to the lungs, which was proportional to the flow rate (Table 1). However, it was not sufficient to keep the bronchial tree adequately warm, even at low rates of ventilation.

**Table 1. Changes over time in the relative activities of THO in the perfusate during perfusion of PA vessels combined.**

<table>
<thead>
<tr>
<th>Group</th>
<th>Time, min</th>
<th>0</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>75</th>
<th>90</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA</td>
<td></td>
<td>1.0</td>
<td>0.94 ± 0.11</td>
<td>0.93 ± 0.08</td>
<td>0.92 ± 0.07</td>
<td>0.90 ± 0.12</td>
<td>0.87 ± 0.06</td>
<td>0.85 ± 0.05</td>
</tr>
<tr>
<td>PA + BA</td>
<td></td>
<td>1.0</td>
<td>0.86 ± 0.06</td>
<td>0.75 ± 0.05</td>
<td>0.63 ± 0.10</td>
<td>0.61 ± 0.04</td>
<td>0.62 ± 0.07</td>
<td>0.62 ± 0.05</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 4 lungs. *P < 0.05 for comparison between groups.

**Table 2. Changes over time in the relative activities of THO in the perfusate during perfusion of PA vessels only or PA + BA vessels**

<table>
<thead>
<tr>
<th>Group</th>
<th>Time, min</th>
<th>0</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>75</th>
<th>90</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA</td>
<td></td>
<td>0.042</td>
<td>0.21 ± 0.03</td>
<td>0.32 ± 0.04</td>
<td>0.34 ± 0.04</td>
<td>0.35 ± 0.05</td>
<td>0.36 ± 0.05</td>
<td></td>
</tr>
<tr>
<td>PA + BA</td>
<td></td>
<td>0.34 ± 0.07</td>
<td>0.39 ± 0.06</td>
<td>0.58 ± 0.08</td>
<td>0.64 ± 0.11</td>
<td>0.62 ± 0.09</td>
<td>0.63 ± 0.10</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 4 lungs. *P < 0.05 for comparison between groups.
Other conditions may increase the relative contribution of the bronchial arterial system to heat-exchange processes. The bronchial circulation may undergo profound changes during certain pathological conditions and may increase from its normal physiological level. With a constant cardiac output, changes in expired gas temperature after repeated exposure to dry and cold gas were interpreted as changes in mucosal blood flow (13). Pathological conditions under which the bronchial microvasculature can respond by increasing flow rate are numerous and include chemical, hormonal, immunologic, and thermal stimuli (1, 2, 35). In addition, blood flow in the bronchial microvasculature is locally regulated and also responds to changes in ventilation (2, 17, 21). For example, the hyperventilation of exercise leads to an increase in bronchial vascular perfusion in humans (17, 21). In the study of Baile et al. (2), hyperventilation with dry gas up to 12–15 l/min was used, which is severalfold different from the conditions of this study; hyperventilation with dry warm gas increased bronchial blood flow by 2–3 times, and with dry cold gas by 1.5–2 times. The severity of hyperventilation or heat loss determines the magnitude of the increased bronchial vascular flow. However, the increase in ventilation, which leads to augmentation of bronchial blood flow, also increases the heat flux from the bronchial tree. It is unlikely that the increase in bronchial blood flow would be more substantial than the increase in heat loss, otherwise one would not observe deep cooling of the bronchial tree during hyperventilation in the isolated lung preparation, which lacks systemic reflexes, including possible change in mucosal blood flow due to hyperventilation or cooling. To address the possible effects of increased bronchial blood flow, we used two different bronchial arterial perfusion pressures during conditions of normal ventilation. This increased bronchial blood flow did not produce significant changes in the indexes of heat exchange. Because bronchial blood flow has, at least, severalfold less potency in its ability to affect the indexes of heat exchange, even if it increases during hyperventilation, it is likely that the effects will be balanced by the increased heat loss produced by hyperventilation. We cannot rule out the possibility that if the bronchial blood supply is increased severalfold by a reactive hyperemia of the bronchial mucosa in the nonisolated, intact whole body, its relative contribution may become substantial. This is a limitation of the current approach using isolated, perfused lung preparations.

Human studies provide strong support to the findings in perfused dog lungs. Immediately after the initiation of cardiopulmonary bypass, pulmonary arterial blood flow ceases as all the venous blood is diverted to the bypass circuit, but the arterial return from the circuit via the aortic arch provides continued perfusion of the bronchial arteries. We did not measure bronchial blood flow in humans, but it should be substantial (4), and anastomotic bronchopulmonary flow may even be higher than the prebypass level because pulmonary arterial perfusion was stopped. This provides a condition that is comparable to the isolated perfused dog lung preparation. A switch to ventilation with cool, dry gas will cause the bronchial mucosal temperature (and thus the expired gas temperature) to decrease. During selective perfusion of the bronchial arteries, there was a substantially lower rate of heat exchange compared with perfusion of both the pulmonary and bronchial systems. With only bronchial arterial blood flow, the mean time constant of temperature decay decreased significantly from 35 to 56 s, and peak expired gas temperature decreased by an average of 1.4°C. These values were obtained only after 5 min of ventilation, and it is likely that longer periods of ventilation would further increase this difference. In combination, these observations provide additional experimental evidence in support of previous observations made in humans and animals, suggesting that the bronchial circulation alone is not adequate to completely condition inspired gas during even during moderate ventilation loads (8, 19, 20).

To further investigate the physiological roles of the two systems of lung circulation, the rates of distribution of water into the parenchymal tissues and expired gas were evaluated by using THO. Previous transient extraction studies have used THO to measure interstitial fluid volume changes after the development of pulmonary edema (5, 6). These transient distribution techniques showed a very rapid rate of water exchange (5) and are based on the assumption that the distribution of water is flow limited. In the experiments reported here, we measured overall water exchange in the lower respiratory system and observed a slower rate of water distribution (half-time 133 min), which is at least two orders of magnitude lower than previously observed (5). The rate of water distribution during the perfusion of the pulmonary circulation alone was fourfold lower than during combined perfusion of the pulmonary and bronchial circulations. This discrepancy suggests that, during isolated perfusion of the pulmonary arterial system, substantial volumes of the interstitial tissues are either poorly perfused or not perfused at all. This is consistent with previous findings suggesting the substantial role of the bronchial circulation in lung fluid balance (11). Pare et al. (22) demonstrated that systemic venous hypertension and fluid overload increased the lung water content and consequently increased pulmonary resistance. Using canine lungs isolated in situ and perfused via the pulmonary and the bronchial arteries, with lymphatic canulas placed to analyze flow, we demonstrated that the filtration of fluid from the bronchial vessels was the main source for the lymph formation (29) and the source of proteins in the peribronchial interstitium (4). The bronchial circulation has been shown to substantially contribute to edema formation occurring after smoke inhalation (1, 7).

Elements of the pulmonary interstitium may be considered as one functional unit that serves as a reservoir for distribution of fluids and is drained either by the lymphatic system or by other routes. The pulmonary interstitium may be subdivided into parenchymal con-
nnective tissue, situated inside the alveolar walls; the peripheral connective tissue; and the axial connective tissue, which comes from the hilum and in which the pulmonary arteries and airways are embedded (14). It is likely that selective pulmonary arterial perfusion allows the exchange of water between the capillary volume and the first constituent of the pulmonary interstitium, whereas the other two components serve as a slow-exchanging nonperfused reservoir, consistent with what was observed in our THO distribution studies. In the case of the selective bronchial arterial perfusion, all of the interstitial volumes are supplied with water, and it is likely that the exchange of THO in the peripheral and axial connective tissue occurs even faster than in the parenchymal tissue.

The degree of mucosal hydration of the bronchial tree is affected by the rate of water evaporation and regulated by the ion composition and osmolality of the mucosal secretions, the geometry of the airways, the activity of the cilia, and the hydrostatic pressure of the mucosal blood vessels (36). Our results indicate that water content of the expired gas was unchanged regardless of which circulatory system was perfused. It is likely that, in the absence of bronchial arterial perfusion, flow through vascular anastomoses into the bronchial mucosa is minimal. Central connective tissue spaces are therefore poorly perfused, and the overall rate of THO exchange is low. In the presence of a large, unperfused space that serves as a sink, the water in the expired gas will be diluted by water without THO from the peribronchial spaces, which diminishes the ratio of relative distribution to 0.42. When the bronchial arteries are perfused, the interstitium and mucosa are filled with THO, which distributes rapidly, and the distribution ratio is close to unity.

The exchange of both substances and heat between tissues can, in general, be presented by the concepts of diffusion-limited and flow-limited processes, depending on the permeability of the barriers (6). Heat has the highest conductivity (or coefficient of thermal diffusion) compared with the diffusion coefficient of all other substances; thus its exchange is certainly flow limited. The majority of osmotically driven water transport in the lung microvascular endothelial cells occurs by a transcellular route through the water channels (33), which can limit the osmotic diffusion coefficient (10). Water exchange in alveolar capillaries occurs predominantly by diffusion and may be permeability limited. The situation is different for the bronchial circulation, in which filtration is likely to occur in physiological conditions because the hydrostatic pressure is as high as in the systemic vessels. The bronchial blood flow provides enough water for hydration of mucosa and saturation of the inspired gas, although its volume flow is not sufficient to adequately warm the bronchial tree during ventilation with dry gas. The blood flow in the pulmonary artery is orders of magnitude higher and serves as a sufficient heat source for this process.

In summary, in the presence of pulmonary circulation, bronchial arterial blood flow contributes minimally to heat exchange, although it is important in water transport to the bronchial mucosa.

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