Bronchial vascular contribution to lung lymph flow

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Wagner, Elizabeth M., Sandralee Blosser, and Wayne Mitzner. Bronchial vascular contribution to lung lymph flow. J. Appl. Physiol. 85(6): 2190–2195, 1998.—The lymphatic vessels of the lung provide an important route for clearance of interstitial edema fluid filtered from pulmonary blood vessels. However, the importance of lung lymphatics for the removal of airway liquid filtered from the systemic circulation of the lung has not been demonstrated. We studied the contribution of the bronchial vasculature to lung lymph flow in anesthetized, ventilated sheep (n = 35). With the bronchial artery cannulated and perfused (control flow = 0.6 ml·min⁻¹·kg⁻¹), lymph flow from the efferent duct of the caudal mediastinal lymph node was measured 1) during increased bronchial vascular perfusion (300% of control flow); 2) with a hydrated interstitium induced by a 1-h period of left atrial hypertension and subsequent recovery, both with and without bronchial perfusion; and 3) during infusion (directly into the bronchial artery) of bradykinin, an inflammatory mediator known to cause changes in bronchial vascular permeability. Increased bronchial perfusion for 90 min resulted in an average 35% increase in lung lymph flow. During left atrial hypertension, the increase in lung lymph flow was significantly greater with bronchial perfusion (339% increase over baseline) than without bronchial perfusion (138% increase). Furthermore, recovery after left atrial hypertension was more complete after 90 min without bronchial perfusion (91%) than with bronchial perfusion (63%). Infusion of bradykinin into the bronchial artery resulted in a prompt and prolonged 107% increase in lung lymph flow. This was not seen if the same dose was infused into the pulmonary artery. Thus, bronchial vascular transudate contributes significantly to lymph flow from the efferent duct of the caudal mediastinal lymph node. These results demonstrate that lymph vessels clear excess fluid from the airway wall and should be considered when evaluating the effect of vascular leak in airway obstruction.

bradykinin; bronchial artery; hydrostatic edema; hyperpermeability; lung water

The lymphatic system provides an important drainage mechanism for fluid being filtered from pulmonary blood vessels. As fluid is filtered, lymph flow increases and thereby removes excess fluid from the lung. However, if the rate of filtration exceeds the capacity for lymphatic removal, then the excess fluid will accumulate in perivascular and peribronchial cuffs (21). The rate of lymph flow has been correlated with the rate of filtration from the pulmonary vasculature but not with the amount of fluid that has accumulated (13). Even during conditions of permeability edema where extra-vascular fluid accumulation is elevated, lymph flow parallels fluid filtration and not overall lung water (17). Although the lymphatic vessels course through the perivascular cuffs, there appears to be little or no mixing between the lymphatic fluid and the interstitial fluid in the cuffs (7). This observation raises several questions regarding how edema that may form in the airway wall is cleared. Bronchial capillaries and post-capillary venules have been shown to leak fluid under several pathological conditions (11). There exist four potential pathways by which this fluid can leave the lung: 1) via reabsorption directly back into the vasculature; 2) by moving through the interstitium directly into the peribronchial-perivascular cuffs; 3) through lymphatics directly adjacent to large pulmonary vessels; or 4) by bulk transport into the airway lumen and subsequent clearance via mucociliary removal (5).

Anesthesia of healthy sheep (24–42 kg) of mixed breeds was induced with ketamine (1 g im) and maintained throughout the surgical and experimental periods with pentobarbital sodium (15 mg/kg loading dose and 20 mg/kg hourly dose). Sheep were paralyzed with pancuronium bromide (2 mg iv), and, after tracheostomy, they were mechanically ventilated with warmed, humidified air at a tidal volume (12 ml/kg) and rate (12–15 breaths/min) sufficient to ensure blood gases within the normal range. Supplemental oxygen was provided, and, after thoracotomy, all sheep were placed on 5 cmH₂O positive end-expiratory pressure. Airway pressure was measured at a sidearm of the tracheal cannula. Catheters were inserted into the femoral vein for anesthetic infusion, into one femoral artery for systemic arterial pressure measurement, and into the other femoral artery to supply the pump used to perfuse the bronchial artery. After right lateral thoracotomy at the sixth intercostal space, the efferent duct of the caudal mediastinal lymph node was cannulated and lymph was collected in a beaker hung from a force transducer. The tail of
the lymph node was clamped to eliminate systemic contributions to lung lymph flow (20). A left lateral thoracotomy was performed between the fifth and sixth ribs to allow direct access to the bronchoesophageal artery as it exits the aorta. The thoracic, tracheal and esophageal branches of the bronchoesophageal artery were ligated. After infusion of the anticoagulant heparin (20,000 U S Pharmacopoeia units), the bronchial artery was cannulated with an 18-gauge catheter inserted directly into the vessel. The catheter was secured in place, and the bronchial branch of the bronchoesophageal artery was perfused with autologous blood from the femoral artery at a flow controlled by a calibrated roller pump (Gilson) and set initially at a flow of 0.6 ml·min⁻¹·kg⁻¹, a value within the reported normal range for sheep (4). Bronchial artery pressure was measured at a side port of the inflow cannula. A balloon-tipped catheter (30-ml Foley) was placed in the left atrium through an incision in the atrial appendage. To help maintain systemic arterial pressure during left atrial pressure elevation, all sheep were given 500 ml of lactated Ringer solution intravenously over the course of 1 h. Measurements of hemodynamic variables were made with Gould transducers and recorded on a Grass recorder. A 30-min stabilization period followed surgery.

Protocols

Three experimental protocols were employed to determine the bronchial vascular contribution to lung lymph flow.

Protocol 1. In this protocol, we sought to quantify the lung lymph flow changes after alterations in bronchial blood flow and perfusion pressure for short (30-min) or prolonged (90-min) time periods. In a group of sheep (n = 5), lung lymph flow was measured during alternating 30-min periods of control, low (<6 ml/min), or high (2–3 times control) flow over the course of 150 min. In an additional group of animals (n = 5), lung lymph flow was measured during control bronchial blood flow (90 min) followed by a 90-min period of high blood flow (300% control flow).

Protocol 2. This protocol was designed to determine whether, under conditions of a hydrated interstitium, the bronchial circulation contributes to fluid filtration and an increase in lung lymph flow or whether it removes fluid. We reasoned that to see a significant effect of the bronchial circulation might require a priming of the interstitial sumps. Thus we studied the effects of different levels of bronchial blood flow during and after a period of left atrial hypertension. In the first series of studies, left atrial pressure was elevated to 20 mmHg by inflating a balloon catheter in the left atrium while maintaining bronchial blood flow at control level. The increase in lung lymph flow was measured during this 60-min period of left atrial hypertension. Left atrial pressure was decreased back to control level, and lung lymph flow was measured for the subsequent 90 min during either conditions of high bronchial blood flow (300% control flow; n = 6) or during conditions in which perfusion through the bronchial circuit was stopped (n = 6). In addition, the increase in lung lymph flow during the period of left atrial pressure elevation with control bronchial artery perfusion of these two groups of animals was compared with a third group of sheep (n = 5), in which the bronchial artery was obstructed before left atrial hypertension.

Protocol 3. In the third protocol, we sought to quantify the contribution of the bronchial vasculature to lung lymph flow after this circulatory bed was selectively challenged with an inflammatory mediator known to cause bronchial vascular fluid extravasation. Bradykinin (10⁻⁸ M; 1 ml/min for 10 min) was infused directly into the bronchial artery. Because of the vasodilatory properties of bradykinin, bronchial blood flow was increased (only during the infusion) to maintain bronchial artery perfusion pressure at its level before the bradykinin infusion. Lung lymph flow was measured before, during, and for 60 min after bradykinin infusion (n = 4). To control for the potential effects of bradykinin on pulmonary vessels downstream from the site of bronchopulmonary anastomoses, the same bradykinin-delivery regimen was applied to the pulmonary artery through the proximal port of the Swan-Ganz catheter and lung lymph flow was measured. In additional animals, Evans blue dye (0.565 mg/ml; 2 ml/min), which binds to albumin, was infused concomitantly with bradykinin infusion (10 min; n = 3) or 15 min after bradykinin infusion (n = 3) to determine whether bronchial vascular permeability remained altered after bradykinin infusion. In these experiments, after an intravenous bolus injection of saturated KCl (10 ml) to stop the heart, the bronchial vasculature was flushed for 5 min with physiological salt solution, the lungs were removed, and samples (0.2–0.5 g) of second- and third-generation bronchi of the left upper and the right middle lobes were removed. The samples were weighed and, after the dye was extracted from the tissue with formamide (5 ml; Sigma Chemical), they were heated (50°C) for 48 h and measured spectrophotometrically at 620 nm (Beckman).

Data Analysis

Statistical significance was determined by Student’s t-test for paired and unpaired observations as appropriate. Analysis of variance was used to determine changes in lung lymph flow in the two series of experiments described for protocol 1. Duncan’s multiple-range test was used to compare the means at different time points. Differences were considered significant when P ≤ 0.05. Values are reported as means ± SE.

RESULTS

Bronchial blood flow for the entire group of 35 sheep (weight 29 ± 1 kg) in which the bronchial artery was initially set at 0.6 ml·min⁻¹·kg⁻¹ was 18 ± 1 ml/min and resulted in a bronchial perfusion pressure of 97 ± 4 mmHg. Baseline lung lymph flow averaged 4.5 ± 0.4 ml/h, pulmonary arterial pressure was 14.6 ± 0.8 mmHg, left atrial pressure was 5.9 ± 0.3 mmHg, and mean arterial pressure was 84 ± 3 mmHg.

In protocol 1, short periods of altered bronchial blood flow had no significant effect on lung lymph flow (Fig. 1). After 30 min of control bronchial flow, lung lymph flow (4.8 ± 1.0 ml/h) did not differ from that after 30 min of increased bronchial blood flow (5.0 ± 1.4 ml/h) or decreased bronchial blood flow (4.7 ± 1.0 ml/h; P = 0.69). Furthermore, baseline (0 min) lymph flow (4.3 ± 1.1 ml/h) was not different from that at 150 min (4.8 ± 1.2 ml/h; P = 0.51), demonstrating that, over the total time period, lung lymph flow remained constant. However, in the next series of experiments when a sustained period of increased bronchial blood flow (55 ± 4 ml/min) was imposed, lung lymph flow increased significantly by 28% over baseline after 60 min of increased perfusion and 35% by 90 min (P = 0.01). The absolute changes in lymph flow from baseline are shown in Fig. 2. Average bronchial artery inflow pressure in this group was 220 ± 16 mmHg during the period of high
blood flow. The change in lung lymph flow after 90 min of control flow was not different from baseline. Lymph flow at both the 150- and 180-min time points was significantly greater than the 90-min control-flow time point ($P = 0.05$ and $P = 0.01$, respectively). Pulmonary microvascular pressures (left atrial pressure + 0.4[pulmonary arterial pressure − left atrial pressure]) at 90 min and 180 min were not significantly different ($8.8 ± 0.6$ vs. $8.7 ± 0.6$ mmHg; $P = 0.535$).

In protocol 2 experiments, hydrostatic edema was generated by inflating a balloon-tipped catheter in the left atrium and thereby elevating left atrial pressure to $19.4 ± 0.5$ mmHg and pulmonary arterial pressure to $26 ± 1$ mmHg ($n = 17$). In the experiments with control bronchial perfusion, on elevating left atrial pressure, bronchial artery pressure increased to $138 ± 7$ mmHg. The average increase in bronchial artery pressure ($42 ± 3$ mmHg) observed was significantly greater than the average increase in left atrial pressure ($13 ± 1$ mmHg; $P < 0.001$). One hour of left atrial hypertension caused a significant increase in lung lymph flow from an average baseline of $4.2 ± 0.5$ to $16.2 ± 0.9$ ml/min ($n = 12$; $P < 0.01$). Pulmonary microvascular pressure increased from baseline ($10.4 ± 0.6$ mmHg) to $20.5 ± 0.6$ mmHg. After left atrial pressure was decreased, lung lymph flow was measured during the recovery time with high bronchial blood flow ($62 ± 3$ ml/min) and an initial inflow pressure of $217 ± 18$ mmHg or with no bronchial blood flow. After 90 min of high-blood-flow conditions, lung lymph flow decreased by $48%$ to $8.3 ± 0.8$ ml/min. However, this level of lymph flow was significantly greater than the original baseline level ($P < 0.01$). After 90 min of no bronchial blood flow, lung lymph flow ($5.7 ± 1.0$ ml/h) was not statistically distinguishable from paired baseline values ($4.5 ± 0.9$ ml/h; $P = 0.11$). As seen in Fig. 3, the changes in lung lymph flow between the two bronchial blood flow groups after 90 min of recovery were significantly different from each other ($P = 0.05$). Pulmonary microvascular pressure during this recovery phase was similar in the two bronchial blood flow groups (high flow: $11.2 ± 0.8$ mmHg vs. no flow: $9.8 ± 1.0$ mmHg; $P = 0.32$).

The changes in lung lymph flow during left atrial hypertension with control bronchial perfusion ($n = 12$) were compared with the increase observed in an additional series of experiments when the bronchial artery was obstructed before the period of left atrial hypertension ($n = 5$). The results are presented in Fig. 4. Baseline lung lymph flow did not differ between the no-flow group ($5.6 ± 0.9$ ml/h) and control blood flow group ($4.2 ± 0.5$ ml/h; $P = 0.16$). Left atrial pressure was elevated to the same level in the no-flow group ($19.4 ± 0.4$ mmHg), and pulmonary microvascular pressure ($19.2 ± 0.9$ mmHg) was not different from what was seen in the group with bronchial perfusion ($P = 0.254$). The change in lung lymph flow during left atrial hypertension and no bronchial blood flow was significantly less ($7.7 ± 0.5$ ml/h) than what was seen when the bronchial artery was perfused at control flow ($12.0 ± 0.7$ ml/h; $P < 0.01$).
Changes in lung lymph flow after the direct infusion into the bronchial artery of bradykinin, an inflammatory mediator known to cause bronchial vascular fluid extravasation, was studied in protocol 3. The results showing lung lymph flow in four sheep during a 10-min infusion of 10^{-6} M bradykinin are presented in Fig. 5. A significant 6.7 ± 2.4 ml/h (107%) increase in lung lymph flow was observed by 20 min (P = 0.02). Despite the termination of infusion of bradykinin after 10 min, lung lymph flow remained significantly elevated for the duration (60 min) of the experiment. To maintain bronchial artery pressure constant during the bradykinin infusion, bronchial blood flow was increased to 43 ± 5 ml/min. This represents a decrease in bronchial vascular resistance (inflow pressure/flow) from the control of 7.2 ± 0.8 to 2.52 ± 0.1 mmHg·ml^{-1}·min (P < 0.01). We also tested whether the bradykinin administration into the bronchial artery caused leakage from pulmonary or bronchial capillaries. If there were substantial bronchial venous drainage into the pulmonary capillaries, then some leakage could have occurred from these vessels. When bradykinin was delivered at the same rate directly into the pulmonary artery through the proximal port of the Swan-Ganz catheter, lung lymph flow did not alter from control (6.0 ± 0.9 vs. 5.6 ± 1.6 ml/h at 30 min; n = 3).

To determine whether fluid exudation from the bronchial vasculature continued despite cessation of bradykinin infusion, Evans blue dye was infused in another group of sheep either during bradykinin infusion or 15 min after termination of bradykinin infusion. The amount of Evans blue dye extracted from six to eight bronchial samples from left and right lungs was averaged for each animal. The average dye concentration recovered from Airways during bronchkinin infusion (21 ± 4 µg/g of airway tissue) was significantly greater than that extracted from airway tissue infused with dye 15 min after the termination of bradykinin (8 ± 4 µg/g; P = 0.04). Thus, despite the maintained elevation of lung lymph flow observed at 25–35 min in Fig. 5, Evans blue dye extravasation was significantly decreased during this time interval relative to that during bradykinin infusion.

**DISCUSSION**

The overall goals of this study were to determine the extent to which the bronchial vasculature could contribute to lung lymph flow. In each of the three protocols, the bronchial circulation was shown to increase significantly lymph flow from the efferent duct of the caudal mediastinal lymph node, which typically is thought to reflect pulmonary vascular transudate. Results from the first series of experiments demonstrated that, when bronchial vascular filtration pressure was increased by increasing bronchial blood flow for a sustained period of time, lung lymph flow increased. In this experiment, the lymph flow increased only by ∼35%, but the magnitude of the increase in lymph flow is likely related to the increase in fluid filtration. Although we measured the magnitude of the increase in arterial perfusion pressure, we could not measure the increase in pressure in the microvessels that are presumed to leak. Because the predominant site of leakage from airway vessels has been shown to be in postcapillary venules (11), there may have been only a small increase in the filtration pressure applied in this protocol with increased arterial pressure. Changes in the filtration pressure in the leaky venules are more closely matched to changes in downstream pressure, because the site of filtration is located downstream from the arterial resistance vessels. This filtration limitation associated with increased arterial pressure was circumvented in the second protocol where left atrial pressure was increased. With a left atrial pressure of 20 mmHg, there was an approximate 300% increase in lymph flow after 60 min. With increases in left atrial pressure, filtration can occur from both the pulmonary and bronchial blood vessels, so the increased lymph flow could have resulted from transudation from either circulation. With a return of left atrial pressure to control, this increase in lymph flow gradually returned to baseline if there was no bronchial blood flow. However, if the bronchial circulation was perfused at high flow during the recov-
ery period, the lymph flow remained substantially elevated. This observation suggests that the conditions of a hydrated interstitium in conjunction with the extended period of elevated microvascular filtration pressure prolonged the period of bronchial vascular fluid flux during high flow. Furthermore, it confirms that fluid leakage from the bronchial vessels was a major contributor to the observed increase in lymph flow. This was further substantiated by the observation that the overall increase in lymph flow was considerably attenuated if bronchial perfusion was stopped prior to left atrial pressure elevation (Fig. 4).

In general, the contribution of the bronchial circulation to overall fluid balance in the lung has received little attention. Paré and colleagues (15) demonstrated that systemic venous hypertension (right atrial pressure elevation) in combination with fluid volume overload caused an increase in lung water and a significant increase in lung resistance. These authors suggested that airway edema resulting from bronchial vascular fluid filtration could promote airflow obstruction. However, Charan et al. (3) were unable to demonstrate an increase in lung lymph flow when they selectively elevated the bronchial venous pressure of the extrathoracic airways that are perfused by the bronchial vessels and that drain through the right heart. Jayr and Matthay (10) showed that, in the absence of pulmonary blood flow, even very low levels of bronchial blood flow were important for the clearance of excess alveolar liquid. By using a different experimental approach, Fukue et al. (6) also demonstrated that, during conditions of no pulmonary blood flow, bronchial vascular perfusion could remove excess interstitial fluid in the lung. The involvement of the bronchial vasculature in either contributing to or removing edema fluid from the lung after a hydrostatic stress has not been extensively studied and has been made difficult by the presence of the larger pulmonary vasculature. However, the contribution of the bronchial vasculature in eliciting permeability edema of the airways has been proposed for an array of inflammatory mediators (11, 18) as well as during inhalation injury (1, 9). As will be discussed below, whether fluid extravasation is synonymous with edema is, however, unclear. If the extravasated fluid can be readily removed, then there will be no airway edema.

The third protocol examined the effects of airway permeability edema on lung lymph flow. Bradykinin has been shown to cause the opening of endothelial gaps of postcapillary venules of the airways, resulting in fluid and protein extravasation (11). We observed a rapid and significant increase in lymph flow after infusion of bradykinin into the bronchial circulation at a dose that was also shown to have no effect on the pulmonary capillaries. The increase was large and sustained for at least 1 h. Thus it appears that lymph flow from the caudal mediastinal node can be dominated by fluid extravasation from just the airway blood vessels. Perhaps the most puzzling aspect about the observed increase in lymph flow after bradykinin infusion was its duration. With the hydrostatic edema, when the pressure was returned to control, the lymph flow fell toward control. Others have shown that, during both hydrostatic and permeability edema in the pulmonary vasculature, lymph flow parallels changes in filtration (13, 17). That lymph flow remained elevated with the permeability edema suggested that either extravasation persisted or that lymphatic vessels associated with airways respond and maintain increased pumping for as long as edematous conditions persist. However, persistent extravasation is not consistent with the known action of bradykinin. McDonald (11) demonstrated that the effect of this drug was very short lived, lasting a few minutes at most, and refractory to further challenges. In a small subset of sheep in protocol 3, Evan's blue dye extravasation, a marker of albumin flux and increased permeability, was determined during and after bradykinin administration. The appearance of this marker in the airway wall was significantly reduced at the time when lymph flow remained elevated and was not decreasing. These results are in accord with McDonald's observations of transient endothelial gap formation. If this is true, then there must be another reason for the prolonged elevated lymph flow. That the results obtained were not the direct effect of bradykinin acting on the pumping capability of lymphatics or on the function of the caudal mediastinal lymph node is suggested by the prolonged time course of elevated lymph flow after the infusion of bradykinin was terminated. Another possibility is that bradykinin affected the mobility of water in the airway wall, such that it maintained access to the initial lymphatics. At the present time we cannot distinguish among these or other possibilities, but it does appear that the lymph flow response to fluid leakage from the bronchial vessels is unlike that observed after more general pulmonary edema.

Several studies have suggested that fluid leakage from the bronchial circulation can lead to sufficient thickening of the airway wall to cause airflow obstruction (8, 14, 19). However, in order for such a mechanism to exist, there must be consideration not only of the possible vascular leakage but also of the potential clearance pathways for this extravascular water. The potential for lung lymphatics to clear extravasated fluid from the airway wall has largely been ignored in these studies. In the present study we have shown that lung lymph flow can be altered significantly by interventions designed to cause fluid leakage from the bronchial vasculature. Periods of increased pressure in the bronchial vessels, either through increases in blood flow or during left atrial hypertension, led to significantly increased lung lymph flow through the efferent duct of the caudal mediastinal lymph node. When the elevated pressures returned to control, there was a gradual recovery of lymph flow toward control. However, if we caused changes in vascular permeability in the bronchial circulation, lymph flow remained elevated for prolonged time periods. These experiments confirm that one operational pathway for drainage of excess airway liquid is through the same lymphatic system that drains fluid transudate from the pulmonary vasculature. There may also be drainage via lymphatics that travel along the airway and exit from the hilum, but
there is no a priori reason to expect the flow in these channels to behave qualitatively differently from that of lymphatics entering the caudal mediastinal lymph node.

The sequence of events associated with fluid leakage from the pulmonary circulation has been known for many years (21). Fluid leakage from the pulmonary capillaries is immediately drawn into the perivascular interstitial space by virtue of the subpleural pressure there. As that space fills, fluid next accumulates in the interstitial space around the airways, forming the so-called peribronchial cuffs. Whether these cuffs are in or around the airways is a semantic point, because, beyond the lobar bronchi, there is no membranous structure that clearly defines the outer wall of intraparenchymal airways (23). As edema develops there is a simultaneous increase in lymph flow from the lung (13).

Although several anatomic studies have documented the extensive network of lymphatics throughout the airway wall (12, 22), the physiology of lymphatic drainage from the airway wall has not been studied. If the sequence of events associated with airway edema mimics that associated with pulmonary edema, then we might expect to find that early fluid leakage from the bronchial circulation similarly is drawn to the perivascular space. This would be consistent with previous histological observations showing minimal increases in airway wall area after leakage from the bronchial circulation (2). Continuing the parallel with leakage from the pulmonary circulation, we would then expect the lymph flow to increase as well. Indeed, this is what has been observed with damage to the bronchial vessels (permeability edema) after inhalation injury (1) and in the present study with the delivery of an inflammatory peptide and with increases in hydrostatic pressure. Because the bronchial circulation has such a small surface area compared with that of the pulmonary circulation, the quantitative effect of fluid transudate from it would be expected to be much less. Thus the fact that we observed such large increases in lymph flow (2- to 3-fold) with bradykinin and increased pressure is rather remarkable. The magnitude of the changes we observed is similar to what is often observed with more generalized pulmonary edema (16). This means that either the pulmonary lymphatics are preferentially arranged to remove excess fluid from the airways or that, with the capacity to deal with large amounts of pulmonary fluid, all of the relatively small amount of airway fluid can be readily cleared. Whatever the explanation, the ramifications are that it appears that the lung is capable of readily removing excess fluid from the airway wall. Given this capability, the notion that fluid leakage from the bronchial circulation might be sufficient to thicken the airway and cause airflow obstruction seems quite unlikely. For this to happen there would need to be relatively massive amounts of fluid leak from the airway.

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Received 1 December 1997; accepted in final form 18 August 1998.

REFERENCES


