

EDITORIAL**PULMONARY VASCULAR TONE AND THE ANESTHESIOLOGIST**

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The lung is the necessary link in transporting oxygen from the air to the blood. In this process, the pulmonary capillaries provide the critical air-blood interface. The thinness of the pulmonary capillary wall is conducive to fluid leakage and pulmonary edema, which could impair oxygenation of the blood. The pulmonary capillaries must maintain adequate perfusion, but it is essential that the perfusion is regulated so that gas exchange is not impaired by excessive fluid leakage. This balance is achieved by modulation of pulmonary vascular resistance (PVR), which is brought about by changes in vascular smooth muscle tone in the pulmonary arterioles.

Physiological studies over the last 40 years have led to a better understanding of the factors influencing pulmonary vascular tone. These factors can be divided into gravity dependent and non-gravity dependent factors¹. As a result of gravitational effects, both blood flow and ventilation increase linearly with distance down the normal upright lung; however, the increase in blood flow is disproportionate to the increase in ventilation². This results in the alveoli at the apex of the lung being relatively underperfused, and the alveoli at the base of the lung being relatively overperfused². The non-gravity dependent factors include passive and active mechanisms. Passive mechanisms are due to changes in lung volume and cardiac output. An asymmetric U-shaped relationship exists between lung volume and PVR¹. When lung volume is either increased or decreased from the functional residual capacity (FRC), PVR increases³⁻⁵. At lung volumes above FRC, the increase in PVR is related to extravascular compression of small intra-alveolar vessels by the surrounding alveoli. Positive end-expiratory pressure (PEEP) increases PVR through a similar mechanism. The increase in PVR below the FRC is due to mechanical kinking of large extra-alveolar vessels³⁻⁵. In the atelectatic lung, the mechanism of increased PVR is active hypoxic pulmonary vasoconstriction (HPV) (see below).

The normal adult pulmonary circulation is a low-pressure, low-resistance circuit that accommodates the entire output of the right ventricle. Understanding passive influences in the pulmonary circulation is essential in identifying active vasodilation or active vasoconstriction (Table 1)^{6,7}. An increase in pulmonary blood flow (PBF) accompanied by no change or a slight increase in pulmonary artery pressure (Ppa) is consistent with a passive decrease in PVR, secondary to distension and/or recruitment of previously nonperfused pulmonary vessels. A passive increase in PVR would be suggested by a decrease in PBF accompanied by a relatively constant Ppa. However, an increase in Ppa in the face of no change or a decrease in PBF, would imply an increase in PVR due to active vasoconstriction. Conversely, a decrease in Ppa in the face of no change or an increase in PBF would imply an increase in PVR due to active vasodilation. The latter changes are often observed during the administration of sodium nitroprusside¹. In patients with pulmonary hypertension, where

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the vessels are rigid and less distensible, Ppa sharply increases with any increase in PBF. Increased Ppa and PVR is a universal feature of acute respiratory failure⁷.

Table 1. Mechanism of change in pulmonary vascular resistance (PVR), as predicted from observed changes in pulmonary blood flow (PBF) and pulmonary artery pressure (Pap).			
PBF		Pap	Change in PVR
↑		→	Passive Decrease
↓		→	Passive Increase
→		↓	Active Decrease
↑		↓	Active Decrease
→		↑	Active Increase

Horizontal arrow indicates no change or small increase or decrease.

The normal pulmonary circulation also responds passively to increases in downstream pressure, i.e., pulmonary capillary wedge pressure, as has been demonstrated in exercising healthy men⁸. Despite marked reductions in the pulmonary pressure gradient, PBF is well maintained by passive reductions in PVR. This passive distension of the pulmonary vasculature, while minimizing resistance to flow, also increases the vulnerability of the lung to fluid filtration from its capillaries, and the formation of edema. An increase in pulmonary venous pressure (Pvp) leading to pulmonary edema, may play a role in the genesis of the adult

respiratory distress syndrome (ARDS)^{1,7}.

Three major categories of active mechanisms influence pulmonary vascular tone^{1,9}: 1) tissue-derived autocrine or paracrine substances. Substances causing vasodilation include nitric oxide (NO), endothelin, and prostaglandin (PGI₂) and substances causing vasoconstriction include PGF₂, thromboxane and leukotriene. 2) alveolar gases, especially low oxygen (see below), and 3) neurohumoral factors, including circulating catecholamines and catecholamines released by sympathetic nerve fibers and the renin-angiotensin system. The pulmonary vascular endothelium plays a fundamental role as a source of vasoactive substances and as a location for activation or deactivation of blood-borne vasoactive substances. The active control of pulmonary vascular tone is extremely complex and involves multiple mechanisms, both local and remote, interacting in complex fashions. It is beyond the scope of this editorial to discuss these mechanisms in detail. The reader is referred to a more comprehensive review⁹.

Hypoxic pulmonary vasoconstriction (HPV) is an adaptive mechanism whereby blood is diverted away from poorly ventilated alveoli to better ventilated alveoli, thus decreasing the shunt flow and protecting PaO₂. Because it is unique to the pulmonary circulation and perhaps the most potent active vascular control mechanism, HPV has been an area of intense investigation since it was initially described in 1946¹⁰. It is present in all mammalian species, and can occur in the whole lung, a lobe, or a segment. The HPV response occurs primarily in the pulmonary arterioles, which are in close proximity to small bronchioles and alveoli and is a function of both alveolar (P_AO₂) and mixed venous oxygen tension, but P_AO₂ has a much greater influence^{1,11-13}.

The molecular mechanism underlying HPV remains uncertain, although various theories have been proposed⁹. One theory involves a closure of K⁺ channels by hypoxia, leading to smooth muscle depolarization, Ca²⁺ entry, and smooth muscle contraction. A second theory suggests that HPV is initiated by a reduction in oxidative phosphorylation. A third theory proposes that oxygen tension regulates the production of reactive oxygen species, which control transmembrane Ca²⁺ flux via a direct action on sulfhydryl groups in the Ca²⁺ channel protein of the vascular smooth muscle cell.

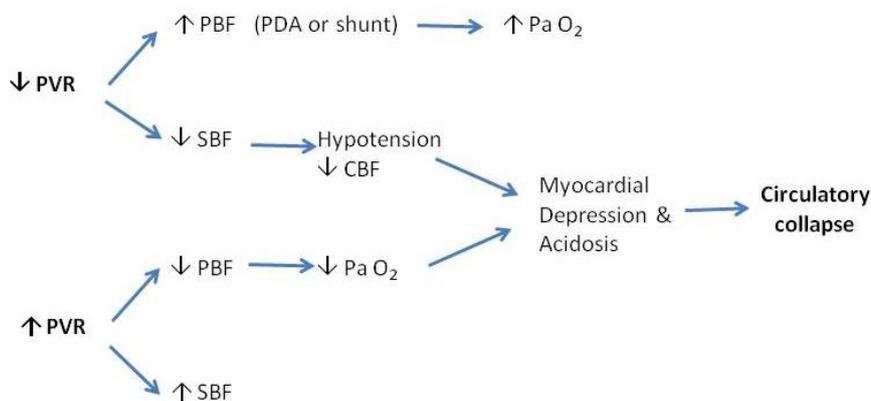
The clinical effects of HPV can be observed in four scenarios in humans. First, HPV is critical for fetal development by minimizing perfusion of the unventilated lung. Second, at high altitudes (or breathing a low oxygen concentration), HPV increases (or even doubles) Ppa, whereas the wedge pressure remains constant^{1,14}. The increased Ppa enhances perfusion to the apical alveoli, resulting in a higher PaO₂. High altitude pulmonary hypertension is an important component in the development of cor pulmonale¹⁵. Third, in patients with lung disease, during one-lung ventilation, and in cases of mainstem intubation, HPV causes diversion of blood to the non-hypoxic lung, thus minimizing intrapulmonary shunting and normalizing regional ventilation/perfusion relationships^{1,16}. Fourth, in patients with chronic obstructive lung disease, asthma, or mitral stenosis, the administration of a pulmonary vasodilator can cause inhibition of pre-existing HPV, and decreased PaO₂^{1,17}.

Because the pulmonary vessels are highly distensible, any condition that raises Ppa will passively inhibit HPV. This can occur with mitral stenosis, volume overload, hypothermia, thromboembolism, and use of vasoactive drugs^{1,18,19}. Pulmonary vasodilator drugs (isoproterenol, sodium nitroprusside, nitroglycerin), infection, and alkalosis can directly inhibit HPV and increase right-to-left intrapulmonary shunting. A selective application of PEEP to only the non-diseased lung can increase PVR and divert blood back into the diseased lung^{1,20}. Both iv and inhalational anesthetics have been studied for their inhibitory effect on HPV¹. Although the results have not always been consistent, it is generally accepted that iv anesthetics have no effect on HPV, while inhalational anesthetics have a slight inhibitory effect¹.

There are many clinical scenarios in which control of PVR plays a pivotal role in achieving cardiovascular stability. Two will be addressed in this editorial. The survival of neonates with hypoplastic left heart syndrome (HLHS) depends on: 1) a patent ductus arteriosus (PDA) (or the creation of a palliative central shunt) to provide systemic blood flow (SBF), and 2) a balanced level of PVR relative to systemic vascular resistance (SVR), since both pulmonary and systemic circulations are supplied from a single ventricle in a parallel fashion (Fig. 1)²¹⁻²³. An excessive decrease in PVR causes an increase in PBF at the expense of SBF, a "pulmonary steal" phenomenon. This results in decreases in both systemic and coronary blood flow, leading to myocardial depression, metabolic acidosis, and circulatory collapse despite a high PaO₂ due to the elevated PBF. Conversely, an excessive increase in PVR reduces PBF, leading to reductions in PaO₂, and ultimately myocardial depression and circulatory collapse, despite initially high systemic and coronary blood flows.

Fig. 1

Balance between PVR and SVR is essential for survival of patients with HLHS before or after creation of a palliative shunt



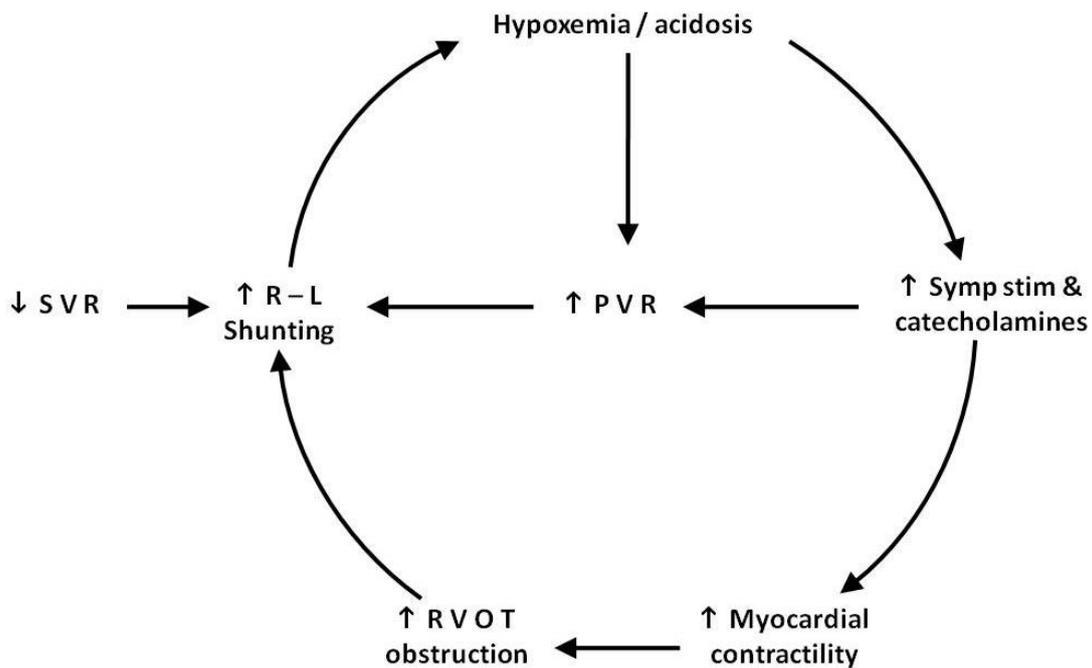
See text for details. Abbreviations: PVR, pulmonary vascular resistance; PBF, pulmonary blood flow; SBF, systemic blood flow; CBF, coronary blood flow; PDA, patent ductus arteriosus.

If PaO₂ is relatively high (PaO₂ >50) in patients with HLHS, decreasing ventilation to allow PaCO₂ to increase (and pH to decrease), generally increases PVR and decreases PBF and PaO₂²¹. Lowering FIO₂ and increasing PEEP may also be necessary to decrease PBF, thus paradoxically decreasing PaO₂²¹. These measures result in increased SBF. In the presence of low PBF with resultant hypoxemia (PaO₂ <20 mm Hg), hyperventilation to a lower PaCO₂ (20-25 mm Hg), in addition to other measures to decrease PVR, can improve PaO₂ to viable levels (30-40 mm Hg). These maneuvers, although difficult to maintain, are useful in the perioperative period and in the critical care setting in maintaining the balance between PVR and SVR, which is essential for survival of HLHS patients.

Another situation where a delicate balance between the SVR and PVR is necessary is in patients with tetralogy of Fallot (TOF) (pulmonary stenosis or atresia, an overriding aorta, ventricular septal defect, and right ventricular hypertrophy)²⁴. In these patients, right-to-left shunting and cyanosis are worsened by increased right

ventricular outflow tract obstruction, elevated PVR and reduced SVR. Furthermore, increased myocardial contractility due to sympathetic activation or administration of β -adrenergic agonists may promote infundibular spasm, resulting in infundibular shutdown^{24,25}. Factors increasing PVR, including hypoxemia and acidosis, can lead to a further decrease in PBF, an increase in right-to-left shunting, and worsening of hypoxemia. Reduction in SVR also increases shunting across the ventricular septal defect. Sudden episodes of hypoxemia in TOF patients are due to spasm of the right ventricular outflow tract, which results in further decrease of PBF and increased right-to-left shunting. Once initiated, a vicious cycle of increased hypoxemia and acidosis develops, which requires immediate treatment (Fig. 2)^{24,25}. Increasing SVR with phenylephrine or another α -adrenergic drug is recommended. In cyanotic pediatric patients with TOF, infusing phenylephrine until systolic arterial blood pressure was increased by 40 mmHg has been demonstrated to raise PaO₂ by an average of 14 mmHg and to reduce right-to-left shunt by an average of 25%^{26,27}. Careful administration of a small doses of β -adrenergic antagonists and enhancing preload can also be helpful. Attempts should be made to decrease PVR by correcting acidosis, decreasing PaCO₂ and adjusting FIO₂^{24,25}.

Fig. 2
Vicious cycle in patients with tetralogy of Fallot



See text for details. Abbreviations: SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; RVOT, right ventricular outflow tract.

The manuscript by Mahdi et al. in this issue addresses the effect of moderate hypocapnia in a limited number of patients with elevated PVR following surgery to correct mitral valve stenosis. The findings provided “proof of concept” that hypocapnia is an effective pulmonary vasodilator in these patients. It was demonstrated

that a 30 min duration of moderate hypocapnia was a simple, safe, and inexpensive technique, which reduced PVR by one-third. The authors concluded that hypocapnia would provide a bridge until pulmonary vascular tone begins to normalize following surgery for mitral valve stenosis. This study provides a springboard for future research to answer pertinent questions. Among them are: Does the reduction in PVR persist if the exposure to hypocapnia is extended beyond 30 min? Does the decrease in PVR vary as a function of the degree of hypocapnia? Is the technique of induced hypocapnia, as an intervention to reduce PVR, applicable to patients with pulmonary hypertension from other causes?

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