THE ENIGMA OF HIGH ALTITUDE PULMONARY OEDEMA

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Every year some people climb a mountain and die there from pulmonary oedema. Sometimes they climb too high too fast, sometimes they exert themselves unusually vigorously and occasionally they know they are prone to high altitude pulmonary oedema and cannot escape down to the valley wherein lies the chance of rapid recovery. For all these proven cases of HAPE there are probably a number of others who develop mild symptoms or a subclinical condition and recover without diagnosis. The pathophysiology of HAPE is unresolved but some observations provide a clue:

Susceptibility

* Individuals who have had HAPE tend to develop it again on re-exposure to hypoxia suggesting predisposition.
* There is usually a delay of 24 - 36 hrs after arrival at altitude before pulmonary oedema develops. It is precipitated by exercise and cold.
* High altitude dwellers are not immune. They may develop "reentry" HAPE after a sojourn of 3 or more days at low altitude.
* In the Japanese population HAPE is associated with human lymphocyte antigens DR6 and DQ4 although it has not been considered an immunogenetic disease [1].

Pulmonary Circulation

* High pulmonary artery pressure is a cardinal feature and precedes the development of HAPE [2]. Impaired of left ventricular function is not the cause. Pulmonary vasoconstriction occurs mainly at arteriolar level and is not homogeneous. Reducing hypoxic pulmonary vasoconstriction with vasodilators prevents the development of pulmonary oedema and treats acute pulmonary oedema with improvement in symptoms and gas exchange [3, 4, 5].
* Subjects who are susceptible to HAPE exhibit haemodynamic differences at sea level. Their pulmonary artery pressure is higher [6] and they have an exaggerated pulmonary artery pressure response to exercise [7].
* Absence of the right pulmonary artery predisposes to HAPE [8].

Lungs

* There is a reduced hypoxic ventilatory response that may worsen alveolar hypoxia and hence pulmonary hypertension [9, 10, 11].
* Some studies have shown small lung volumes in HAPE susceptible subjects [10, 12].
* Bronchoalveolar lavage in patients with HAPE has shown high concentrations of protein and cells [13].

Neuro-endocrine

* There is enhanced sympathetic activation in response to hypoxia [14].
* Salt and water retention precedes the development of pulmonary oedema [15].

Inflammation

* Virus infections predispose to HAPE and cause increased fluid leak into the lung [16].
* Inflammatory markers are measurable once HAPE is established but do not appear to precede it.

Haemostasis
* Thrombi have been found in the small pulmonary arteries of patients who succumb to HAPE [17].

Recovery
* The pulmonary oedema normally resolves rapidly on descent to low altitude.
* In cases where the patient does not descend or perish, the oedema may resolve spontaneously after about 5 or 6 days, although a small number of people have chronic pulmonary oedema until they descend.

How can this evidence be reconciled? The overperfusion hypothesis proposes that patchy arteriolar vasoconstriction leads to inhomogeneous perfusion of the lung in HAPE [18]. This results in excessive blood flow in some regions of the lung with increased capillary filtration pressure. Capillary stress failure, rather than capillary rupture, has been shown in isolated lungs when transmural pressure rises rapidly causing epithelial and capillary rupture [19]. Others have proposed that leakage may occur at arteriolar level [20].

There is as yet no unifying hypothesis to explain the mechanism of oedema formation based on all the observed facts. Perhaps the implication of this is that there may be more than one mechanism.

Haemodynamic changes in the pulmonary circulation appear to play a central role in most cases. The pulmonary circulation behaves as if it is less distensible: hence the association with a circulation of reduced size as in absence of a pulmonary artery and small lungs, and more vasoconstriction in susceptible subjects. It is the presence of smooth muscle in small arteries that determines their ability to vasoconstrict rather than differences in severity of vasoconstriction. The complexities of the haemodynamics are largely unexplored and so it remains uncertain whether haemodynamic changes alone or an additional trigger mechanism are required to initiate pulmonary oedema. The pathogenic role of vascular "remodeling" in response to hypoxia has hardly been considered, but might be important given the time from altitude exposure to the development of oedema.

It appears likely that inflammation caused by infection may be a separate precipitating factor for HAPE. In the absence of infection the limited evidence favours inflammation developing after pulmonary oedema is established rather than preceding its formation. Once the pulmonary vessels begin to leak an inflammatory response would be expected. HAPE has been compared to other non-cardiogenic forms of pulmonary oedema caused by raised intra-cranial pressure, reperfusion of the pulmonary circulation after surgery for pulmonary embolism or atresia and heroin overdose [21].

These share hypoxia, pulmonary hypertension and sympathetic activation in their

pathogenesis, but they seem to lend little help to understanding HAPE. Can diving induced pulmonary oedema which is probably not related to hypoxia but, like HAPE, is preventable with nifedipine provide any clues? In evolutionary terms the development of the pulmonary circulation was essential for the survival of the living creatures that left the sea to live on dry land. Some of us have exulted in travelling to the highest places on the land. In doing so we are peculiarly vulnerable to drowning in our own juices.

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