Chapter 19

RED BLOOD CELLS AND HEMOGLOBIN IN HYPOXIC PULMONARY VASOCONSTRICTION

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Abstract: Nitric oxide (NO) plays an important role in the modulation of hypoxic pulmonary vasoconstriction; in turn, red blood cells (RBCs) augment HPV by hemoglobin-mediated oxidation and inactivation of NO. In addition, scavenging of reactive oxygen species by RBCs may play a role in augmentation of HPV. NO delivery and/or production by RBCs does not appear to be important in the control of pulmonary vasomotor tone. This review will discuss regulation of HPV by RBCs with an emphasis on hemoglobin-NO interactions. In addition, the review will discuss how biologic (S-nitrosation) or pharmacologic (cross-linking) modification of hemoglobin may affect pulmonary circulatory-hemoglobin interactions.

Key Words: pulmonary blood flow, gas exchange, oxygen delivery

INTRODUCTION

Vasoconstriction of small pulmonary arteries and arterioles occurs in response to alveolar hypoxia. In the presence of regional shunt or low ventilation-to-perfusion, this hypoxic pulmonary vasoconstriction (HPV) acts to divert blood flow away from hypoxic lung regions, thus minimizing the effects of lung pathology on the arterial PO$_2$. In the presence of global lung hypoxia, HPV results in pulmonary hypertension.

HPV kinetics are rapid, and HPV is undoubtedly an intrinsic property of pulmonary vascular smooth muscle. It is generally agreed that HPV is initiated by opening of L-type calcium channels and an increase in intracellular calcium. The location of the “hypoxia sensor” may be the mitochondria, but the role of reactive oxygen species (ROS) in transducing this signal is a subject of intense debate. Despite the localization of sensor and effector mechanisms for hypoxic pulmonary
vasoconstriction to pulmonary vascular smooth muscle cells, extrinsic factors certainly modify the response. In particular, the pulmonary vascular endothelium modulates hypoxic pulmonary vasoconstriction through production of arachidonic acid derivatives, nitric oxide (NO), and endothelin, and perhaps other yet undefined mediators. In addition, it is clear that the red blood cell is necessary for the full expression of hypoxic pulmonary vasoconstriction via a variety of potential mechanisms, including interactions with nitric oxide (NO), other reactive oxygen species, purines, and endothelial interactions. The remainder of this review will discuss the roles that red blood cells play in the modulation of hypoxic pulmonary vasoconstriction, with particular emphasis on the importance of NO and hemoglobin (Hb) in this interaction.

MODULATION OF HPV BY NO

Multiple levels of evidence suggest an important role for NO in the modulation of HPV, including marked augmentation of HPV in isolated lungs, intact animals, and human subjects after inhibition of NO synthesis, (3, 8, 12, 24, 41, 53, 66, 72, 74, 76), and in mice with targeted disruption of the endothelial nitric oxide synthase (eNOS) gene. (31) Administration of inhaled NO results in inhibition of hypoxic pulmonary vasoconstriction. (33, 67, 75) There appear to be species differences in the role that NO plays in regulation of pulmonary vascular resistance during normoxia and hypoxia, with NO playing an important role in mice, rats, rabbits, pigs, sheep, and humans, but less so in dogs.(18)

Given that NO is continually produced by pulmonary vascular endothelium and airway epithelium, it is remarkable that HPV is not tonically inhibited. The inhibitory effect of NO on HPV appears to be blunted by the capacity for red blood cells to take up and inactivate NO, as discussed below. In addition, an immediate fall in NO production during acute hypoxia due to reduced NOS activity may act to enhance hypoxic pulmonary vasoconstriction (29, 46, 70).

MODULATION OF HPV BY RED BLOOD CELLS AND HEMOGLOBIN: INITIAL STUDIES

Augmentation of HPV by blood was demonstrated by Duke et al in isolated, perfused cat lungs more than 50 years ago.(28) McMurtry et al later identified the role of the red blood cell in this response when they showed that isolated rat lungs perfused with colloid solution, plasma, or plasma plus platelets had rapidly decaying hypoxic pulmonary vasoconstriction when compared to lungs perfused with blood or plasma plus red blood cells. (58) Although they showed that cyclooxygenase played no role in augmentation of HPV by red blood cells, they were unable to identify a mechanism to explain their observations.

Later, potentiation of hypoxic pulmonary vasoconstriction by red blood cells was described in both rat and cat lungs, but not in lungs from swine and hamsters (39, 40). Later investigations by Hakim suggested that species differences in augmentation of HPV by red blood cells were due to differences in muscular pulmonary vessel size, and/or red blood cell deformability changes in response to hypoxia. (38, 39) Weissmann et al found that red