Non-ventilatory functions of the lung—Influence on the cardiovascular system

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This article affords the reader an understanding of the ability of the lungs to affect concentrations of potent vasoactive hormones in circulating blood, enumerates situations in which this ability may be altered, and examines the possible consequences of such alterations in circulating vasoactive hormones.

Although concerned primarily with gas exchange, the lungs have other functions which are unrelated to ventilation. The cells and enzyme systems of the pulmonary vascular bed change the biological activity of a variety of substances presented to them via the pulmonary circulation. The lungs have the ability to clear certain vasoactive hormones from the pulmonary blood and to synthesize or activate others, which then enter the blood leaving the pulmonary circulation. Thus, the lungs can alter arterial blood concentration of vasoactive compounds.

Evidence for the role of the lung in modifying circulating vasoactive substances can be found in the literature dating back to the first quarter of this century. Starling and Verney recognized the metabolic role of the lung, as indicated by their experiments on the formation of urine in which an isolated lung was included in the system to prevent vasoconstriction in the isolated perfused kidney. Page later demonstrated that extracts of lung tissue could inactivate a "serum vasoconstrictor substance" which was eventually identified as serotonin.

Only recently, however, have there been detailed investigations on the ability of the lung to remove certain vasoactive substances. Clearance of such vasoactive substances is now recognized as an important pulmonary function that can be altered in certain disease states and be influenced by drug treatment.

Vasoactive substances metabolized at the pulmonary endothelial surface without uptake from the plasma

Bradykinin, a potent vasodepressor kinin, is formed in the blood by a series of reactions. The first step is the activation of one of the kallikreins, a specific proteolytic enzyme that acts on plasma kininogen to yield bradykinin and other kinins. The kinins are powerful substances which can cause vasodilation, increased vascular permeability, and contraction of certain vascular smooth muscles. Activation of bradykinin can occur in a variety of conditions including pulmonary edema, anaphylaxis, and endotoxic and hemorrhagic shock. Without participation of lung tissues in the removal of bradykinin from the circulation, its destruction by blood alone would result in a half life shorter than two circulation times. Ferreira and Vane found that bradykinin infused into the right atrium is largely destroyed in the few seconds it takes the blood to reach the aorta, suggesting...
that bradykinin is somehow inactivated by the pulmonary circulation.\textsuperscript{5}

Anatomical evidence has shown that bradykinin is inactivated by enzymes on or very close to the innermost surface of the endothelial cells which line the pulmonary vasculature.\textsuperscript{4} There are vesicles opening to the lumen (caveolae) containing structural components which may represent clusters of enzymes involved in the hydrolysis of bradykinin. The enzymes involved in this degradation differ from those degrading bradykinin in the blood and kidney.\textsuperscript{6} Adenosine nucleotides may also be inactivated in the same manner by exposure to the luminal endothelial surface.

In contrast to bradykinin, angiotensin I is activated to angiotensin II which is the most potent hypertensive agent known. Angiotensin II has 10-50 times the pressor activity of angiotensin I in the systemic circulation. Enzyme renin, when released by the juxtaglomerular cells of the kidney, reacts with a plasma glycoprotein, angiotensinogen, to form angiotensin I. Angiotensin I is a decapeptide which is a relatively inactive pressor substance. When introduced into the venous system a considerable fraction of it is converted to angiotensin II by the time the blood has reached the systemic circulation.\textsuperscript{7}

The converting enzyme for angiotensin I has long been known to exist in the plasma, but the enzyme's plasma activity is too low to account for this rapid conversion. The converting enzyme forms angiotensin II by specifically cleaving off the C-terminal dipeptide. This conversion is now known to take place mostly in the lung where the converting enzyme activity is higher than in any other organ. Some extrapulmonary conversion can occur, but peripheral tissues seem to be more concerned with inactivating angiotensin II. In the lungs the converting enzyme for angiotensin I appears to be bound to the cell membrane surface, whereas in the vascular endothelium the converting enzyme seems to be intracellular and therefore, less accessible to the plasma.\textsuperscript{8} The different handling of the angiotensin I by the vascular beds of the systemic circulation and pulmonary circulation suggests that endothelial functions may not be the same in different parts of the body.

It is now believed that the converting enzyme for angiotensin I in the lungs is identical with the enzyme kininase that inactivates bradykinin. Angiotensin I and bradykinin, hormones which have opposite effects on blood pressure, have these points in common with regard to pulmonary metabolism:

1. Both angiotensin I and bradykinin disappear almost completely from the blood in one pass through the lungs.
2. Both conversions apparently take place on the luminal surface of the pulmonary endothelial cell.
3. Factors such as certain snake venoms which potentiate the action of bradykinin also inhibit the conversion of angiotensin I to angiotensin II.

Consistent with these findings a converting enzyme has been isolated from the lung that converts angiotensin I to angiotensin II and also inactivates bradykinin.\textsuperscript{9}

The ability of the lungs to eliminate a hormone which lowers the blood pressure (bradykinin), while also forming a hormone which raises the blood pressure (angiotensin II), suggests that the lungs may play a role in blood pressure regulation. The clinical importance of these actions is illustrated by the successful treatment of some forms of hypertension by the drug captopril, an orally active inhibitor of angiotensin I converting enzyme.

Due to the location of the lungs within the circulation and the characteristics of their normal function, it seems evident that the lungs have the capacity to vary the amount of angiotensin II and bradykinin entering the systemic arterial circulation. The lungs receive the entire cardiac output, which can vary from 5-7 L/min at rest up to 40 L/min during strenuous exercise. Not all lung capillaries are open at one time. Because the angiotensin I converting enzyme is located on the luminal surface of the pulmonary endothelial cell, the factors influencing the circulating amounts of angiotensin II and bradykinin include vascular surface area, caliber of vessels, rates and distribution of pulmonary blood flow, and arterio-venous shunting.

**Vasoactive substances metabolized intracellularly after uptake from plasma**

Serotonin (5-hydroxytryptamine) is a biogenic amine found in a variety of cells including platelets (8-9\%), brain neurons (1-2\%), and intestinal chromaffin cells (90\%). Serotonin is important in the functioning of platelets in blood coagulation, as a neurotransmitter in the central nervous system, and in vascular smooth muscle as a potent vasoactive substance. Approximately 65\% of the quantity injected into the right atrium disappears in a single circulation through the lung.

Strum and Junod\textsuperscript{11} found that carrier-mediated serotonin uptake in the lungs was localized to
the endothelial cells and that uptake was dependent on sodium potassium ATPase activity. Inside the pulmonary endothelial cell serotonin (5-HT) is metabolized to 5-hydroxyindoleacetic acid (5-HIAA) partially by monoamine oxidase.

The clinical significance of pulmonary uptake and metabolism of serotonin is manifold. Grubly and associates have postulated that inhibition of 5-HT uptake may increase plasma serotonin levels and thus cause venous thrombosis by platelet aggregation. This may occur during cardiopulmonary bypass. Tricyclic antidepressants also inhibit the uptake of serotonin and norepinephrine in the lungs so that appreciable quantities gain access into the systemic circulation.

A second vasoactive substance taken up and metabolized by the lung is norepinephrine. The pharmacological effects of norepinephrine disappear rapidly after intravenous injection. About 25% of norepinephrine is removed in one circulation through the lungs in anesthetized man. The site of norepinephrine uptake is distinct from that responsible for serotonin uptake since neither amine influences the pulmonary uptake of the other. It is possible pharmacologically to block the action of norepinephrine and not serotonin and vice versa. The clinical implications of pulmonary uptake of norepinephrine are seen in lung disease where the endothelial cells are damaged and uptake is inhibited, resulting in elevated circulating levels of norepinephrine which can lead to hypertension.

The lungs are a major site for enzymatic inactivation of prostaglandins E and F after uptake by the pulmonary endothelial cell. Prostaglandin A is relatively unaffected by pulmonary metabolism.

### Vasoactive substances synthesized within the lung and released to the blood

The membranes of all cells contain arachidonic acid which is synthesized from linoleic acid, an essential fatty acid present in food. Arachidonic acid is metabolized to prostacyclin (PGI2), prostaglandin (PGE2, PGE1, PGD2) or thromboxane. These prostaglandins are synthesized by a multi-enzyme complex referred to as prostaglandin synthetase which is present in relative abundance in the lung.

Prostaglandin E2 (PGE2) is a potent vasodilator substance which is released during the anaphylactic response and may contribute to the hypotension seen in this condition. Prostaglandin F (PGF) constricts blood vessels and bronchi and raises the arterial blood pressure. It has been found that mechanical stretching of the lung leads to discharge of large quantities of prostaglandins, mostly PGE2.

In an effort to see whether pulmonary release of PGE2 was sufficient to contribute to the hypotension seen with mechanical ventilation, Kita-mura and associates monitored arterial blood pressure both before and after large doses of aspirin (a PGE inhibitor) during mechanical ventilation. The results suggest that from 30% to 40% of the fall in blood pressure with positive pressure hyperinflation and hyperventilation could be mediated by prostaglandin E2. Thus, it appears that part of the fall in blood pressure, exclusive of the mechanical impediment to venous return, may arise from the release of prostaglandin E2 by mechanical stretching.

### Physiological consequences of the metabolic pathways of vasoactive substances in the lung

The physiological significance of pulmonary metabolic function has not been assessed fully. The pulmonary circulation, which receives all of the cardiac output, is well fitted to monitor and control levels of circulating vasoactive hormones and thus influences cardiovascular responses produced in the arterial circulation.

As stated previously, norepinephrine and serotonin are removed from the pulmonary circulation in man. Defects in pulmonary metabolism of these hormones may be implicated in some clinical conditions. For example, venous thrombosis following cardiopulmonary bypass surgery could be due to platelet aggregation resulting from failure to clear serotonin from venous plasma.

The anesthetic gases halothane and nitrous oxide inhibit pulmonary removal of norepinephrine in the isolated rabbit lung and halothane abolishes inactivation of norepinephrine in dogs. These findings could have clinical significance not only due to the fact that halothane allows a higher concentration of amines to reach the arterial circulation but because halothane also sensitizes the myocardium to circulating catecholamines.

The physiological roles of prostaglandin E and F metabolism and synthesis by the lung are still unclear, but there seems to be no doubt of their pathological significance. There is experimental evidence that prostaglandins are released from the lung by various stimuli, and it has been suggested that the bronchial constrictor effect of PGF2 may play a role in bronchial asthma. If for some reason inactivation of prostaglandins by the
lung is diminished, their accumulation could have a pharmacological effect. It has been demonstrated that prostaglandin plasma levels are elevated in endotoxin shock, secondary to an impaired degradation mechanism. This may account for some of the circulatory changes such as hypotension seen with this condition. As mentioned earlier, PGE₂ synthesis also has been implicated as a cause for the hypotension occurring during mechanical ventilation with large tidal volumes.

There is little data on the physiological or pathological consequences of the alterations in the ability of the lung to inactivate bradykinin and form angiotensin II. But conditions such as total lung bypass during cardiac surgery, pulmonary embolus, and emphysema (where the lung microcirculation is compromised or obliterated) may have cardiovascular changes due to the interruption of this enzymatic pulmonary metabolic pathway.

Questions still remain about the cardiovascular effects of the pulmonary metabolism of vasoactive hormones. Does the lung have a role in the control of blood pressure? Despite the uncertainty, one point can be made without reservation: The lung is more than an intricate mechanical ventilator for gas exchange. It has considerable influence on the metabolic function of the body as a whole.

REFERENCES


AUTHORS

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