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EDITORIAL

High altitude pulmonary oedema: who gets it and why?

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High altitude pulmonary oedema is a life-threatening condition which can affect otherwise healthy individuals travelling at altitude. Common clinical features are breathlessness, chest pain, cough and haemoptysis, and these features often occur against a background of symptoms of mountain sickness, such as headache, nausea, insomnia and dizziness. The incidence of high altitude pulmonary oedema is difficult to assess but attempts have been made; in 1976 HACKETT and RENNIS [1] showed that 2.5% of trekkers passing through Pheriche (4243 m) in the Khumbu region of Nepal suffered from high altitude pulmonary oedema (HAPE). Since the syndrome occurs in otherwise fit people and high altitude travel is becoming more common due to the increasing adventurousness of holiday makers, it would be very useful to be able to predict which individuals are likely to get into trouble if they travel to altitude. In order to make this prediction, we need to know the cause of high altitude pulmonary oedema but, at the present time, no single cause has been found.

Excessive breathlessness with high altitude travel has been known about since pre-Christian times but it was not until 1960 that the condition was recognized as a separate entity [2]. Since this clinical description, there have been many attempts to explain the cause of the syndrome. These have included left ventricular failure, pulmonary thromboembolism, pneumonia, excessive pulmonary hypertensive response to hypoxia, inadequate ventilatory response to hypoxia, excessively leaky pulmonary capillaries on exposure to hypoxia and stress failure of the pulmonary capillaries. There are several important clinical features of the syndrome which may point to its aetiology. It is rare below 2,000 m altitude. The incidence is increased by exercise at altitude and also if cold conditions prevail. There is no relationship between HAPE and physical fitness, as measured by maximum oxygen consumption, but there is marked individual susceptibility - an individual who has suffered HAPE before is likely to get it again even though they are apparently otherwise entirely well. When catheter studies have been performed prior to treatment, it has been found that HAPE is often associated with severe pulmonary hypertension. In addition, bronchoalveolar lavage studies have shown that the pulmonary oedema fluid is rich in protein [3], and the fluid may contain inflammatory mediators [4].

It is now clear that HAPE is not due to left ventricular dysfunction. We know this because the oedema is protein-rich and the wedge pressure, when measured, is usually normal. HAPE is also unlikely to be due to pulmonary thromboembolism. Where intravascular pulmonary artery thrombosis is seen on postmortem, it is likely that these thrombi have occurred *in situ* rather than embolising from other parts of the body. For many years, it was held that HAPE was due to pneumonia but this is now known to be untrue, although the patients are often feverish and inflammation may be important [5]. The more likely factors in the aetiology of HAPE are: 1) abnormally brisk vasoconstrictor response to hypoxia; 2) inadequate ventilatory response to hypoxia; and 3) leak or stress failure of the pulmonary capillaries.

There now appears to be no doubt that the response of the pulmonary vasculature to hypoxia is extremely important in the aetiology of HAPE. The reasons for this assertion are as follows. Cardiac catheterization usually demonstrates severe pulmonary hypertension prior to treatment. The condition is more common where there is absence of a pulmonary artery [6, 7] and pulmonary flows are higher. Cold, a known precipitating factor in HAPE, is known to raise pulmonary artery pressure [8]. Even when pulmonary artery pressure has not actually been measured, chest radiographic images will often show an increase in pulmonary artery size suggesting high intraluminal pressures [9]. Humans and animals who live successfully at high altitude tend to have thinner pulmonary arteries and a diminished pulmonary vasoconstrictive response to hypoxia [10, 11]. High altitude pulmonary oedema can be both prevented and treated with calcium antagonists, which are known pulmonary vasodilators [12].

From the above, it is clear that the pulmonary circulation is implicated but additional factors, such as leaking capillaries, may also be important, particularly since it is necessary to explain the high protein content of the oedema [13]. Although it is difficult to prove that hypoxia *per se* causes leak in the pulmonary capillaries, it is likely that the finding of diminished vital capacity on exposure to hypobaric hypoxia is due to leak of fluid into the interstitium [14]. A major argument against the view that high pulmonary artery pressures cause HAPE is that the leak occurs downstream from the vasoconstriction. This anomaly may be explained by HULTGREN'S observation that the pulmonary oedema is patchy [15]. If the vasoconstriction that occurs in response to hypoxia occurs more in some pulmonary arteries than others then this would account for the fact that some capillaries are exposed to very high pressures whereas others are protected. This patchy vasoconstriction would also explain West's theory of HAPE - stress failure of the pulmonary

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capillaries. West's group have shown by electron microscopy that excessive pressure on thin walls of the unprotected capillaries can lead to breaks in the capillary endothelial layer and leak of protein fluid and blood cells into the alveolar space [16]. Whilst it seems very likely that changes in the pulmonary circulation in response to hypoxia are responsible, at least in part, for HAPE, the role of the hypoxic ventilatory response is more controversial. Some studies have suggested that subjects with a history of high altitude pulmonary oedema have a lower hypoxic ventilatory response [17], but others maintain that this correlation was not valid [18].

It seems clear that an idiosyncratic and excessive pulmonary vascular vasoconstrictive response to hypoxia is the primary event in the aetiology of HAPE. This vasoconstrictive response is patchy and, as a consequence, there is an increase in pressure on some capillaries, which are made more leaky by the effect of hypoxia on their integrity. The result of this is leakage of protein rich fluid and sometimes blood into the alveolar space. If hypoxic ventilatory response is important, then this could precipitate the suggested chain of events by allowing excessive alveolar hypoxia. From the above, it is clear that attempts to predict HAPE in otherwise fit individuals should concentration on the pulmonary vascular responses to hypoxia and possibly also the ventilatory responses to hypoxia. Clearly, any test to be performed on healthy individuals must be noninvasive and have a low incidence of false negative results. The most promising test has been the measurement of the pulmonary vascular response to hypoxia using Doppler echocardiography. This test relies on the fact that when pulmonary hypertension develops there is an abnormally short acceleration time in the pulmonary artery in relation to total ejection time, and also that higher pressures in the right ventricle result in blood refluxing through the tricuspid valve. The acceleration time and the ejection time can be measured by echo. The velocity of the refluxing blood can be measured by Doppler and is directly proportional to the pressure developed in the right ventricle and, hence, to pulmonary artery pressure. This method has been used by YAGI *et al*. [19] and VACHIERY *et al*. [20]. Both these studies found that subjects with a previous history of HAPE had excessive pulmonary vascular responses as measured by noninvasive means. Unfortunately, because of the range of responses obtained, they could not predict whether a particular individual would experience difficulties. This, ultimately, must be the aim of any predictive test.

The other method of prediction, based on the effect of hypoxia on ventilation has been pioneered by RICHALET *et al.* [21]. He makes subjects exercise to 30% of their maximum oxygen consumption ($\dot{V}'_{O_2,max}$) under hypoxic conditions and measures changes in heart rate and arterial oxygen saturation. Using this test, RICHALET *et al*. [21] claim that they can predict high altitude pulmonary oedema in the majority of cases, but confirmation of this success is necessary.

As reported in this issue of the Journal, in an attempt to solve the problem once and for all, HOHENHAUS *et al*. [22] have combined hypoxic ventilatory responses and hypoxic pulmonary vascular responses as predictive tests. They took 10 subjects with a history of HAPE, 10 subjects with a history of acute mountain sickness, and 10 controls. In each subject, they measured the ventilatory response to hypoxia (HVR), the ventilatory response to hypercapnia and the hypoxic pulmonary vascular response (using Doppler echocardiography). They found that HVR was lower in the HAPE susceptible subjects compared with nonsusceptible controls but not different from subjects susceptible to acute mountain sickness. Doppler measurement of pulmonary vascular response to hypoxia did not lead to further discrimination between HAPE susceptible and acute mountain sickness susceptible subjects. The pulmonary vascular response did appear to be different in HAPE susceptible subjects from controls but, as in the study of VACHIERY *et al.* [20], predictions could not be made on an individual basis.

All this is very disappointing to those interested in high altitude physiology who would like to be able to predict responses to high altitude. The most promising avenue of research must be the response of the pulmonary circulation to hypoxia. But, until we can be certain that we can adequately predict the response of individuals to altitude we must ensure that everyone who travels to altitude receives adequate advice on acclimatization schedules and what to do if symptoms develop. The most important part of that advice will of course be, "if in doubt, descend".

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