Chapter 1

Physiological Function of Hypoxic Pulmonary Vasoconstriction

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1. Introduction

Hypoxic pulmonary vasoconstriction (HPV) clearly has a role in reducing perfusion through the lung in utero to enhance \( O_2 \) delivery to the systemic circulation. It may also have a role in adults to improve the balance of blood perfusion to ventilation in the lung to optimize gas exchange, although some have suggested that this is a vestigial response (17). This chapter will look at the physiological role of HPV in the fetus and the adult.

2. History of Hypoxic Pulmonary Vasoconstriction

Investigators from as early as the 1930s were aware that men at altitude in the Andes mountains had an enlarged right heart as seen by electrocardiogram, chest X-ray and autopsy compared to men at sea level (29, 34). This was thought to be due to hypoxia, “anoxica anoxia”. How the right heart became hypertrophied was unclear until the recognition in 1946 that pulmonary vessels constricted to hypoxia (46). von Euler and Liljestrand were exploring the regulators of pulmonary blood flow in cats into which they had implanted a rigid tube and flange through the side of a pulmonary artery to measure pulmonary artery pressure. In 9 cats they measured a mean pulmonary artery pressure of 17 mmHg when the cats spontaneously inhaled air or were artificially ventilated. They noted that when the cats were ventilated with 10-11\% \( O_2 \) that there was a distinct rise in pulmonary artery pressure. They did not measure cardiac output with hypoxia but did note only a small rise in pulmonary artery pressure with occlusion of one main pulmonary artery, causing double the blood flow to the remaining right lung, or only a modest rise in pulmonary artery pressure with muscular exercise. They felt the rise in pulmonary artery pressure when the cats received hypoxic ventilation was out of proportion to the rise seen with the flow-
induced change in pulmonary artery pressure, suggesting a direct effect of hypoxia to constrict the pulmonary vessels. They also examined CO$_2$ and found a lesser response. CO$_2$ may enhance HPV more than it constricts by itself (7). Subsequent to these classic studies, many other investigators have confirmed that there is a rise in pulmonary artery pressure in most cases in animals or humans with little or no rise in cardiac output caused by inhalation of 10% O$_2$ (31).

3. Physiologic Characteristics of Hypoxic Pulmonary Vasoconstriction

In humans and adult animals the alveolar oxygen tension (P$_{O_2}$) needs to reach 60 mmHg or lower to initiate pulmonary vasoconstriction (5, 26). In newborn sheep, however, there is evidence of active hypoxic tone even when being ventilated with 30% F$_{O_2}$ (5). This enhanced sensitivity to alveolar hypoxia in the newborn probably accounts for the well-known flip/flop of the circulation in the newborn when weaning from the ventilator during which suddenly pulmonary vascular resistance is high and the fetal shunts have opened again. At an alveolar oxygen of 60 mmHg or greater, there is little pulmonary vasoconstriction to hypoxemia even when the mixed venous P$_{O_2}$ is as low as 10 mmHg (26). Although as alveolar hypoxia gets more severe, mixed venous hypoxemia may become a more important stimulus to pulmonary vasoconstriction. Nevertheless, the greater responsiveness of lung vessels to alveolar than to vascular hypoxia has led to the assumption that lung vessels autoregulate flow in response to local alveolar ventilation so that poorly ventilated alveoli with low O$_2$ concentrations produce vasoconstriction to shift perfusion to better ventilated alveoli.

HPV characteristically has an onset of action in seconds and can be sustained for hours if the hypoxia is regional (43). Diffuse hypoxia tends to reach an early peak rise in pulmonary artery pressure which then tails off over time (44). HPV can be as focal as a lobule (10) or in a larger area, including one lung or both lungs. The ability of the lung vessels to constrict and shift blood flow from one region to another depends on the size of the area made hypoxic (25). If the whole lung is hypoxic, then the lung vessels constrict diffusely and pulmonary artery pressure rises as the heart pumps harder to overcome the rise in pulmonary vascular resistance, allowing cardiac output and oxygen delivery to the tissues to stay as normal as possible. On the other hand, if the hypoxia is regional then the local vasoconstriction can effectively shift blood flow with only a very small rise in pulmonary artery pressure to other well ventilated areas of the lung which are compliant and can receive more flow. The anesthetized dog in Figure 1A shifted 54% of the perfusion from its left lung to the right well-ventilated lung in response to 100% N$_2$ for 7 mins to the left lung (13). The mean pulmonary artery pressure only increased from 14 to 15 mmHg to achieve this diversion and the stimulus to the HPV was alveolar hypoxia (P$_{A\_O_2}$, 25 mmHg) since the