Role of veins in regulation of pulmonary circulation

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Gao, Yuansheng, and J. Usha Raj. Role of veins in regulation of pulmonary circulation. Am J Physiol Lung Cell Mol Physiol 288: L213–L226, 2005; doi: 10.1152/ajplung.00103.2004.—Pulmonary veins have been seen primarily as conduit vessels; however, over the past two decades, a large amount of evidence has accumulated to indicate that pulmonary veins can exhibit substantial vasoactivity. In this review, the role of veins in regulation of the pulmonary circulation, particularly during the perinatal period and under certain pathophysiological conditions, is discussed. In the fetus, pulmonary veins contribute a significant fraction to total pulmonary vascular resistance. At birth, the veins as well as the arteries relax in response to endothelium-derived nitric oxide and dilator prostaglandins, thereby assisting in the fall in pulmonary vascular resistance. These effects are oxygen dependent and modulated by cGMP-dependent protein kinase. Under chronic hypoxic conditions, pulmonary veins undergo remodeling and demonstrate substantial constriction and hypertrophy. In a number of species, including the human, pulmonary veins are also the primary sites of action of certain vasoconstrictors such as endothelin and thromboxane. In various pathological conditions, there is an increased synthesis of these vasoactive agents that may lead to pulmonary venous constriction, increased microvascular pressures for fluid filtration, and formation of pulmonary edema. In conclusion, the significant role of veins in regulation of the pulmonary circulation needs to be appreciated to better prevent, diagnose, and treat lung disease.

pulmonary vasoactivity; hypoxia; pulmonary hypertension; edema

IN THE PULMONARY CIRCULATION, veins serve not only as channels through which oxygenated capillary blood flows into the left atrium, but they also regulate fluid filtration pressures in the upstream capillary network via active vasomotion. Changes in venous tone regulate both distention and recruitment of alveolar wall capillaries and thus ventilation-perfusion matching in the lung. Over the past two decades, a significant body of information about these vasoactive functions of the pulmonary veins has been published, primarily from our laboratory, so that now many more researchers include the study of pulmonary veins when investigating the pulmonary circulation. However, the importance of pulmonary veins in regulation of pulmonary circulation is still not fully appreciated; hence, a review of this subject is timely. This review will outline the existing data on the contribution of veins to total pulmonary vascular resistance, the mechanisms of active regulation of both arteries and veins, highlighting the heterogeneity in the behavior of arteries and veins, the developmental changes in the role of veins in regulating pulmonary vascular resistance, and the differential pulmonary vascular remodeling that occurs in arteries and veins in response to hypoxia and other chronic stimuli. Many reports have been published recently on the distinctly separate molecular regulation of the development of arteries and veins in the lung, emphasizing the point that the heterogeneous behavior of pulmonary arteries and veins is largely predetermined. Most of these topics have been comprehensively reviewed elsewhere, and the reader will be referred to them.

CONTRIBUTION OF VEINS TO TOTAL PULMONARY VASCULAR RESISTANCE

In the lung, circulation consists of three longitudinal vascular segments that are arranged in series: the arteries, the microvessels, and the veins. Although it is clear that in systemic circulation, the arterioles are the major sites of resistance (15), there is still some confusion as to the relative contribution of arteries, capillaries, and veins to total resistance to flow in the lungs. Much of the controversy has arisen because the data in the literature related to pulmonary circulation have varied depending on the method used to partition resistances in the vascular segments of the lung, the experimental conditions under which the lungs were studied, and the age of the animal and species studied. In addition to direct measurement of pressures in the main pulmonary artery and left atrium, pressures have been measured at other sites within the pulmonary circulation using direct and indirect methods. Most of the attempts were made to measure the pressures at the junction between the arterial tree and capillary network and between the capillary network and the venous tree. This allowed for the partition of the pulmonary circulation into the three longitudinal segments: the arteries, the capillaries, and the veins, and for the study of the functional behavior of these segments separately. For example, using micropipettes, direct measurement of pressures in small precapillary and postcapillary arterioles and venules, 1–10 μm in diameter, have been obtained (10), and small 1- to 2-mm-diameter catheters have been passed into
small arteries in the lung to directly measure small venular pressures (108). By indirect methods such as the vascular occlusion technique (49), circulation has also been partitioned into three vascular segments. Calculation of microvascular filtration pressures has allowed the partitioning of circulation into an upstream and downstream segment from a midfiltration point (2). In general, with the use of these techniques in adult lungs, the veins appear to contribute the least resistance to flow, ranging from 7% of total resistance in the rabbit lung (114) to 30% in the adult cat lung (100), with the major portion of vascular resistance residing in small pulmonary arteries and capillaries. Thus in the adult lung, because the pulmonary veins are thin walled and sparsely innervated, they act mainly as conduit vessels to drain oxygenated blood into the left ventricle (32, 85). However, other investigators, from measurement of venular pressures using small catheters, have found that a substantial portion of the total pulmonary vascular resistance is in veins (75, 92, 147). Similarly, from detailed morphometric measurements of cat lung, 49% of the total vascular resistance was calculated to be in veins, which the authors attributed to the branching pattern of the veins and the viscoelastic properties of the vessel walls (169). The wide range of values for venous resistance in adult lungs shown in Fig. 1 may be due to differences in experimental conditions (species, lung volume, basal vasomotor tone) and methods used for partitioning vascular resistances in the lung.

In the adult lung, the major sites of resistance appear to be the microvessels and capillaries. The contribution of microvessels and capillaries to total pulmonary vascular resistance is 40% in the adult dog (10) and 90% in the adult ferret (121). This is intriguing because the high distensibility of capillaries and the large surface area of the microvascular network should make this segment impose the least resistance. One explanation may be that much of the experimental data have been obtained in lungs that have been experimentally perfused with steady flow. In vivo, flow is pulsatile, which may reduce the resistance of microvessels significantly by facilitating recruitment of the capillaries. Alternatively, with increasing age, alveolar size also increases, which would result in stretching and/or compression of the alveolar wall and capillary lumen, accounting for the increasing microvascular resistance with age.

In the younger animal, on the other hand, vascular resistance seems to reside mainly in arteries and veins of the lung (40, 118, 119), with a shift to the microvascular segment occurring with increasing age (114), as shown for the ovine species in Fig. 2. Data from morphometric studies of human (31), pig (125), and rat (91) lungs support these findings, which show that the pulmonary arteries have a thicker smooth muscle coat in the neonatal period and that the vascular smooth muscle decreases in mass with age, resulting in a larger luminal diameter with advancing age. The high fractional resistance in the arteries and veins of the neonatal lung may also be due, in part, to higher vasomotor tone in the perinatal period (116). The high vasomotor tone in the fetal lung falls dramatically at birth but remains higher than in the adult lung during the neonatal period. There are also differences in the geometry of the vasculature, the branching pattern, and the viscoelastic behavior of the vessels, which would account for the higher resistance in the arteries and veins in the younger animal. In neonatal lambs, veins contribute 40% to total pulmonary vascular resistance. This large fractional resistance in veins is present even in the absence of vasomotor tone. Because the caliber of the blood vessels in any vascular network depends on the transmural pressures and the pressure-volume behavior of the vessels (compliance or distensibility), it has been argued that this apparent high resistance in veins might be due to the low transmural pressures present in the veins. However, in neonatal lamb lungs, when we perfused the lungs in reverse, i.e., from the left atrium to the pulmonary artery, and the veins were distended with high transmural pressures, fractional resistance in veins was the same as in arteries during forward flow, suggesting that the geometry of the arterial and venous networks was similar in newborn lambs.

The distensibility of veins and, therefore, the resistance imposed by them varies in different species. In dog (86, 137) and rabbit (20) lungs, veins are less distensible than arteries, and they contain fibrous tissue and collagen in the vessel wall.
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This also makes the veins in these species less vasoactive. However, in sheep (72), cow, guinea pig, llama, pig, and rat, pulmonary veins are more muscular and they also demonstrate significant vasoreactivity. In cat (169), in vessels smaller than 2 mm in diameter, the compliance of veins is similar to that of arteries. Thus, under basal conditions, the contribution of veins to total vascular resistance also depends on the species being studied, in addition to the age of the animal, basal vasomotor tone, and conditions of flow and vascular distention.

MECHANICAL FACTORS THAT INFLUENCE VENOUS RESISTANCE IN LUNGS

An increase in blood flow rate does not always affect pressures in the filtering segment of the lung, i.e., in the capillaries. In adult lung, flow can be increased threefold before any appreciable change in pulmonary artery pressure is detected. The effect of an increase in blood flow on microvascular pressures depends on the initial state of the pulmonary vascular bed, i.e., the state of recruitment of the capillary bed. When the lung is already fully recruited, increases in blood flow result in large increases in pulmonary artery and venous pressures (57). Similarly, when the total vascular surface area is reduced, an increase in flow will also markedly increase vascular pressures in the lung (28, 78). The consequences of an increase in flow rate and the resultant increase in capillary filtration pressures become important in the presence of lung injury when small increases in filtration pressure may significantly increase fluid and protein filtration (166).

In adult sheep, Coates et al. (26) found that when cardiac output was increased by infusion of isoproterenol without any change in ventilation, there was no increase in pulmonary artery or left atrial pressures and no suggestion of an increase in microvascular filtration pressures, indicating that when the lung vascular bed is only partially recruited, large increases in blood flow are accommodated with increases in the perfused surface area in the filtering segment, and there may be little change in vascular pressures. In neonatal lambs, when blood flow through the lungs was increased by the opening of an external shunt between the carotid artery and the jugular vein, lymph flow increased without a change in lymph protein concentration, indicating an increase in perfused surface area but no change in microvascular pressures (37). If microvascular filtration pressure had increased, lymph flow would have increased with a concomitant decrease in lymph protein concentration. However, under conditions of maximal or submaximal recruitment, increases in blood flow can cause significant increases in microvascular and venous pressures, both in the neonatal (116, 148) and adult (57, 78) lung. Also, in situations where fractional venous resistance is high (115) or venous distensibility is low (39), increases in blood flow rate will shift the filtration midpoint upstream toward the pulmonary artery (166) resulting in microvascular filtration pressures that approach the pressure in the pulmonary artery. This is shown graphically in the case of neonatal lamb lungs but not in adult rat lungs in Fig. 3. Very large increases in pulmonary blood flow and a shift in microvascular pressures toward the pulmonary artery pressure may account for the development of capillary stress failure and pulmonary edema in elite athletes and racehorses and is thought to be the pathogenesis of acute pulmonary hemorrhage in the very preterm baby with immature lungs (87).

The resistance to flow in the circulation is determined by both vascular geometry and blood viscosity. Hematocrit is an important determinant of blood viscosity, and in the macrocirculation, the effect of an increase in hematocrit is an increase in resistance to flow in many organs, including the lungs (9, 70, 99, 101). At the microcirculatory level, however, little is known about how the increase in hematocrit affects the distribution of pressures in the filtering segment of the lung. Considerable work has been done on the effects of hematocrit on the systemic microvessels, although these data cannot be used to explain the events in the pulmonary microcirculation. In fact, in the pulmonary capillary bed, there may be large numbers of unrecruited capillaries that can be recruited and opened for transit of red blood cells. Also, the size and distensibility of pulmonary capillaries are probably larger than those of the systemic circulation. The effect of an increase in perfusate hematocrit and apparent viscosity on segmental vascular resistances was studied in isolated perfused rabbit lungs (122) (Fig. 4). In this study, an increase in hematocrit resulted in an increase in total pulmonary vascular resistance mainly due to an increase in resistance in small arteries and veins. There was no effect of hematocrit in capillaries and large conduit arteries and veins. The effect of a large increase in resistance in small veins is that the pressures in upstream fluid filtration sites in capillaries will increase significantly, resulting in increased fluid and protein filtration in the lung. This nonhomogeneous effect of hematocrit in the different longitudinal segments of the lung is important since the very large increase in small venous resistance has a great impact on lung fluid filtration. The larger increase in resistance in small veins compared with small arteries may be due to the fact that intraluminal pressures are lower in veins than in arteries, resulting in smaller transmural diameters in these vessels and a greater hindrance.

Fig. 3. When fractional venous resistance is high under baseline conditions (lamb lungs), the effect of a 3-fold increase in blood flow rate is to push microvascular pressures closer to pulmonary artery pressure. In lungs with low fractional venous resistance, as in the rat, this effect of blood flow is not as prominent.
vasodilation primarily by elevating cGMP levels following the activation of soluble guanylate cyclase. cGMP is hydrolyzed by phosphodiesterases (67, 160).

Nearly two decades ago, Edwards et al. (35) found that nitrovasodilators were more effective in increasing cGMP levels and, therefore, in inducing relaxation in pulmonary veins, than in arteries of adult cows. Subsequently, it was found that a number of agents induced equal or greater endothelium-dependent relaxation in pulmonary veins than in arteries of sheep and pigs (4, 6, 36, 167). In perinatal sheep, not only acetylcholine (an EDNO-dependent vasodilator) but also exogenous nitric oxide causes a greater increase in the intracellular content of cGMP and relaxation in pulmonary veins than in arteries. However, both vessel types respond similarly to 8-bromoguanosine 3′,5′-cyclic monophosphate, a cell membrane-permeable analog of cGMP (Fig. 5). These data suggest that the reason for the difference in EDNO-dependent relaxation between arteries and veins lies upstream of cGMP (79).

In adult pigs, the amount of endothelial nitric oxide synthase (eNOS) protein and its activity are higher in pulmonary veins than in arteries (11). In lungs of fetal lambs, immunolabeling and immunoblot analyses show that staining for eNOS and soluble guanylate cyclase is more pronounced in veins than in arteries (156). In fetal and newborn lambs as well as in adult pigs, phosphodiesterase activity is more pronounced in pulmonary arteries than in pulmonary veins (11, 104). Thus the functional consequences of the differences in the activities of eNOS, soluble guanylyl cyclase, and phosphodiesterases may be the greater relaxation responses to the nitric oxide-cGMP pathway in pulmonary veins.

There is a maturational change in EDNO-mediated relaxation of pulmonary veins. For instance, acetylcholine is ~10-fold more potent in relaxing pulmonary veins of newborn than of fetal lambs. The relaxation is endothelium dependent and is abolished by nitro-L-arginine, suggesting that it is mediated by EDNO (45, 46). In adult sheep, acetylcholine causes contraction of pulmonary veins, regardless of the presence of the endothelium (151). Bradykinin causes EDNO-mediated relaxation of pulmonary veins of newborn but not fetal lambs (45, 46). In pigs, the maximal relaxation to acetylcholine is less in fetal pulmonary veins than in veins of 14-day-old newborn lambs (4). In sheep, the rate of hydrolysis of cGMP is faster in fetal veins than in the newborn, suggesting that faster degra-
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Fig. 6. Top: relaxations of pulmonary veins of newborn lambs induced by 8-Br-cGMP. Vessels were preconstricted to a similar tension with endothelin-1 (3 × 10⁻⁶ M to 10⁻⁴ M), Rp-8-Br-PET-cGMPS, 3 × 10⁻⁵ M; H-8, 10⁻⁴ M; KT-5720, 5 × 10⁻⁵ M. Data are shown as means ± SE; n = 6 for each group. *Significant difference between control and vessels treated with Rp-8-Br-PET-cGMPS or H-8 (P < 0.05). Bottom: effects of Rp-8-Br-PET-cGMP (3 × 10⁻⁵ M), H-8 (10⁻⁴ M), and KT-5720 (5 × 10⁻⁵ M) on protein kinase G (PKG) activity of pulmonary veins. (−)cGMP, without cGMP; (+)cGMP, in the presence of cGMP (5 × 10⁻⁵ M). Data are shown as means ± SE; n = 4 for each group. *Significantly different from basal activity without added cGMP (P < 0.05).

Fig. 7. Concentrations of 8-BrcGMP and 8-BrcAMP that elicit 50% of maximum vasodilation (EC₅₀) of ovine pulmonary arteries (PA) and veins (PV) of term fetus (143–147 days of gestation) and newborns (6–13 days). Active tension of vessels was first raised to a similar level with endothelin-1 (3 × 10⁻⁷ M to 6 × 10⁻⁹ M). Data are shown as means ± SE; n = 5 for each group. *Significantly different from those treated with 8-BrAMP (P < 0.05).

were much more sensitive to the cGMP analog than to the cAMP analog (Fig. 7). Therefore, it appears that the nitric oxide-cGMP-PKG pathway may play a more important role in regulating the relaxation responses of pulmonary arteries and veins in the perinatal period than the cAMP-PKA pathway.

The responses of both fetal pulmonary arteries and veins to cGMP are modulated by changes in oxygen tension. In ovine fetal pulmonary veins, after 4 h of incubation in oxygen at 140 mmHg, relaxation responses to the cGMP analog were significantly greater than those in veins incubated at an oxygen tension of 40 mmHg (Fig. 8). The effect of oxygen was abrogated by Rp-8-Br-PET-cGMPS, a selective inhibitor of PKG type I. PKG activity, PKG type I protein content, and PKG type I mRNA are greater after 4 h of exposure to oxygen at 140 mmHg than at 40 mmHg. This indicates that in fetal pulmonary veins, oxygen exposure increases PKG-mediated relaxation to cGMP. At birth, after the initiation of respiration, the oxygen tension to which pulmonary veins are exposed increases from <25 mmHg in utero to 100 mmHg postnatally. It appears that the oxygen-dependent upregulation of PKG activity in veins may facilitate the relaxation of pulmonary veins at birth (43). Although cGMP-mediated relaxation of pulmonary arteries of fetal lambs is also enhanced after oxygenation, the effect of oxygen on the arteries seems less sensitive to PKG inhibition. It remains to be determined whether other mechanisms, such as cGMP-gated ion channels, play a more important role in the oxygen-dependent potentiation of cGMP-mediated relaxation of pulmonary arteries (56, 80).

In juvenile rabbit lungs, adenosine causes substantial relaxation of both vessel types, which is partially attenuated by inhibition of eNOS and by removal of the endothelium (142). In guinea pig lungs, histamine and sodium nitroprusside relax arteries more than veins (133). In monkey lungs, histamine induces endothelium-dependent relaxation of pulmonary veins that is attenuated or abolished by treatment with hemoglobin, a scavenger of nitric oxide, and by methylene blue, an inhibitor of soluble guanylyl cyclase (88). Thus significant species...
In the pulmonary circulation, PGI2 production appears to be age dependent. PGI2 production is the same in adult ovine pulmonary arteries and veins. However, resistance vessels (diameter <1 mm) of adult ovine lungs synthesize more PGI2 than similar-sized fetal vessels. Hypoxia (<50 mmHg of oxygen tension) attenuates PGI2 production by fetal pulmonary arteries and veins of all sizes (>3 mm, 1–3 mm, and <1 mm in diameter) but has effect only in 1- to 3-mm-sized adult arteries. The greater sensitivity of PGI2 production in fetal vessels to oxygen tension might be important for facilitating the fall in pulmonary vascular resistance at birth with the onset of breathing and oxygenation (60).

Potassium channels. Potassium ion channel activity is a major determinant of cell membrane potential and is an important regulator of vascular smooth muscle tone. In blood vessels, four main classes of K+ channels have been described based on their biophysical and pharmacological properties. They are ATP sensitive (KATP), inward rectifier (Kir), large-conductance Ca2+-activated K+ (BKCa), and voltage-gated K+ (KV) channels (5, 27, 124, 139). In rat lungs, 4-aminopyridine and Ba2+ (inhibitors of KV and Kir K+ channels, respectively) cause veins to contract (94). Pulmonary veins have a coaxial structure, with layers of cardiomyocytes (pulmonary vein cardiomyocytes) arrayed externally around a subendothelial layer of typical smooth muscle cells [pulmonary venous smooth muscle cells (PVSMC)] (162). Whole cell patch-clamp recordings indicate that both Kir and KV channels are present in pulmonary vein cardiomyocytes. In contrast, PVSMCs contain mainly BKCa channels. The presence of Kir, BKCa, and KV channels in pulmonary veins has been demonstrated by immunoblotting and by RT-PCR (94).

In pigs and fetal lambs, relaxation of pulmonary veins induced by levromakalim, the KATP channel opener, is blocked by glibenclamide, the KATP channel blocker, suggesting that KATP channels are operative (12, 150). In lungs of newborn, 3-, 6-, 17-day-old, and adult pigs, levromakalim induces relaxation of precontracted pulmonary veins, which is inhibited by glibenclamide. Maximal relaxation increases between birth and 6 days, with no change in EC50. At all ages, except in the newborn, relaxation is partially inhibited by N5-monomethyl-L-arginine, an inhibitor of eNOS. Indomethacin, a cyclooxygenase inhibitor, attenuates relaxation in veins of 6- and 17-day-old animals. These findings indicate a possible role for KATP channels during normal postnatal relaxation of pulmonary veins, with the involvement of EDNO and dilator prostaglandins (12).

CONSTRUCTORS OF PULMONARY ARTERIES AND VEINS

When subjected to various stimuli, pulmonary veins exhibit substantial vasoconstriction and contribute a significant portion to total pulmonary vascular resistance (88, 113, 115, 121, 123, 168). In a variety of species, including the human, pulmonary veins show a greater sensitivity than arteries to a number of vasoconstrictor stimuli, such as endothelin (ET) (3, 13, 153, 161), platelet-activating factor (PAF; 47, 111, 135), thrombox-

Fig. 8. Top: relaxations of PA and PV of fetal lambs to 8-Br-cGMP after 4 h of incubation under hypoxic and normoxic conditions (PO2 30 and 140 mmHg, respectively). Vessels were precontracted to a similar tension with endothelin-1. Data are shown as means ± SE; n = 6 for each group. *Significant difference between vessels incubated under hypoxic and normoxic conditions (PO2 30 and 140 mmHg, respectively). \( \Delta \) Significant difference between vessels incubated under hypoxia and normoxia in the presence of Rp-8-Br-PET-cGMPS (PKG-I; 3 \times 10^{-5} M, P < 0.05). Bottom: PKG activity in pulmonary vessels after 4 h of incubation under hypoxia and normoxia (PO2 30 and 140 mmHg, respectively). (-)cGMP, without cGMP; (+)cGMP, in the presence of cGMP at 5 \times 10^{-6} M. Data are shown as means ± SE; n = 4 for each group. *Significantly different from those without cGMP; †significantly different from those incubated under hypoxia (P < 0.05).

Fig. 9. Effect of prostaglandins on basal tension of PA and PV of newborn lambs. Experiments were performed in the presence of indomethacin (10^{-5} M). Data are shown as means ± SE; n = 5 for each group. *Significant difference between arteries and veins (P < 0.05).
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Table 1. Vasocostructions of pulmonary veins vs. arteries

<table>
<thead>
<tr>
<th>Stimuli</th>
<th>Species</th>
<th>Actions</th>
<th>Methods</th>
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<tr>
<td>Endothelin-1</td>
<td>rat</td>
<td>contraction: PV &gt; PA</td>
<td>scanning electron microscopy</td>
<td>3</td>
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<tr>
<td>guinea pig</td>
<td>contraction: PA &lt; PV</td>
<td></td>
<td>isolated vessel tension recording</td>
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<tr>
<td>fetal, newborn, and adult sheep</td>
<td>sensitivity: PV &gt; PA</td>
<td></td>
<td>isolated vessel tension recording (3rd generation vessels)</td>
<td>153</td>
</tr>
<tr>
<td>human</td>
<td>pD2: PA, 9.64; PV, 10.36</td>
<td></td>
<td>isolated vessel tension recording</td>
<td>161</td>
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<tr>
<td>PAF</td>
<td>ferret</td>
<td>PA: relaxation; PV: contraction</td>
<td>isolated vessel tension recording</td>
<td>47</td>
</tr>
<tr>
<td>dog</td>
<td>increase in capillary pressure mainly due to venoconstriction</td>
<td>isolated lung perfusion</td>
<td>135</td>
<td></td>
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<tr>
<td>pig</td>
<td>PA: unresponsive; PV: contraction</td>
<td>isolated vessel tension recording</td>
<td>111</td>
<td></td>
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<tr>
<td>TxA2</td>
<td>dog</td>
<td>increase in pulmonary vascular resistance mainly due to venoconstriction</td>
<td>isolated vessel tension recording</td>
<td>134, 143</td>
</tr>
<tr>
<td>sheep</td>
<td>PA: unresponsive; PV: contraction</td>
<td>isolated vessel tension recording</td>
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<tr>
<td>sheep</td>
<td>PV: constriction</td>
<td>measuring pressures in 20-80-μm diameter venules by micro puncture</td>
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<td>newborn lamb</td>
<td>pulmonary hypertension is primarily due to venoconstriction</td>
<td>isolated vessel tension recording</td>
<td>165</td>
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<td>human</td>
<td>PV: contraction [EC50 (−log M): 8.60]</td>
<td>isolated vessel tension recording</td>
<td>158</td>
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<tr>
<td>Leukotrienes</td>
<td>sheep</td>
<td>LTD4 increases resistance of large PV</td>
<td>pulmonary arterial wedge pressures recording in awake sheep</td>
<td>102</td>
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<td>pig</td>
<td>LTD4 causes contraction of PV in the presence of nitro-l-arginine</td>
<td>isolated vessel tension recording</td>
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<tr>
<td>cow</td>
<td>PV: contraction</td>
<td>isolated vessel tension recording</td>
<td>14</td>
<td></td>
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<tr>
<td>human</td>
<td>contractions to LTC4 &amp; LTD4 PV &gt; PA</td>
<td>isolated vessel tension recording</td>
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<tr>
<td>Acute hypoxia</td>
<td>rat</td>
<td>contraction: PV &gt; PA</td>
<td>isolated vessel tension recording</td>
<td>168</td>
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<tr>
<td>guinea pig</td>
<td>PV: contraction</td>
<td>isolated vessel tension recording (pulmonary venules, effective lumen radius: 116 μm)</td>
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<td>ferret (3- to 5-wk-old and adult)</td>
<td>arterial and venous resistances increase equally</td>
<td>measuring pressures in 20-50-μm diameter arterioles and venules by micropuncture</td>
<td>121</td>
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<tr>
<td>dog</td>
<td>PA and PV: constriction</td>
<td>isolated perfused lobes, measuring diameters of arterioles and venules with videomicroscope</td>
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<tr>
<td>newborn lamb</td>
<td>contributing equally to the increase in total pulmonary vascular resistance constriction: PV &gt; PA</td>
<td>measuring pressures in 20-80-μm diameter arterioles and venules by micropuncture</td>
<td>115</td>
<td></td>
</tr>
<tr>
<td>cow</td>
<td>sheep</td>
<td>prolonged hypoxia enhances responsivity of PV but not PA to hypoxia</td>
<td>isolated vessel tension recording</td>
<td>36</td>
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<tr>
<td>Chronic hypoxia</td>
<td>sheep</td>
<td>prolonged hypoxia enhances responsivity of PV but not PA to hypoxia</td>
<td>isolated vessel tension recording (0.5- to 2-mm inner diameter)</td>
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PA, pulmonary arteries; PV, pulmonary veins; PAF, platelet-activating factor; TXA2, thromboxane A2; LTC4, leukotriene C4; LTD4, leukotriene D4; pO2, the negative logarithm of the molar concentration of the agonist that produces 50% of the maximum possible response.

Therefore, in lung disease with hypoxia and/or increased synthesis of these vasoactive agents, venous constriction can aggravate the situation by promoting edema formation. The role of some important vasoactive mediators will be discussed below.

Endothelins. In the rat (3), sheep (153, 161), and human (13), endothelin-1 (ET-1) is a more potent constrictor of pulmonary veins than of arteries. The most notable effect of ET-1 in the rat lung is focal constriction of small veins (3). In lungs of term fetal lambs, small veins (internal diameter ~273 μm) are ~10-fold more sensitive to the constrictor effect of ET-1 than small arteries (internal diameter 169 μm) (161). In guinea pigs, however, the effect of ET-1 is more pronounced in pulmonary arteries than in corresponding sized veins (19).

In pigs, ET-evoked contraction of pulmonary arteries is mediated by endothelin A (ETa) receptors, whereas in veins, it is mediated by both ETa and endothelin B (ETb) receptors (145, 167). In isolated rabbit pulmonary vein, ET-induced constriction is not affected by the Ca2+ channel antagonists verapamil, nifedipine, or nicardipine, but is greatly attenuated by 3 mM LaCl3 and Ca2+-free media. Thus extracellular Ca2+ appears to enter the cell via nonpotential-dependent channels that can be blocked by La3+. Studies also suggest that vascular constriction caused by ET in rabbit pulmonary veins involves activation of both phospholipase C and protein kinase C, but not phospholipase A2 (140).

ET may also modulate pulmonary vessel tension by stimulating the release of EDNO and prostacyclin. EDNO-mediated relaxation induced by ET is greater in pulmonary veins of pigs than in arteries; ET-1 causes a fourfold greater increase in prostacyclin release in pulmonary veins compared with arteries (167). In lung vessels of adult sheep, pretreatment with indomethacin and SQ-29548 significantly attenuated venous constriction to ET, whereas arterial constriction was unaffected. These results suggest that ET-induced contraction of ovine pulmonary veins may be via a thromboxane A2 (TXA2)-prostaglandin H2 mechanism (153).

ET has several other effects in the lung, such as an increase in lung endothelial cell growth factor (21) and stimulation of release of catecholamines (109). In isolated perfused rat lungs, ET-1 causes a pressor response associated with an increase in microvascular pressure and an increase in lung weight (126). Because ET-1 is a more potent constrictor of pulmonary veins than arteries in a number of species including human (3, 13,
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PAF. Ibe et al. (59) were first to describe an important physiological function for PAF in maintenance of high vaso- motor tone in the fetal pulmonary circulation. They demonstrated, by using specific PAF receptor antagonists infused into fetal lambs in vivo, that PAF contributes significantly to maintenance of high tone in the pulmonary circulation in utero. Consistent with the observed high pulmonary vasomotor tone, they found very high circulating levels of PAF in the fetus, which fell dramatically after birth with the onset of oxygenation (59, 61, 64).

PAF synthesis by fetal pulmonary venous smooth muscle cells is more than twofold greater than by arterial cells. This difference in PAF synthesis may be due to greater expression of phospholipase A2 protein as well as greater acetyltransferase activity in venous smooth muscle cells (62). Hypoxia increases PAF synthesis in fetal lung vascular smooth muscle cells, more in pulmonary venous than in arterial cells (62), so that in the hypoxic environment of fetal lungs, there is more PAF available for binding to its receptor in pulmonary vessels. Ibe et al. (65) also reported that PAF receptor (PAF-R) gene mRNA expression as well as PAF-R density is high in fetal lungs, both of which decrease within 2 h after birth, returning to a new intermediate level after a few weeks of life. Binding to the PAF-R is greater in veins than in arteries. Hypoxia significantly upregulates PAF-R binding and PAF-R protein level, especially in fetal pulmonary venous smooth muscle (Fig. 10) (62).

PAF is inactivated by acetylhydrolase (PAF-Ah) (61, 62, 96, 98, 110, 138). In fetal and newborn lamb lungs, activity of PAF-Ah is significantly attenuated by hypoxia (61, 62, 129), suggesting that enzymatic degradation of PAF in fetal pulmonary vasculature is low, resulting in a high level of PAF-Ah in fetal lungs. In ovine fetal pulmonary vein smooth muscle (61, 62), PAF-Ah activity is significantly less than activity in arteries. In hypoxia, PAF-Ah activity in veins is 48% of activity in arteries and 11% of activity during normoxia, suggesting a slower PAF clearance in ovine fetal pulmonary veins. Therefore, the combination of high PAF synthesis and low PAF catabolism by PAF-Ah in fetal veins should mean that a high PAF level will be available for binding to the receptor. These factors all account for this unique role for PAF as an important endogenous mediator of increased tone in pulmonary veins of the fetus, accounting in part for the large fractional resistance in veins of the ovine fetal lamb.

In isolated perfused dog lungs, PAF causes edema by increasing capillary pressure predominantly due to venoconstriction (135). PAF induces contractions of isolated porcine pulmonary veins, whereas the arteries are unresponsive (111). In ferret lungs, PAF induces an endothelium-dependent constriction of the veins but an EDNO-dependent relaxation of the arteries (47) (Fig. 11). These data indicate that in a number of species, PAF is a pulmonary venoconstrictor, and that when synthesized in abnormal amounts in the mature lung, it will lead to a tendency for edema formation. In isolated rat lungs, PAF administration stimulated the release of PGE2 into the venous effluent and increased lung weight, a measure of edema formation. Perfusion of rat lungs with PGE2 causes pulmonary edema, which is largely prevented by inhibition of \( \text{K} \text{V} \).

\( \text{TxA}_2 \). \( \text{TxA}_2 \) is a potent constrictor of pulmonary veins in a number species, including dog (71, 134), sheep (73, 113, 165), and human (158). It causes constriction of human pulmonary veins via prostaglandin receptor subtypes TP and EP1 (158). \( \text{TxA}_2 \) is a poor constrictor of pulmonary arteries in dogs (143) and...
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sheep (73). In isolated perfused dog lungs, the stable TxA2 analog causes a threefold increase in pulmonary vascular resistance, exclusively due to pulmonary venoconstriction. The change is accompanied by an increase in pulmonary capillary pressure with progressive lung weight gain. These results suggest that pulmonary veins may play an important role in the development of pulmonary hypertension and edema when TxA2 production increases (134).

Leukotrienes. Evidence from isolated pulmonary vessel studies suggests that leukotrienes may contribute to pulmonary edema formation during anaphylaxis in cattle (14). In lungs of sheep (102), cows (14), and human (131), leukotrienes, in particular leukotriene C4 (LTC4) and/or D4 (LTD4), are more potent constrictors in veins than in arteries. In fetal and newborn lambs, the release of leukotrienes B4 and LTC4 induced by calcium ionophore A-23187 or arachidonic acid is greater in isolated pulmonary veins than in arteries (58, 63). In sheep, LTD4 causes contraction of the pulmonary veins mainly by elevating thromboxane (102). In pigs and human, LTC4 or LTD4 may also cause EDNO-dependent relaxation of the pulmonary veins (6, 107, 131).

Acute Hypoxic Pulmonary Vasoconstriction

Acute hypoxic pulmonary vasoconstriction is a physiological response whereby circulating blood is diverted away from hypoxic alveoli to optimize the matching of perfusion with ventilation. The primary site of resistance to flow in the pulmonary circulation under both normal and hypoxic conditions is thought to be the precapillary pulmonary arterioles (7). However, numerous studies have shown that hypoxia causes vigorous constriction of pulmonary veins in a variety of species including rat (168), guinea pig (155), ferret (121), dog (53), sheep (115, 132), and cow (36). In some instances, acute hypoxia induces significantly greater contraction of pulmonary veins than of arteries, such as in rats (168) (Fig. 12).

In porcine pulmonary veins with endothelium, acute hypoxia induces contraction that is partially blocked by nitro-L-arginine. Bradykinin-induced relaxation is abolished by hypoxia. These results suggest that inhibition of EDNO may be involved in hypoxia-induced contraction of pulmonary veins (36). Because oxygen is an essential substrate for nitric oxide synthases, it is conceivable that hypoxia may facilitate vasoconstriction by inhibiting the synthesis of EDNO (66, 79). Other studies indicate an important role for cyclooxygenase products in the hypoxic vasoconstrictor response of pulmonary veins.

In porcine pulmonary veins both with and without endothelium, acute hypoxia induces a contractile response that is partially blocked by indomethacin (36).

Pulmonary Vascular Responses to Chronic Hypoxia

Abnormal vasoconstriction and changes in vessel morphology are two prominent pathological features in lungs subjected to chronic hypoxia (68, 97, 128). A study utilizing electron microscopy has provided morphological evidence of vasoconstriction of small pulmonary veins in rats exposed to hypoxia for 28 days (34). Vascular remodeling occurs not only in pulmonary arteries but also in veins in a number of species including rat (34, 146), sheep (69), and human (23, 157). In humans, the changes in veins consist of medial hypertrophy and arterialization of bundles of smooth muscle cells within the venous intima (157). In patients with primary pulmonary hypertension, intimal and adventitial thickening of pulmonary veins <250 \( \mu \)m in diameter was observed in approximately one-half of the subjects studied (23).

There is very limited information on the mechanisms underlying hypoxia-induced remodeling of pulmonary veins. In rats, expression of Big ET-1 is more abundant in pulmonary veins than in arteries. After exposure to hypoxia for 7 or 14 days, expression of Big ET-1, endothelin converting enzyme, and ET receptors increased in small pulmonary veins. Increases in medial thickness, wall thickness, and immunoreactivity for \( \alpha \)-smooth muscle actin were also observed together with the upregulation of ET-1 and ET receptors in small pulmonary veins (146). The actions of ET-1 are mediated by two different receptors, namely ET\( \alpha \) and ET\( \beta \). Chronic hypoxia augmented contraction of rat pulmonary veins but not that of arteries induced by sarafotoxin 6c, a selective ET\( \beta \) agonist. In contrast, contractions of both vessel types to ET-1, which activate ET\( \alpha \) and ET\( \beta \), were reduced by chronic hypoxia (77).

In adult sheep, after 20 h of hypoxia, subsequent hypoxia had no effect on pulmonary arteries but caused the veins to contract vigorously. Prior incubation of the veins with catalase (a scavenger of reactive oxygen species), indomethacin, or SQ-29548 (the TxA2-prostaglandin H\( _2 \) receptor antagonist) significantly reduced the response to hypoxia. Veins preexposed to hypoxia are more reactive than control veins to U-46619, a TxA2 analog. This suggests that hypoxia may increase the production of reactive oxygen species, which in...
turn modifies production of, metabolism of, and/or tissue responsivity to TXA2-prostaglandin H2 (132).

PAF has been shown to play a role in persistent pulmonary hypertension of the newborn (PPHN) (18, 105, 106). Circulating plasma PAF level was noted to be high in newborn infants with PPHN, with the levels falling dramatically when their clinical condition improved (18). In adult rats, a role for PAF in chronic hypoxia-induced pulmonary hypertension has been reported. PAF receptor antagonists attenuated hypoxia-induced pulmonary hypertension and pulmonary vascular remodeling (106) in rats, indicating a PAF-R-mediated mechanism. PAF also appears to be involved in remodeling of pulmonary veins in chronic hypoxia-induced pulmonary hypertension in neonatal calves; the veins had markedly increased expression of PAF-R in their smooth muscle cells (unpublished observations, Ibe BO and Raj JU).

The role of EDNO in chronic hypoxia-induced changes in pulmonary veins is less clear. In sheep, when pulmonary hypertension was induced by continuous pulmonary artery air embolization for 1 day, both large- and medium-sized pulmonary veins became resistant to nitro-L-arginine inhibition. The mechanism of nitro-L-arginine resistance appears to be due to the upregulation of a K+ channel-mediated backup vasodilator mechanism that can compensate for the loss of nitric oxide-mediated relaxation (74).

In general, after chronic hypoxia, in most species, there appears to be greater remodeling and vasoconstriction of the pulmonary arteries than veins. Nevertheless, this review indicates that there is also significant remodeling of pulmonary veins, such that the physiological consequence of increased venous resistance has to be considered in situations of chronic hypoxia-induced pulmonary hypertension. Further studies are required to explain why the response of pulmonary arteries and veins to chronic hypoxia is different.

**ROLE OF PULMONARY VENOUS CONSTRICION IN DEVELOPMENT OF PULMONARY EDEMA**

Although venous constriction, by increasing microvascular pressures, can cause distention and recruitment of capillaries, with the possibility of better ventilation-perfusion matching, a major negative consequence is increased fluid filtration and the tendency toward edema formation. It is generally believed that most baseline lung fluid filtration occurs across alveolar wall capillaries, i.e., at least 50% or more of total fluid flux occurs at this site. However, considerable experimental evidence exists that fluid filtration also occurs across thin-walled corner vessels, the extra-alveolar precapillary arterioles, and postcapillary venules. Because the pressure is higher in arterioles, there is likely to be greater fluid filtration from this site than from the low-pressure venules. However, if the filtration coefficient is lower in venules, then a small increase in venular pressure will result in the filtration of large amounts of fluid and protein. This is particularly true in situations where there is injury to the capillaries and small venules. In humans with any degree of lung injury, if the conditions of increased vascular permeability with an increase in filtration pressure coexist, the lung will have a great tendency to edema formation. It is important to realize that potentially there can be two patients with identical pressures in the pulmonary artery and left atrium, but if one of them has any degree of venous constriction, the pressures within the filtering vessels of the lung will be greatly elevated, and that patient will be more prone to developing fulminant pulmonary edema.

A number of bioactive agents, such as PAF, ET, thromboxane, and leukotrienes, by causing venous constriction, can increase pulmonary capillary pressure and thus promote pulmonary edema formation (21, 48, 96, 126, 130, 170). Increased synthesis of these agents is associated with lung injury and disease.

**SUMMARY**

In the last two decades, a large body of evidence has accumulated indicating that the pulmonary vein is not a simple conduit but rather an active player in regulation of pulmonary circulation. This is particularly true during the perinatal period, i.e., in the fetus and newborn. Although other laboratories, in addition to ours, have published data on pulmonary venous reactivity in the perinatal period in a number of animal species, nevertheless, there is still some doubt as to the importance of pulmonary veins in the human fetus and newborn. This is because pulmonary vessels from the human fetus and newborn are difficult to obtain for study, although some data exist in the adult human pulmonary vein (13, 23, 131, 157, 158, 159). Data from other animal species indicate that pulmonary venous activity is affected by a variety of agents, including EDNO, prostaglandins, ET, PAF, and thromboxane. The release and/or actions of EDNO and PGI2 are modulated by oxygen. Hence, these agents may play an important role in the transition from fetal to neonatal life, a period when the pulmonary vasculature is exposed to dynamic changes in oxygen tension.

In comparison with pulmonary arteries, studies in pulmonary veins are few and limited, and many questions remain to be answered. In particular, the mechanisms underlying the heterogeneous behavior of pulmonary arteries and veins need to be defined. The contribution of genetic and molecular determinants of vascular structure and function contrasts against the contribution of environmental modifiers such as differences in blood flow, shear rate, vascular pressure and distention, and oxygen tension on vascular behavior of the pulmonary arteries and veins needs further study. Finally, continuing new information on the vasoactive behavior of pulmonary veins will likely lead to new therapeutic interventions. For instance, although it has been known for a long time that atrial natriuretic peptide is more potent as a vasorelaxant of pulmonary arteries than of veins (67, 89), it was recently found that C-type natriuretic peptide (CNP) is a very potent dilator of pulmonary arteries and thromboxane. The release and/or actions of EDNO and PGI2 are modulated by oxygen. Hence, these agents may play an important role in the transition from fetal to neonatal life, a period when the pulmonary vasculature is exposed to dynamic changes in oxygen tension.

Thus the high selectivity of CNP could be of some therapeutic use in the treatment of pulmonary edema caused by venoconstriction.

This review of the heterogeneous behavior of pulmonary arteries and veins to a variety of vasodilator and constrictor agents emphasizes the fact that the pulmonary circulation is likely to respond in a complex manner to changes in local and circulating vasoactive mediators. Regional changes in vascular resistance within the pulmonary circulation will affect blood flow and fluid filtration differently, and a good understanding of the biology of the pulmonary vasculature is necessary for accurate prediction of the vascular responses. Also, since the measurement and detection of venous vasoactivity is not easy
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in a clinical setting, awareness and knowledge of the potential venous responses in the lung will enable the astute clinician to anticipate the pathological consequences.

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