Progress in Cardiovascular Diseases 52 (2010) 485–492
www.onlinepcd.com

New Insights in the Pathogenesis of High-Altitude Pulmonary Edema

Urs Scherrer*, Emrush Rexhaj, Pierre-Yves Jayet, Yves Allemann, Claudio Sartori

Department of Internal Medicine and the Botnar Center for Extreme Medicine, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

Abstract High-altitude pulmonary edema is a life-threatening condition occurring in predisposed but otherwise healthy individuals. It therefore permits the study of underlying mechanisms of pulmonary edema in the absence of confounding factors such as coexisting cardiovascular or pulmonary disease, and/or drug therapy.

There is evidence that some degree of asymptomatic alveolar fluid accumulation may represent a normal phenomenon in healthy humans shortly after arrival at high altitude. Two fundamental mechanisms then determine whether this fluid accumulation is cleared or whether it progresses to HAPE: the quantity of liquid escaping from the pulmonary vasculature and the rate of its clearance by the alveolar respiratory epithelium. The former is directly related to the degree of hypoxia-induced pulmonary hypertension, whereas the latter is determined by the alveolar epithelial sodium transport. Here, we will review evidence that, in HAPE-prone subjects, impaired pulmonary endothelial and epithelial NO synthesis and/or bioavailability may represent a central underlying defect predisposing to exaggerated hypoxic pulmonary vasoconstriction and, in turn, capillary stress failure and alveolar fluid flooding. We will then demonstrate that exaggerated pulmonary hypertension, although possibly a conditio sine qua non, may not always be sufficient to induce HAPE and how defective alveolar fluid clearance may represent a second important pathogenic mechanism. (Prog Cardiovasc Dis 2010;52:485-492)

High-altitude pulmonary edema is a life-threatening condition occurring in predisposed but otherwise healthy individuals. It thereby allows studying underlying mechanisms of pulmonary edema in the absence of confounding factors, such as coexisting cardiovascular or pulmonary disease, and/or drug therapy. Pulmonary edema results from a persistent imbalance between forces that drive water into the airspace of the lung and the biological mechanisms for its removal.[1,2] There is evidence that some degree of asymptomatic alveolar fluid accumulation may represent a normal phenomenon in healthy humans shortly after arrival at high altitude.[3] Two fundamental mechanisms then determine whether this fluid accumulation is cleared or whether it progresses to HAPE. After arrival at high altitude, the amount of alveolar fluid depends on the quantity of liquid escaping from the pulmonary vasculature on the one hand and on the rate of its reabsorption by the alveolar respiratory epithelium on the other hand. The former is directly related to the degree of hypoxia-induced pulmonary hypertension, whereas the latter is determined by the alveolar epithelial sodium transport. Over the past decade, it has been established that HAPE represents a prototype of a distinct form of pulmonary edema in humans, resulting from the conjunction of alveolar fluid flooding induced by exaggerated hypoxic pulmonary hypertension and impaired alveolar fluid clearance related to defective pulmonary transepithelial sodium transport. In the following, we will review this evidence.

Statement of Conflict of Interest: see page 491.

* Address reprint request to Urs Scherrer, Department of Internal Medicine, BH 10.640, Centre Hospitalier Universitaire Vaudois, CH-1011 Lausanne, Switzerland.

E-mail address: urs.scherrer@chuv.ch (U. Scherrer).

Exaggerated hypoxic pulmonary hypertension

Exaggerated pulmonary hypertension is a hallmark of HAPE,[4,5] and several observations indicate that it

0033-0620/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.pcad.2010.02.004

Abbreviations and Acronyms

ET-1 = Endothelin-1

HAPE = High-altitude pulmonary edema

NO = nitric oxide

PFO = patent foramen ovale

contributes to its pathogenesis. Anatomical (congenital absence of the right pulmonary artery, pulmonary artery occlusion from granulomatous mediastinitis)[6,7] or functional (Down syndrome)[8,9] abnormalities that facilitate pulmonary hypertension are risk factors for developing HAPE at relatively low altitude (1500-2500 m). Lowering of pulmonary artery pressure with pharmacologic agents of different types has beneficial effects in HAPE.[10] Most importantly, pharmacologic prevention of exaggerated pulmonary hypertension in HAPE-prone subjects reduces the incidence of pulmonary edema during high-altitude exposure.[11,12]

To cause pulmonary edema, the elevated pulmonary-artery pressure has to be transmitted to the capillaries. For this to occur, one has to postulate that there exist pulmonary regions where capillaries are not protected by constricted resistance vessels. This appears to be the case because, in patients suffering from HAPE, the perfusion of regions of the lung with radiographic evidence of pulmonary edema is much greater than the one of the regions without edema (Fig 1).[13] Consistent with this concept, pulmonary capillary pressure is considerably higher in patients with HAPE than in those without pulmonary edema.[14] Using the arterial occlusion method, which most likely measures pressures in vessels close to 100 μm in diameter, we found that, at 4559 m, pulmonary capillary pressure was on average 16 mm Hg (range, 14-18 mm Hg) in HAPE-prone subjects who did not develop pulmonary edema and 22 mm Hg (range, 20-26 mm Hg) in those who developed HAPE. These findings suggest that, in HAPE-prone subjects, the pulmonary capillary pressure threshold value for alveolar fluid flooding is roughly 20 mm Hg. It is possible that, in addition to inhomogeneous hypoxic pulmonary vasoconstriction resulting in regional overperfusion of capillaries in nonprotected areas,

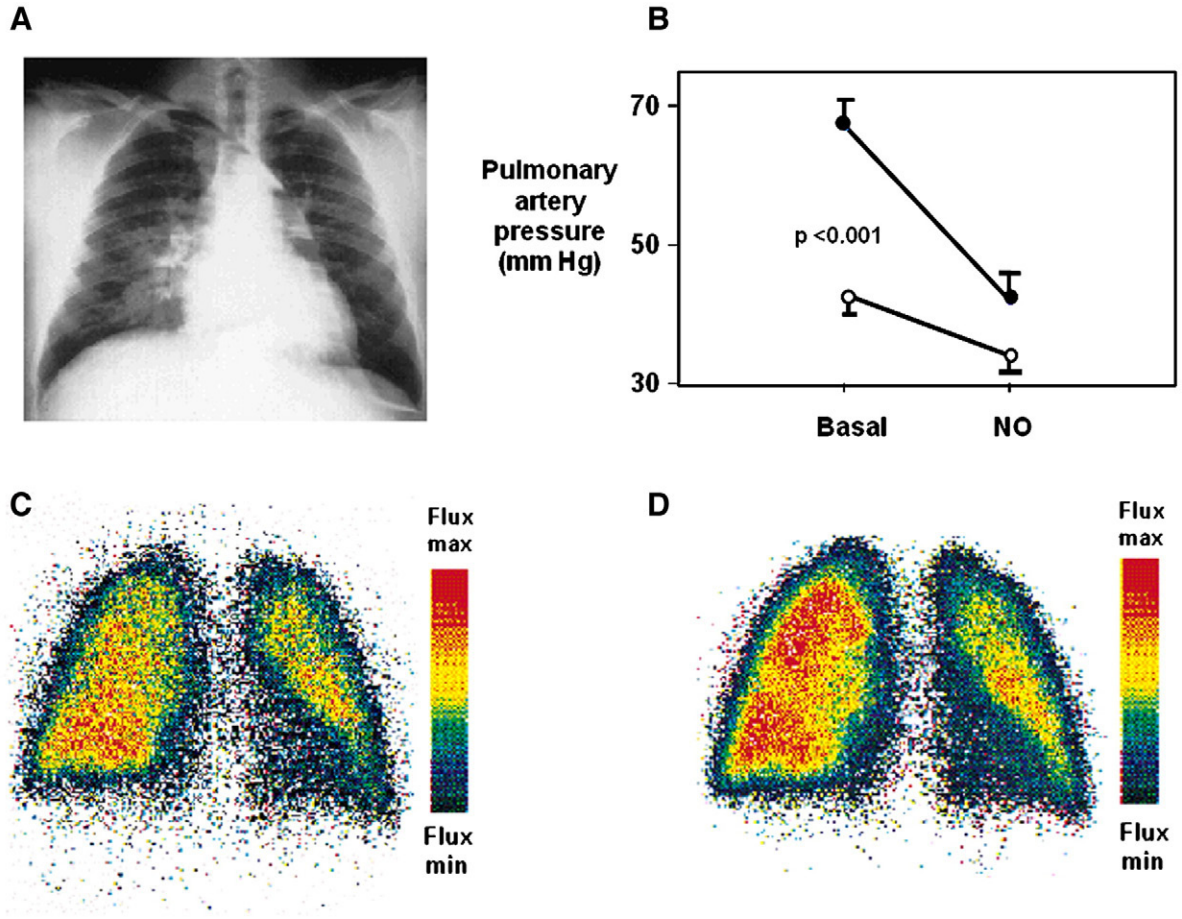

Fig 1. Effects of NO inhalation on pulmonary blood flow and systolic pulmonary-artery pressure in HAPE-prone subjects. The chest x-ray film (A) was obtained a few minutes before the first lung-perfusion scan (B) was obtained. The second scan (D) was obtained 20 minutes after the start of NO inhalation (40 ppm). The inhalation of NO, which induced a significantly greater reduction of the pulmonary-artery pressure in HAPE-prone than HAPE–resistant subjects (C), redistributed blood flow away from edematous regions of the lungs and toward nonedematous regions (adapted from Scherrer et al[13]).