High Altitude Pulmonary Edema

New horizons

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Over the last three decades, increased awareness and education have lessened the instances of high altitude pulmonary edema (HAPE) encountered by otherwise healthy, active sojourners to high altitude. HAPE had been described in Europe as early as the late 1700s and in South America in the late 1800s and 1900s, when it was thought to be pneumonia and/or fluid in the lungs from heart failure. But it was not until the 1950s and 1960s in Peru and the United States that HAPE was recognized as a distinct disease unrelated to infection or heart failure that could afflict otherwise healthy, young and middle-aged individuals. Although not nearly as common as acute mountain sickness (AMS) and occurring more commonly at slightly higher altitudes (3000 meters or above), HAPE, unlike AMS, can be fatal.

The purpose of this article will be to review what is known about HAPE and its underlying pathophysiology. We will also provide an update on the latest research and insight into the underlying mechanism of the disease, which results in a potentially fatal leak of fluid into the lungs. References are provided for more exhaustive reviews, but this piece is intended only to tantalize the reader about the current research—research that will one day lead to better understanding as well as better prevention and treatment of HAPE.

BACKGROUND

Clinical presentation

The primary predisposing factor to developing HAPE is not allowing enough time for acclimatization. Rapid ascent, as in all altitude illnesses, is the primary predisposing factor to becoming ill. Recognition of the signs and symptoms of HAPE by the victim and his/her group members should lead to proper decision making that optimizes the chance for survival and quick recovery. Unless trauma or weather conditions prevent a victim’s descent, no one should die from HAPE.

How rapid an ascent is too rapid? The question is difficult to answer, because there is tremendous individual variability in the time course of acclimatization. In this modern world of fast travel, everyone tries to get to their destination as quickly as possible. Unfortunately, this can lead to HAPE in people who, if they had ascended more slowly, would not have become ill.

Climbing, trekking or recreational parties traveling to high altitude must be educated regarding the risk and signs of developing HAPE. Any time a party member can not keep up and develops signs of inordinate shortness of breath, exercise intolerance and cough with a rapid heart rate, HAPE must be suspected. Pulse oximeters, which are now available, accurate and inexpensive, can provide guidelines for people who are having trouble oxygenating their blood, a condition that may be a reflection of early or evolving HAPE. As the disease
progresses, coughing may produce pink, frothy sputum, which is accompanied by very low oxygen saturation levels. It is at this point that the disease can progress rapidly to death.

Over the past decade, the guidelines for treatment of HAPE for recreational and climbing parties have changed. For instance, in high altitude resort areas such as in Colorado, it used to be routine for physicians to evacuate individuals at great expense and inconvenience by ambulance or helicopter to a low altitude hospital. Experience has shown that in most cases, evacuation is not necessary. In these communities, healthcare facilities are usually available. If the patient’s oxygen saturation level can be elevated to 90 percent or higher with portable oxygen, and if they have friends or family with them, they can be sent back to their accommodations with portable oxygen. As long as they can be observed by friends and a physician is available in case the condition worsens, there is no need to evacuate. If, on the other hand, it is the physician’s clinical judgment that the patient is critically afflicted with HAPE, then evacuation is mandatory. If the disease is recognized quickly enough, most individuals recover quickly from HAPE, and they can often return to climb or ski again on the same trip.

On the other hand, in the field setting of a climb or trek where medical care is not available, evacuation to a lower altitude while the victim is still able to walk on his or her own is essential to prevent progression of the disease and possibly death.

**Pathophysiology**

**Pulmonary Hypertension**

The first description of HAPE in the English medical literature was made by Charles S. Houston in a *New England Journal of Medicine* report in 1960. At the same time, Herbert N. Hultgren, Chief of Cardiology at Stanford University Medical School, was adventuring in the high altitude mining towns of Peru, where he observed and described a number of cases of HAPE. Over the next 15 years, Dr. Hultgren did some landmark research studies of the cardiopulmonary characteristics of people with HAPE. These studies, which have subsequently been confirmed on numerous occasions, demonstrated that individuals with HAPE did not have congestive heart failure. They did, however, have accentuated pulmonary artery pressures compared to healthy individuals at high altitude.

These findings remain a seminal characteristic of HAPE-susceptible individuals. They suggest that upon ascent, such individuals develop higher pressures in the blood vessels of the lung. The pressures may stretch and damage these fragile blood vessels in such a way that fluid leaks from the intra- to the extravascular space in the lung tissue. This fluid leak then enters the alveolar space, and the ability of the lung to obtain oxygen from the air is impaired.

The Campaña Margharita hut sits on the summit of Monte Rosa (4800 meters) in the northern Italian Alps. In an insightful and bold clinical study in 1991, Bartsch and colleagues tested the hypothesis that HAPE-susceptible individuals, who have high pulmonary artery pressures when they go to high altitude, could avoid developing HAPE if the rise in pressures was minimized. The drug nifedipine is a calcium-channel blocker known to attenuate the sharp rise in pulmonary artery pressures. Nifedipine was used to treat HAPE-susceptible subjects before and during the ascent to the Monte Rosa hut. Bartsch and colleagues evaluated the subjects after the ascent with clinical exams, chest x-rays and a Doppler ultrasound estimation of pulmonary artery pressures. The results showed that nifedipine minimized the rise in pulmonary artery pressures and prevented the development of HAPE in these individuals, many of whom would have been expected to become sick.
This elegant field study, based on previous research and sound physiologic principles, resulted in a practical clinical application. It is now recommended that HAPE-susceptible patients be prescribed nifedipine upon and during their stay at high altitude resorts or regions of climbing and trekking. Good studies, however, have not been done to prove the efficacy of nifedipine to treat HAPE once it has developed.

Using the same physiologic principle of the relationship between pulmonary vasoreactivity and HAPE, this same Monte Rosa group used nitric oxide (NO) to look at its effect upon pulmonary gas exchange of oxygen and carbon dioxide and distribution of perfusion of blood to the lungs of individuals with HAPE. Although this intervention is not practical in high altitude settings, NO selectively decreased pulmonary artery pressures. The study showed that nitric oxide increased perfusion of blood to areas of the lung that were not edematous, thus improving oxygenation. It also furthered the understanding of the physiology of the gas exchange, ventilation and perfusion of blood to the lung in HAPE.

In this regard, it is important to acknowledge that each person’s reaction to stress from a physiologic and biochemical standpoint is different. These differences make each individual’s ability to adapt unique.

The biochemistry of nitric oxide is no different. Nitric oxide, the focus of intense research in medical science, is produced in many vascular beds of the body. Researchers have recently found that in rats taken to simulated high altitude, the adhesion of white blood cells and subsequent inflammation in tissue capillaries, which may lead to further edema formation in the tissues of the body, are decreased with three weeks of acclimatization. This process appears to be mediated by an increase in NO synthesis. The study suggests that NO plays a role in the acclimatization process.

A breakthrough in the understanding of HAPE occurred in the 1980s under the directorship of Peter Hackett. With the use of bronchoscopy in climbers with HAPE, studies at the Denali Medical Research Camp at 4300 meters characterized the nature of the edema fluid. These studies gave further insight into the mechanism of the leak in the lung. They showed a very high protein content in the alveolar fluid, suggesting a large pore leak into the lung tissue and alveoli. In fact, the values were higher than any other patients previously described. The studies also found evidence of inflammation, which can also contribute to loss of integrity of the endothelial lining of the small blood vessels in the lung. The question then became: “Is the leak in HAPE secondary to damage of the pulmonary small blood vessels by very high pressures, or is it secondary to violation of the integrity of the blood vessel lining by inflammation?” The logistics and nature of the studies in the field at high altitude did not allow investigators to answer this question.

Inflammation

Although high pressures are the primary mechanism of edema formation in the lung, inflammation may be a confounding factor. In a recent study on Monte Rosa, bronchoalveolar lavage was performed at the onset of HAPE. No inflammatory mediators were found. The findings suggest that high pressures create the break in the vascular wall, leading to subsequent leak in the tissues. The inflammation that was found in earlier studies are probably a response to the initial leak.

In Summit County, Colorado, at little less than 3000 meters, the inflammatory mediator leukotriene E4 was found in the urine of HAPE patients, a discovery that goes hand-in-hand with the lavage studies. But what is more interesting is that about two-thirds of
HAPE Schema. The diagram represents a proposed mechanism for the development of HAPE. HAPE-susceptible individuals may have some or all of the inherent characteristics or encountered stresses that lead to the leak of fluid from the blood vessels to the tissue of the lung. For instance, some of the genetic traits include a blunted breathing response upon ascent to high altitude, which leads to lower levels of oxygen in the lungs and blood; a stronger vasoconstrictive response in the pulmonary circulation, which leads to higher pressures and stress on the endothelial lining; slower clearance of fluid from epithelial lining of the alveolar airspace; and a lower production of the natural vasodilator nitric oxide (NO) during acclimatization. Some of the encountered stresses include the common denominator, high altitude; rapid ascent without time to acclimatize; cold, which accentuates the pulmonary vasoconstrictive response; exercise, which increases stress in the blood vessels; concomitant viral illnesses, which may impose some degree of weakness on the lining cells of the lung; and other inflammatory mediators, which are a result of the initial leak of proteins from the blood. Of all of these, high pressures in the pulmonary vasculature appear to be the most important factor in initiating the leak.
the patients had a history of a viral upper respiratory infection before or during their development of HAPE. One could speculate that the viral infections resulted in an increase of inflammatory mediators, which make the endothelial lining of the blood vessels more vulnerable to the subsequent increase in pressures that they will experience upon ascent.

**Ventilation**

Another physiologic response that is essential to acclimatization to high altitude is an increase in breathing. Although this response is generally predictable, everyone experiences it to a greater or lesser degree, and the response is probably inherent. Studies on Denali and in Japan and Europe have shown that individuals whose responses are more blunted than healthy controls upon ascent are more susceptible to developing HAPE. By not being able to increase ventilation adequately, one can not optimize the obtaining of oxygen from the air at high altitude where the oxygen availability is less. Individuals with a blunted response, therefore, do not have as much oxygen in their lungs or blood. Subsequently, they may have a more intense pulmonary vascular response and higher pulmonary artery pressures. One could then speculate a mix of physiologic characteristics: a blunted breathing response and a more intense pulmonary pressure response, which act in concert to make the likelihood for developing HAPE greater (see HAPE schema on right).

**Fluid Clearance from the Lung**

Another area of recent HAPE research has dealt with the ability of the epithelial lining of the alveoli in the lung to reabsorb fluid that has developed there. This process, requiring moving of fluid across the membrane with energy from sodium-potassium (ATPase), appears to be slower in HAPE-susceptible individuals. This response is probably linked to genetic factors. One could speculate that those whose capability to clear fluid from the alveoli is impaired have prolongation of their clinical course.

**Future Directions**

Based on what is known from previous research in the field of HAPE, investigators still have an exciting array of questions to ask to understand the mechanism of HAPE and thus develop better preventative and therapeutic interventions.

Questions for ongoing research are as follows:

- What are the sequence of physiologic, cellular, and biochemical reactions that precede HAPE?
- Are there interventions that can mitigate these accentuated reactions and thus prevent HAPE?
- What more can we learn from the HAPE-susceptible victims?
- Do they have characteristics that are identifiable as genetic markers of physiologic responses?
- What is the role of NO in acclimatization and how does it pertain to HAPE?
- What is the role of alveolar clearance of fluid in the predisposition to and prolongation of the course of HAPE?
HAPe is fortunately an uncommon, albeit potentially fatal, altitude illness. Some individuals are predisposed to developing HAPe, particularly if they do not allow time for adequate acclimatization. Each individual undergoes the process of acclimatization differently and thus may be more or less susceptible to the development of all altitude illnesses. Allowing time for acclimatization is still the best preventative measure; recognition of symptoms early should minimize the chance that anyone becomes gravely ill or dies from HAPe. Enough clinical and practical information is available to develop even better educational programs for the sojourner to high altitude and to his/her physicians, travel partners, or high altitude guides. Awareness and prevention are certainly the best ways to attack HAPe.

Medical research, begun by great pioneers such as Charlie Houston, Herb Hultgren and others, has led to further insight into the mechanism of this non-cardiogenic form of pulmonary edema occurring in otherwise healthy individuals. Understanding at the physiologic, cellular, molecular, and genetic levels will be forthcoming. When it does, it will be another example of the human will to understand the mechanism of diseases and thus prevent the unnecessary loss of people who enjoy the many wonders of the high altitude environment.

Suggested References


Dr. Robert “Brownie” Schoene began climbing in the Shawangunks while in medical school 30 years ago. As a pulmonologist at the University of Washington in Seattle, he was a climber-scientist on the 1981 American Medical Research Expedition to Mt. Everest. Also in the 1980s, he conducted research on Denali with Peter Hackett, participated in the high altitude chamber study Operation Everest II and studied high altitude dwellers in Chile and Peru. His particular interests in high altitude are physical performance and HAPE. He is a professor of medicine at the University of Washington.