Angiogenesis in bronchial circulatory system after unilateral pulmonary artery obstruction

NIRMAL B. CHARAN AND PAULA CARVALHO
Pulmonary Research Laboratory, Veterans Affairs Medical Center, Boise, Idaho 83702; and Division of Pulmonary/Critical Care Medicine, Department of Medicine, University of Washington, Seattle, Washington 98195

Charan, Nirmal B., and Paula Carvalho. Angiogenesis in bronchial circulatory system after unilateral pulmonary artery obstruction. J. Appl. Physiol. 82(1): 284–291, 1997.—We studied the effects of left pulmonary artery (LPA) ligation on the bronchial circulatory system (BCS) by using a sheep model. LPA was ligated in the newborn lambs soon after birth (n = 8), and when the sheep were ~3 yr of age anatomic studies revealed marked angiogenesis in BCS. Bronchial blood flow and cardiac output were studied by placing flow probes around the bronchial and pulmonary arteries in four adult sheep. After LPA ligation, bronchial blood flow increased from 35 ± 6 to 134 ± 42 ml/min in ~3 wk (P < 0.05). We also studied gas-exchange functions of BCS ~3 yr after the ligation of LPA in newborn lambs (n = 4) and used a control group (n = 12) in which LPA was ligated acutely. In the left lung, O2 uptake after acute ligation was 16 ± 3 ml/min and was similar to the chronic model, whereas CO2 output in the control group was 27 ± 3 ml/min compared with 79 ± 12 ml/min in the chronic preparation (P < 0.05). We conclude that LPA ligation causes marked angiogenesis in BCS that is capable of performing some gas-exchange functions.

OVER A CENTURY ago, Virchow made observations that ligation of a pulmonary artery rarely resulted in pulmonary infarction (16) and that the bronchial arteries that supply the occluded lung increased in size (17). Since then, several other studies have confirmed that unilateral occlusion of the pulmonary artery stimulates angiogenesis that subsequently results in marked hypertrophy of the bronchial circulatory system in that lung (7, 13). It has been estimated that these changes develop progressively and reach a peak in ~18 mo to 2 yr and that most of the increase occurs in the first 3 mo (1, 19). The magnitude of this increase over time, however, has not been systematically determined.

The significance of this profound angiogenesis in the bronchial circulatory system, which results in marked increases in bronchial blood flow after pulmonary artery obstruction, is not known. There is some evidence that suggests that in the absence of pulmonary circulation the expanded bronchial circulation may participate in gas exchange (11). However, because the bronchial circulation carries arterial blood with high PO2, it should not be important in O2 uptake (VO2) but could play a role in CO2 output (VCO2).

In this study, we systematically investigated the anatomic as well as the physiological changes in the bronchial circulatory system that occur after unilateral pulmonary artery obstruction.

METHODS
Anatomic study. Eight newborn lambs (within 1 wk of birth) were sedated with xylazine (0.25 mg/kg) ~30 min before surgery. After induction of anesthesia with intravenous injection of 1–2.5 ml of 5% thiamylal sodium, the lambs were intubated and connected to an anesthesia machine (Ohmeda Anesthesia System Excel 210, Madison, WI). Anesthesia was maintained with 1–2% halothane. The animals were placed in a right lateral decubitus position, and, under sterile conditions, a left thoracotomy was performed through the fifth intercostal space. The hilum of the left lung was dissected without opening the pericardium. The left pulmonary artery was exposed and was ligated with “0” silk. We chose the left pulmonary artery for ligation because it is easily accessible through the left thoracotomy. The chest was closed, and the animals were allowed to recover. These lambs were subsequently returned to a holding facility where they were allowed to grow. When the sheep were 1–3 yr of age, they were brought back to the laboratory and anesthetized again as described above. Four of the sheep first underwent gas-exchange studies as described below. Subsequently, all eight sheep had anatomic studies performed according to a previously described technique (4). A brief summary of the technique is as follows. Under anesthesia, the sheep were killed by exsanguination, and a left thoracotomy was performed. The bronchoesophageal artery was identified, and the aorta was clamped both proximally and distally to the origin of this artery and opened with a vertical incision. The bronchoesophageal trunk was cannulated through the opening in the aorta and secured with “0” silk. Saline was infused into the bronchial artery at a pressure of ~80–100 Torr to flush the bronchial circulatory system. The lungs were continuously ventilated during this procedure. A cast of the bronchial circulatory system was then prepared by infusing Batson's solution (Polysciences) into the bronchoesophageal artery until it appeared as effluent through the pulmonary vein into the left atrium and the pleural vessels on the surface of the lungs were filled. Lungs were kept inflated during infusion of the Batson's solution. After the casting material had set in the vessels, the heart and lungs were removed from the thorax, and the tracheobronchial tree was filled by pouring clear Batson's solution into the trachea. Because filling of alveolar space with casting material makes examination of casts more difficult, we let the casting material set for some time before filling the tracheobronchial tree. With this technique, we were able to fill only the airways without flooding the alveolar spaces. The lungs were suspended in air, and the casting material was allowed to harden for ~24 h. Then the tissue was digested by submerging the preparation in a saturated solution of potassium hydroxide for 48–72 h. The specimens were washed with tap water, and the gross anatomy was studied.

Increases in bronchial blood flow after pulmonary artery obstruction. After flow probe placement, it usually takes a few days to get a satisfactory signal. Therefore, we performed two thoracotomies in each sheep. The first thoracotomy was...
performed to place the flow probes, and, ~1 wk later, a second thoracotomy was done to ligate the pulmonary artery. This allowed us to accurately measure changes in the bronchial blood flow soon after the occlusion of the pulmonary artery.

Four adult sheep were fasted for 24 h and then sedated with xylazine (0.25 mg/kg) ~30 min before surgery. After induction of anesthesia with intravenous injection of 10–15 ml of 5% thiopental sodium, this sheep were intubated and connected to an anesthesia machine (Ohmeda Anesthesia System Excel 210). Anesthesia was maintained with 1–2.5% halothane. The animals were placed in a right lateral decubitus position and, under sterile conditions, a left thoracotomy was performed through the fifth intercostal space. Depending on the size of the pulmonary artery, a 16- or 24-mm ultrasonic flow probe (Transonic Systems) was placed around the pulmonary artery to monitor cardiac output. The bronchoesophageal artery was dissected, and a 2-mm ultrasonic flow probe was placed around the common bronchial branch of the bronchoesophageal artery to continuously measure the bronchial blood flow. The left lung was reexpanded, and the chest wall was closed. The animals were allowed to recover for ~1 wk or until the flow probes were giving good signals and both pulmonary as well as the bronchial blood flows had stabilized. Under anesthesia, a second thoracotomy was then performed, and the left pulmonary artery was ligated. The chest wall was closed, and the sheep were allowed to recover again. The flow probes were connected to a dual-channel blood flowmeter for simultaneous recording of cardiac output and bronchial blood flow. In awake sheep, the bronchial blood flow and the cardiac output were monitored at regular intervals for ~3–4 wk. Four other sheep were used as control animals. These sheep were prepared exactly the same way as the experimental group, including two thoracotomies; however, in this group of sheep the left pulmonary artery was not ligated.

Gas exchange with bronchial circulation. To study whether the hyperexpanded bronchial circulation participates in gas exchange, four newborn lambs that had undergone the left pulmonary artery ligation within 1 wk of birth were studied. In this animal model, the experimental left lung is supplied by only the bronchial circulation, whereas the control right lung has both pulmonary as well as the bronchial contributions. This chronic preparation causes profound angiogenesis in the bronchial circulation that results in marked increases in bronchial blood flow through that lung. The sheep were anesthetized, and a left thoracotomy was performed at the fifth intercostal space. The hilum of the left lung was dissected, and pulmonary vein was isolated. Through a purse-string suture, a small silastic catheter was placed into the left pulmonary vein and advanced toward the periphery of the lung. The pulmonary vein was ligated close to its termination into the left atrium to prevent regurgitation of left atrial blood into the pulmonary vein. This catheter allowed us to obtain blood samples from the pulmonary vein draining the left lung. Systemic arterial blood was obtained through a catheter placed in the carotid artery. Through a tracheostomy, a bifurcated endotracheal tube was placed to collect expired gases separately from the left and the right lungs. These expired gas samples were collected for 3 min in a Douglas bag, and the volume of this gas was measured with a spirometer. A sample of this gas was analyzed for PO2 and PCO2 by using a blood gas machine (BM-53, Radiometer) calibrated for the expected partial pressures of PO2 and PCO2. From these data, VO2 and VCO2 were calculated. This preparation also allowed us to produce systemic hypoxemia by ventilating the right lung with hypoxic gas mixture, and the alveolar PO2 in the experimental left lung could be further increased by ventilating the left lung with hyperoxic gas mixture. We could also stop the ventilation to the left lung but keep the animal oxygenated by ventilating the right lung. Sheep were ventilated with different gas mixtures for 15 min, and data were collected during the last 3 min of this experimental period. We also used an acute model as control, where 12 anesthetized adult sheep were studied immediately before and after left pulmonary artery ligation as described above. However, in this acute model we studied VO2 and VCO2 with room air ventilation only.

Statistical analysis. A one-way analysis of variance for repeated measures was used to compare changes in bronchial blood flow after pulmonary artery obstruction, and Dunnett’s test was used to compare baseline values with other experimental means. Comparisons of VO2 and VCO2 between experimental and control groups were made by using an unpaired t-test. P < 0.05 was regarded as significant. The data are represented as means ± SE.

RESULTS

Anatomic studies. Ligation of left pulmonary artery in the newborn lambs stimulated angiogenesis that resulted in hypertrophy of the bronchial circulatory system in all eight animals. The bronchoesophageal artery, as it originated from the aorta, had markedly increased in size (Fig. 1), reaching a diameter of ~5–8 mm. This is in contrast to our previous observations where we found that in normal healthy sheep the bronchoesophageal artery is usually 1–2.5 mm in diameter (4). The common bronchial artery had a tortuous course as it reached the carina. At the tracheal carina, the bronchial artery divided into a right and a left bronchial branch (Figs. 2 and 3). The right bronchial branch was normal in size, but the left bronchial artery had markedly increased in size. The left bronchial artery and its branches continued to have a tortuous course as they descended down the left bronchus (Fig. 3). The smaller branches of the bronchial vessels formed a dense microvascular plexus around the left bronchial tree and eventually filled the pulmonary capillaries. Compared with this, the bronchial microvascular plexus around the right bronchial tree was normal (Figs. 2 and 3).

There was also marked enlargement of vessels that supply the visceral pleura (Fig. 4). Some of these vessels were direct continuation of the bronchial vessels that supply the terminal airways that penetrated the lung and coursed on the surface of the lung beneath the visceral pleura. Other pleural vessels arose from the esophageal branch of the bronchoesophageal artery, traversed through the pulmonary ligament, and supplied the visceral pleura of the caudal lobe of the left lung.

During this study, we encountered one interesting incidental finding because of a technical error. In two newborn lambs, because of the inability to identify the left pulmonary artery correctly, we unintentionally occluded the superior pulmonary vein of the left lung instead of the left pulmonary artery. We did not detect the problem until these sheep were killed. Interestingly, both of these sheep also had developed marked angiogenesis of the bronchial circulatory system in the
territory of the left superior pulmonary vein. These sheep were not included in any other study, and we report this incidental finding just for interest.

Changes in bronchial blood flow. There was a marked individual variation in the bronchial blood flow among animals. The bronchial blood flow immediately before pulmonary artery ligation was 35 ± 6 ml/min (Fig. 5). After pulmonary artery ligation, the bronchial blood flow progressively increased over the next 3 wk in all four sheep, although there was variability in the magnitude of increase in flow among individual sheep (Fig. 5A). By 3 wk, the bronchial blood flow had increased to 134 ± 42 ml/min (P < 0.05), representing approximately a fivefold increase in flow, and then appeared to reach a plateau. Although the cardiac output showed a downward trend at day 24, it was not significantly different from other values (Fig. 5B). In the control group, the bronchial blood flow before pulmonary artery occlusion was 42 ± 3 ml/min; after the second thoracotomy it did not change significantly, and by day 24 it was only 25 ± 4 ml/min (Fig. 5A). At day 24, the bronchial blood flow in the experimental group was significantly higher than that in the control group (P < 0.05).

Gas exchange with bronchial circulation. Table 1 shows VO₂ and VCO₂ after acute left pulmonary artery ligation in adult sheep (n = 12) and in the chronic preparation where the bronchial circulation was allowed to hypertrophy for 1–3 yr. After acute ligation of the pulmonary artery, VO₂ from the left lung decreased from 148 ± 40 to 16 ± 0.05 ml/min; this value was comparable to that found in the chronic sheep preparation. In contrast, VCO₂ from the left lung after the acute ligation was 27 ± 3 ml/min but it was 79 ± 12 ml/min in the chronic sheep preparation with pulmonary artery ligation (P < 0.05). In the chronic preparation (n = 4), when the sheep was made hypoxic by ventilating the right lung with hypoxic gas mixture (Table 2), VO₂ from the left lung increased from 15 ± 3 to 63 ± 6 ml/min (23% of total VO₂). The PO₂ in the pulmonary vein draining the left lung during this experimental condition and when the left lung was being ventilated with room air was 70 ± 8 Torr (alveolar-to-arterial O₂ difference of 16 Torr). This suggests that the arterial...
Fig. 2. Best example of lung cast prepared from another sheep in which pulmonary artery had been ligated soon after birth. Batson’s solution colored with yellow pigment was infused into bronchoesophageal artery. Trachea was filled with clear Batson’s solution. Dense bronchial microvascular plexus surrounding left bronchial tree is filled with yellow casting material. In contrast, right bronchial tree has rather sparse bronchial vascular plexus.

Fig. 3. Close up photograph of same cast shown in Fig. 2. Photograph has been taken at main carina to show common bronchial artery dividing into right bronchial and left bronchial branches. Only short stump of common bronchial artery is present in this cast (arrow). Right bronchial artery is normal in size. In comparison, left bronchial branch going to left bronchial tree has markedly enlarged. Also note that compared with right side, left bronchial artery is strikingly tortuous. There is some filling of alveolar capillaries around left main stem bronchus.
blood that perfused the bronchial microvasculature was getting further oxygenated. This observation was confirmed by ventilating the left lung with inspired O\textsubscript{2} fraction (F\textsubscript{IO2}) of 1.0 and at the same time keeping the systemic arterial P\textsubscript{O2} (Pa\textsubscript{O2}) low by ventilating the right lung with a hypoxic gas mixture (Pa\textsubscript{O2} = 48 ± 4 Torr). In addition, we found that the P\textsubscript{O2} in the left pulmonary vein further increased to 319 ± 46 Torr. During ventilation of the left lung with F\textsubscript{IO2} of 1.0, we were unable to measure V\dot{O}2 and V\dot{CO2} because of technical difficulties. With systemic hypoxemia, V\dot{CO2} from the left lung remained unchanged (70 ± 10 ml/min). When we stopped ventilation of the left lung (maintaining ventilation to the right lung), the systemic arterial blood had a P\textsubscript{O2} of 72 ± 4 Torr and arterial PCO\textsubscript{2} of 44 ± 5 Torr, and the simultaneously measured pulmonary venous blood gases in the left lung had a lower P\textsubscript{O2} but essentially unchanged arterial PCO\textsubscript{2}.

DISCUSSION

We have previously found that causing experimental empyema in a sheep model stimulates angiogenesis in

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Table 1. V\dot{O}2 and V\dot{CO2} in both experimental and control groups of sheep

<table>
<thead>
<tr>
<th>Experimental Condition</th>
<th>V\dot{O}2, ml/min</th>
<th>V\dot{CO2}, ml/min</th>
<th>R</th>
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<tbody>
<tr>
<td>Baseline (n = 12)</td>
<td></td>
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<tr>
<td>Left lung</td>
<td>148 ± 40</td>
<td>118 ± 10</td>
<td>0.79</td>
</tr>
<tr>
<td>Right lung</td>
<td>138 ± 20</td>
<td>130 ± 10</td>
<td>0.94</td>
</tr>
<tr>
<td>Acute (n = 12)</td>
<td></td>
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<tr>
<td>Left lung (PA ligation)</td>
<td>16 ± 3</td>
<td>27 ± 3</td>
<td>1.69</td>
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<tr>
<td>Right lung (control)</td>
<td>198 ± 20</td>
<td>192 ± 20</td>
<td>0.96</td>
</tr>
<tr>
<td>Chronic (n = 4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left lung (PA ligation)</td>
<td>15 ± 3</td>
<td>79 ± 12*</td>
<td>5.27</td>
</tr>
<tr>
<td>Right lung (control)</td>
<td>209 ± 10</td>
<td>186 ± 20</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = no. of sheep. V\dot{O}2, O\textsubscript{2} uptake; V\dot{CO2}, CO\textsubscript{2} output; R, respiratory quotient; PA, pulmonary artery. *Significantly different compared with corresponding value in acute group, P < 0.05. 

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Fig. 4. Surface of left lung of same sheep shown in Fig. 1. There are large bronchial arteries on surface of lung underneath visceral pleura.

Fig. 5. A: changes in bronchial blood flow after ligation of left pulmonary artery in adult sheep. B: changes in cardiac output. ○, Experimental group with ligated left pulmonary artery (n = 4); ●, control group in which pulmonary artery was left intact (n = 4). Day 0, day of pulmonary artery ligation. *Significantly different compared with control group, P < 0.05.
the bronchial circulatory system, which can be detected as early as 3 days after introduction of infection in the pleural space (3). In the present study, we found that the pulmonary artery ligation in newborn lambs also stimulates angiogenesis, resulting in marked proliferation of the bronchial circulatory system. When the pulmonary artery is ligated in the adult sheep, the bronchial blood flow gradually increases and reaches a maximum value in ~3 wk. We also found that after acute pulmonary artery ligation, some VO₂ and VCO₂ can occur from the bronchial circulation, and chronic pulmonary artery ligation, which causes marked hypertrophy of the bronchial circulation, results in a further increase in these values.

Several investigators have studied the effects of pulmonary artery ligation on the bronchial circulatory system in acute as well as in chronic models (5, 9, 12, 14). In acute model, the bronchial blood flow has been studied soon after ligation of pulmonary artery. Kowalski et al. (8) used the radiolabeled microsphere technique in rabbits and found that occlusion of pulmonary artery resulted in a progressive fall in bronchial blood flow over the first 4 h and remained diminished at 24 h. In other long-term studies, the bronchial blood flows were generally studied only at a specified time after pulmonary artery obstruction. These studies show that enlargement of the bronchial arteries starts in ~2–3 days after ligation of the pulmonary artery (5, 18), becomes moderately enlarged in ~1–2 wk, and develops marked hypertrophy by 2–4 wk (5, 10, 12, 18). Our study is unique because we used a flow probe to monitor sequential changes in bronchial blood flow measurements without killing the animals at different time intervals. We found that the bronchial blood flow began to increase in ~4 days, was about three times the control value within 1 wk of pulmonary artery obstruction, and reached a maximum value of 134 ml/min in ~4 wk. These findings are in agreement with those of Liebow et al. (9), who also found that the bronchial blood flow had increased in excess of 100 ml/min in ~2 wk after ligation of the left pulmonary artery in dogs. Because two thoracotomies could have resulted in changes in bronchial blood flow, we used a control group of animals and found no significant change in bronchial blood flow in this group of animals, indicating that surgery by itself does not cause significant angiogenesis in the bronchial circulatory system. It is also possible that placement of the flow probe around the bronchial blood artery could have restricted further enlargement of the vessel and, if the probe was not placed around the bronchial artery, there could have been further increases in flow. In this sheep model, we were able to study the flows for only 3–4 wk after flow probe placement because, beyond that period, flow readings became rather unreliable. Thus we report only 24-day data and, from this study, we are not able to establish whether the maximal value of bronchial blood flow that we observed 3 wk after pulmonary artery ligation would have remained unchanged over the subsequent years. Nevertheless, this study does provide some serial data that suggest progressive development of angiogenesis in the bronchial circulatory system after pulmonary artery obstruction.

Although marked expansion of the bronchial circulation has been described in patients with congenital absence of unilateral pulmonary artery, this phenomenon has not been systematically studied in an animal model. In this study, we found that ligation of pulmonary artery in newborn lambs resulted in profound angiogenesis in the bronchial circulation (Fig. 2). Our findings are in agreement with those of Liebow et al. (10), who found in adult dogs that the bronchial circulation had developed marked expansion 12 wk after pulmonary artery ligation. We also observed that whenever there was marked angiogenesis in the bronchial circulatory system, it was always associated with tortuosity of the bronchial arteries. The explanation for this could be that during the angiogenic process, the bronchial arteries increase not only in diameter but also in length, which results in tortuosity of the vessel. The mechanism involved in this progressive enlargement of bronchial circulatory system after pulmonary artery ligation is not known. Weibel (18) suggested that the initial increase in bronchial blood flow is due to hemodynamic factors and that angiogenesis begins only after 5 days. Thus it is possible that increases in bronchial blood flow during the first 3 days of pulmonary artery obstruction could be due to dilatation of the bronchial microvasculature. Development of angiogenesis that leads to marked enlargement of the bronchial circulatory system is likely to be mediated by release of angiogenic factors by the pulmonary endothelial cells. Indeed, there has recently been some evidence that suggests that endothelin-1 may play a role in bronchovascular angiogenesis that occurs after pulmonary artery obstruction (6). It can be speculated that marked

### Table 2. Effects of varying alveolar-to-arterial O₂ tensions on VO₂ and VCO₂ from left lung in sheep in which left pulmonary artery was ligated at birth

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Systemic Arterial Blood Gases</th>
<th>Pulmonary Venous Blood Gases</th>
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<tbody>
<tr>
<td></td>
<td>PABO₂</td>
<td>PABCO₂</td>
</tr>
<tr>
<td>Normoxemia (left lung = RA ventilation)</td>
<td>87 ± 7</td>
<td>37 ± 4</td>
</tr>
<tr>
<td>Severe hypoxemia (left lung = RA ventilation)</td>
<td>34 ± 4</td>
<td>33 ± 5</td>
</tr>
<tr>
<td>Systemic hypoxemia and left lung hyperoxia</td>
<td>48 ± 4</td>
<td>29 ± 3</td>
</tr>
<tr>
<td>No ventilation in left lung</td>
<td>72 ± 4</td>
<td>44 ± 5</td>
</tr>
</tbody>
</table>

Values are means ± SE in Torr. PABO₂, arterial PO₂; PABCO₂, arterial PCO₂; RA, room air. Note: barometric pressure = 690 Torr. *Significantly different compared with corresponding value in normoxic group, P < 0.05.
decreases in pulmonary blood flow result in an absence of shear forces across the pulmonary endothelial cells and that this decrease in shear forces provides stimulation for angiogenesis. This is consistent with our findings that ligation of pulmonary artery as well as incidental ligation of pulmonary vein resulted in angiogenesis in the bronchial circulatory system.

The functional importance of such a marked degree of angiogenesis in the bronchial circulatory system after unilateral pulmonary artery obstruction is not known. It is unlikely that the main purpose of this angiogenesis is to prevent necrosis of lung tissue because necrosis should take place soon after the occlusion, whereas angiogenesis in the bronchial circulatory system takes a few days to develop. It has been suggested that the hyperexpanded bronchial circulation has some gas-exchange functions. Several investigators have looked into this possibility. For example, Bloomer et al. (2) occluded the left pulmonary artery in dogs and found that although there was a small amount of VO₂ from the left lung, it was insufficient to sustain life for more than a few minutes in the absence of ventilation in the right lung, even 21 mo after ligation of the pulmonary artery. Similarly, Lilker and Nagy (11) occluded the left pulmonary artery in seven adult dogs and studied them 6–12 mo later. They found that from the experimental left lung VO₂ was 11% and VCO₂ was 15% of the total. Compared with this study, we found that in our chronic sheep model where the bronchial artery had been ligated at birth, VO₂ from the left lung was 7% and VCO₂ was 30% of the total. The reason for finding much higher VCO₂ in our study could be due to the fact that we ligated the pulmonary artery at birth because, compared with ligation of the pulmonary artery in adult animals, this is known to cause far more pronounced increases in the bronchial blood flows. Because the bronchial circulation is perfused with systemic arterial blood, it should not pick up much O₂. Indeed, Viola and Abbate (15) described a patient in whom, after surgical ligation of the left pulmonary artery, there was no VO₂ from the left lung; however, the uptake reached 80 ml when the right lung was supplied with a low O₂ mixture. In our acute as well as chronic sheep model, only 7% of VO₂ were from the left lung, but this also increased when sheep were made hypoxic, presumably by increasing alveolar-to-arterial O₂ difference in the left lung. This finding is also consistent with that of Lilker and Nagy (11), who also found that with systemic hypoxemia VO₂ increased from 11 to 29% of the total. In this model, it is difficult to establish whether the site of gas exchange is in the airways or in the bronchial capillaries. Because the bronchopulmonary anastomoses are generally precapillary in sheep (4), it is likely that gas exchange occurred at the alveolar level rather than in the airways. When we ventilated the left lung with 100% O₂, the pulmonary venous PO₂ was only 319 Torr, which suggests that the pulmonary capillaries may have altered in some manner, causing a diffusion barrier to O₂. The other possible explanation for this finding is that there are direct communications between the bronchial microvasculature and the pulmonary veins, resulting in a mixing of the hypoxic systemic arterial blood with well oxygenated blood coming from the pulmonary capillaries. If direct bronchial-to-pulmonary venous communications do exist in this chronic pulmonary artery-ligated sheep preparation, they must not be numerous. This notion is in agreement with our previous study in sheep, where we found that most of the bronchopulmonary communications are precapillary (4).

Thus we conclude that chronic ligation of unilateral pulmonary artery causes marked angiogenesis in the bronchial circulatory system, which results in progressive increases in bronchial blood flow. This increase in bronchial blood flow may perform some gas-exchange functions.

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Address for reprint requests: N. B. Charan, Section of Pulmonary/Critical Care Medicine (111), Veterans Affairs Medical Center, 500 West Fort St., Boise, ID 83702–4598.

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