THE INFLUENCE OF HYPOXIA ON THE PULMONARY MICROCIRCULATION

FINAL REPORT

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I. Summary of Progress

The objective of this research has been to study the effect of hypoxia on the pulmonary microcirculation. It has been well established that the pulmonary circulation has a vasopressor response to airway hypoxia. However, there is controversy over which vessels account for the increased resistance to blood flow. From the literature, it seems entirely possible that there is both a pulmonary arterial and a pulmonary venous component to this response. There is also evidence indicating that part of the response is intrinsic to the lung itself and another part is mediated by the sympathetic nervous system.

A large part of the confusion stems from the inability of available techniques to resolve adequately the components of the pulmonary microcirculation under in vivo conditions. For this reason, we developed a technique of implanting a transparent window in the chest wall of the dog to permit direct visualization of the pulmonary microcirculation. Considerable effort was devoted to the successful development of a system for arresting movement of the surface of the lung during spontaneous respiration. It was then possible to study the microcirculation using a surface illuminating microscope at magnifications up to oil immersion. It was also possible for us to control the animal's physiological condition such that his blood gases, blood pressures, and cardiac output were within normal limits during control conditions. Observation of the microcirculatory flow patterns, the microscopic appearance of the tissue, and conventional histologic preparations of the tissue immediately under the window all indicated that the microscopic field we were studying was functioning normally.

THE EFFECT OF HYPOXIA ON THE MICROCIRCULATION

One of the changes we noted during the administration of hypoxic gas mixtures was an increase in the number of perfused capillaries. In order to
quantitate the number of recruited capillaries, a method was developed for
taking motion pictures of the lung at a wavelength corresponding to the
maximum hemoglobin absorption band. This system produced pictures which
rendered the single red blood cells in sharp contrast to the surrounding
lung tissue. By projecting these images onto appropriate grids, we have been
able to determine with reasonable precision the change in capillary density
using well established stereologic techniques.

Results thus far indicate that previously unperfused capillaries become
perfused with blood during hypoxia. The recruitment occurs both in the
upper portions of the lung (zone 2), and to a lesser extent, in the dependent
lung (zone 3). We were not able to correlate the capillary recruitment
response to changes in cardiac output or to the magnitude of the rise in
pulmonary artery pressure accompanying hypoxia. Because left atrial pressure
was unchanged in our animals during hypoxia, the implication was that con-
striction in pulmonary veins accounted for the recruitment.

We have recently made a considerable effort to develop a reliable
technique for measuring the pulmonary vein to left atrial pressure gradient.
It is hoped that this technique will provide a positive correlation between
an elevation of pulmonary vein pressure and capillary recruitment. If this
correlation can be demonstrated, a technique will be available that will
permit study of venomotor events in the lung. Because there are few methods
available for these kinds of studies, a number of pharmacological experiments
on the pulmonary veins can be made to determine the nature of the control
of their response to hypoxia (sympathetic? α? β? etc.)

VASOMOTION IN THE PULMONARY MICROCIRCULATION

Our initial objective in the development of the thoracic window technique
was to determine visually which vessels constricted with hypoxia in the lung.
We have not been able to demonstrate constriction of any kind in arterioles, capillaries, or venules during hypoxia. A possible explanation for this is the histologic absence of smooth muscle in vessels of the size that lie on the surface of the lung (<100 microns).

A protocol was designed to demonstrate whether constriction or dilation was present in arterioles or venules under a wide variety of conditions: (1) Norepinephrine was infused in an attempt to cause constriction. This drug approximately doubled pulmonary vascular resistance in quantities that we used. (2) Blood pressure in the arterioles and venules was passively raised by elevating left atrial pressure. This was accomplished by an occlusion device placed around the ascending aorta. It was possible to make steady-state studies with left atrial pressure being as high as 30 torr. (3) Finally, isoproterenol was infused in sufficient quantities to double cardiac output in an attempt to see whether increased flow would cause a change in the caliber of the small vessels.

To our surprise, none of these maneuvers caused any visible caliber change in arterioles or venules. We did, however, see marked changes in capillary perfusion. All three maneuvers caused recruitment of new capillaries. The recruitment response was: increased $P_{\text{la}} >$ increased $P_{\text{Pa}}$ (norepinephrine) $>$ increased cardiac output (isoproterenol).

From these pilot studies it would appear that the capillaries are very sensitive to changes in pressure within them and respond by recruiting new capillaries for blood to flow through. The arterioles and venules, however, do not constrict or dilate under these conditions.

THE EFFECT OF POSITIVE ALVEOLAR PRESSURE ON THE PULMONARY MICROCIRCULATION

The effect of increased $P_A$ was studied on the top of the lung at a point approximately 15 cm above the heart (zone 2). A single positive pressure
breath was given in the form of a transient square wave. At a $P_A = 10 \text{ cm H}_2\text{O}$ capillary pressure still exceeded $P_A$ so blood flow continued, although at a diminished rate. Raising $P_A$ to $20 \text{ cm H}_2\text{O}$ caused a marked slowing of flow. When $P_A$ was elevated to high levels ($> 60 \text{ cm H}_2\text{O}$), flow in the venules continued in the forward flow direction but was very slow; flow in the arterioles was reversed as blood was forced out of these vessels. When $P_A$ was reduced to atmospheric pressure, the flow patterns rapidly returned to normal. Thus, the pulmonary microcirculation seems to be extremely sensitive to alveolar pressure changes.

Observations on the lack of vasomotion in arterioles and venules but their sensitivity to alveolar pressure changes raise some interesting questions about compliance of the pulmonary vasculature and how it functions as a blood reservoir. It is not clear at this time why the arterioles and venules are so sensitive to alveolar pressure changes, but resist caliber alteration when pressure is varied from within. Additional points that require further investigation are how positive alveolar pressure effects phasic or temporal ventilation perfusion relationships and what the effect of intermittent positive pressure respiration might be on normal pulmonary microcirculatory flow patterns.
II. Publications


