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High Altitude Pulmonary Edema

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1. Introduction

High altitude pulmonary edema (HAPE) is a form of high altitude idiopathy that occurs in a minority of people upon either the first or subsequent exposure to high altitudes. It is triggered by a shortage of oxygen and certain other predisposing factors, all of which lead to a sudden increase in pulmonary arterial pressure, increase in lung blood volume, disturbance of pulmonary circulation, and leakage of fluid in microcirculation into the pulmonary interstitium and alveoli. The clinical symptoms of this condition include dyspnea and hacking cough.

HAPE is a severe type of acute high altitude disease, typically occurring at altitudes above 4,000 meters. However, cases have been reported at altitudes as low as 2,261 meters in Xining, China. HAPE is a rapid-onset condition that can progress and change quickly, especially during the first stage of high altitude exposure, usually within a week, peaking within three days. According to a report based on 332 cases, 63% of HAPE patients presented symptoms within three days, and the fastest onset was after only a few hours. HAPE occurs mostly in unacclimatized sea-level residents when they first ascend to high altitudes or acclimatized individuals ascending from lower to higher altitudes. It can also occur in long-term high altitude residents or high altitude natives undertaking excessive physical activities or in those who return to high altitudes after living in low-altitude areas for a period of time. HAPE patients can recover after short-term treatment and continue to stay at high altitudes. However, improper treatment may lead to negative effects. The incidence rate is closely related to the altitude, rapidity of exposure, season, the individual's physical condition, and the intensity of activity.

2. Epidemiology

2.1 Incidence rate

1. Population Incidence

The incidence rate of HAPE varies significantly between China and the others country reports, for example it ranges between 0.15% and 9.9% in Chinese report. The incidence rate is higher in kids and teenagers than in adults. For instance, data collected from the Andes Mountain area of Peru reports that the incidence rate was 10% in children aged 2-12, 17% in teens aged 13-20, and 3% in adults over 21.

2. Hospitalization rate

Due to the differences in location and population served, different treatment facilities have reported rather different hospitalization rate. The Menon hospital, at an altitude of 3,450 meters, treated 101 HAPE patients over two years, accounting for 5-10% of all inpatients in the department of internal medicine; a hospital in Changdu (Tibetan), at an altitude of 3,200 meters, treated 33 HAPE patients over 11 years, accounting for 0.37% of all inpatients in the internal medicine department and 6.28% of all inpatients with high altitude diseases; the General Hospital of the Tibet Military Region, at an altitude of 3,658 meters, treated 2,853 HAPE patients from 1956 to 2005, accounting for 89.6% of all inpatients with high altitude diseases during the same time period.

3. Age Distribution

Reports from the Andes and Rocky Mountain areas show higher incidence in children, but occurrences in children below 2 years old are rare and the maximum age of all HAPE patients covered in these reports was found to be 53 years old. In the General Hospital of the Tibet Military Region, the youngest HAPE patient was 1 year old and the oldest one was 63 years old. We think that HAPE can occur at any age, but children and young adults are more susceptible.

4. Gender Differences

HAPE can occur in both males and females. Many reports show higher incidence in males, mainly because more males travel to high altitude areas. In mountaineering and high altitude medical research teams, male participants are more common, hence a higher reported incidence of HAPE in males. Horrobin et al. mentioned that in Kenyan mountain areas there were many female mountaineers, none of whom developed HAPE. However Hultgren et al. reported that among 97 lifelong mountain residents, HAPE occurred mainly in females.

5. Racial Differences

It has been shown that there is no significant difference in HAPE incidence between Peruvian Indians and Caucasians in the plateau areas of Peru. However, some have suggested that the Sherpa of Nepal have a lower HAPE incidence than the Indians of Peru. They point out that the Indians have only inhabited the Andes for about 10,000 years, whereas the Sherpa, originally from the Tibetan Plateau, have lived in high altitude areas for several tens of thousands of years. Therefore, the Sherpa may be more adapted to high altitudes environment than Peruvian Indians. Our investigation found that, on the Tibetan Plateau, HAPE incidence in native Tibetans was lower than in Han immigrants. In the 923 HAPE cases treated by the General Hospital of the Tibet Military Region over the past ten years, there was only one Tibetan patient. Recently we have retrospectively analyzed for severe acute mountain sickness of 3184 Inpatients cases in General Hospital of Tibet Military region Hospitalization from June 1956 to June 2005, and in which the incidence and clinical characteristics of native Tibetan plateau were analyzed.The results detected 24 cases of high altitude native Tibetan suffering severe cases of acute mountain sickness, high altitude pulmonary edema 21 cases and high altitude cerebral edema 3 cases in them, incidence of severe acute mountain sickness in native Tibetan population was 0.75% (24/3184).

6. First and Repeated Exposure to High Altitudes

Whether triggered by the patient's first or a subsequent exposure to high altitude, HAPE onset usually takes place between one and seven days, but it can start as early as three hours or as

late as ten days after exposure. Occasionally, HAPE is triggered in high altitude residents by such factors as fatigue. For those who travel to high altitudes by plane, the typical time of HAPE onset is within three days. Data collected from Peru and the U.S. suggest that high altitude residents are likely to develop HAPE when returning to the plateau after spending typically one to three weeks on the plains. In Tibetan areas, HAPE tends to be triggered when residents spend typically three to six weeks on the plains before returning.

7. Mode of Transportation to High Altitude Area

Traveling to high altitude areas, whether on foot, by ground vehicle, or by airplane, can trigger HAPE. In recent years, as more people take airplane flights to the Tibetan Plateau, the number of HAPE patients who have arrived by plane has substantially increased. Among the 2,853 HAPE patients treated by the General Hospital of the Tibet Military Region between 1956 and 2005, 2,054 patients were traveled to Tibet by airplane.

8. Occupation and Labor Intensity

HAPE can occur in individuals of all occupations when they are exposed to high altitudes, but it is more common in those engaged in heavy physical labor. For instance, during the Qinghai-Tibet Highway, construction workers have a higher HAPE incidence than drivers, who in turn have a higher HAPE incidence than travelers taking rides. Those who are rapidly exposed to high altitudes and extreme fatigue are particularly susceptible to HAPE. Therefore, individuals engaged in physical activities at high altitudes, such as plateau mountaineering, alpine skiing, or traveling to high altitudes are all at risk for HAPE. In addition, HAPE is more likely to occur in young boys, as they tend to be more active and less willing to rest than young girls and adults.

9. Season of Onset and Changes in Climate

HAPE can occur in any season, but in general it is more common in the winter and spring. Earlier statistics from domestic show the onset of HAPE to be distributed mostly from November to March of the next year. More recent data suggest an increase in the prevalence of HAPE between January and October, mainly because there have been more people traveling to and from the plateau or engaging in high altitude activities during this period.

10. Upper Respiratory Tract Infection and Acute mild mountain sickness

Upper respiratory tract infection can also trigger HAPE. Among the 865 HAPE patients treated by a Tibetan hospital in Lhasa, 30% had already had a previous upper respiratory tract infection at the time of onset. It is suggested that upper respiratory tract infection may trigger HAPE because contracting an upper respiratory tract infection after reaching a high altitude substantially worsens the shortage of oxygen.
A minority of those who show Acute mild mountain sickness (AMMS) may develop HAPE without prompt treatment. Among the 230 HAPE cases reported by a hospital in southern Xinjiang, 112 (47%) started out with AMMS. From this it can be concluded that, when developing acute or even minor AMMS or upper respiratory tract infection, one should rest and receive immediate treatment to prevent the condition from progressing to HAPE.

11. Individual and Familial Susceptibility

It has been reported that there are patients who develop severe HAPE more than two times, up to four times. Analysis on the 923 HAPE cases treated by a hospital in Lhasa showed that 27% of the patients returning to high altitudes developed HAPE two or more times, two of

them even seven times. In our clinical experience we have seen one worker developing HAPE eight times. It is worth pointing out that some HAPE patients, when returning to high altitudes from the plain, may still develop HAPE again even if they take active measures to prevent it, such as bed rest, oxygen inhalation, and medicine.

Some reports have shown that HAPE can co-occur in fathers and sons, brothers, and mothers and daughters. In Tibetan, Zhang reported HAPE occurring in three generations of one family, suggesting that familial and individual factors are involved in patients' susceptibility to HAPE. Animal studies have also shown species and individual differences in susceptibility to HAPE.

2.2 Fatality rate and cause of death

1. Fatality Rate

A collection of data showed that among 160 HAPE cases that occurred between 1958 and 1965 in China, the fatality rate was 9.4%. In recent years, due to substantial improvements in medical conditions and the promptness of treatment, the fatality rate has decreased significantly. For instance, among the 923 cases of HAPE treated by the General Hospital of the Tibet Military Region in the northern Tibetan plateau, the fatality rate was 0.33%.

2. Cause of Deaths

When treated promptly, most HAPE patients can recover in three to five days. However, death still occurs occasionally, and the causes can be generally summarized as belonging to one of the following categories: 1) Delay in diagnosis or treatment due to poor transportation and substandard medical conditions in remote areas. 2) Deterioration of the patient's general condition caused by undiagnosed and untreated complications such as heart failure, shock, massive pulmonary embolism, severe lung infection, and cerebral encephaledema/encephalorrhagia. 3) Severe HAPE may cause instant death, and co-occurring pulmonary embolisms or encephalorrhagia can also lead to death.

In summary, the incidence of HAPE is closely related to factors such as the mode of transportation to high altitude regions, the rapidity of exposure to high altitudes, the altitude itself, the medical support received, and individual susceptibility. Fatigue, upper respiratory tract infection, and excessive mental stress are all important triggers of HAPE. HAPE mostly occurs at altitudes above 3,000 meters because there are more immigrants at these altitudes. HAPE is not clearly correlated with age or gender. With the increasing of knowledge on HAPE and improvements to medical conditions, the fatality rate of HAPE has become extremely low.

3. Causes and predisposing factors

HAPE is a disease that occurs at high altitudes, its main cause being scarcity of oxygen. All factors that aggravate oxygen shortage in the body lower the body's tolerance to low oxygen levels, or add load to pulmonary circulation can trigger HAPE. The most common predisposing factors include cold, fatigue, and upper respiratory tract infection.

1. Cold

Cold is a basic feature of plateau weather. The temperature on the Tibetan Plateau is on average more than 20°C lower than the temperature at sea level on the same latitude. At night, wind blows downwards from the snow-covered mountaintops, further accelerating

the drop in body surface temperature and making the night at high altitudes especially cold. Under external conditions, extreme coldness accompanied by wind and snow, the body will speed up its metabolism and consume more oxygen. At the same time, sympathetic excitability will become elevated, increasing the venous blood return from the peripheral veins, especially those on the surface of the skin, increasing the load of pulmonary circulation. In addition, pulmonary arterioles contract, inducing or aggravating pulmonary hypertension and eventually triggering HAPE.

2. Fatigue

Physical labor can increase oxygen demand ten times. Physical labor further aggravates oxygen shortage. In addition, physical labor at high altitudes increases the release of catecholamine, and hyperventilation can cause respiratory alkalosis, decrease the concentration of $PaCO_2$, and lead to venoconstriction in the systemic circulation and subsequent increases both in the cardiac output of the right side of the heart and in pulmonary blood volume. Physical labor may further increase the pulmonary arterial pressure and decrease the concentration of $PaCO_2$. Those who engage in excessive mental labor may also be susceptible to HAPE due to bodily fatigue.

3. Upper respiratory tract infection

Upper respiratory tract infection often causes fever, which increases oxygen consumption. If complicated by bronchitis, causing coughing and an increase in bronchial secretions, it will affect pulmonary ventilation and cause damage to the alveolar epithelia, impeding the generation of surface-active substances. According to statistics from Lhasa, 30% of HAPE cases were triggered by upper respiratory tract infections; data from southern Xinjiang showed 29%.

4. Excessive mental stress

Mental stress, anxiety, and fear can increase the release of catecholamine, which in turn increases pulmonary arterial pressure and triggers HAPE.

5. Rapidity of exposure to high altitudes

Among those who quickly enter the plateau areas by ground vehicle or by plane without adaptation trainings, the incidence of HAPE is substantially higher than in those who come by slower means. This is because rapid exposure to high altitudes leads to acute oxygen shortage, in which the body does not have enough time to adapt and shows extremely poor tolerance to low oxygen levels.

6. Sleep and hypnotic drugs

During sleep, the horizontal position of the body increases pulmonary blood volume (500 ml more than an upright position). The shallow breathing that takes place during sleep, especially the periodic or irregular breathing accompanied by temporary apnea can aggravate the oxygen shortage.

The incidence of HAPE mainly depends on the altitude, temperature, and adaptability of the body. High altitudes, low temperatures, and failure to acclimate are three basic factors that trigger HAPE. Individuals may not develop HAPE when only one factor is present. With two factors, the incidence rate is still not high. However, when all three factors are present, one is much more likely to develop HAPE. The incidence rate will increase further if there are other coexisting conditions. Those who are exposed to high altitudes without a thorough

physical examination may have undetected organic cardiovascular diseases, organic diseases of the respiratory tract, liver, brain or kidney, malnutrition, or hypoproteinemia.

4. Pathogenesis

The incidence of HAPE is closely correlated with oxygen shortage at high altitudes. Currently, it is believed that the following processes are important: an excessive increase in the pulmonary arterial pressure, an increase in the permeability of the pulmonary capillaries, and impairment in alveolar epithelium water clearance. Among these three, an excessive increase in the pulmonary arterial pressure is the key link.

4.1 Excessive increase in the pulmonary arterial pressure

In 1904, Plumier et al. observed that low oxygen levels could lead to pulmonary hypertension. In 1964, Hultgnen performed right cardiac catheterization on four acute HAPE patients and found that in both the clinical and the recovery periods their pulmonary arterial pressures were significantly higher than that of control subjects at the same altitude, but their right arterial pressures, pulmonary venous pressures, and pulmonary capillary pressures were all essentially normal. There are several ways in which hypoxia that occurs at high altitudes can lead to pulmonary hypertension.

1. Pulmonary vasoconstriction caused by hypoxia

Hypoxic pulmonary vasoconstriction can redirect blood flow from low-oxygen alveolar regions to alveoli with higher oxygen content, which improves the ventilation/perfusion ratio and gaseous exchange, allows sufficient oxygenation of the blood, and increases arterial partial pressure of oxygen. However, pulmonary hypertension over a long period of time can also cause a series of pathophysiological changes and become an important pathologic basis of the initiation and development of HAPE.

Studies on the mechanisms of hypoxic pulmonary vasoconstriction have demonstrated that, at low oxygen levels, the calcium concentration and transmembrane inflow of calcium ions in the pulmonary arterial smooth muscle cells are both significantly increased. As hypoxia the distribution of ions across the membranes of the pulmonary arterial smooth muscle cells, calcium and sodium ions flow into the cells and potassium ions flow out, causing the resting membrane potential to decrease, approaching its excitation threshold. This depolarization of the pulmonary arterial smooth muscle cells leads to increased reactivity of the pulmonary vessels and increased tension in the pulmonary arterioles and pulmonary arteriolar contraction. Some investigators believe that hypoxia directly changes the transmembrane potential of the pulmonary artery smooth muscle cells, leading to calcium ion inflow and decrease of excitation threshold of these cells, which then causes the smooth muscles of the arterioles to contract. In addition, vasoactive substances such as prostaglandin, thromboxane A_2, angiotonin, and histamine may serve as regulators or synergists in hypoxic pulmonary vasoconstriction. However, persistent pulmonary hypertension caused by hypoxia may involve many vasoactive substances, the importance of each varying depending on the specific conditions.

Hypoxic pulmonary vasoconstriction doubtlessly leads to pulmonary hypertension. As to how the pulmonary hypertension causes HAPE, currently there are three hypotheses.

a. Regional maldistribution of blood flow. It has been proposed that when those who are sensitive to hypoxia at high altitudes are exposed to low-oxygen environments, their

muscle arterioles contract rigorously and precapillary resistance increases, while their non-muscle arterioles expand under pulmonary hypertension. The sudden increase in the hydrostatic pressure in the afflicted areas, plus other factors, can cause HAPE. As the changes described above occur in some but not all pulmonary arterioles and capillaries, the pathological changes manifested in the HAPE are usually regional, in accordance with the patchy distributions of edema in HAPE observed via X-ray.

b. At high altitudes, as hypoxia leads to sudden increases in pulmonary arterial pressure, this high pressure in turn causes closed capillaries to instantly open. The abrupt increase in the capillary pressure then causes fluid to leak out.
c. It has been proposed that fluid does not leak out through the capillaries but rather directly through the walls of pulmonary arterioles under the pulmonary hypertension caused by hypoxia.

2. Increases in the resistance to pulmonary venous return

The left ventricle is a relatively large, muscular organ that needs to overcome the high pressure and high resistance of systemic circulation to pump blood. At high altitudes, when oxygen shortage is minor, the body can employ a series of adaptive mechanisms on levels ranging from the systemic to the cellular to alleviate the damage to myocardia caused by hypoxia. However, when oxygen shortage is severe (such as may occur in cases of rapid ascent, excessive physical activity, and severe cold), there is no time for the body to set up these adaptive mechanisms of antihypoxia on the cellular level. In this case, hypoxia will cause direct damage to myocardia, especially those on the left side of the heart. Although left heart failure is not the main cause of HAPE, in clinical situations, cardiac agents have proven to be effective to a certain extent. Animal studies have also shown that compensation in heart function can significantly affect the progress of hypoxic pulmonary hypertension.
When the myocardial damage induced by oxygen shortage exceeds a certain degree, the function of the left heart decompensates, causing an increase in the left ventricular end diastolic pressure (LVEDP) and in the left atrial pressure (LAP). This in turn boosts pulmonary hypertension and contributes further to the development of pulmonary edema. Pulmonary edema impedes gaseous exchange and oxygenation, and the resulting decrease in arterial partial pressure of oxygen further aggravates myocardial anoxia and damage. Increases in high altitude pulmonary blood volume cause an increase in the pulmonary venous resistance.

3. Increases in pulmonary circulation blood volume

Increases in pulmonary blood volume are another important factor that can elevate pressure in pulmonary circulation. It has been shown that 48-72 hours after healthy soldiers were airlifted from sea level to 3,658 meters, their pulmonary blood volumes increased by 82%. This is because oxygen shortage acts on the central nervous system and causes increased sympathetic excitability. Increased sympathetic excitability results in the large-scale release of catecholamines. At the same time, due to the increase in resistance in the peripheral vessels, the left ventricular load increases and cardiac output decreases while left atrial pressure increases. Pulmonary venous return is impeded, causing blood to fill the blood vessels of the lungs. The increased blood supply and reduced blood output in the pulmonary circulation increase pulmonary blood volume. The compensatory erythrocytosis and increase in both water and sodium retention caused by hypoxia increase blood volume in general, including pulmonary blood volume, which also leads to pulmonary edema.

4. Formation of micro-thrombi in the pulmonary vessels

The formation of micro-thrombi in the pulmonary circulation is a pathological feature of HAPE. Autopsies of HAPE patients have found extensive blockages by thrombi in the pulmonary capillaries and some in the branches of the pulmonary veins and arteries, demonstrating that the formation of thrombi in the pulmonary vessels is relatively important to the pathogenesis of HAPE. Due to extensive micro-thrombus formation in the pulmonary capillaries and in other organs such as the brain, the liver, the spleen, the kidney, and the intestine, it has been suggested that hypoxic pulmonary hypertension results from abnormal coagulation and general thrombus blockage of the pulmonary capillaries.

As to the mechanism by which micro-thrombi form in the pulmonary vessels, it is generally believed that as the levels of fibrinogen and anti-fibrinoclase released by the liver increase and levels of fibrinoclase activators released by the lung decrease, the resulting abnormal fibrinolysis is an important pathophysiological basis of the formation of micro-thrombi in the pulmonary vessels. Singh et al. proposed that hypoxia could lead to damage to the fibrinoclase system and that this damage might disturb the dynamic balance between the formation and dissolution of fibrin, causing fibrin to build up in the pulmonary vessels and hence cause the formation of micro-thrombi.

Studies have shown that during the initial stages of HAPE, there are substantial increases in the level of platelet factor 3, and in the release of ADP, resulting in decreased platelet mobility. They have also found that, in HAPE patients, the levels of plasma immunoglobulins, including IgG, IgA, and IgM, all increase significantly. IgG and IgM can adhere to the surface of platelets and change their electrophoretic mobility, increasing platelet adhesivity and release of ADP. ADP can promote the utilizing of platelet factor 3, which further speeds up the coagulation process. Imbalances in cellular immune function cause immune complexes to build up. As the immune complexes activate blood coagulation factors, they further aggravate blood clotting in the blood vessels. The aforementioned weakening of the cellular immune function co-occurs with a decrease in the dissolution activity of fibrin. When the dissolution activity of fibrin improves, cellular immune function also recovers. In addition, recent studies have found that the magnesium content of erythrocytes and leukocytes increases significantly in healthy individuals who adapt well to high altitudes, but in HAPE patients it decreases significantly. Magnesium can alleviate coagulation by expanding blood vessels, stabilizing fibrinogen and platelets, and accelerating the dissolution of fibrin.

4.2 Increases in the permeability of the pulmonary capillaries

It has been reported that when dogs were placed at a simulated altitude of 6,401 meters, the flow of lymph in the right lymphatic duct increased. After inhaling pure oxygen, lymph flow decreased, the lymphatic duct expanded, but there was no sign of blockage. The causes of lymph flow increase included increased pressure and increased permeability resulting from pores opening in the walls of the lymphatic ducts in a low-pressure, low-oxygen environment. When the dogs' arterial oxygen saturation dropped to 75% (corresponding to an altitude of 5,200 meters), the lymph flow began to increase. When the arterial oxygen saturation dropped to 52.5% (corresponding to an altitude of 6,100 meters), the lymph flow increased substantially. Once red blood cells enter the lymph, the capillaries are considered damaged. Schoene collected bronchoalveolar lavage fluid from HAPE patients in a lab at an altitude of 4,400 meters by branchofiberoscope. Component analysis showed elevated

protein content, even higher than that in the edema fluid collected from adult respiratory distress syndrome (ARDS) patients. All these directly demonstrate that HAPE results from the leakage of fluid, protein, and even blood formed elements caused by the increased permeability of the pulmonary capillaries, suggesting that HAPE is a type of protein-rich, high-permeability pulmonary edema. In 1991, West JB et al. successfully simulated the pathophysiological process of HAPE in the laboratory by increasing the pulmonary arterial pressure of laboratory animals. He observed that when the rabbits' pulmonary capillary pressure reached 40 mmHg, the endothelia of the pulmonary capillaries and alveoli and sometimes even all the linings of the alveoli started to rupture.

The mechanisms by which the pulmonary capillary permeability increases may include the following factors.

1. Direct damage to the respiratory membrane structure

According to studies, under emergency conditions involving hypoxia, the endochylema of the pulmonary capillary and alveolar endothelial cells become condensed, causing the cells to shrink, which in turn expands the intercellular space of the alveolar capillary membranes and increases their permeability.

2. Decrease in secretion of alveolar surfactants

The alveolar surfactant is a type of phospholipin secreted by alveolar epithelial type II cells. When the lung tissues experience shortages of oxygen and blood, the normal metabolism of the alveolar epithelial type II cells is disturbed, and the secretion of this substance decreases. In high altitude, secretion of this substance may decrease, causing the permeability of the barrier between the capillaries and lung tissues to increase, leading to HAPE.

3. Increases in levels of acidic metabolites in local tissues

The anaerobic metabolism increases and the acidic metabolites accumulate, causing the physicochemical properties of the adhesion substance between the capillary endothelial cells to change and the basilar membrane to denature, which eventually leads to increased capillary permeability.

4. Respiratory tract infection

Any respiratory tract infection can directly damage the pulmonary capillaries and tissues through inflammatory metabolites and bacterial toxins, increasing their permeability. It is already known that hypoxia can induce inflammatory reactions involving immunocytes and epithelial cells, and therefore it can be deduced that high altitude hypoxia may induce the secretion of inflammatory cytokines, causing HAPE by producing pulmonary extravasation. To understand the relationship between inflammation and the pathogenesis of HAPE, researchers measured the levels of several inflammation mediators under hypoxia, including interleukin-6 (IL-6), interleukin -1 receptor antibody (IL-1ra), and C reactive protein (CRP). The moderate increase of these inflammatory markers reflects the presence of general local inflammation and suggests that inflammation may be involved in the pathogenesis of HAPE. Another study measured continuously the level of NO, a marker of respiratory inflammation, in the expiratory air of human subjects, and found that at 4,359 meters, the 13 subjects who were also HAPE patients among 28 subjects did not show trend of elevated NO levels during the clinical period, found the NO content in the expiratory air of subjects during their stay at high altitudes was 30% lower, indicating that respiratory tract infection does not precede HAPE.

5. Increases in plasma fibrinogen and the decreases in the dissolution activity of fibrin cause fibrin to accumulate in the pulmonary capillaries, forming thrombi that block them. This increases the permeability of the capillary walls.

4.3 Impairment of water clearance by the alveolar epithelium

HAPE results from unbalanced fluid secretion and reabsorption in the alveoli. In particular, the amiloride-sensitive epithelial sodium channel (ENaC) is involved in 40-60% of the re-absorption processes. It has also been found that β2 antagonist, which activates epithelial sodium channels (ENaC), also promotes water clearance in the lungs. In addition, *in vitro* studies have found that hypoxia inhibits Na+/K+-ATPase activity in alveolar epithelial type II cells as well as the co-transportation of Na, K, and Cl. This all suggests that hypoxia impedes the transmembrane re-absorption of water and sodium in epithelial cells.

4.4 Increases in sympathetic excitability

Studies have found that sympathectomy or blockage of cervical sympathetic nerves can eliminate HAPE. This suggests that the pathogenesis of HAPE is clearly related to sympathetic excitability. It has been found that the subjects' sympathetic excitability instantly increased at 3,500 meters, reaching a peak value within 24-72 hours, which is exactly the period of time during which HAPE is most likely to occur.

4.5 Individual susceptibility

Given the same conditions, the incidence of HAPE shows differences along racial, individual, and age lines. A study reported that among the 43 patients with recurrent HAPE, thirty-two developed HAPE 2 times, seven 3 times, three 4 times, and one 6 times. This shows that individual susceptibility is one of the factors for the incidence of HAPE. When comparing HAPE patients to normal subjects, researchers have found that the chest circumferences and chest anteroposterior diameters of acute HAPE patients are both longer than those of controls. In addition, there are more circular muscle fibers on the pulmonary arteriolar walls of the acute HAPE patients. Individual differences in internal factors such as the tissue structure of the pulmonary vessels and immune function status may lead to individual differences in sensitivity, tolerance to hypoxia, and other steps of the pathogenesis of HAPE.

In summary, the pathogenesis of HAPE is complex, involving many steps. Currently well-accepted factors include the following:

a. Hypoxia directly damages pulmonary capillary endothelial cells and expands or destroys the intercellular space, leading to general damage to the structure of the air-blood barrier, which causes blood plasma to leak directly into the alveolar space.
b. Hypoxia damages alveolar epithelial type II cells, diminishing their ability to secrete surfactants, leading to a decrease in alveolar surface tension, which causes the fluid and proteins in the pulmonary capillaries likely to leak out.
c. Hypoxia prompts the alveoli to release cytokines such as histamine, serotonin, interleukin-1, interleukin-6, leukotriene E4, tumor necrosis factor, and C-reactive protein, causing capillary permeability to increase.
d. Hypoxia prompts pulmonary arteriole constriction and an increase in vascular resistance, resulting in pulmonary hypertension. At the same time, sympathetic excitability increases and blood is redistributed, leading to an increase in pulmonary blood volume and body fluid retention, which causes capillary hydrostatic pressure to increase and fluid components to leak out, further aggravating HAPE.

5. Pathological changes

The pathological changes involved in HAPE mainly occur in the lungs. Visual inspections reveal increases in the volume, weight, and surface moisture of the two lungs and that the

peripulmonary membrane has become stretched, rubbery, and dark red in color. When pressed, pink spumous fluid streams to the surface. Under optical microscope, expansion of the pulmonary capillaries is observed, with red blood cells accumulating inside and bleeding around the vessels. The middle layers of the muscular pulmonary arterioles thicken, the elastic layers appear serrated, and the arterioles muscularize. The pulmonary arterioles are expanded and interrupted and capillary thrombi are formed. The bronchioles and alveoli present hyaline membranous edema, and the alveolar ducts become filled with blended protein fluid or cluttered red blood cells. The capillaries in the alveolar septum expand, with blood accumulating inside and forming thrombi. Under electron microscope, unformed edema fluid with low electron concentration is observed inside the pulmonary alveolar space. Red blood cells accumulate, the capillaries in the alveolar septum expand, the intercellular space between endothelial cells enlarges, and the endothelial cells swell. The number of pinocytotic vesicles and some vacuolated were increased. The alveolar epithelial type I and type II cells swell, shedding surface microvilli. The perinuclear space of the alveolar epithelial type II cells expands, and the laminated bodies in their cytoplasts increase in number and show vacuolization.

6. Clinical manifestation

Like those of other types of acute pulmonary edema, the clinical manifestation of HAPE includes dyspnea, cyanopathy, cough, the production of large amounts of white or pink spumous phlegm when coughing, and moist rales in one or both lungs.

6.1 Symptoms

At the early stage, the most common symptoms of HAPE include severe headache, dyspnea, palpitations, shortness of breath, chest tightness, chest pain, panic, extreme fatigue, weakness, persistent dry cough, worsened nighttime insomnia, pale complexion, and moist, cold skin. As the condition progresses, the above symptoms worsen, and patients may experience severe dyspnea, an inability to lie flat, and coughing out spumous phlegm, which is initially white or faint yellow in color and later turns pink, in some worse cases gushing out of the mouth and nose. Most patients display dysphoria while a minority experience hypersomnia, in some cases accompanied by altitude coma.

6.2 Signs

One distinctive sign of HAPE is moist pulmonary rales. In severe cases, moist rales can be heard in all regions of both lungs along with wheezing and phlegm. The cardiac sound is often masked. In mild cases, moist rales can be heard at the base of one or both lungs. Most patients display cyanosis in the lips, nail beds, and parts of the face. Due to dyspnea, patients often take bed rest in a semi-reclining position. About two thirds of patients experience fever, usually at 37.5-39^{o}C. If body temperature persists over 38.5^{o}C, it usually indicates complicating upper respiratory tract infection. Signs also include increased heart rate, loud or splitting P2, and grade 2-3 systolic murmur in the apex region of the heart. Some patients exhibit sulcus terminalis cordis expansion, possibly with diastolic gallop, jugular vein distention, hepatosplenomegaly, and edema complicated in some cases by cardiac insufficiency. Compared to other acute pulmonary edemas, HAPE has the following distinctive clinical features:

a. At early stages, HAPE patients only show symptoms of mild AMS, such as headache, dizziness, palpitations, insomnia, anorexia, and nausea. As these can be early symptoms of HAPE, they must be addressed with caution. Pulmonary auscultation may show normal results, but X-ray examination will reveal typical infiltrated shadows.
b. In some patients, HAPE progresses very rapidly, with acute onset and severe symptoms. Patients experience extreme dyspnea, asphyxia, and rales in all lung regions, quickly reaching impending death status. They may exhibit bloody pleural fluid in one or both lungs before death.
c. Patients tend to have high blood pressure, fine pulse, tachycardia, loud or splitting P2, and either a mild systolic murmur or diastolic gallop in the apex region of the heart. Only a few also experience right heart failure.
d. Some patients mainly show neurological and psychiatric symptoms, which often include headache, vertigo, diplopia, vomiting, phrenitis, and irritation. A minority of patients exhibit symptoms of derangement, meningeal irritation, or even coma. Further examination typically reveals increased pressure in the cerebrospinal fluid and edema in the optic papilla. In these cases, encephaledema often co-occurs, as can be detected by encephalic CT or MRI examination.
e. At the onset of HAPE, there is usually no fever, but some patients show low fever and intolerance to coldness.

6.3 Diagnostic examination

a. Hemogram: The leukocyte count is typically normal or mildly increased; about 40% patients have a count over 10000/mm^3. The highest count recorded in our study was 64000/mm^3. The neutrophilic granulocyte count also increases mildly. If the leukocyte and neutrophilic granulocyte counts continue to rise, it usually indicates concurrent infection.
b. X-rays: HAPE patients often show unilateral or bilateral flake-like or cloudy shadows centered at the porta pulmonis, mostly in the right lung. A minority of patients show large patchy or butterfly/batwing shadows. The apex regions of the lung are usually clear. At early stages, there is only thickening of the lung markings, also called pulmonary interstitial edema.
c. Electrocardiography: Manifestations of HAPE on the electrocardiogram include nodal tachycardia, right axis deviation, right bundle branch blockage, sharply tented P waves or P pulmonale, T wave inversion, and ST segment depression.
d. Blood gas: HAPE patients show substantial decreases in levels of PaO_2 and SaO_2, which are not only lower than those of healthy controls but also significantly lower than those of mild AMS patients.
e. Pulmonary function: HAPE mainly features decreases in the expiratory flow rate or diffusion capacity.
f. Hemodynamics: The pulmonary arterial pressure and resistance to the pulmonary artery are significantly increased. Left atrial pressure remains normal. The pulmonary capillary wedge pressure and cardiac index remain normal or decrease slightly.

7. Clinical classification

Using clinical signs and symptoms and the results of diagnostic examination, HAPE can be classified into three types: mild, moderate, and severe.

1. Mild HAPE: Characterized by mild dyspnea, coughing, coughing out small amounts of spumous phlegm, focal moist rales at the base of one or both lungs, respiratory rate of 20-30 breaths/minute, pulse rate under 100 beats/minute, bilateral thickening of lung markings, or cloudy spots at the base of the lungs visible on sternal X-ray.
2. Moderate HAPE: Characterized by substantial dyspnea, chest pain, chest tightening, coughing out large amounts of white or pink spumous phlegm, moist rales at the base of both lungs spreading over other pulmonary regions, respiratory rate of 30-40 breaths/minute, pulse rate of 110-120 beats/minute, bilateral thickening of lung markings, and flake-like or cloudy shadows at the base of the lungs visible on sternal X-ray.
3. Severe HAPE: Characterized by polypnea, panic, inability to lie flat, coughing out large amounts of pink spumous phlegm, severe cough, considerable blowing systolic murmur upon examination of the apex region of the heart or pulmonary valve area, moist rales sounding like boiling water in all pulmonary regions, bilaterally symmetrical cloudy shadows centered at the porta pulmonis or bilaterally symmetrical butterfly/batwing shadows visible on sternal X-ray, heart enlargement, clear protruding of the pulmonary trunk, and in some cases signs of heart failure including jugular vein distention, hepatomegaly, and edema in both lower extremities.

8. Diagnosis and differential diagnosis

8.1 Diagnosis and diagnostic criteria

1. Clinical diagnostic criteria

In China, the clinical diagnosis of HAPE is mostly based on the clinical diagnostic criteria recommended in 1995 by the Chinese Medical Association's third national medicine academic seminar. These criteria have been approved by the International Society for Mountain Medicine. The criteria include the following:

a. Upon recent exposure to high altitudes (usually considered to be 3,000 meters or more above sea level), the subject experiences dyspnea at rest, chest stress and tightening, cough, coughing out white or pink spumous phlegm, malaise, or decreased activity.
b. There are unilateral or bilateral moist rales or wheezing sounds in the pulmonary field, central cyanosis, tachypnea, and tachycardia.
c. X-ray shows unilateral or bilateral flake-like or cloudy infiltrated shadows centered at the porta pulmonis, often scattered and irregularly distributed but sometimes fused into a large patch. The podoid is normal in most cases, but sometimes signs of pulmonary hypertension and right heart enlargement can also be observed.
d. Other cardiac and pulmonary diseases, such as myocardial infarction and heart failure are excluded by clinical and electrocardiographic examinations. Pneumonia is also excluded.
e. Symptoms quickly improve after bed rest, oxygen inhalation treatment, or descending to a lower altitude, and signs shown by X-ray disappear within a short period of time.

2. Criteria for early diagnosis

As we gain a deeper knowledge of HAPE and accordingly improve both protective and therapeutic measures, clinically typical HAPE cases have become rare. If we continue to refer to the previous diagnostic criteria, it will be difficult to identify HAPE patients. For this reason, we carried out a study funded by the National Sci-Tech Support Plan and proposed the following as the criteria for early diagnosis of HAPE:

a. Upon recent exposure to high altitudes (usually considered to be 3,000 meters or more above sea level), the at-rest subject experiences palpitations, chest tightening, dyspnea, and coughing with or without small amounts of white spumous phlegm.
b. There is local, unilateral or bilateral coarse breathing with or without focal moist rales. There is also central cyanosis, tachycardia (>100 beats/minute), and tachypnea (>24 breaths/minute).
c. Early routine X-ray examination shows a decrease in transmittance of the lungs, blurred or increased lung markings, and the presence of ground-glass opacity or small patchy shadows in the lung. CT scan shows increased number and thickening of lung markings, ground-glass opacity, nodular shadows, scattered or isolated alveolar edema on terminal bronchioles, and fine reticular shadows.
d. Routine blood examination shows increases in the leukocyte count and the proportion of neutrophilic granulocytes.
e. Arterial blood gas examination shows persistent hypoxemia accompanied by mild respiratory alkalosis.
f. Electrocardiographic examination shows nodal tachycardia, clockwise rotation, sharply tented P waves, and so on.
g. Ultrasonic cardiogram shows early, prominent, persistent pulmonary hypertension.
h. All symptoms quickly improve after treatment such as bed rest, oxygen inhalation, decreasing pulmonary arterial pressure, and diuresis.

It should be noted that criteria a-c must be met first. Conditions in d-h are then evaluated. The criteria are then combined collectively to produce an accurate early diagnosis. In clinical practice under aforementioned criteria, if we also refer to the severities of the condition and of the signs, the features and sizes of the shadows on the chest film, make proper diagnoses, and give prompt, effective, on-site treatment, it is completely possible that we will be able to keep early-stage HAPE under control.

8.2 Differential diagnosis

1. Adult respiratory distress syndrome

a. Differences in the cause of disease: The fundamental cause of HAPE is oxygen shortage at high altitudes and low pressure leading to disturbed pulmonary circulation and body fluid maldistribution, of which oxygen shortage is the cause. ARDS is the secondary lesion of the lung tissues directly or indirectly caused by trauma or severe infection, in which oxygen shortage is the consequence.
b. Differences in pathological changes: Both show high levels of permeability edema. However, HAPE features short duration, fibrosis of the interstitial tissues and alveolar walls, thickening of the interstitium, only mild hyperplasia in the epithelial cells of alveolar walls, and a full recovery without sequelae. ARDS may evolve into subacute and chronic conditions, such as alveolar wall fibrosis. Chronic patients may exhibit pathological changes in general bronchopneumonia, which can eventually lead to prominent fibrosis of the interstitium and the alveoli and the pathological changes of emphysema.
c. Differences in reaction to oxygen inhalation: After treatments such as oxygen inhalation and measures that decrease pulmonary arterial pressure, most HAPE patients can quickly improve and recover in 2-7 days. Only in rare cases will patients die, usually due to a long delay before treatment, extreme severity of the condition, or complication

by adult respiratory distress syndrome. ARDS usually features more severity and a longer duration, often with hemosputum or hemorrhagic sputum and unilateral or focal tubular sound with few moist rales. Oxygen inhalation, even high-pressure oxygen inhalation and assisted respiration, is often not effective. The fatality rate is relatively high, usually between 40% and 70%.

d. Differences in X-ray manifestations: HAPE often shows flake-like or cloudy shadows spreading outward from the porta pulmonis, mostly scattered at the middle and lower fields and rarely fused into large patch. The X-ray film of ARDS patients typically shows patchy shadow at the edges of the lungs, in server cases fused into a large patch. At the terminal stage, "white lung" is manifested, and the pulmonary shadows gradually disappear.

2. High altitude pneumonia

High altitude pneumonia and upper respiratory tract infection can trigger HAPE, and HAPE tends to be complicated by high altitude pneumonia. Therefore, we should carefully differentiate the two in both diagnosis and treatment.

a. Differences in cause: HAPE is caused by hypoxia under low-oxygen, low-pressure conditions at high altitudes. High altitude pneumonia is pulmonary inflammation caused by bacteria, viruses, allergies, or inhalation of hazardous substances such as kerosene or gasoline.
b. Differences in clinical manifestation: Both show increases in body temperature and hemogram. However, high altitude pneumonia usually has a rapid onset with chills and high fever. Body temperature reaches 39-40^{o}C within hours and continues to rise, causing enecia. Both the leukocyte and the neutrophilic granulocyte counts increase significantly, reaching up to 20-30×10^{9}/L. Mostly neutrophilic granulocytes can reach more than 80%. There is also a left shift of nuclei, observable toxic granulations, and vacuoles in the cytoplasts. In comparison, HAPE patients usually do not have fever higher than 38.5^{o}C, and their leukocyte and neutrophilic granulocyte counts only increase slightly.
c. Differences in clinical signs: HAPE patients cough typical spumous hemosputum or pink spumous phlegm, which can gush out from mouth and nose when large amounts are present. High altitude pneumonia patients first cough mucus and then purulent or rusty sputum.
d. Differences in X-ray manifestation: HAPE often shows either intense shadows with different densities, shapes, and sizes, or spotty, flake-like, cloudy shadows. Lesion margins of HAPE were blurred and not constrained by the interlobar fissures. The above signs are widely scattered in both lungs. High altitude pneumonia shows increased numbers of lung markings and decreased transmittance of the lung fields at early stages. Later spotty, flake-like shadows of different sizes can be observed, sometimes fused into patchy shadow, but usually limited to one pulmonary lobe or one pulmonary segment.

9. Complications

9.1 High Altitude Cerebral Edema

High altitude cerebral edema (HACE) is a common complication of HAPE, as verified by clinical examinations, lab examinations, and autopsies. Because patients may have one or

both of these two diseases, we should take great caution in diagnosis and treatment. HAPE patients often show signs and symptoms such as headache, vomiting, hypersomnia, and coma, which relate to increased intracranial pressure and cerebral edema. Fundus examination sometimes shows papilledema and fundus hemorrhage, and lumbar puncture often shows increased cerebrospinal fluid pressure. Such cases merit special attention during diagnosis and treatment.

Shortly after rapid exposure to a high altitude environment, blood within the body is redistributed via neural, fluid regulation. The vasomotion of the blood vessels in some organs undergo prominent changes resulting in large amounts blood moving to important organs, such as the lung, heart, and brain, ensuring their oxygen supply and normal function. However, if the blood flow volume, rate, and pressure in these organs become too high, disruption to microcirculation may occur. In particular, in the lung and brain, where low-pressure space is normally present, it can easily cause fluid to leak out into neighboring tissues, leading to edema. HAPE and HACE share some common pathogenesis, for the most part in the pathological changes in hemodynamics. HACE and HAPE may occur separately or jointly, sometimes in succession. Severe HAPE and large amounts of extravasation from the alveoli seriously impair oxygen uptake from the external environment, aggravating hypoxemia, which promotes the hemangiectasis of the cerebral blood-vessels via neuroendocrine regulation induced by severe hypoxia of the brain tissue. The resulting increase in cerebral blood flow and blood volume then further aggravates cerebral edema. However, HACE escalates the extravasation of pulmonary tissue and worsens HAPE via neural, fluid regulation. When HACE extends to the respiratory and cardiovascular centers of the medulla oblongata, respiration is inhibited and blood pressure drops, in severe cases leading to cerebral hernia, which can cause respiratory circulation failure or even sudden cardiac arrest, resulting in vicious circle. This is an important cause of death among patients with HAPE complicated by cerebral edema.

9.2 Cerebral infarction

Cerebral infarction is another common complication of HAPE, possibly induced by the following: 1) Acute erythrocytosis occurs due to excessive erythropoiesis triggered when the body is exposed to altitudes above a certain elevation. The compensatory erythrocytosis in the plasma leads to a significant increase in blood viscosity. Blood flow rate decreases and blood cells cluster together, resulting in increased contact between the platelets and the blood vessel walls, rendering the blood more likely to coagulate. 2) Wade et al. proposed that disturbances in cerebral circulation might play a major role in generating cerebral thrombosis. HAPE complicated with HACE is an important cause of disturbances in cerebral microcirculation, which slows down the blood flow and increases the blood viscosity of the patient, leading to cerebral thrombosis. 3) At high altitudes, the generation of blood coagulation factor in the plasma increases, creating a hypercoagulative condition. The blood of High altitude polycythemia (HAPC) patients is already in a hypercoagulative state, and second hyperfibrinolysis can easily occur. 4) HAPE patients have severe hypoxemia, which may result in damage to blood vessel endothelial cells. The above changes caused severe damage to the pulmonary capillary endothelial cells of HAPE patients, boosting platelet adhesion and activating the blood coagulation system, finally leading to cerebral thrombosis.

9.3 Multiple Organ Dysfunction Syndrome

Patients with HAPE complicated by cerebral edema are prone to multiple organ dysfunction syndrome (MODS). Patients show symptoms including headache, chest tightness, shortness of breath, nausea, aggravated vomiting, and abnormal psychological behavior. Auscultation can reveal aggravated pulmonary rales; fundus examination may show spotting or patchy bleeding in the retina and papilledema; there is gastrointestinal hemorrhage or fecal occult blood, hematuria, or proteinuria; chest X ray of most patients show enlarged hilar shadows, unilateral or bilateral cloudy shadows of uniform density in the lung field, in some cases fused into large, dense, patchy unilateral or bilateral shadows of uniform density; encephalic CT reveals decreased brain parenchymal density, narrowed bilateral cerebral ventricles, and the shallower, narrower sulci; laboratory examination will reveal increased leukocyte counts, often above 13.0×10^9/L, increased bleeding and clotting time, increased fibrinolytic activity, and increases in thromboxane B2, vWF, fibrinogen, tissue-type plasminogen activator and inhibitor in the plasma, increased levels of D-dimers, increased levels of alpha-granular membrane protein, significantly decreased levels of 6-keto-PGF1a and antithrombin III, and severe dysfunction of the coagulation and fibrolysis systems.

AMS complicated by MODS has been underemphasized and the diagnostic yield has been low. Our investigation shows that 2.5% of AMS cases are complicated by MODS, which is considerable. We need to improve early diagnosis and early detection because early treatment is crucial in reducing the fatality rate of AMS complicated by MODS.

10. Prevention and treatment

10.1 Prevention

1. Protection of susceptible populations from exposure to high altitudes

Physical examinations, especially inspections of cardiac and pulmonary functions, should be performed on individuals who are about to travel to high altitude areas. Those with heart and/or lung ailments should be advised against exposure to high altitudes.

2. Prevention of respiratory tract infection

Individuals with respiratory tract infections are more susceptible to HAPE at high altitudes. Those who catch upper respiratory tract infections before planned trips to high altitude areas should first seek treatment and only make the trip after full recovery. Prior to high altitude exposure, one should perform cold resistance exercises. After arrival, one should take active measures to keep warm and prevent respiratory tract infection.

3. Acclimatization to hypoxia

Prior to high altitude exposure, one should receive hypoxic training using masks or hypoxic respirators to increase the body's tolerance to hypoxia so as to promote high altitude acclimatization.

When possible, one should ascend to higher altitudes gradually and multisteply rather than rapidly ascend to higher altitudes to avoid body damage. Before traveling to high altitude regions, individuals should familiarize themselves with the climate characteristics and geological environment of the area and familiarize themselves with preventative treatments for high altitude diseases.

4. Reduction and control of activity level

During the first week of high-altitude exposure, one should take proper rest, reduce or avoid intense physical activity, avoid fatigue, and minimize oxygen consumption. Normal physical activity should be resumed only after the body is acclimatized to the hypoxic environment.

5. Administration of prophylactic medicine

a. Chinese traditional medicine
   There are four courses of Chinese traditional medicines that may serve to prevent HAPE:
   Compound codonopsis tablets: Take orally. Start 3 days before hypoxia exposure, 3-5 tablets/dose, 3 doses each day. Continue for 5-7 days after hypoxia exposure.
   Ginseng and astragalus pollen tablets: Take orally. Start 3 days before high altitude exposure, 5 tablets/dose, 3 doses/day. Continue for 5-7 days after high altitude exposure.
   Rhodiola rosea oral solution: Take orally. Start 3 days before high altitude exposure, 10 ml/dose, 3 doses/day. Continue for 5-7 days after high altitude exposure.
   Compound rhodiola capsules: Take orally. Start 3 days before high altitude exposure, 2 capsules/dose, 3 doses/day, continue for 5-7 days after high altitude exposure.
b. Glucocorticoid preparations
   Dexamethasone: Take orally. Start 1 day before high altitude exposure, 5 mg/dose, 3 doses/day. Continue for 2 days after high altitude exposure.
c. Carbonic anhydrase inhibitors
   Nephramid (a.k.a. acetazolamide): Take orally. Start 1 day before high altitude exposure, 250 mg/dose, 3 doses/day. Take for 2-3 days.
   Methazolamide (a.k.a. Ni Mu Ke Si): Take orally. Start 1 day before high altitude exposure, 25-50 mg/dose, 3 doses/day. Take for 2-3 days.
d. Calcium antagonists
   Nifedipine: Take orally. Start 1 day before high altitude exposure, 10 mg/dose, 2 doses/day or sublingual administration 10 mg/dose, 3 doses/day. Take for 1-3 days.
e. Beta2- receptor stimulants
   Salbutamol: Inhale. Start 1 day before high altitude exposure, 125 μg/dose, 2 doses/day. Continue for 2-3 days after high altitude exposure.
f. Phosphodiesterase inhibitors
   Sildenafil: Take orally. Start 1 day before high altitude exposure, 50 mg/dose, 3 doses/day. Continue for 2-3 days after high altitude exposure.
   Tadalafil: Take orally. Start 1 day before high altitude exposure, 10 mg/dose, 1 dose/day. Continue for 2-3 days after high altitude exposure.

10.2 Treatment

Accurate, effective early-stage treatment usually quickly improves symptoms. Therefore, early diagnosis and timely treatment are crucial to controlling the course of the disease and prognosis.

1. Oxygen inhalation or hyperbaric oxygen therapy

Oxygen inhalation can substantially decrease pulmonary arterial pressure in HAPE patients and quickly alleviate hypoxia and the series of clinical symptoms that it causes. HAPE

patients should in general use continuous administration of low-flow oxygen (4-6 L/minute). For patients with severe hypoxia, high-flow continuous oxygen may be administrated (8-10 L/minute) but for no longer than 24 hours in order to avoid oxygen toxicity. If the symptoms include excessive spumous phlegm, an appropriate amount of alcohol may be added to the oxygen humidifying containers for froth suppression.

Hyperbaric oxygen treatment can temporarily remove hypoxia for HAPE patients. Most patients show symptom improvement after 1-2 treatments and achieve recovery after 2-3 treatments. However, for a minority of patients, HAPE signs and symptoms worsen after departure from the hyperbaric oxygen chamber, which can be associated with disease severity variance and individual difference. Therefore, when treating HAPE patients with hyperbaric oxygen therapy, caution should be taken to acknowledge individual variability and monitor the severity of the condition.

2. Nitric oxide inhalation

Inhalation of low-concentration nitric oxide can quickly, selectively alleviate the pulmonary hypertension caused by hypoxia. The inhalation method is as follows: Mix 10 ppm nitric oxide with pure air and inhale through a nasogastric feeding tube at 3-5 L/minute, 30-60 minutes/treatment and 2-3 treatments/day. Patients with mild or moderate HAPE typically recover after 2-3 days. For severe HAPE patients, the duration and daily frequency of the inhalation treatments should be increased accordingly.

Inhaled nitric oxide can be oxidized into NO^{2-} and NO^{3-} in high-oxygen environments and can accumulate in the blood, which will damage the blood cells. For this reason, when treating HAPE patients with nitric oxide, simultaneous inhalation of high concentration oxygen should be avoided. Animal studies have shown that the effects of inhaling concentrations of nitric oxide ranging from 5-80 ppm on decreasing pulmonary arterial pressure are statistically the same.

3. Aminophylline

Aminophylline is the drug of choice for standard HAPE treatment. It can quickly diminish pulmonary arterial and vena cava pressure and decrease right atrial venous return volume. It can also be cardiotonic, diuretic and a smooth muscle relaxant and can reduce resistance in the systemic circulation, improving the heart function.

Regular dose: 0.25g diluted to 20ml 10-50% glucose, intravenously injected at an even speed. It can be repeated after 4-6 hours. For mild HAPE patients, administer 2 times/day. For severe patients, upgrade to 0.5g/administration, and increase the frequency of administration according to the severity.

4. Anticholinergic agents

Atropine and anisodamine can treat pulmonary vasospasms. They also decrease resistance in the pulmonary blood vessels, improve pulmonary microcirculation, keep pulmonary blood flow unimpeded, and prevent blood clotting and pulmonary thrombosis inside the blood vessels.

Regular dose: Atropine 2-5 mg/0.5hour. Anisodamine (654-2) 20-40 mg/0.5 hour, intravenous drip.

5. Dexamethasone

Dexamethasone can be used in both treating and preventing HAPE. Regular dose: 10 mg, IV injection, 2 times/day for no more than 3 days. For patients with comorbid conditions such

as epilepsy, peptic ulcer, high blood pressure, or diabetes mellitus, dexamethasone should be taken with caution or contraindicated.

6. Diuretics

Nicorol: 10 mg IV injection, 1 dose/day; Nephramid: Take orally.250 mg/dose, 3 doses/day; Drugs that alleviate pulmonary hypertension: nifedipine: 10-20 mg/dose orally or sublingually, 2 doses/day. Sodium nitroprusside: IV drip, 10-20 mg/dose.

7. Cardiotonics

Cedilanid: IV injection, 0.4-0.8 mg. Strophanthin K: IV injection, 0.125-0.5 mg.

8. Sedatives

Morphine hydrochloride: 5-10 mg, subcutaneous injection. In severe cases, dilute 5 mg to 20 ml 10% glucose and administer IV injection. For some patients with anxiety symptoms, Valium may be used with caution, but its inhibitory effects on breathing should be monitored.

9. Antibiotics

HAPE is very likely to be complicated by pulmonary infection. When the two diseases co-occur, each aggravates the other and the situation becomes difficult to control. In treating HAPE, broad-spectrum antibiotics are usually used to prevent and treat infection. Patients with mild symptoms should take broad-spectrum antibiotics (e.g. amoxicillin, norfloxacin, trimethoprim and sulphame-thoxazole etc.) orally for anti-infection purposes, and control the intake of sodium chloride to avoid worsening the HAPE. The commonly used antibiotics include the following:

a. Amoxicillin: Take orally, 1g/dose, 3 doses/day.
b. Norfloxacin: Take orally, 0.2g/dose, 3 doses/day.
c. Trimethoprim and sulphame-thoxazole: Take orally, 1-2 tablets/dose, 2 doses/day, take orally.
d. Levofloxacin: Take orally, 0.1-0.2 g/dose, 2 doses/day.
e. Penicillin (still the first choice): 4,800,000-6,400,000 units diluted in 250-500 ml glucose or saline, IV drip, 1-2 times/day. Contraindicated in patients clinically significant allergy to penicillin.
f. Ampicillin sodium/sulbactam sodium: For mild infections, 1.5g/day in 2-3 IM injections. For moderate infections, 4-9g/day in 3-4 IM injections. For severe infections 9-12g/day in 2-3 IV drips.
g. Cefamezin: 2g/dose, 3 doses/day, IV drip.
h. Cefradine: 100-150 mg/kg/day, IV drip.
i. Lincomycin hydrochloride: 0.6g/dose, 1-2 doses/day, IV drip.
j. Ciprofloxacin Lactate: 0.2g/dose, 2 doses/day, IV drip.

10. Decent to lower altitude

When possible, patients should be quickly transferred to lower altitudes (below 3,000 meters) for further treatment. After leaving the hypoxic environment, the elevated pulmonary arterial pressure can quickly return to normal levels and the series of symptoms caused by hypoxia quickly disappear. However, descent treatment is only applicable in less remote areas within a relatively short amount of time. In remote mountain areas where transportation conditions are extremely poor and continuous oxygen supplies cannot be guaranteed in transit, it is for the best to administer on-site treatment.

When transferring patients to lower altitudes, the following should be noted: 1) Transportation utilities: fast, stable transportation utilities are preferable, e.g. helicopter, truck, heavy medical vehicle, small ambulance. 2) Accompanying crew: there should be one doctor and one nurse, or at least one medical professional who can perform effective treatment through the transfer. 3) The patient in should assume a semireclining position during descent to keep the airway clear. 4) Patients with high altitude coma should assume a semireclining position. Head movement and vehicle pitching should be minimized to prevent cerebral hernia. 5) The driver should proceed slowly when road conditions are rough so that the patient's position can remain relatively stable. 6) The accompanying crew should read and record vital signs and give effective treatment when needed. 7) If a patient passes away, the time and order of vital sign loss should be recorded and body position should respectfully be kept unchanged.

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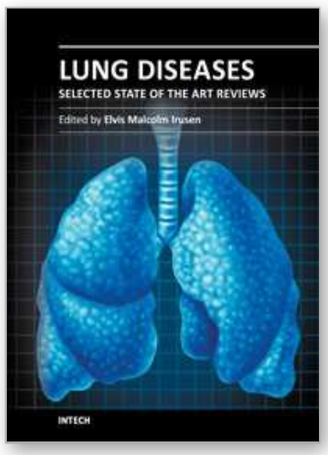
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