SPECIAL REPORT

Some Basic and Clinical Challenges in the Pulmonary Circulation*

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It is a special honor to deliver the Simon Rodbard lecture. Dr. Rodbard was an intense, bright person with a fine critical mind. His early analysis of the hemodynamic properties of the pulmonary circulation provided a major advance and led to the later contributions of John West and Solbert Permutt. I do not believe it an exaggeration to suggest that he anticipated the zonal distribution of blood flow in the lung as a function of gravity, the application of Starling resistor theory to the pulmonary vascular bed, and the concept of the pulmonary vascular waterfall long before these were appreciated by others. He also provided classic contributions in the field of pulmonary edema. In his memory, I have decided to discuss five challenges presented by the pulmonary circulation: (1) the mechanism of hypoxic pulmonary vasoconstriction (HPV); (2) the role of vasoconstriction in pulmonary vascular disease; (3) the progressive nature of pulmonary hypertension; (4) the role of primary pulmonary venous obstruction in pulmonary vascular disease; and (5) the role of direct pulmonary artery-to-pulmonary vein communications in disease.

MECHANISM OF HYPOXIC PULMONARY VASOCOSTRICTION (HPV)

Thirty-four years ago, von Euler and Liljestrand[1] opened a new era in our understanding of the pulmonary circulation. They showed that the inhalation of hypoxic gas mixtures produced pulmonary vasoconstriction. This observation not only provided insight into a specific regulatory mechanism; it showed for the first time that the pulmonary vascular bed was not a simple system of tubes which reacted passively to a series of hydrodynamic factors imposed by the heart, on one hand, and by the airways, pulmonary parenchyma, and pleura on the other. The pulmonary circulation was subject to important regulatory processes which operated actively and not passively. It is now clear that when alveolar Po2 values drop below 60 mm Hg, there is substantial constriction of pulmonary arterioles (HPV). When the hypoxia is regional, vasoconstriction is regional; when hypoxia is global, vasoconstriction is global.

In the adult, the major biologic value of HPV is to optimize the oxygen content of blood leaving the lung by shunting blood away from poorly ventilated areas, thereby increasing the Po2 and saturation of arterial blood. It does so at a price: an increase in pulmonary vascular resistance and right ventricular work. During fetal life, HPV, which is better developed than in the adult, is required for survival and adult HPV may represent a useful ontogenic residual.

The mechanism by which hypoxia is translated into vasoconstriction has been an important focus for investigation and has given rise to a massive number of studies. There is a general impression that elucidating the mechanism would provide a major breakthrough, both for understanding of the pulmonary circulation and for our ability to manage various pulmonary diseases. Most pulmonary diseases are characterized by either regional or general reductions in lung oxygen tensions. Unraveling HPV might permit us to modify this important component of many pulmonary diseases.

In recent years there have been at least two excellent overall reviews of HPV, one by Fishman[2] and one by Bergofsky.3 My discussion will differ somewhat by focusing on cellular and biochemical factors.

The most honest summary of present knowledge is to say we do not know the mechanism of hypoxic pulmonary vasoconstriction. Existing evidence suggests five possible mechanisms. One model suggests

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that HPV results from direct excitation-contraction. Hypoxia produces a direct change or a neurally mediated change in the concentration of some pre-existing constituent in pulmonary vascular smooth muscle which causes constriction. This mechanism appears unlikely.

A second model suggests that a pulmonary artery constrictor substance (PACS) is released from some lung cell types during hypoxia. PACS diffuses into the vascular smooth muscle. No such agent has been demonstrated and there is compelling evidence which makes this possibility unlikely.

Another model suggests that there is an O_2 sensor located within some lung cell which senses low PO_2 and initiates the release of PACS resulting in constriction. A review of existing evidence shows major problems with this model.

Another model suggests that hypoxia decreases the release of a pulmonary artery vasodilator substance (PADS) from some lung cell type and the reduction in vascular tone results in vasoconstriction. Although an attractive model, it also does not fit all of the experimental observations that are available.

The final model (Fig 1) suggests that regional pulmonary vascular resistance reflects the balance between two agents—PADS and PACS. One lung cell type A secretes PACS and responds to hypoxia by a decreased release of PADS, possibly the result of processes originating from a biochemical sequence whose rate-limiting enzyme has a low affinity for O_2. The second lung cell secretes PACS. Pulmonary vascular tone at any time is related to the balance of activity of these two agents. Hypoxia shifts the balance to vasoconstriction. In respect to this possibility, recent attention has been focused on the prostaglandins. The synthesis of some of the prostaglandins is sensitive to O_2 supply. These agents are elaborated by pulmonary endothelial cells, as well as other lung cell types. It would be elegant to have the source of the regulatory agents originate in pulmonary endothelial cells because of their juxtaposition to pulmonary vascular smooth muscle. Some of these agents are pulmonary vasodilators and others are pulmonary vasoconstrictors.

Kadowitz and others have suggested that vasodilator prostaglandins (such as prostacyclin, PGI_2) contribute to maintenance of the low pressure state of the pulmonary circulation. Vasoconstriction would result from the inhibition of synthesis of the prostaglandin pulmonary vasodilators. Hydralazine is a pulmonary vasodilator which aborts hypoxic pulmonary vasoconstriction in the dog. Following the use of prostaglandin synthetase inhibitors, hypoxic pulmonary vasoconstriction is no longer inhibited by hydralazine, suggesting that the mechanism of vasodilation involves the prostaglandin system. Infusion of arachidonic acid attenuates HPV in the dog, presumably by increasing the synthesis of PGI_2, a prostaglandin pulmonary vasodilator. Even (as seems likely) if not the primary mediator of HPV, it is reasonable to believe that the prostaglandin system modulates pulmonary vascular resistance in this and a variety of other physiologic and pathophysiologic circumstances.

A model using an interplay between vasodilator and vasoconstrictor agents fits all of the data which are available.

To summarize this section, we do not know the mechanism of HPV. My speculations go as follows:

Hypoxic pulmonary vasoconstriction is mediated by the local release of agents in the lung close to the pulmonary vascular smooth muscle. These agents are released by some special cell(s) in the lung. Conceivably one cell type involved might be the pulmonary endothelial cell. HPV is mediated by chemical reactions which are O_2 requiring, but involve at least one reaction catalyzed by an enzyme with a relatively low affinity for O_2. These reactions either decrease the production or release of a vasodilator agent (PADS) or alternatively alter the balance between PADS and a vasoconstrictor substance (PACS).

**ROLE OF VASOSPASM IN PULMONARY DISEASE**

Vasospasm may be defined as an abnormal, rapid,
time-limited contraction of vascular smooth muscle, resulting in a decrease in the diameter of a vessel. In the systemic circulation, vasospasm is recognized as an important pathogenic factor in a variety of vascular disorders (cerebral, coronary, peripheral). Not uncommonly, systemic vasospasm is mediated by the sympathetic nervous system. There is little reason to doubt an important role for vasospasm in the pulmonary vascular bed. However, unlike the systemic circulation, pulmonary vasospasm tends to be clinically silent, producing no equivalent to angina in the coronary circulation or focal neurologic signs in the cerebral circulation. Nor is there a simple, direct way to document pulmonary vasospasm objectively. As a result, its existence must be inferred from indirect evidence.

Three examples may be cited. Bronchial asthma is not generally regarded as a disorder with important consequences for the pulmonary circulation and the right ventricle. Measurements of pulmonary artery pressure during acute asthma may show frank elevation. However, there have not been systemic studies of pulmonary hemodynamics during acute paroxysms of the disease. Perfusion lung scans in acute asthmatics frequently reveal focal to diffuse loss of perfusion which may be mistaken for pulmonary embolism. There is, of course, fotal alveolar hypoxia as well as altered airway pressures, both of which may increase pulmonary vascular resistance. In addition, several chemical mediators released by the immunologic cascade of asthma produce pulmonary vasoconstriction as well as bronchial constriction. A model for this is shown in Figure 2. Histamine, serotonin, and slow reacting substance-anaphylaxis (SRS-A) are released from mast cells in the pulmonary parenchyma by a series of immunologically mediated events. These mediators diffuse into pulmonary vascular smooth muscle and produce vasospasm. Histamine is a potent pulmonary vasoconstrictor. In the pulmonary circulation, the H₁ blocker, chlorpheniramine, prevents the vasoconstrictive effect of infused histamine. This suggests that H₁ receptors are involved. Histamine apparently produces vasoconstriction by a direct effect on the smooth muscle. Serotonin, which is found in the mast cells and platelets of many species, is a potent and consistent pulmonary vascular constrictor in a number of species. SRS-A has recently been identified as a group of substances, collectively called leukotrienes, derived from fatty acids by a group of enzymes, lipo-oxygenases. The metabolic sequence is similar to the generation of prostaglandins from fatty acids by the enzyme cyclo-oxidogenase. SRS-A acts as a pulmonary vasoconstrictor. Given the known physiologic activities of these agents, it is reasonable to assume that pulmonary vasospasm, like bronchospasm, is an integral part of severe bronchial asthma.

The role of pulmonary vasospasm in pulmonary embolism is less precisely defined. The major cause of vascular obstruction is the mechanical impact of the clot. However, there is not always a close correlation between the amount of vascular bed which is mechanically occluded and the degree of pulmonary hypertension. Relatively small clot burdens may be associated with severe pulmonary hypertension. There is little question that a series of mediators are released both from the surface of clots and from injured lung cells. It is probable that some of these mediators are capable of producing both bronchoconstriction and pulmonary vascular spasm in non-embolized segments of the lung. As a result, a degree of pulmonary hypertension may develop which is disproportionately great for the amount of vasculature which is mechanically occluded.

A different mechanism for pulmonary vasospasm is probably operative in the Cre§t syndrome (calcinosis, Raynaud’s phenomenon, esophageal dysfunction, sclerodactyly, telangiectasia) variant of scleroderma. Pulmonary hypertension and increased pulmonary vascular resistance is found in a disproportionately high percentage of these patients. The pulmonary hypertension tends to occur early in the course of the syndrome, may be found in the virtual absence of interstitial lung disease, and is found in association with Raynaud’s phenomenon. When structural vascular lesions are found, these involve small and medium-sized pulmonary arteries. There

**Figure 2.** Proposed mechanism for pulmonary vasospasm in bronchial asthma. The release of histamine, serotonin, and slow-reacting substance A by an antigen-antibody reaction is followed by the diffusion of these agents into pulmonary vascular smooth muscle producing vasoconstriction.
is intimal proliferation or thickening with narrowing or obliteration of the vessel lumen. These lesions are similar or identical to those found in the digital arteries of patients with scleroderma and Raynaud's\(^7\) and in the renal arteries of patients with scleroderma kidney.\(^8\) There may be the deposition of serum globulin IgG and the complement component, Clq, similar to those described in the interlobular renal arteries in scleroderma.\(^9\)

Similar lesions of the pulmonary blood vessels have been described in systemic lupus erythematosus, dermatomyositis, and rheumatoid arthritis. Given these correlations, it may be speculated that the early pulmonary hypertension in the Crest variant may be considered as a Raynaud's phenomenon of the pulmonary vasculature. There is the development of hyper-reactive pulmonary vessels and, with recurrent episodes of pulmonary vasospasm (Raynaud's phenomenon of the lung), there is the ultimate development of structural changes in the vessel wall and persistent pulmonary hypertension.

It is of some interest that up to 30 percent of patients with primary pulmonary hypertension show Raynaud's phenomenon\(^10\) in the digits, and a hyper-reactive pulmonary vascular bed may be important in the pathogenesis of a variety of other causes of pulmonary hypertension.

Why should pulmonary blood vessels become hyper-reactive? In Raynaud's phenomenon, in the systemic circulation, the autonomic nervous system appears to be involved. Could this be true in the pulmonary circulation as well? Even if not true, this speculation permits a discussion of a major challenge in the pulmonary circulation. Autonomic nerves invest pulmonary blood vessels, but their role is almost completely obscure and this problem is an important gap in knowledge. I will speculate that vasospasm in the Crest syndrome occurs as follows (Fig 3): the deposition of immune complexes in the wall of pulmonary muscular arteries sensitizes them to that increased traffic along sympathetic fibers and results in vasospasm.

In summary, I conclude that pulmonary vasospasm exists, that it is an important pathogenetic mechanism, and that the development of methods for detecting and quantitating vascular spasm in the lung is a major challenge.

The Progressive Nature of Pulmonary Hypertension

Extensive hemodynamic studies over substantial periods of time, which outline the natural life history of pulmonary hypertension, are lacking. However, there are clinical observations indicating that once pulmonary hypertension develops (whatever its cause), there are further increases in pulmonary vascular resistance with time and, so to speak, pulmonary hypertension begets further pulmonary hypertension.

One line of evidence involves structural changes that develop with time in patients with pulmonary hypertension independent of the cause. These include medial hypertrophy of muscular pulmonary arteries, plexiform lesions, dilatation lesions, intimal thickening and sclerosis, pulmonary atherosclerosis, and thickening capillary basement membranes.\(^11\) These changes tend to increase flow resistance and thereby increase pulmonary pressures progressively. The pathogenetic link between persistent pulmonary hypertension and the development of these non-specific structural changes is not at all clear.

It is generally not appreciated that acute increases in pulmonary artery pressure may be accompanied by widespread small thromboses in situ of small pulmonary arteries and veins.\(^12\) It is of some interest that PG \(I_2\), which is a pulmonary vasodilator, is also a potent anticoagulant.\(^13\) Perhaps attenuation of the release of this agent not only leads to pulmonary hypertension (see above), but to widespread thromboses in situ in the low pressure pulmonary circulation. Although these thrombotic lesions may resolve, some do undergo organization, producing additional increases in vascular resistance.

There are a variety of circumstances in which chronic decreases in regional pulmonary perfusion are accompanied by the ultimate development of generalized pulmonary hypertension. These include unilateral pleural disease,\(^14\) multiple regional stenoses of the pulmonary artery,\(^15\) and regional pulmonary artery coarctation.\(^16\)

It has been suggested that the development of pulmonary hypertension is related to the elabora-
tion of a humoral agent from the hypoperfused lung segments.\textsuperscript{14} A similar sequence of events in the kidney was designated the "Goldblatt kidney" and led to the identification of the renin-angiotensin system. Although pulmonary "renin" has not been identified, this sequence of events might be described as the "Goldblatt lung."

We conclude that pulmonary hypertension does beget pulmonary hypertension. Effective nonspecific measures to decompress pulmonary pressures might prevent some of the late vascular complications of this disorder.

**PULMONARY VENOUS OBSTRUCTIVE DISEASE**

The consequences of increased pulmonary venous pressure resulting from primary disorders of the heart have long been recognized. Disorders such as mitral stenosis and left ventricular failure are common causes of pulmonary venous hypertension. However, primary disorders involving pulmonary veins, independent of cardiac disease, have not been the focus of intense study. There are several major pathophysiologic consequences. One is the development of pulmonary capillary hypertension leading to transudative pulmonary edema because of the unbalancing of Starling forces across the pulmonary capillary wall. Thus, obstructive diseases of the pulmonary veins can produce transudative pulmonary edema despite normal cardiac function. Pulmonary venous disease leads to pulmonary arterial hypertension related to increased pressures generated proximal to the obstruction, to the development of a more positive interstitial pressure related to interstitial pulmonary edema, and to alveolar hypoxia. This leads to increased pressure work of the right ventricle and may lead to right ventricular failure.

Table 1 classifies the basic primary pulmonary venous obstructive diseases on an etiologic basis. There are a number of disorders which produce structural obstruction of pulmonary veins. The prototypic disorder is pulmonary veno-occlusive disease. This is a disorder of unknown etiology in which there are diffuse intimal obstructive lesions in many small sized branches of the pulmonary venous system. The cause is unknown. The clinical picture includes severe progressive pulmonary edema and progressive pulmonary hypertension with ultimate right heart failure. Wedge pressures tend to be normal because the major site of involvement is venular and proximal to confluence of pulmonary veins. Thus, there is the development of a substantial pulmonary capillary—"large" pulmonary vein gradient. Wedge pressures, which measure large pulmonary vein pressure distal to the site of obstruction, may be normal.\textsuperscript{17} Pulmonary veins may occasionally be the site of endophlebitis, leading to pulmonary edema. Depending on the site of involvement, wedge pressures may be normal or high. Tumor obstruction of pulmonary veins, producing extensive compression of large-sized pulmonary veins, can result in pulmonary edema. A similar sequence has been described with fibrosing mediastinitis. Pulmonary veins may undergo thrombosis in situ. This, for example, is seen during transplant rejection of the lungs. Finally, there may be congenital absence of some branches of the pulmonary venous system.

Disorders associated with functional obstruction of pulmonary veins have only recently been considered as an important pathogenetic mechanism for pulmonary edema. In some patients with acute myocardial infarction there may be the development of acute pulmonary edema with normal wedge pressures. It may be speculated that the injured myocardium released mediators which specifically cause pulmonary venular constriction.

The pulmonary edema associated with pulmonary embolism and normal wedge pressures may also be caused by mediator release from the surface of clots.\textsuperscript{18}

It may be speculated that a variety of other disorders of the lungs will be described in the future which have as their common denominator increased flow resistance in the pulmonary venous system.

**DIRECT PULMONARY ARTERY TO PULMONARY VEIN SHUNTS**

The term "shunt" has been widely adopted and in the jargon of the chest physician describes the entry of mixed venous blood into the arterial circulation without exposure to alveolar air. In most patients, this occurs because of non-ventilated alveoli, and there is no direct anatomic communication between pulmonary arteries and pulmonary veins.

We have shown that, at least in severe liver disease, there is another kind of lung shunt. This
Shunt consists of direct anatomic connections between branches of the pulmonary artery and veins. These shunt vessels are at least 30 to 60 micra in diameter, and as much as 50 percent of the cardiac output may flow through these vessels.\textsuperscript{19} Shunt vessels may be detected by using a modified lung perfusion scan in which the deposition of both pulmonary and extrapulmonary radioactivity are measured. Macroaggregates with diameters between 30-60 micra are injected into the right side of the circulation. These particles cannot pass through pulmonary capillaries which are about 8 micra in diameter (Fig 4). In patients with shunt vessels greater than 30-60 micra, the aggregates pass through the shunts to the left side of the circulation and are deposited in extrapulmonary sites and can be detected by appropriate scanning technique.

In the normal subject, less than 7 percent of radioactivity can be detected in extrapulmonary sites. In patients with true vascular shunts, there is significantly higher deposition of extrapulmonary radioactivity. The major pathophysiologic consequences of these vessels is the development of arterial hypoxemia and the presence of true vascular shunts is presumably a major cause of arterial hypoxemia in the 40 percent or so of cirrhotics with low arterial $O_2$ tensions.

The existence of these shunt vessels in liver disease poses a number of intriguing questions. One is whether similar pulmonary artery-to-pulmonary vein communications are present in the normal lung. The data are conflicting. Beads up to 500 $\mu$m in diameter injected into the pulmonary artery were recovered from pulmonary venous blood in several studies.\textsuperscript{20} Using morphologic methods or corrosion casts, some workers found small anastomotic channels in small number\textsuperscript{21} in the normal lung, while other workers could not demonstrate any at all.\textsuperscript{22} It is possible to estimate that if such channels do exist in the normal lung, they are physiologically inconsequential as the upper limit of flow through them must be less than 7 percent of the total cardiac output.

A second question is whether such shunts exist in the normal lung in a collapsed state and only become physiologically important when a given critical opening pressure is exceeded, say with pulmonary hypertension. There is no clearcut answer to this question.

A third question is whether there are disease states, in addition to liver disease, that cause such shunts to develop. Unexplained arterial hypoxemia is found in patients with bronchogenic carcinoma, with kyphoscoliosis, and with pulmonary embolism. Perhaps systematic studies in such patients would extend the list of disease states associated with this form of shunt.

Perhaps the most interesting question of all is what regulates flow resistance and pressure in these shunt vessels. It does seem clear that the resistance to flow (through these shunt vessels) is low, since these patients appear to have low or normal pulmonary artery pressures despite marked increase in cardiac output.\textsuperscript{19}

A clue to the regulation of the hemodynamics of these vessels comes from the work of Daoud et al.\textsuperscript{23} They noted that the inhalation of hypoxic gas mixtures did not evoke pulmonary vasoconstriction in a group of cirrhotic patients. They speculated that cirrhosis was associated with altered metabolism of a chemical agent responsible for HPV. There is a much simpler and, therefore, more appealing explanation of these results (Fig 5). Assume that the shunt vessels are derived from and regulated as systemic vessels and not as pulmonary blood vessels. During hypoxia there would be pulmonary arteriolar vasoconstriction, but vasodilation of the shunt vessels with a relative increase in flow through the
shunt vessels and no increase in total pulmonary vascular resistance. The “failure” of pulmonary vasoconstriction, therefore, suggests (to me) that the shunt vessels may be regulated like systemic vessels. If so, it would seem that if we understood the regulation of pulmonary hemodynamics in severe liver disease, then we would understand the mechanism of hypoxic pulmonary vasoconstriction. We have thus come full circle, and it is time to conclude.

A specific summary of such a diffuse talk might list the following conclusions:

1. We do not know the mechanism of HPV, but continued search for the Yin of PACS and the Yang of PADS should be rewarding.
2. Pulmonary vasospasm does exist and is a major factor in many lung diseases.
3. Pulmonary hypertension begets additional pulmonary hypertension, which explains the progressive nature of pulmonary hypertension in many patients.
4. Intrinsic obstructive disorders of pulmonary veins are involved in some forms of pulmonary edema.

5. True vascular shunts between pulmonary arteries and pulmonary veins are found in severe liver disease and may be present in other disorders. Understanding the regulation of flow through these vessels could provide major insight into the normal regulation of the pulmonary circulation.

For those of you who may feel discomforted, I can only quote Charles Darwin:

“Many of the views which have been advanced are highly speculative, and some, no doubt, will prove erroneous; but I have, in every case, given the reasons which have led me to one view rather than to another . . . False facts are highly injurious to the progress of science, for they often endure long; but false views, if supported by evidence, do little harm, for everyone takes a salutory pleasure in proving their falseness . . .”

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REFERENCES

References may be obtained by writing to the author.