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THE INFLUENCE OF HYPOXIA ON THE PULMONARY MICROCIRCULATION

FINAL REPORT

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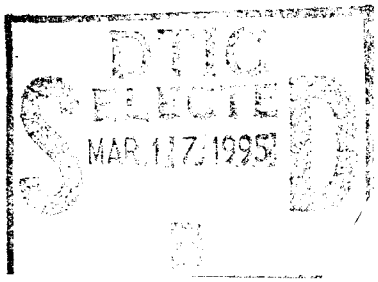

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I. Summary of Progress

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 constriction 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_{la} > increased P_{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 cm H_2O capillary pressure still exceeded P_A so blood flow continued, although at a diminished rate. Raising P_A to 20 cm H_2O caused a marked slowing of flow. When P_A was elevated to high levels ($\leq$ 60 cm H_2O), 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

1. Wagner, W.W. and Filley, G.F.: Cinemicrography of the in vivo lung (motion picture). Presented at:

   a) The 47th Ann. Meeting Fed. Amer. Soc. Exper. Biol., Atlantic City, 1963.
   b) The Ann. Meeting Amer. Assoc. Adv. Science, Cleveland, 1963.
   c) The Ann. Meeting Amer. Heart Assoc., Los Angeles, 1963.

2. Wagner, W.W. and Filley, G.F.: Cinemicrography of the in vivo lung. (abstract). Israel J. Exptl. Med., 11: 112, 1963.

3. Wagner, W.W. and Filley, G.F.: Microscopic observation of the lung in vivo. Vascular Dis., 2: 229, 1965.

4. Wagner, W.W., Barker, D.B. and Filley, G.F.: The bioengineering of cinemicrography of the lung in vivo. San Diego Biomedical Engineering Symposium 7: 95, 1967.

5. Wagner, W.W., Barker, D.B. and Filley, G.F.: A photographic method for quantitating blood flow in the pulmonary microcirculation. J. Biol. Photo. Assn., 35: 95, 1967.

6. Wagner, W.W.: Pulmonary microcirculatory observations in vivo under physiologic conditions. J. Appl. Physiol. 26: 375, 1969.

7. Wagner, W.W.: Interpretation of in vivo microscopic changes of the pulmonary microanatomy. Anes. and Anal. 49: 843, 1970.

8. King, E.G., Wagner, W.W., Ashbaugh, D.G.: Pulmonary microanatomical alterations after fat embolism. Amer. Heart Assn., Los Angeles, 1970.

9. King, E.G., Wagner, W.W., Ashbaugh, D.G., Latham. L.P. and Halsey, D.R.: Alterations in pulmonary microanatomy after fat embolism. Chest 59: 524, 1971.

10. Wagner, W.W., Latham, L.P. and Halsey, D.R.: The effect of hypoxia on the pulmonary microcirculation. In press. National Conference on Research Animals in Medicine, Washington, D.C., 1972.

11. Wagner, W.W. and Latham, L.P.: Vasomotion in the pulmonary microcirculation. IN: Small Vessel Angiography, Ed. S.K. Hilal, C.V. Mosby Company, St. Louis, Mo., 1973.

12. Wagner, W.W., Latham, L.P. and Halsey, D.R.: The effects of hypoxia and high alveolar pressure on the pulmonary microcirculation. Chest 63: 41S, 1973.