

REVIEW

Bronchial vascular congestion and angiogenesis

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ABSTRACT: The bronchial vasculature is the systemic arterial blood supply to the lung. Although small relative to the pulmonary blood flow, the bronchial vasculature serves important functions and is modified in a variety of pulmonary and airway diseases.

Congestion of the bronchial vasculature may narrow the airway lumen in inflammatory airway diseases, and formation of new bronchial vessels (angiogenesis) is implicated in the pathology of a variety of chronic inflammatory, infectious and ischaemic pulmonary diseases. The remarkable ability of the bronchial vasculature to remodel has implications for disease pathogenesis.

The contributions of the bronchial vasculature to the pathogenesis of pulmonary disease are reviewed in this article.

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The bronchial circulation is ideally situated to play an important role in lung defence and in the pathogenesis of a number of airway diseases. The bronchial microvasculature provides nutrient blood flow to the airway epithelium and is important for proper functioning of the mucociliary escalator. Bronchial blood flow is responsive to changes in neural and humoral stimuli and plays a role in conditioning of inspired air. The focus of this review is the potential involvement of the bronchial vasculature in contributing to the pathogenesis of a variety of airway diseases. In particular, we have focused on the possibility of airway narrowing as a consequence of bronchial vascular congestion, and the remarkable proliferative capacity of the bronchial vessels in response to a variety of pulmonary diseases.

Bronchial vascular congestion

Hyperaemia of the bronchial vasculature is often included in descriptions of the pathology of asthma. An example of hyperaemia of the bronchial vasculature is shown in figure 1. This photomicrograph shows a cross-section of a human airway from a patient who died of asthma. The apparent increase in the size and number of vessels inside and outside the smooth muscle layer is clearly visible, suggesting that vascular dilation and proliferation (angiogenesis) could be important components of the airway wall remodelling in asthmatic patients. The airway vasculature is of considerable interest in asthma because it can contribute to the excessive airway narrowing, which is characteristic of this disease. A diagram of an airway (fig. 2) illustrates the two bronchial vascular plexuses: the peribronchial plexus, located in the adventitial space between the muscle and the surrounding lung parenchyma; and the submucosal vascular plexus, located beneath the epithelial layer. Dilation, exudation

or transudation from these vessels could contribute to the excessive airway narrowing observed in asthma. Relaxation of the bronchial vascular smooth muscle and/or an increase in the intravascular pressure will lead to congestion of these vessels. This bronchial vascular congestion could result in a reduction in the area of the airway lumen and/or an increase in the outer diameter of the airway. The latter effect could uncouple the airway smooth muscle from the load applied by the elastic recoil of the lung. Tethering by the alveolar attachments to the outside of the airways is thought to be an important mechanism limiting airway smooth muscle shortening and airway narrowing [1]. The regional lung deflation that accompanies adventitial thickening or oedema, could cause a regional loss of lung recoil. To measure the potential effect of these changes, it is important to know how much space the bronchial vessels normally occupy and whether they could significantly narrow the lumen if they became engorged.

These questions have been addressed in several studies [2–5], the results of which are summarized in table 1. In our laboratory, BAILE and co-workers [2] have recently carried out a study in anaesthetized sheep to determine whether bronchovascular engorgement results in significant airway narrowing, by administering aerosols of the bronchial vascular dilator, histamine, and the bronchial vascular constrictors, phenylephrine and methoxamine. Pulmonary resistance was measured, as an indicator of airway narrowing, before and after the aerosol challenge; airway blood flow was measured using the radioactive microsphere technique. Morphometric techniques were used to measure the blood volume of the airway wall and the contribution of vascular area to the thickness of the airway wall. In these studies, care was taken to ensure that no blood was lost from the lung during excision and fixation. Immediately after recording

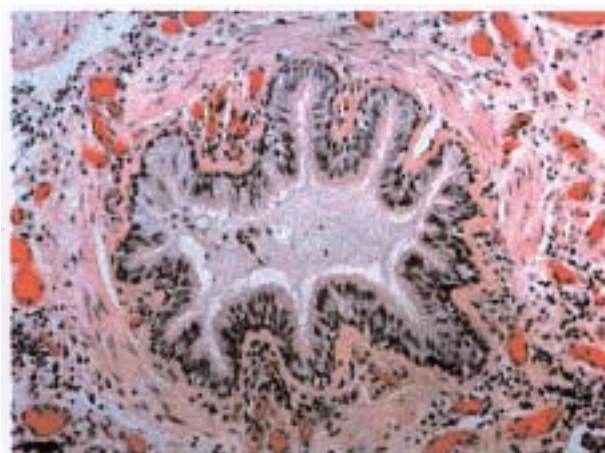


Fig. 1. — Photomicrograph showing a cross-section of a small bronchiole from a patient who died of asthma. An increase in the size and number of vessels is visible inside and outside the smooth muscle layer. (From the archives of J.C. Hogg).

the maximal increase in pulmonary resistance in response to aerosol challenge, the ventilator was turned off at end-inspiration, ligatures around the hilum of the lung were tied tightly and saturated potassium chloride was injected into the heart. The lungs were excised and the left lung frozen in liquid nitrogen. Lung tissue samples were processed for histology using a freeze substitution technique. The contribution of bronchial vessels to the airway wall area inside and outside the smooth muscle layer was measured using cross-sections of the trachea and intraparenchymal bronchi.

Physiological measurements showed that inhalation of aerosolized histamine tripled pulmonary resistance,

whereas there was no change in airway resistance after inhalation of the aerosolized alpha-agonists, methoxamine and phenylephrine. Airway blood flow doubled in response to aerosolized histamine, but was unchanged after the alpha-agonists. Results of the morphometric analysis of the trachea showed that blood vessels made up 34% of the wall, and that the aerosolized drugs had no effect in increasing or decreasing the percentage of the wall made up of blood vessels. In the intraparenchymal bronchi, both inside and outside the smooth muscle layer, bronchial blood vessels made up approximately 15 and 21% of the area of the bronchial wall, and aerosolized histamine caused a 50–60% increase in the blood volume. The inhaled alpha-agonists had no significant effect. Calculation of the theoretical decrease in luminal area required to achieve a tripling in pulmonary resistance showed that this was substantially more than the increase in airway wall area observed after inhalation of the aerosolized histamine. Even if we assumed that the entire increase in wall area took place at the expense of the luminal area (*i.e.*, 100% encroachment), less than 20% of the decrease in the area of the airway lumen could be accounted for by bronchovascular congestion. Although we concluded from this study that bronchial vascular congestion contributes little to airway narrowing, the measurements were limited to larger airways (bronchi).

Using a different technique, CORFIELD and co-workers [7] also examined the effect of changing airway mucosal thickness on airway diameter. In a perfused canine tracheal segment, they used a microprocessor-controlled surface probe to accurately measure small changes in mucosal thickness produced by different vasoactive drugs. Results showed that bronchial vascular dilators increased mucosal thickness, and that phenylephrine, a bronchial vascular constrictor, decreased mucosal thickness. Using this technique, changes in mucosal thickness could be due to changes in the tracheal blood volume, but could also be attributable to tissue oedema and mucus secretion. CORFIELD and co-workers [7] concluded that mucosal thickening secondary to acute vascular congestion and/or oedema had little effect on decreasing luminal area in large airways.

MARIASSY *et al.* [3] also carried out a morphometric study to examine the possibility that bronchial vascular congestion may contribute to narrowing of the airway lumen. To maximize the effect of bronchial vascular congestion, they perfused the pulmonary and bronchial vasculature of anaesthetized sheep with fixative (glutaraldehyde) at varying pressures, before and after maximal vasodilation using intravenous sodium nitroprusside. The results showed that the microvascular volume fraction comprised 12–16% of the subepithelial tissue area, and that vascular congestion doubled this fraction (~30%).

Table 1. — Bronchial vascular areas

First author [Ref.]	Lung region (species studied)	Condition	Airway wall area		% Total
			Inner	Outer	
BAILE [2] (sheep)	Trachea	Control	34±10		
		Histamine	30±6	NA	NA
		Phenylephrine	34±8		
	Cartilaginous bronchi	Methoxamine	30±8		
		Control	15±1	21±2	18±2
		Histamine	24±4	31±6	28±5
MARIASSY [3] (sheep)	Trachea	Phenylephrine	18±5	25±4	23±3
		Methoxamine	19±6	35±7	25±5
		Control	11±1		
	1 mm bronchioles	PH	11±1	NA	NA
		PH+V	22±5		
		Control	16±1		
	0.5 mm bronchioles	PH	21±2	ND	ND
		PH+V	29±3		
		Control	15±3		
WAGNER [4] (sheep)	Range of airway sizes (0.2–2.5 mm), mostly membranous	PH	22±4		
		PH+V	31±7	ND	ND
		Control	3±1	12±1	
		↑ PLA	8±0.7	16±2	ND
		Pap control	4±0.2	12±1	
KUWANO [5] (humans)	Membranous airways, range of sizes	↑ PLA+Pap	9±1	17±0.7	
		Control	0.6±9	8±4	~4.8
		COPD	0.3±0.1	7±4	~4.1
		Asthma	3.3±4	13±8	~8.9

Values are presented as mean±SEM. PH: pulmonary hypertension ($P_{sa}=100$ mmHg, $P_{pa}=40$ mmHg); PH+V: pulmonary hypertension and vasodilation ($P_{sa}=100$ mmHg, $P_{pa}=40$ mmHg, sodium nitroprusside); ↑ PLA: increased left atrial pressure; P_{ap} : papaverine; COPD: chronic obstructive pulmonary disease; P_{sa} : systemic artery pressure; P_{pa} : pulmonary artery pressure; NA: not applicable; ND: not determined.

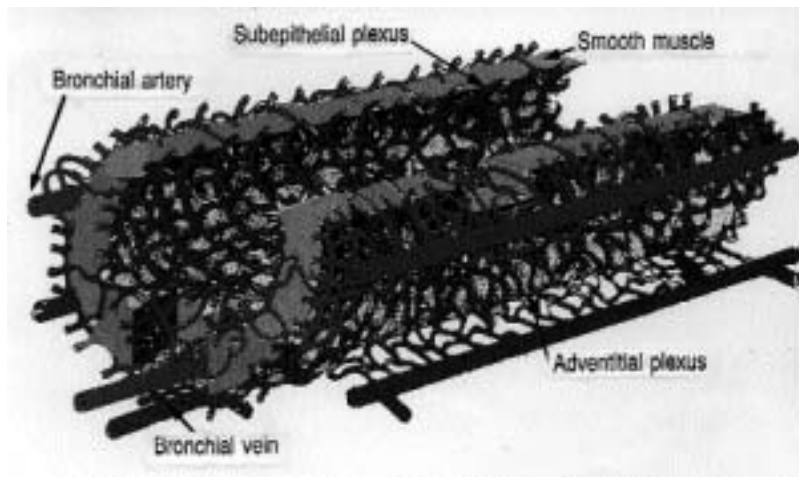


Fig. 2. — Segment of the tracheobronchial tree, illustrating the two bronchial vascular plexuses located on either side of the smooth muscle layer. (Modified from [6]).

BLOSSER and co-workers [8] and WAGNER and MITZNER [4] have recently examined the potential role of bronchovascular congestion on airway narrowing using two different approaches. In the study by BLOSSER and co-workers [8], the bronchial artery of anaesthetized sheep was perfused for 3 h at a rate set to 300% of its baseline blood flow. Morphological assessment of the airways showed that, although there was measurable airway oedema and an increase in the vascular area external to the smooth muscle layer, the amount of airway narrowing produced was small. WAGNER and MITZNER [4] perfused the bronchial artery of anaesthetized sheep under three different conditions designed to produce vascular congestion: increased bronchial blood flow; increased left atrial pressure; and increased left atrial pressure when airway and vascular smooth muscle were relaxed by bronchial arterial infusion of papaverine. Results of the morphometric analysis showed that, although bronchial vascular congestion was associated with a small reduction in airway luminal area, airway narrowing was primarily related to airway smooth muscle contraction rather than to engorgement or oedema. Although it is possible that bronchial vascular congestion could alter the bronchial smooth muscle function, this has not been studied. Because WAGNER and MITZNER [4] examined small airways, their studies extend those of BAILE *et al.* [2], and results suggest that there is no greater effect of vascular congestion in smaller airways than in large airways.

Another approach [9] has been to measure airway dimensions using high resolution computed tomography (HRCT). Airway narrowing was produced by inducing bronchial vascular congestion by rapid infusion of large volumes of isotonic saline or blood into anaesthetized dogs. Infusion of 500–1,000 mL blood produced a very slight airway narrowing, whereas infusion of isotonic saline (1,000–3,000 mL) produced more substantial airway narrowing. These results suggest that most of the airway narrowing was related to extravasation of fluid from the bronchial vasculature; the airway wall thickening was due to oedema rather than to vascular congestion.

There are limited data on the volume occupied by bronchial vessels in human airways. There is, however,

some evidence for an increase in the size and number of bronchial vessels in the airways of asthmatic subjects, suggesting that vascular congestion and angiogenesis may play a part in the airway remodelling that characterizes asthma. KUWANO and co-workers [5] compared the morphology of peripheral airways of patients who died of asthma with those of asthmatic patients who died of other causes. The asthmatic lungs were also compared with lungs that had been resected for peripheral neoplasms from patients who had normal lung function (table 2) (forced expiratory volume in one second (FEV₁) >80 % pred), and from patients who had mild chronic obstructive pulmonary disease (FEV₁ <80 % pred). The smooth muscle area and the tissue areas inside and outside the smooth muscle layer were measured. In addition,

the fraction of the inner and outer wall occupied by bronchial vessels and the number of bronchial vessels within each of these areas were also measured. Results from this study showed a considerable increase in the absolute area occupied by submucosal and adventitial tissue and smooth muscle in the asthmatic subjects; this was especially evident in the airways of the patients who had died of asthma. There was also an increase in the fractional area occupied by blood vessels in the two tissue compartments; again, this was most striking in the airways of patients who had died of asthma. Similar results have been reported by JAMES and co-workers [10]. They showed an increase in the number of bronchial venules in cartilaginous airways of asthmatic subjects, when compared to those of control subjects.

The stimulus for angiogenesis in asthma is unclear. Increased bronchial arterial flow caused by the local release of vasodilatory mediators could secondarily result in remodelling and proliferation of the vasculature. Increased flow results in increased endothelial shear stress, stimulating endothelial release of nitric oxide and tending to decrease shear by causing vascular smooth muscle relaxation. If there is chronic increase in blood flow and shear stress, it is possible that more definitive adaptive mechanisms are called into action, allowing a permanent increase in the cross-sectional area of the microvasculature. Alternatively, the local release of proinflammatory and mitogenic cytokines, that accompanies the chronic inflammation of asthma, could stimulate the vasculature proliferation. There is evidence that connective tissue cells and airway smooth muscle proliferate in chronic asthma, possibly stimulated by these cytokines. The bronchial vasculature could respond as a bystander to these potent growth factors. There is evidence for the increased expression of transforming growth factor- β (TGF- β) and platelet-derived growth factor (PDGF) in the airways of asthmatic subjects [11, 12].

In summary, there is little evidence that acute bronchial vascular congestion contributes significantly to airway narrowing, at least in animal models. In chronic asthma, an increase in the size and number of bronchial vessels, which appears to correlate with severity of asthma, suggests that bronchial vascular angiogenesis accompanies the airway remodelling that has been described

Table 2. – Clinical data for asthmatic subjects

Case No.	Age yrs	Sex	Duration yrs	FEV1 % pred	Clinical severity	Specimen obtained	Cause of death
1	26	M	-	-	Severe	PM	Asthma
2	20	F	-	-	Severe	PM	Asthma
3	57	M	-	-	Severe	PM	Asthma
4	64	F	-	-	Severe	PM	Asthma
5	62	F	-	-	Severe	PM	Asthma
6	39	F	-	-	Severe	PM	Asthma
7	27	F	14	110+	Severe	PM	Asthma
8	20	F	20	-	Severe	PM	Asthma
9	21	M	17	87+	Severe	PM	CO poisoning
10	21	M	17	-	Severe	PM	Cardiac arrhythmia
11	55	M	30	-	Mild	PM	Anaphylaxis
12	41	M	15	91*	Moderate	SR	-
13	51	F	22	87*	Moderate	SR	-
14	47	F	10	82*	Moderate	SR	-
15	41	F	3	111*	Mild	SR	-

+: last recorded FEV1 % pred before death; *: Preoperative FEV1 % pred. M: male; F: female; FEV1: forced expiratory volume in one second; % pred: percentage of predicted value; PM postmortem specimen; SR: surgically resected lung.

in these patients. It is possible that changes in vascular volume within this remodelled microvasculature could lead to an augmentation in airway narrowing and, perhaps, changes in airway smooth muscle function.

Angiogenesis of the bronchial vasculature

In contrast to the pulmonary circulation [13], the bronchial circulation has a remarkable ability to proliferate. Leonardo da Vinci is generally given the credit for being the first person to demonstrate the presence of new bronchial vessels (angiogenesis) forming a dense plexus around a cavitary lesion in a human lung [14]. Since Leonardo's time, there have been many reports documenting hypertrophy and angiogenesis of the bronchial circulation in response to a variety of stimuli, including chronic lung infections, pulmonary artery occlusion, lung tumours and lung transplantation.

Chronic lung infections

Bronchiectasis is the most common pulmonary condition associated with proliferation of the bronchial vasculature. Anatomical abnormalities, such as dilation and tortuosity of the bronchial arteries and large bronchopulmonary anastomoses due to angiogenesis, have been clearly described [15, 16]. Hyperplasia of the bronchial circulation in bronchiectasis also results in increases in bronchial blood flow, ranging from normal to as high as 35% of cardiac output [17–21].

The anatomical changes and angiogenesis in the bronchial vasculature can have significant haemodynamic consequences. Most of the bronchial blood flow drains into the pulmonary circulation *via* large bronchopulmonary anastomoses, and this may affect measurements of pulmonary arterial pressures and mixed venous oxygen saturation during pulmonary artery catheterization. Pulmonary arterial occlusion (wedge) pressures can range from 30–50 mmHg in bronchiectatic regions to normal pressures in the main pulmonary artery and its branches [22]. Oxygen saturation measured in the main pulmonary artery supplying the bronchiectatic region can be close to that measured in the systemic arterial circulation, whereas oxygen saturation measured in the

main pulmonary artery is usually the same as that of mixed venous blood [23]. It has also been observed, during pulmonary artery catheterization, that systemic arterial blood can sometimes be withdrawn from an unwedged catheter in patients who have bronchiectasis [24]; thus, data on "mixed venous" oxygen saturation obtained in these patients should be interpreted with caution.

Increased bronchial-to-pulmonary anastomotic blood flow and angiogenesis can be detected using angiographic techniques [21, 25]. Characteristic findings are enlarged, tortuous vessels and hypervascularity of the bronchial circulation in the diseased lung. Occasionally, the contrast medium can flow in the direction opposite to normal pulmonary arterial blood flow and pass toward the hilum of the lung; this situation is described as "reverse flow" [25]. This usually occurs in unilateral bronchiectasis, when pulmonary arterial pressure, measured in the main pulmonary artery, is normal. The presence of reverse flow during pulmonary angiography may simulate occlusion of a lobar pulmonary artery, and may be misdiagnosed as a pulmonary embolism. If this is observed, then obtaining blood samples from the distal pulmonary artery for blood gas analysis may be useful in confirming that the angiographic abnormality is due to increased bronchial-to-pulmonary blood flow, rather than to pulmonary embolism.

Considerable angiogenesis of the bronchial vasculature is also found in patients who have lung abscess [26]. The pulmonary arteries supplying the wall of the abscess are usually obliterated by infected thrombi, so that most of the blood supply to the walls of the abscess cavity comes from the bronchial circulation [27]. In addition to the growth of new vessels surrounding the diseased area, there is dilation of the smaller branches of the bronchial artery [15]. A fine, loop-like pattern of bronchial arterial branches surrounding the abscess cavity has also been described [22]. Despite the new vessel growth, there are data to suggest that total bronchial blood flow may not increase in lung abscess. NAKAMURA *et al.* [19] measured bronchial blood flow in four patients and found that it was within normal limits, being less than 1% of the cardiac output.

Similar anatomical findings have been observed in lung abscesses of sheep. Using corrosion casting techniques,

CHARAN *et al.* [13] observed that the bronchial artery was very dilated and hypertrophied. The abscess cavities were surrounded by a dense microvascular plexus, supplied exclusively by the bronchial arteries. Scanning electron microscopy of the inner wall of the abscess cavities revealed a dense plexus of bronchial vessels, with only a few isolated nests of pulmonary alveolar capillaries remaining.

In pulmonary tuberculosis, enlargement of the bronchial arteries was noted as early as 1845 by GUILLOT [28]. These changes were later confirmed and anatomical features elaborated upon by several investigators [15, 27]. The usual features in the tuberculous lungs are distortion, tortuosity, and extensive ramification and proliferation of the bronchial arteries supplying the caseating areas. In addition, systemic arteries from the parietal pleura may enter adhesions between the pleural layers. In contrast, the pulmonary arteries are obliterated due to intimal proliferation and thrombosis. The extent of bronchial vascular proliferation and hypertrophy correlates with the severity of disease. However, in arrested cases of tuberculosis there may be residual changes. As in bronchiectasis, bronchial blood flow is increased in tuberculous lungs, ranging 3–9% of the cardiac output [19, 20, 29]. The oxygen saturation in the pulmonary arteries supplying extensively tuberculous areas can approach the saturation in the systemic blood, and is much higher than the saturation in the mixed venous blood [23]. Similarly, there is an increase in pressure in the pulmonary arteries in the diseased lung.

Infections of the pleural space (empyema) are also associated with angiogenesis of systemic vessels. The visceral pleura is supplied by the bronchial circulation, and, although not studied in detail, there is evidence that angiogenesis occurs in response to inflammation of the pleural space. WOOD and MILLER [15] described bronchial arterial dilation and proliferation, as well as extensive anastomoses with the pulmonary circulation, in one patient who had empyema.

CHARAN and CARVALHO *et al.* [30] produced experimental empyema by intrapleural inoculation of *Streptococcus pneumoniae* in a sheep model. An extensive inflammatory reaction occurred within 6 h, and, at 72 h, the bronchial circulation was studied by corrosion casting techniques, and showed new vessels lining the visceral pleura and forming a plexus. This study indicates that angiogenesis of the bronchial circulation can occur very early in response to inflammation.

The mechanisms involved in angiogenesis in chronic lung infections are not well understood. Lung infections are associated with accumulation of inflammatory cells, including macrophages and neutrophils, and both of these cell types are thought to play an important role in angiogenesis. Activated macrophages promote angiogenesis by producing a wide variety of angiogenic factors, including tumour necrosis factor- α (TNF- α), basic fibroblast growth factor (bFGF), and TGF- β [31]. Angiogenic factors have also been shown to be present in the bronchoalveolar lavage fluid of patients who develop acute lung injury due to a variety of stimuli [32]. These findings support the idea that the inflammatory response in the lung is associated with liberation of several angiogenic factors.

Interleukin-8 (IL-8) has recently been shown to have potent angiogenic activity [33–35], as well as chemotactic

activity for endothelial cells; both of these functions are important for angiogenesis. IL-8 can be produced by neutrophils, especially when they are activated by a phagocytic challenge [36] or by endotoxin [37, 38]. Although the amount of IL-8 produced by activated macrophages is considerably greater than that produced by neutrophils, the number of neutrophils far exceeds the number of mononuclear cells during the inflammatory response, suggesting that neutrophils may also play a role in angiogenesis.

Angiogenesis after occlusion of a pulmonary artery

Over a century ago, VIRCHOW [39] observed that ligation of a pulmonary artery seldom caused pulmonary infarction and that the bronchial arteries supplying the ischaemic lung increased in size [40]. It is now well-established that occlusion of a pulmonary artery to one lung stimulates angiogenesis in the bronchial circulatory system of that lung.

Several investigators have measured bronchial blood flow in patients who have congenital absence of one pulmonary artery. Bronchial blood flows as high as 25% of the cardiac output have been reported [20, 41–43]. The time-frame of this proliferation has also been examined in animal models of occlusion of one pulmonary artery. Bronchial arteries begin to enlarge as soon as 2–3 days after ligation of the pulmonary artery [44, 45]. By about 1–2 weeks, there is moderate enlargement, and considerable hypertrophy occurs by 2–4 weeks [44, 46–48]. Results from another study of adult dogs showed that 3 months after ligation most (~80%) of the hypertrophy had occurred [49]. Similarly, 12 weeks after pulmonary artery obstruction, LIEBOW and co-workers [46] found that this impressive expansion of the bronchial circulation was associated with anastomoses between the bronchial circulation and the pulmonary artery. The anastomoses were precapillary and ranged from 50–200 μm in diameter.

The functional importance of angiogenesis in the bronchial circulatory system after unilateral pulmonary artery obstruction is not clear. Although it has been suggested that the increased bronchial blood flow could augment gas exchange, the fact that the bronchial artery is perfused with fully oxygenated systemic arterial blood makes this unlikely [50]. In a chronic study in dogs, after ligation of the left pulmonary artery, oxygen uptake ($V'\text{O}_2$) and carbon dioxide elimination ($V'\text{CO}_2$) from the left lung was 11 and 15% of the total, respectively [51]. When systemic hypoxaemia was induced, the oxygen uptake from the left lung increased to 29% of the total, suggesting an increased capacity for gas exchange from the enlarged bronchial circulation under hypoxic circumstances.

The mechanism for the remarkable increase in blood flow occurring after pulmonary artery obstruction is also unknown. The initial increase in bronchial blood flow during the first 3 days after pulmonary artery obstruction has been attributed to dilation of the bronchial microvasculature and could be mediated by increased synthesis of nitric oxide [48]. Pulmonary artery obstruction causes an initial decrease in bronchial arterial flow, but within 24 h flow increases, presumably because downstream pressure at sites of bronchial pulmonary anastomoses

decreases. Although this brief increase in bronchial blood flow can be explained haemodynamically, the subsequent progressive increase in flow must be related to vascular remodelling and proliferation. It is possible that the endothelium orchestrates this process in an attempt to keep local shear stress constant. GLAID and co-workers [52] ligated the left pulmonary artery in dogs, and 15 months later studied the lungs. They found an increase in endothelin-1 (ET-1)-like immunoreactivity in the new bronchial vessels in the ligated lung, suggesting that ET-1 may play a role in the bronchial neovascularization. Alternatively, a signal from the relatively ischaemic epithelium, or airway smooth muscle cells could drive the process. The striking localization of the stimulus can be appreciated by examining the cast of the remodelled bronchial vasculature from a sheep, in which the left main pulmonary artery had been ligated soon after birth and the bronchial vessels studied 3 yrs later [53] (figure 3). The main bronchial artery can be seen to divide into a greatly enlarged vessel supplying the left lung and a bronchial artery of normal calibre supplying the right lung. Although the stimulus for vascular proliferation must originate in the microvasculature, the remodelling extends to the large bronchial vessels.

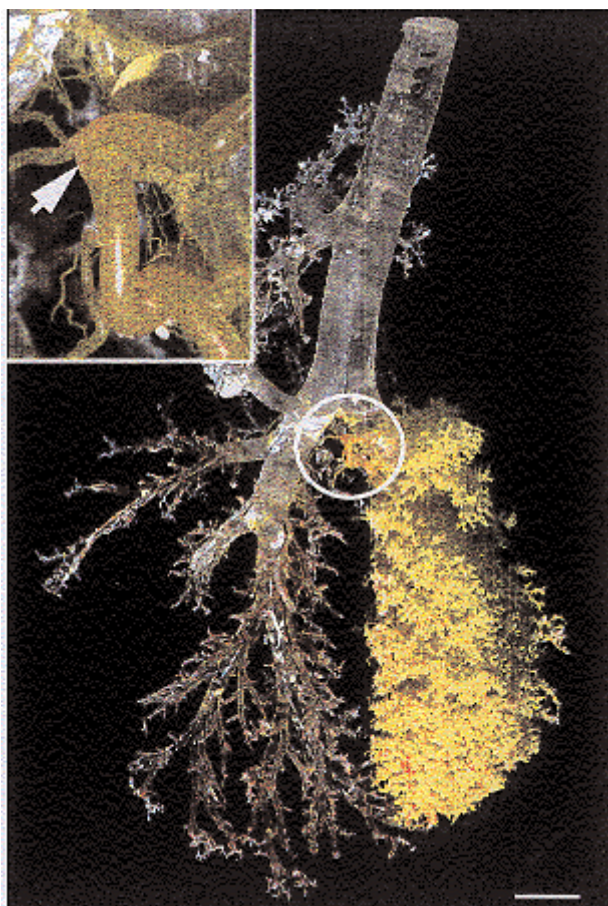


Fig. 3. — Cast of the bronchial vasculature of a sheep made 3 yrs after ligation of the left main pulmonary artery. Note the main bronchial artery dividing into a greatly enlarged vessel supplying the left lung (see insert, white arrow indicates the enlarged bronchial artery), and a bronchial artery of normal calibre supplying the right lung. (Internal scale bar = 3 cm). (Modified from [53]).

Angiogenesis in lung tumours

FOLKMAN [54] was first to propose that the growth of tumours requires a concomitant increase in blood supply, which is achieved through angiogenesis. With few exceptions, lung tumours receive their blood supply from the bronchial circulation. The relative blood supply to lung tumours may depend on their anatomical location and size. Tumours near the hilum of the lung, in rabbits, were always found to be perfused by the bronchial circulation, whereas peripheral lung tumours did not develop a bronchial blood supply until they were 2 mm in diameter [55]. JONAS and CARRINGTON [56] confirmed that larger tumours were always supplied by proliferation of the bronchial arteries and never by proliferation of the pulmonary arteries.

Recently, SMITH *et al.* [57] found an increased quantity of IL-8 in lung tumours, and also showed that the tissue homogenates of tumours had angiogenic properties. Furthermore, they found that addition of neutralizing antisera to IL-8 resulted in considerable attenuation of the angiogenic response, suggesting that IL-8 is an important mediator of angiogenesis in bronchogenic carcinoma.

There is evidence that angiogenesis may be a significant factor in haematogenous metastasis [58]. Angiogenesis in the primary tumour, assessed by density of microvessels, has been shown to correlate positively with recurrence after surgical resection and with the presence of haematogenous metastasis in patients who have lung cancer [59, 60]. In support of this finding, some angiogenic inhibitors, such as the newly described TNP-470, tend to suppress pulmonary metastases, at least in animal experiments [61].

Importance of angiogenesis in the airways after lung transplantation

Airway anastomotic complications remain a cause of morbidity after human lung transplantation. Ischaemia of the donor bronchus results from loss of the bronchial arterial circulation, which is not routinely restored during transplantation. The donor airway depends on connections between the pulmonary and bronchial circulations of the transplanted lung, until adequate bronchial neovascularization takes place. FISHER *et al.* [62] performed transection and reanastomosis of the left main-stem bronchus in dogs. Sixteen days postoperatively, radiographs obtained after aortic injection of radiopaque material showed complete filling of bronchial microvasculature, initially through a network of fine vessels at the bronchial anastomotic site, but later through normal-looking vessels in the airways. These vessels presumably arose as a result of capillary proliferation and subsequent capillary growth to a vessel size of about 35 μ m diameter. Initially, bronchial blood flow appeared lower than normal, but 29 days after surgery bronchial blood flow had reached normal levels. These findings demonstrate that, after transection, there is development of new vessels to re-establish continuity between the transected vessels. BAILE and co-workers [63, 64] have examined the time course of the re-establishment of blood flow to the airways after auto- and allotransplantation in a dog model. Using radioactive microspheres to measure

airway blood flow, they found that microvascular flows both from the bronchial and pulmonary vessels were close to normal by about 3 days after surgery, and increased to three times the normal level by 14 days. Bronchial omentopexy and even bronchial revascularization techniques have been used in an attempt to accelerate neovascularization [65, 66]. Although results from some studies have suggested that omentopexy accelerates the anastomotic revascularization [65], BAILE *et al.* [63] showed no difference in the restoration of flow whether omentopexy was present or not.

In one experimental study in anaesthetized rats, SCHR-AUFNAGEL and co-workers [67] found that applying TGF- α (a well-known angiogenic factor) onto the trachea after it had been severed and resutured, resulted in more rapid revascularization and an extensive capillary growth at the anastomotic site. Fortunately, drugs that are commonly used in organ transplantation, such as methylprednisolone and cyclosporin A, do not appear to inhibit angiogenesis [68]. Thus, it is possible that use of an angiogenic agent may have some use in lung transplantation.

In summary, the bronchial vasculature responds to a variety of stimuli by proliferation and remodelling. These stimuli can be grouped into inflammatory or ischaemic categories. Vascular angiogenesis is obviously an important adaptive process and may function to maintain the viability of pulmonary tissues and structures. However, the remodelling is not without its adverse effects, including the increasing likelihood of airway narrowing, and an increased risk of haemoptysis. More studies regarding the mechanisms causing bronchial vascular dilation and proliferation are necessary, and these may yield information relevant to the phenomenon of angiogenesis.

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