Ischemic Lung Disease, including a New Look at $V_A/Q_c$

Decreases in regional blood flow (ischemia) relative to metabolic requirements is an area of considerable importance. Ischemia in the systemic circulation results in limitations of both $O_2$ and substrate supply, thereby altering cell tissue and organ function. Studies of systemic ischemia have provided substantial insight into the pathophysiology of a variety of vascular diseases.

The possible impact of reduced pulmonary blood flow (the ischemic lung) on the metabolism of lung cells has received scant attention. The major function of the lung is gas exchange and most studies of reduced pulmonary blood flow have focused on the impact of this alteration on pulmonary gas exchange. There is net addition rather than net removal of $O_2$ in pulmonary capillaries and it is easy to forget that there are $O_2$-requiring cells in the lung.

The design of the lung has a number of special features which tend to minimize the impact of reduced blood flow on lung metabolic processes.

The $O_2$ requirements of lung cells are relatively small as compared to total $O_2$ uptake. Moreover, $O_2$ requirements by lung cells do not increase appreciably during peak performance (maximal exercise). As lung cells compete, as it were, with all other cells for $O_2$, this helps insure an adequate $O_2$ supply for nonpulmonary tissues. This, however, tends to obscure the intrinsic requirements of lung cells for $O_2$.

As compared to other cells, lung cells show an unusual pattern of dependence on the circulation. $O_2$ can be supplied directly by diffusion from alveolar air. Thus, $O_2$ supply may be virtually independent of $O_2$ supplied by the circulation. $O_2$ supplied by alveolar air would be maximized by augmented ventilation. Loss of perfusion is deleterious to pulmonary gas exchange, but may be excellent for lung cell $O_2$ supply.

On the other hand, like other cells, lung ischemia limits substrate delivery by the circulation to lung cells. An analysis of the impact of altered ventilation-perfusion ratios in the lung from the metabolic standpoint (metabolic $V_A/Q_c$) would show the following:

<table>
<thead>
<tr>
<th>$V_A$ intact increased</th>
<th>Substrate</th>
<th>$O_2$ Supply</th>
<th>Supply</th>
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<tbody>
<tr>
<td>$Q_c$ reduced or absent</td>
<td>Maintained</td>
<td>Reduced</td>
<td></td>
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<tr>
<td>$V_A$ decreased to absent</td>
<td>Decreased</td>
<td>Maintained</td>
<td></td>
</tr>
<tr>
<td>$Q_c$ decreased to absent</td>
<td>Decreased</td>
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Knowledge of the substrate requirements of various lung cells is scanty. The lung as a whole has an unusually high rate of lactate generation suggesting a high rate of aerobic glycolysis. Two lung cell types, pulmonary artery endothelial cells and lung epithelial cells, show high rates of aerobic glycolysis. Given an obligatory requirement for carbohydrate in the process of glycolysis, the high rate of substrate utilization required for ATP generation by glycolysis and the relative lack of glycogen in the lung, it would be anticipated that the delivery of glucose by the circulation would be particularly important in the lung as compared to other organs.

The lung as compared to most other organs has a dual circulation and the existence of a bronchial circulation provides an alternative source for $O_2$ and substrate delivery by the circulation. However, the precise contribution of the bronchial circulation to lung cell viability under conditions of reduced pulmonary blood flow is not known. It does seem clear that the bronchial circulation is not required for near normal lung function. For example, in human heart-lung transplantation, there is at least acute loss of bronchial blood flow. Despite this, lung cell viability is not compromised and even structures normally supplied by the bronchial circulation remain intact. This is at least true under conditions of normal ventilation and normal pulmonary blood flow. What occurs should there be impairment of ventilation or perfusion is unknown.

A special area of interest involves the various metabolic functions of the lung which do not subserve energy metabolism. A wide variety of metabolic transformations occur in the lung. A number of these are $O_2$-requiring and some undoubtedly process substrates which are delivered by the circulation. As the lung processes the entire cardiac output per heart beat, this system seems well designed, but these metabolic processes would be particularly vulnerable to decreases in pulmonary blood flow. The lung contains a variety of oxygenases and oxidases involved in other than bienergetic pathways. How these pathways are influenced by reduced blood flow and how such changes influence the metabolism of nonpulmonary organs is not clear.

It therefore appears that the lung does require blood flow to preserve its own normal metabolic function, but is relatively resistant to ischemia because of special features of lung structure and function. However, there are a number of specific clinical phenomena which suggest the importance of maintained pulmonary blood flow or suggest undescribed mechanisms for preserving lung cell viability despite reduced or absent pulmonary blood flow.
PARENCHYMAL ABNORMALITIES IN (PRIMARY) 
PULMONARY HYPERTENSION

A variety of forms of pulmonary hypertension are associated with direct nonvascular abnormalities of lung function and abnormalities of lung gas exchange. Dyspnea is common, arterial hypoxemia in the absence of cardiac shunts is exceedingly common, measurements of "small airway" function are usually abnormal, and restrictive pulmonary mechanics are not unusual. Why should parenchymal function become abnormal as a result of vascular disease? It is tempting to ascribe the development of abnormal nonvascular pulmonary function to chronic reductions in pulmonary blood flow. These would occur because various cell types involved in normal pulmonary function become either substrate or O2 deprived.

TRAUMATIC BRONCHIAL RuptURE WITH 
CHRONIC ATELECTASIS

The reverse problem is posed in patients with traumatic rupture of a bronchus. In these patients there may be the development of chronic atelectasis. Lung segments so affected suffer loss of ventilation and presumably blood flow from the pulmonary circulation must be low or absent because of high pulmonary vascular resistance. Despite this, repair of the affected bronchus even after years results in re-expansion of the lung which (in the absence of infection) then seems to function in a reasonably normal fashion. The simplest explanation is that the atelectasis area continues to be supplied at least at a low level by the bronchial circulation. This is speculative and how O2 supply and substrate delivery are maintained during the period of chronic collapse is not clear.

PULMONARY INFARCTION

Irreversible changes in pulmonary tissue following acute loss of pulmonary blood flow is relatively rare. The basis of the usual continued viability of lung cells despite loss of pulmonary blood flow is not entirely clear. Occlusion of large pulmonary artery segments does not usually lead to infarction, nor does occlusion of very small pulmonary artery branches (microocclusion). The basis of these differences is not entirely clear. One factor may be that midsized pulmonary arteries may lack extensive collateral supply from the bronchial circulation. The tendency for infarction to occur seems to increase in areas of pre-existing or co-existing pulmonary disease. Left ventricular failure may also promote infarction, possibly by decreasing bronchial blood flow.

SHOCK LUNG

The pathogenesis of shock lung is not clear. It is well known that in systemic cells, decreased O2 delivery and reduced substrate delivery produce striking changes in cell function. It has recently been suggested that similar changes occur in the lung during shock. Shock usually reduces both pulmonary and bronchial blood flow, as well as the circulatory supply of a number of blood-borne substrates. These alterations presumably would lead to nonspecific injury to a variety of lung cells and initiate the sequence leading to shock lung.

Despite the inadequate nature of our knowledge, it is probably not premature to suggest that ischemia in the lung (ischemic lung disease) is associated with important metabolic abnormalities and that studies of lung cell metabolism under conditions of reduced pulmonary blood flow will provide important new approaches to the understanding and management of pulmonary vascular disease.

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Subtype-Specific Pharmacology
The Magic and the Myth

Thirty-four years ago, Ahlquist concluded that divergent responses of the sympathetic nervous system could be described in terms of two types of adrenergic receptors, alpha and beta. Activation of alpha-adrenergic receptors resulted in constriction of blood vessels, while stimulation of the beta-adrenergic receptor increased heart rate and myocardial contractility. Consistent with most biologic systems, however, the response to various sympathomimetic drugs and blocking agents does not demonstrate absolute specificity. Epinephrine, an endogenous circulating catecholamine, possesses roughly equivalent alpha- and beta-adrenergic activity. Norepinephrine, the endogenous sympathetic neurotransmitter, causes contraction of vascular smooth muscle (alpha-adrenergic effect) but relaxation of airway smooth muscle (beta-adrenergic effect). The synthesis of isoproterenol ushered in an era of "specific" sympathomimetic drugs, but it was readily apparent that the beneficial beta-adrenergic bronchodilator effects of isoproterenol could not be separated from the undesirable cardiotimulatory effects of the drug. Likewise, the widespread use of beta-adrenergic blocking agents for treatment of cardiac, hypertensive, neuropsychiatric, endocrine, and ophthalmologic diseases has produced severe bronchospasm in some asthma patients and patients with chronic obstructive pulmonary disease.

In recent years, the concept of the beta-adrenergic receptors has been modified by the observation that some analogs of beta-adrenergic agonists and blocking agents caused "selective" activation of inhibition of the receptor at different anatomic sites. Beta-adrenoceptors have now been classified as beta1 (heart) and beta2 (lung). Accordingly, terbutaline, salbutamol (albuterol), and several other congeners have been shown to cause "selective" beta2-adrenergic stimulation, while metoprolol and atenolol have been touted as cardioselective beta1-blocking agents.

The subtype-specific approach to the treatment of a number of cardiac and pulmonary diseases is a clinical frontier. Neither the perfect beta1-adrenergic agonist nor the absolutely selective beta2-adrenergic antagonist exists today. Metoprolol, a selective beta1-antagonist, can cause substantial bronchospasm in asthma patients. This is because of the high relative density of beta-adrenoceptors in the lung and the beta1-selectivity of metoprolol is not absolute.

Terbutaline and albuterol cause selective (beta2-adrenergic mediated) airway relaxation when inhaled by nebulizer. However, tachycardia and cardiac arrhythmias may occur after oral ingestion of these drugs, partly from reflex cardiac stimulation resulting from beta2-adrenergic induced relaxation of vascular smooth muscle and partly from direct beta1-adrenergic activity of these drugs. Furthermore, as additional methyl groups are added to the amine end of the catecholamine molecule (providing greater beta2-adrenergic specific activity), the potency and intrinsic activity of the beta2-adrenergic agonists declines. One cannot be absolutely certain that specific beta2-adrenergic activity is desirable, as this could lead to augmented peripheral vascular dilation (a beta2-adrenergic effect) with augmented reflex-mediated beta1-adrenergic effects. This is precisely what one is trying to avoid by administering agonists which possess minimal direct beta1-adrenergic activity.

The point is that the concept of lock-and-key drug membrane receptor model is an oversimplification. Specificity is relative, and at present, "cardioselective" beta-adrenoceptor blockade cannot be achieved. A new generation of subtype-specific drugs may still lead to encounters with some old and familiar problems—those which we have already seen in this generation of cardiac and pulmonary patients.

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