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Fishman A P. Respiratory gases in the regulation of the pulmonary circulation. *Physiol. Rev.* 41:214-80, 1961.
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In a critical review that draws heavily on personal experience, a strong case is made for the predominant role of passive over active mechanisms in the regulation of the normal pulmonary circulation and for intrapulmonary over extrapulmonary mechanisms in the vasomotor control of the pulmonary circulation. Hypoxia is identified as a potent vasoconstrictor and acidosis as an independent, often auxiliary, vasomotor mechanism. The vasomotor effect of carbon dioxide is attributed to the local acidosis that it affects. [The SCI® indicates that this paper has been cited in over 340 publications since 1961.]

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In the mid 1940s, Euler and Liljestrand[1] showed that changing the composition of inspired air can change pulmonary arterial pressure. They were not the first to do so, but they were the first to appreciate fully the implications of their observations. This understanding led them to propose that the respiratory gases operate locally within the lungs to balance automatically alveolar ventilation and blood flow. Their observations were made on open-chest, anesthetized cats; the time was not yet ripe for determining pulmonary blood flow or blood pH.

In 1949, when I came to Cournand's busy laboratory, the preoccupation was with intact, unanesthetized humans. Also, techniques were evolving rapidly for determining some of the parameters that Euler and Liljestrand had to assume, e.g., the cardiac output. Before I came to the laboratory, the observations of Euler and Liljestrand on the pulmonary hypertensive effects of acute hypoxia had been confirmed.[2] However, the results on humans were puzzling in that instead of increasing, as expected, the cardiac output decreased. During my first few months in the laboratory, before I became incorporated into the team efforts, I read the previous publications of the laboratory and was puzzled by the unexpected fall in cardiac output. Upon reviewing the original data books, I found that the arterial blood pH in those subjected to hypoxia was abnormally high, i.e., that they were hyperventilating. It turned out that the reason was a failure to achieve a steady state of the respiration and circulation before the measurements were made. This led to a paper[3] that clarified the problem, showed that cardiac output either remained unchanged or increased during acute hypoxia, and prompted a great deal of additional work on the effects of the respiratory gases on the pulmonary circulation. While doing so, I reviewed all the previous studies that I could find along the same line and became convinced that the literature was inconsistent, in large measure because of the artificial preparations that were being used. In contrast, our human subjects allowed us to investigate integrated response patterns.

The paper that appeared in 1961 provided a critical review of the experiments done since Euler and Liljestrand, pointing at discrepancies from our observations on the intact human. Therefore, it provided a comprehensive survey of all that had been done before and accounted for discrepancies in the light of our own experience. Moreover, by defining clearly the known and the unknown, particularly with respect to the intact organism, it indicated future directions that had to be followed to complete the puzzle. I believe that its value has been primarily in defining an important regulatory mechanism operating under natural conditions and in placing into proper perspective a wide assortment of animal experiments done under artificial experiments. As far as I can tell, neither the substance nor the arguments of the paper have been seriously challenged during the next 25 years and the information presented has served as a sturdy base for taking the next step in exploring the intimate mechanisms, at a cellular level, involved in the regulatory effects of the respiratory gases on the pulmonary circulation.[4] In this role, the article is still timely as an underpinning for studies currently under way around the world.

1. **Euler U S V & Liljestrand G.** Observations on the pulmonary arterial blood pressure in the cat. *Acta Physiol. Scand.* 12:301-20, 1946. (Cited 215 times since 1955.)
2. **Motley H L, Cournand A, Werko L, Himmelstein A & Dresdale D.** The influence of short periods of induced acute anoxia upon pulmonary artery pressures in man. *Amer. J. Physiol.* 150:315-20, 1947. (Cited 240 times since 1955.)
3. **Fishman A P, McClement J, Himmelstein A & Cournand A.** Effects of acute anoxia on the circulation and respiration in patients with chronic pulmonary disease studied during the "steady state." *J. Clin. Invest.* 31:770-81, 1952. (Cited 145 times since 1955.)
4. **Fishman A P.** Pulmonary circulation. (Fishman A P & Fisher A B, eds.) *Handbook of physiology. Section 3: the respiratory system. Volume I: circulation and nonrespiratory functions.* Bethesda, MD: American Physiological Society, 1985. p. 93-166.

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