Iron lung? New ideas about hypoxic pulmonary vasoconstriction

Michael J. Joyner1 and Bruce D. Johnson2
1Department of Anaesthesiology and CTSA and 2Division of Cardiovascular Diseases, Department of Medicine and CTSA, Mayo Clinic, Rochester, MN, USA

The word ‘hypertension’ usually evokes thoughts of slowly rising systemic arterial blood pressure and increased risk for diseases like stroke, heart attack and congestive heart failure. However, hypertension in the pulmonary vasculature is an equally problematic disease (Rich et al. 1987, Rubin, 1997). Clinicians and medical students most often think about ‘primary pulmonary hypertension’, a devastating and idiopathic disease often observed in otherwise healthy young women (Gaine, 2000). Because it is not possible to measure pulmonary blood pressure using a simple cuff in the doctor’s office, this disease frequently goes unnoticed until it is far advanced and may be discovered when the cardiovascular system is challenged by increased cardiac output during pregnancy (Wong et al. 2001). Unfortunately, efforts to dilate selectively the pulmonary circulation and treat primary pulmonary hypertension have been frustrating and truly effective treatment options for this condition are limited. The dogma is that by the time of diagnosis there are ‘structural’ changes in the vessels with a loss of dilator function (Botney et al. 1994). Fortunately, the disease is rare (1–2 cases per 1 million people in the general population).

In contrast to primary pulmonary hypertension, blood pressure in the pulmonary vasculature can rise in response to both acute hypoxia, which can occur in healthy people during activities like mountain climbing, and acute illnesses like pneumonia or the adult respiratory distress syndrome (ARDS) (Moloney & Evans, 2003). Additionally, longer term hypoxia associated with chronic obstructive pulmonary disease, obstructive sleep apnoea or chronic altitude exposure can also evoke a rise in pulmonary pressure leading to secondary pulmonary hypertension. Secondary pulmonary hypertension is also observed in some forms of congenital heart disease where both hypoxia and high levels of pulmonary blood flow contribute. There also appears to be a ‘reactive component’ of the pulmonary vasculature in patients with more classic forms of systolic heart failure (Olson et al. 2007). Circulating hypoxia-sensitive intermediates, such as endothelin-1 and serotonin, are elevated in heart failure, which suggests that low perfusion, venous hypoxia and possibly intermittent dips in oxygen due to central sleep apnoea may contribute to this process (Ghatak et al. 1998; Delgado et al. 2005). As is the case with primary pulmonary hypertension, there may again be ‘structural’ changes in the vessels in these forms of secondary pulmonary hypertension with an eventual loss of dilator function.

In cases of acute pulmonary hypertension associated with hypoxia, calcium agonists (e.g. nifedipine) are often used as prophylaxis for altitude exposure. Vasodilator therapy like inhaled nitric oxide and inhaled prostaglandins can also be effective, but their use is usually limited to the operating rooms or intensive care settings. There is also evidence that sildenafil and similar medications are effective in limiting the rise in pulmonary blood pressure associated with acute exposure to hypoxia (Snyder et al. 2008). The idea is that this approach enhances the effects of locally produced NO and blunts hypoxic pulmonary vasoconstriction. The focus of all of the effective therapies (and many of the ineffective ones too) is on vasodilator therapy targeted at the pulmonary circulation in a way that has minimal impact on systemic blood pressure (McGoon et al. 2004).

In this edition of The Journal of Physiology, Smith et al. (2008) show that infusions of iron can blunt the vasoconstrictor responses to acute hypoxia and that reducing iron availability with desferrioxamine enhances the constrictor response to hypoxia. This finding is important for at least three reasons. First, it sheds light on and raises important questions about the role of iron sensitive hypoxia inducible factors, the integration with various genes and the regulation of vascular tone (and other physiological responses) especially in the pulmonary circulation. It also raises questions about the role of iron in oxygen sensing pathways and production of reactive oxygen species. Second, the observations in the paper raise important questions about the epidemiology and pathophysiology of acute pulmonary vasoconstriction during hypoxia and chronic forms of pulmonary hypertension. Will there be some association between iron status and high altitude illness, such as high altitude pulmonary oedema (HAPE)? Will there be some association between iron status and acute pulmonary hypertension in critically ill patients? Will dysfunction in the pathways that iron operates on to prevent acute pulmonary hypertension during hypoxia be involved with either primary or secondary pulmonary hypertension? Could the more fragile iron status in women be a specific risk factor? Could a screening test for those at risk for primary pulmonary hypertension ever be developed based on some of the ideas in the paper? Third, what new treatment options does the paper suggest and where might clinical trials be targeted? Should sojourners to high altitude take iron supplements? Should hypoxic patients in the intensive care unit receive supplemental iron? Should it be used in cardiac surgery where acute pulmonary hypertension in the peri-operative period is a major challenge especially in children operated on for congenital cardiac defects?

In summary, Smith and colleagues have made a truly elegant observation using non-invasive techniques. The observation centres on one of the fundamental but sometimes life threatening responses to environmental stress that the most robust humans encounter during recreation at high altitude. At the same time it has vast clinical implications for the sickest patients seen in the hospital, and like all good integrative physiology it raises more questions that it answers.

References