Emergency Medicine: Open Access
ISSN: 2165-7548

Zhou, Emergency Medicine 2012, 2:4
DOI: 10.4172/2165-7548.1000113

Review Article Open Access

Severe Acute Mountain Sickness Complicated by Multiple Organ Dysfunction Syndrome

Qiquan Zhou*

Department of High Altitude Diseases, College of High Altitude Military Medicine, Third Military Medical University, China

Introduction

Severe acute mountain sickness accompanied with multiple organ dysfunction syndrome (MODS) is a severe, critical mountain illness characterized by high altitude pulmonary or cerebral edema, complicated by 24 hours of unresponsiveness to treatment and the dysfunction or failure of 2 or more organs. Not only is it a severe illness with a high mortality rate, but the treatment for it, is also very difficult.

Plateau regions have become areas of focus, development and construction in China. With more and more people entering the plateau regions each year for development and tourism, the number of cases of acute mountain syndrome (AMS) has increased dramatically, especially in high altitude regions. High-altitude pulmonary edema (HAPE) and high-altitude cerebral edema (HACE) have become two critical high-altitude diseases most threatening to human beings in the high-altitude environment. They are the primary cause to trigger the high altitude-multiple organ dysfunction syndrome (H-MODS) and lead to mortality. In the past, we had some relatively superficial understanding of severe acute mountain sickness complicated by MODS and there was a lack of systematic research on the subject. Along the course of studying severe mountain diseases and gaining more knowledge and experience with H-MODS, we are achieving a more in-depth understanding of acute, high altitude multiple organ dysfunction. We found that cases of high altitude pulmonary edema, high altitude cerebral edema, acute respiratory distress syndrome (ARDS) and MODS all showed very similar symptoms in high altitude areas. For example, all had hypoxia as a common disease basis and H-MODS as a common adverse outcome [1,2]. Therefore, to further study and improve our understanding about severe acute mountain sickness complicated by MODS will be the key to lowering the mortality and improving prognosis in patients with severe acute mountain sicknesses.

Epidemiological Traits

We researched over 4000 cases of HAPE and HACE at dozens of hospitals in high altitude regions and found the prevailing rate of severe acute mountain sickness complicated by MODS to be at or above 2.5% [3-5]. However, the rate of accurate diagnosis was under 1%. There appears to be an urgent need for improvement in this area. We studied a total of 4095 cases of severe acute mountain sickness of the past 50 years from 11 hospitals on the Qinghai-Tibet Plateau. Of these, 3184 patients were from Tibet, 360 from Qinghai and 551 from Xinjiang. There were 264 cases of cerebral edema alone, 3,739 cases of pulmonary edema alone and 252 cases of both cerebral edema and pulmonary edema. In addition, 3248 cases showed pHAPE and 583 cases had rHAPE. The oldest age of onset was found to be 62 years old, the youngest age of onset was found to be 3 months and the mean age of onset was found to be 23.96 years old. Males made up 3757 cases and females 338. The mean elevation of incidence was 4136.91 m. Time of onset was usually about 30 hours after the patient entered the plateau. First-time high plateau visitors made up 1266 cases and returning visitors made up 2829. There were 12 native patients and 4083 patients from outside the region. Of our patients, 2041 had entered the area via cars and 2054 had entered via airplanes. Severe illness was seen in 1351 and critical illness in 197. The average time of treatment was 5.36 days and the average length of hospital stay was 9.31 days. The screening of the data of these 4095 cases, which was in accordance with the standards of the H-MODS score, resulted in 103 patients meeting the diagnostic criteria for H-MODS, a detection rate of 2.5%. This was reasonably consistent with Wei Gao's report in 2004 [6]. Among these 103 cases of severe acute mountain sickness complicated by MODS, the primary disease of 8 cases was found to be HAPE, 4 cases were found to involve HACE and 91 cases involved both. Of these 103 cases, 19 patients died, 23 were transferred to lower altitude facilities inland for treatment and 61 were cured locally. There were 14 cases involving 3 damaged organs, 25 cases of 4 damaged organs, 34 cases of 5 damaged organs and 30 cases of 6 damaged organs. The organs and organ systems damaged by this condition were, from most to least common, the lung (100%), brain (100%), blood (90%), heart (80%), kidney (61%), metabolic system (42%), liver (25%) and gastrointestinal tract (27%). Rating cases using the APACHE-II system resulted in scores as low as 16 points and as high as 29 points with an average of 21.5 points. After comparing cases of mountain disease alone and mountain disease complicated by multiple organ dysfunction, we found that except the GCS scores of patients with mountain disease complicated by multiple organ dysfunction were significantly lower than those of patients with altitude sickness alone, all other indicators were significantly higher in patients with only high-altitude cerebral or pulmonary edema. The MODS scores in particular were significantly different ($P < 0.01$). This indicates that the degree of organ damage is significantly increased after mountain disease is complicated by multiple organ dysfunctions. The study also found that although cases of MODS in the plateau and in the plains had essentially no differences in nature, hypoxia-based environmental factors gradually became more relevant as altitude increased, affecting to different extent the pathogenesis, clinical symptoms and prognosis of the syndrome. This is why the diagnosis and treatment of H-MODS involves more uncertainty than other types. It is very difficult to make the correct diagnosis using any diagnostic criteria meant for use on the plains. This causes both false negatives and false positives for H-MODS [7].

The condition of acute mountain disease, be it high altitude pulmonary edema or high altitude cerebral edema, if complicated by MODS afterwards, deteriorates rapidly as oxygen intake becomes less efficient. Response to treatment is then usually insignificant if treatment is not timely, mortality is high and prognosis poor. In the 103 MODS patients studied, 19 died, giving the condition a mortality rate of 19.2%. All of these patients died of MODS or multiple organ

***Corresponding author:** Qiquan Zhou, Department of High Altitude Diseases, College of High Altitude Military Medicine, Third Military Medical University, Key Laboratory of High Altitude Medicine, Ministry of Education, Chongqing 400038, China, E-mail: zhouqq9918@yahoo.com.cn

Received March 13, 2012; **Accepted** March 28, 2012 **Published** March 30, 2012

Citation: Zhou Q (2012) Severe Acute Mountain Sickness Complicated by Multiple Organ Dysfunction Syndrome. Emergency Medicine 2:113. doi:10.4172/2165-7548.1000113

failure. Not only does acute high altitude disease complicated by MODS progress rapidly, but indicators of multiple organ or multiple system damage appear. For example, Cr, BUN, LDH, WBC, total bilirubin and platelet counts increase significantly, while partial pressure of oxygen in arterial blood (PaO_2), urine output and GCS scores are significantly reduced. Levels of blood glucose, serum potassium and serum sodium become significantly abnormal. Some patients have melena or mucosal hemorrhage, i.e. the so-called "three high and two low" state: high response, high metabolism, hypercoagulability, low PaO_2 and low state of consciousness. Body temperature does not change as would be expected. Usually there is only a moderate fever, but the white blood cell count is significantly higher, partially reflecting the severity of disease. Currently there is lack of knowledge regarding both the significance and the cause of increased white blood cell counts. Whether the increase in white blood cells is a causal factor in acute high altitude disease complicated by MODS is not entirely certain and merits further study. The oxygenation index and the GCS scale are the indicators that have so far been found to have relatively high value in the diagnosis of H-MODS. These can not only be used for early detection but can also be used to evaluate the prognosis of patients who have experienced high altitude disease complicated by MODS. However, these indicators alone cannot produce accurate diagnoses of H-MODS. They must be used alongside clinical signs and symptoms and laboratory test results. They must definitely not be allowed to admit subjectivity or imagination to the process. In this study, we found that either high altitude pulmonary edema complicated with high altitude cerebral edema or high altitude cerebral edema complicated with high altitude pulmonary edema could develop into H-MODS. Among the 103 cases of acute high altitude disease complicated by MODS here studied, there were 91 cases of high altitude cerebral edema with high altitude pulmonary edema, accounting for 88.3% of the total. There were also 8 cases of high altitude pulmonary edema alone and 4 cases of high altitude cerebral edema alone. We advise that once high altitude pulmonary edema complicated with high altitude cerebral edema or high altitude cerebral edema complicated with high altitude pulmonary edema have been identified, a comprehensive inspection should be conducted as soon as possible to rule out or confirm the possibility of MODS so as to improve the success rate of any treatment.

Acute mountain sickness complicated by MODS is a critical high-altitude illness. According to our study results, the incidence rate is higher than the rate of diagnosis would suggest. The major reason for this is that our understanding of high altitude disease complicated by MODS is still relatively vague. It is actually not difficult for a person familiar with acute mountain sickness complicated by MODS to diagnose it. As long as the individuals or the group suspected of suffering from MODS has recently traveled from the plains to a plateau of altitude greater than 3000 m, the diagnosis can be confirmed if they appear to have enough of the following symptoms: headache, dizziness, nausea, vomiting, lethargy, acute-onset coma accompanied by typical high altitude cerebral edema or pulmonary edema symptoms, a GCS score of 8 or less with significantly abnormal changes in fundus and CSF examinations and either obvious signs of cerebral edema in brain CT or MRI or scattered flocculent cloud-shaped shadows in both lungs in lung CT or plain chest film accompanied by a cough with a large number of frothy sputum or frothy bloody sputum. The patient will also either be unresponsive to treatment for 24 hours or show aggravated, obvious damage to the heart, liver, kidney, gastrointestinal tract, vascular system, or metabolism of other organs or systems under laboratory examination. The patient may also have 3 or more organs or systems that meet the assessment scores consistent with the diagnostic criteria for H-MODS described by Shifan Zhang.

Etiology and Pathogenesis

The cause of acute mountain sickness complicated by MODS is not entirely clear. It may be associated in some patients with the rapid onset or progression of high altitude disease, failure to take timely and effective treatment locally, or failure to transfer patients to lower altitude facilities in time, which lead to the damage of other organs and in some cases complicated with trauma or infections making patients more vulnerable to get multiple organ dysfunction or failure. The mechanism of acute mountain sickness complicated by multiple organ dysfunction is unclear. It may be related to the following factors:

Abnormal regulation mechanisms in signal transduction

In recent years, it has generally been agreed upon that the incidence of MODS is related to delayed apoptosis of polymorphonuclear neutrophils (PMN). Studies have confirmed that hypoxia may act through a variety of pathways in signal transduction, in particular through the excessive activation of neutrophils in the HIF-1 pathway, to delay neutrophil apoptosis. When hypoxia acts on the body, the activity of the amino acid hydroxylase found in oxygen sensing cells is inhibited, causing HIF-1 hydroxylation to weaken and the HIF-1a protein to aggregate inside the cells, form dimers with HIF-1α, therefore enhancing hypoxia-related gene transcription and increasing the expression of apoptosis suppressor genes such as bcl-2 and Mac-1. This may be an important reason for exceptional PMN apoptosis. In addition, delayed PMN apoptosis is also associated with the downregulation of Fas and caspase-3 expression. Power et al found that bacterial lipoproteins (BLP) can inhibit the activity of caspase-3 and delay the PMN apoptosis [8]. However, endotoxins delay PMN apoptosis through induced production of inhibitor of apoptosis protein-2 (cIAP-2), which accelerates the degradation of activated caspase-3 [9]. Hirano et al. found that the use of technical processing in continuous renal replacement therapy (CRRT) in hemodialysis could significantly improve the delay in neutrophil apoptosis by clearing inflammatory factors (IL-6, IL-8, TNFa) from patients' blood, thereby reducing damage to tissues and organs [10]. This indicates that delays in neutrophil apoptosis may be a major cause of tissue damage.

Our study demonstrates that acute hypoxia can cause wall-attached scrolling of PMN, increased adhesion index and prolonged adhesion of the endothelial cells and that this increased adhesion is associated with increased CD18 expression [11]. This indicates that hypoxia can cause excessive activation of PMN. Activated PMN adheres to vascular endothelial cells under the role of chemokines, thus entering inflammatory tissue. It then releases inflammatory mediators through in respiratory bursts and degranulation, damaging the vascular endothelial cells and extravascular tissues. In this way, it is an contributing cause of SIRS and MODS [12]. Activated PMN also produces large amounts of superoxide anions and activated oxygen. These molecules also damage normal tissue cells at the same time as the destruction of microorganisms. Reactive oxygen species (ROS) can also increase the expression level of several cytokines and adhesion molecules such as TNFα, IL-1 and ICAM-1, amplifying their inflammatory effects. ROS can also participate in cell signaling pathways, in which it transmits activation signals from the cytoplasm to the nucleus, inducing the expression of inflammation-related genes and increasing the body's inflammatory response. Activated PMN can synthesize leukotrienes and generate and release platelet activating factor (PAF) and proteases, promoting smooth muscle contraction and increasing vessel wall permeability. PMN degranulation produces large amounts of protease, leading to the degradation of elastin and collagen and the decomposition of the endothelial fibronectin on the surface and

within the matrix of endothelial cells. This isolates the endothelial cells and basement membrane and increases the permeability of the blood vessel wall, thereby worsening altitude pulmonary edema and cerebral edema and promoting the occurrence of H-MODS [13]. Recent studies by West et al have shown that the activity of mitogen-activated protein kinase (MAPK) is enhanced in SIRS patients [14]. After insulin was given, the activity levels of MAPK, PI3K and PKC activity were lowered and TNF production was inhibited, suggesting that signal transduction pathways also play an important role in the pathogenesis of critical high-altitude illness [15].

Activation of inflammatory pathways

Our results indicate the white blood cell count of 93% of our acute mountain sickness complicated by MODS patients to be greater than 12.1×10^9/L, with the highest reaching 63.4×10^9/L and a mean of 19.24×10^9/L, while the average white blood cell count of patients with simple high altitude disease was found to be lower than 12.1×10^9/L [14]. This indicates that an increase in the number of leukocytes plays an important role in the onset of acute mountain sickness complicated by MODS. A great deal of evidence indicates that neutrophils are critical in causing acute respiratory distress syndrome (ARDS) not only because they can trigger inflammation but also because they are involved in subsequent tissue damage [17]. Further studies on cases of high altitude cerebral edema and high altitude pulmonary edema have shown that after the occurrence of acute mountain sickness, there is often activation of inflammatory mediators and cytokines. Bailey et al. observed that both the level of IL-6 and C-reactive protein in acute high altitude patients and that total creatine phosphate kinase activity was increased [18]. Studies by Hartmann et al. confirmed that under exposure to high-altitude hypoxia, the expression of IL-6, IL-1 receptor antagonist and C-reactive protein were upregulated in the circulating blood, showing that high-altitude hypoxia can induce the expression of a variety of cytokines, thereby supporting the hypothesis that the inflammatory response takes part in the pathogenesis of HAPE [19]. Our study further showed that pro-inflammatory mediators TNF-α, IL-1, IL-2, IL6 and IL-8 were increased significantly in the blood acute high altitude patients, while anti-inflammatory mediators such as IL-4 were significantly reduced [16]. Due to the imbalance between the pro-inflammatory and anti-inflammatory media and the release of a large number of oxygen-derived free radicals and lysosomal enzymes, a delay in treatment can eventually lead to damage to the endothelial cells and parenchymal organs and to multiple organ dysfunction and even failure. Takahashi et al found that neutrophils' production of too much anti-inflammatory media can lead to inflammatory immunosuppression and might also cause the occurrence of systemic inflammatory response syndrome (SIRS) [20]. Yiming et al. found in a study of UTI blockage that in the progression of SIRS to multiple organ dysfunction syndrome (MODS), UTI can regulate inflammatory reactions by upregulating anti-inflammatory factors and down regulating pro-inflammatory factors, thereby blocking the progression of SIRS to MODS [21]. Although there was no direct evidence of the involvement of inflammatory mediators in the pathogenesis of H-MODS, our study did find that the white blood cell counts of patients with altitude sickness complicated by MODS were significantly higher than those of patients without MODS. In addition, the variety of pro-inflammatory cytokines in mountain sickness patients was significantly higher than in healthy people on the plateau, but that of anti-inflammatory cytokine was significantly lower than in healthy people on the plateau. This shows that inflammatory mediators are involved in the pathogenesis of high altitude disease complicated by MODS [16].

While examining the serum and bronchoalveolar lavage fluid of patients with high altitude pulmonary edema, we found that levels of C-reactive protein and immunoglobulins IgG, IgA and IgM were significantly higher in the peripheral blood of high-altitude pulmonary edema patients and there were not only many proteins, red blood cells and white blood cells but also a great deal of C-reactive protein and a large number of immunoglobulins (IgG, IgA and IgM) and complements (C3, C4). The above evidence shows that inflammatory reactions do exist in acute mountain sickness patients and that inflammatory injury plays an important role in the progression of acute mountain sickness.

In recent years, studies have shown that the production of large amounts of inflammatory mediators by the inflammatory cell after activation by some kind of damage results in uncontrolled inflammatory response, which is an important step in the progression of systemic inflammatory response syndrome (SIRS), compensatory anti-inflammatory response syndrome (CARS) and MODS (MODS). Acute mountain sickness is a non-infectious inflammatory disease, so there may be a defense response to the inflammation. First, a pro-inflammatory state is created upon hypoxia and then pro-inflammatory mediators TNFα, IL-1, IL-6 and platelet activating factor (PAF) are released sequentially. To prevent the pro-inflammatory media from causing damage, the body also releases anti-inflammatory factors, such as IL-4 and IL-10, reducing the initial proinflammatory response. However, due to the damage that high-altitude hypoxia will have already caused many organs and systems, the regulation of early pro-inflammatory response is lost, resulting in an over active inflammatory response. Excessive release of the pro-inflammatory cytokines TNFα, IL-1 and PAF causes an exaggerated inflammatory response and leads to serious tissue damage, diffuse microvascular injury and even MODS. Larson and Horak thought that the occurrence of SIRS and subsequent occurrence of MODS were also closely related to levels of macrophage migration inhibitory factor (MIF) and the functions and states of Th1 and Th2 in the blood [22]. O'Mahony et al. found that, in the case of mechanical ventilation, the presence of endotoxin, even without acute lung injury, could increase the generation of lung pro-inflammatory cytokines, promoting damage to the lungs and other organs [23]. For this reason, Zhu et al came to consider the lung to be the trigger organ for MODS [24].

Activation of coagulation pathway

As hypoxia stimulates a response, various inflammatory cytokines are released and promote coagulation. This study notes the elevation in blood coagulability and the hypercoagulable status associated with the activation of fibrinolysis suppression in patients with HACE. High-altitude hypoxia, increased erythropoiesis and higher Hb concentration were found to make the blood much more viscous even without these other factors. In addition, increased fibrinogen concentration and increased activity of plasminogen activator inhibitor-1 (PA1-1) further increased blood coagulation. A study by Rupert et al. found that administering antagonists to plasminogen activator inhibitor did not cause this coagulation to cease [25]. Severe hypoxia can also cause injury to vascular endothelial cells and further activate the blood coagulation factor. This can also initiate the intrinsic clotting process. In addition, the release of a variety pro-inflammatory cytokines in the body can induce the expression of tissue factors, initiating the extrinsic clotting process and accelerating thrombin generation. At the same time, the increased inflammatory response caused by endothelial damage leads to neutrophil activation, the adhesion of neutrophils to endothelial cells and the further release of inflammatory cytokines, all of which promotes vascular endothelial dysfunction. Tissue factor is also the key medium for connecting the immune system to coagulation

as well as the main material for coagulation. It interacts with activated coagulation factor XII to form a complex that can activate coagulation factors X and XI. With the activation of coagulation factors XI, VII and V, coagulation cascade is formed. These ultimately produce large amounts of thrombin and significantly increase procoagulant activity. Under high altitude exposure, not only blood coagulation is enhanced. Fibrinolytic activity is increased as well. The study by Jianhua et al. found that under high-altitude hypoxia exposure, levels of AT III and t PA were significantly lower than in plains areas and that they decreased as altitude increased but went up again as the subject spent more time in the high-altitude area [26]. Levels of PLG, DD, PAI, α2 PI and Fg were significantly higher in subjects at high altitudes than in subjects in the plains after 7 days at altitude of 3700 m above sea level, after 7 days at 5380 m and after 6 months at 5380 m, increasing with the increased altitude and decreasing with time of residence. After 6 months at 3700 m, however, there was no significant difference from measurements of subjects living on the plains, indicating that, under high-altitude hypoxia, coagulation disorders are present and shown in the activation of coagulation and fibrinolysis accompanied by inhibition of fibrinolysis leading to disruption of the balance between coagulation and fibrinolysis, leaving the blood both more prone to coagulation and less prone to fibrinolysis. It is particularly true for acute mountain sickness patients under high altitude exposure that the activation of the coagulation process is always accompanied simultaneously by the activation of fibrinolytic system. A study by Jianhua et al. found that HAPE patients had significant hypercoagulability and increased fibrinolytic activity, which led to an interruption of the balance between coagulation and anticoagulation [27]. Kaur et al. found that the concentration of D-dimers in serum from patients with high altitude pulmonary edema was significantly higher in general [28]. D-dimers are degradation products with specificity for cross-linked fibrin in plasmin hydrolysis. While their presence in the body is normally very small or even undetectable, the concentration of D-dimer in plasma was significantly increased in patients with acute mountain sickness, suggesting that the activation of the coagulation system is accompanied by activation of the fibrinolytic system. However, the activation of fibrinolytic system is accompanied by the formation of fibrinolysis inhibitors, so coagulation activity is enhanced, which ultimately leads to disseminated intravascular coagulation or even multiple organ damage.

Gastrointestinal mucosal injury and reduced barrier function

High-altitude hypoxia causes not only gastrointestinal motility disorders and digestive secretion dysfunction but also pathological injury to the gastrointestinal mucosa. According to a report by Wu et al. the endoscopy results of 22 climbers at 5020 m showed that 13 out of 22 cases (59%) experienced gastric and duodenal mucosal damage, 3 of these cases involved acute gastric mucosal damage (2 of superficial ulcer and 1 of hemorrhagic gastritis), 2 involved duodenal ulcers and 1 case involved gastric ulcers [29]. Recavarren et al. also reported the existence of serious gastric mucosal injury in the gastric mucosal biopsy of the Peruvian Alps [30].

Hypoxia can also cause reduction in the secretion of secretory IgG by the gastrointestinal mucosa, thus weakening the function of the mucosal barrier and leading to intestinal epithelial necrosis, damaged integrity of the intestinal mucosa, lead to the invasion of bacteria and toxins. A study by Diebel et al. also showed that ischemia or hypoxia to the intestinal epithelials can cause excessive activation and delay in apoptosis of neutrophils, leading to SIRS, MODS, or distant organ failure [31]. Our study shows that in patients with severe acute mountain sickness accompanied by severe gastrointestinal disorders, high-altitude gastrointestinal dysfunction is one of the causes of severe acute mountain sickness complicated MODS and should never be ignored [32,33]. Animal studies have shown that, under high altitude exposure, rats experienced intestinal mucosal atrophy, mucosal barrier dysfunction, increased intestinal permeability, translocation of mesenteric lymph nodes and spleen bacteria. Starvation under high-altitude conditions was found to increase the degree of intestinal mucous damage, promote the translocation of bacteria and endotoxins and cause systemic inflammatory response. This was found to be an important cause of H-MODS incidence. Glutamine pretreatment has certain protective effects with regard to gastrointestinal mucosal injury due to the high altitude environment. It can reduce gastrointestinal mucosal injury, bacterial translocation and systemic inflammatory response.

In addition, severe high-altitude hypoxia can also weaken the mucosal barrier by reducing the HIF-1a. Under normal circumstances, intestinal bacteria can produce a bacterial product called sodium butyrate, which has a protective effect on intestinal epithelial cells. However, under hypoxic conditions, sodium butyrate inhibits the transcriptional activity of HIF-1 by reducing the binding activity of intestinal epithelial hypoxia response element [34]. Sodium butyrate is a histone deacetylase inhibitor that can increase the level of histone acetylation, enhance the transcriptional activity of certain genes and upregulate CD86 and CD80 molecules of NB4 cells. The expression of CD86 is mediated by NF-Kβ and expression of NF-Kβ is increased by sodium butyrate. Once the intestinal barrier function is damaged, then, intestinal bacteria enter the blood. In this way, the bacterial product sodium butyrate leads to the activation of NF-Kβ, thus initiating the NF-Kβ signal transduction pathway.

Severe hypoxia can also induce the inflammatory response in both immune and epithelial cells. This generates a large number of inflammatory cytokines that cause exudation in the lungs. Both TNFa and IL-1 are the initiators of inflammatory injury. After TNFα binds to its receptor, the signaling pathway of the transcription factor NF-Kβ is activated. Through the activation of transcription factors, the monocyte-macrophage cells secrete more PAF, IL-1, IL-6, IL-8 and TNFα, causing the cytokine cascade and the expansion of the injury. Meanwhile the expression of adhesion molecules by the WBC and endothelial cells enhances neutrophil phagocytosis and a variety of proteolytic enzymes and oxygen radicals are released, leading to expansion of the inflammatory reaction and eventually multiple organ dysfunction.

Effects of hypoxic brain injury on the onset of H-MODS

The brain is the biggest consumer of oxygen in the body and the organ most sensitive to hypoxia. Patients often experience neuropsychiatric abnormalities after entering high altitude areas. Upon quick ascent to en elevation of over 5000 m, the effect of hypoxia on the central nervous system becomes serious. It can involve not only brain dysfunction but also severe brain edema and extensive necrosis with softening accompanied by blood-brain barrier and vascular endothelial cell injury, which can further increase brain edema, causing severe brain dysfunction. Hackett and Roach pointed out that the incidence of high altitude cerebral edema is mainly due to vascular leakage, which he believed was caused by over-release of IL-1 and NO due to hypoxia, leading to changes in the tight junctions of brain capillary endothelial cells [35]. These he believed to be caused by the increase in membrane permeability induced by oxidation stress [35-37]. Felinski et al also confirmed from the treatment aspect that the formation of cerebral edema is related to the increase of blood-brain-barrier

permeability [38]. A study by Velasco and Bailey et al. [37] also showed that the incidence of high altitude cerebral edema is related to vascular autoregulation disorders [39,40]. Because high altitude cerebral edema is generally accompanied by increased intracranial pressure, it not only causes disturbances of consciousness shown as drowsiness or coma but also injury to the limbic system, causing ataxia and oppression of the brain tissue leading to hernia formation in severe cases, in turn causing the central nervous system dysfunction and over-excitement of the sympathetic nervous system leading to the redistribution of systemic blood flow, excessive pulmonary vascular perfusion leading to increased fluid filtration and hypoxia-induced damage leading to an increase of pulmonary vascular permeability, all of which inducing HAPE and aggravating the dysfunction of other organs. In this way, high altitude cerebral edema is often associated with high altitude pulmonary edema. These two conditions interact with each other and cause rapid deterioration. This shows hypoxic brain injury is an important causal effect and provides a pathological basis for multiple organ dysfunction.

Clinical Manifestations

After the onset of severe acute mountain sickness complicated by MODS, the patients not only experienced the general manifestations of acute mountain sickness, such as headache, chest tightness, shortness of breath, coughing, pink bubble sputum, nausea, vomiting, psychotic disorders, behavioral abnormalities in small number of patients, sleepiness or lethargy in most patients and varying degrees of coma and other symptoms in some patients, but also additional symptoms, such as spasm, gastrointestinal bleeding or fecal occult blood, decreased urine output, increased body temperature, faster heart rate and declined blood pressure in severe cases.. During physical examination 97% of the patients showed cyanosis, with some showing facial edema, significantly increased myocardial enzyme activity, increased levels of urine creatinine, increased total bile acids and serum alanine aminotransferase activity, generally increased serum electrolytes, increased white blood cell count, reduced platelet count and significantly prolonged clotting time. ECG examination often revealed cardiac arrhythmia or tachycardia, usually right axis deviation and an incomplete right bundle branch block or atrial fibrillation. Fundus examination suggested papilledema, retinal hemorrhage, or a large flame-shaped hemorrhage coexisting with diffusive spotted bleeding in both retinas. Plain chest film or CT examination often showed cloudy shadows with uniform density appearing in unilateral or bilateral lungs and occasionally showed patchy shadows with uniform density. GCS scores were found to be under 8. Brain CTs and MRI examinations showed that most patients experienced reduced density of the brain parenchyma on one or both sides, brain ventricles narrowing on both sides, shallow sulci, corticomedullary demarcation vague in both cerebral hemispheres, lenticular nuclei on both sides of the corpus callosum and globus pallidus, swelling of the temporal lobe and either reduced density of or multiple scattered patchy shadows involving the cortex and medulla.

Clinical Diagnosis

For a long time, due to spotty awareness of high-altitude MODS, it has been difficult to create consistent diagnostic criteria. Some people believe that there is no difference between MODS in plateau and plains regions; therefore, they advocate the use of the same diagnostic criteria for both environments. However, this is a misconception. Both our own team that of Zhang Shifan found it difficult to make a correct diagnoses for high-altitude MODS using either Marshall's diagnostic criteria (designed for the plains) or Chinese Lushan diagnostic criteria, coming up with both false negatives and diagnoses of exaggerated seriousness. We found that, although there is not much difference in nature between plateau and plains MODS, hypoxia-based environmental factors increase in significance with increased altitude, changing to varying degrees the pathogenesis, clinical disease symptoms, treatment and prognosis of MODS. This discrepancy can significantly change diagnostic criteria, creating more uncertainty and variability in the diagnosis and treatment of high-altitude organ dysfunction syndrome than plains areas. For this reason, using plains diagnostic criteria alone is not practical on the plateau. We first proposed definition and scoring criteria for high altitude MODS.

(H-MODS) after many years of clinical and experimental research, but these criteria were proposed for high-altitude trauma and infection and are not suitable for the altitude sickness with MODS. We then revised and improved these criteria and later proposed an integrated scoring system for high-altitude systemic inflammatory response syndrome and acute mountain sickness syndrome. However, we still felt that the scoring system had a certain gap between it the actual occurrences of severe acute mountain sickness complicated by MODS. We then made further revisions and, after multi-center clinical cohort studies and animal experiments in a high altitude gradient of similar altitude, the scoring and diagnostic criteria for severe acute mountain sickness complicated by multiple organ dysfunctions were finally established. After a few years of trials by a number of high-altitude hospitals, this system was proven to be more convenient in use and more specific in scoring than the plains-based systems and the criteria were confirmed to be of good practicability and maneuverability. With further addition, revision and improvement, the current diagnostic criteria were ultimately established [41].

The scoring and diagnostic criteria for severe acute mountain sickness complicated by MODS are as follows: (1) Acute onset. (2) Disease symptoms or index as listed in the table shown in populations with rapid ascent to high altitudes. (3) 24 hours of unresponsiveness to treatment for typical AHAR/HAPE/HACE disease symptoms. (4) Any positive item for any of the 3 organs listed in Table 1.

Clinical Rescue and Treatment

Principles of classified diagnosis and staged treatment

Upon being admitted to a hospital, patients with severe acute mountain sickness with MODS are first sorted according to disease priorities. In addition to conventional therapy for altitude sickness, the patients receive enhanced monitoring of complications. For patients with multiple organ damage, in addition to conventional treatment, which consists of such things as bed rest, oxygen therapy and supportive care, comprehensive treatment for expanding the blood vessels, decreasing the pulmonary artery pressure, diuretic dehydration etc. The comprehensive therapy shows very good effects.

Stage I (mild): Diagnosis must take place after moderate physical activity. State I patients will show difficulty in breathing and cough and spitting white foam sputum. One side of the lower lung fields will produce moist rales. The breath rate will be under 25 times per minute. The heart rate will be over 110 beats per minute with no arrhythmia. Chest X-rays will show infiltrative shadows over more than 1/4 of the lung area, more limited to the lower right lung and appearing to be scattered spot (plaque-like) shadows. Hemogram will be normal. The patient may also have a headache, nausea and vomiting. The frequency of the vomiting will be more than 5 times per day, accompanied by lethargy, trance, or mental disorders, papillary edema and cerebrospinal fluid pressure over 200 mm H_2O. These symptoms will disappear or be

Organ	Index	Stage 1 (points)	Stage 2 (points)	Stage 3 (points)	Stage 4 (points)
Heart	SBP (mmHg)	≤ 90	+ Liquid ≥ 90	+ Liquid + CVAD ≥ 90	+ Liquid + CVAD≤90
	Heart rate (times/min)	90-100	111-120	121-140	≥ 141 ≤ 50
	Zymography (CK/LDH)	≥ Normal high limit	≥ 1 times normal high limit	≥ 2 times normal high limit	≥4 times normal high limit
Lung	PaO_2/ FiO_2	≤ 220	150-219	75-149	≤ 75
	Respiratory rate (times/min)	≥ 22	26-35	36-45	≥ 46 ≤ 5
	SaO_2(%) continuous oxygen inhaling	≤ 90	79-60	59-45	< 45
	Coughing, sputum	Significant	Cough with large amounts of foam sputum	Large amounts of heavy foam sputum	Large amounts of plink foam sputum
	Signs	Wet/dry rales at the end of one lung	Wet rales at the ends of both lungs	Bubble sounds in both lungs	Big bubble sounds in both lungs
	Chest x-ray results	Cloud shadows over 1/4 of lung	Cloud shadows over 1/2 of lung	Cloud shadows Over 1 side of lung	Cloud shadows over both sides of lung
Brain	GCS score	14-13	12-10	9-7	≤ 7
	Disturbance of consciousness	Drowsiness or lethargy	Mild coma	Moderate coma	A deep coma
	Fundus examination	Papilledema	Retinal hemorrhage	Papilledema + punctate hemorrhage	Papilledema + patchy hemorrhage
Liver	TBI (μmol/L)	≤ 16	17-40	41-80	81-120
	ALT/AST	≥ 0.5 times normal	≥ 1 times normal	≥ 2 times normal	≥ 3 times normal
	GPT/GOT	≥ 0.5 times normal	≥ 1 times normal	≥ 2 times normal	≥ 3 times normal
Kidney	Cr (μmol/L)	101-200	20-350	351-500	≥ 501
	Urine output (ml/h)	≤ 40	≤ 30	≤ 20	≤ 10
Metabolism	Bood glucose (mmol/L)	7-9	10-15	16-21	≥ 22
	Serum sodium (mmol/L)	≤ 134 ≥ 146	≤ 130 ≥ 150	≤ 125 ≥ 155	≤ 110 ≥ 160
	Serum potassium (mmol/L)	≤ 3.5, ≥ 4.5	≤ 3.0, ≥ 5.0	≤ 2.5, ≥ 5.5	≤ 2, ≥ 6.0
	pH	≥ 7.45	≥ 7.5	≥ 7.55	≥ 7.6
Digestion	Loss of appetite	Mild	Medium	Heavy	No appetite
	Abdominal pain and/or bloating	Bloating	Bloating without bowel sounds	Paralytic ileus	Paralytic intestinal obstruction
	Gastrointestinal bleeding	None	Positive occult blood (+)	Hemafecia	Melena, hematemesis
Blood	WBC (×109/ L)	≥ 10	≥ 12.0, ≤4.0	≥ 20.0, ≤ 3.0	≥ 30.0, ≤ 2.0
	PLT (× 109/ L)	< 120	100-70	69-40	≤ 39
	Bleeding/coagulation time	Negative	> normal	> or < 0.5 times normal	> or with DIC
Accumulated Points		8	16	24	32

Table 1: High altitude disease complicated by MODS, scoring and diagnostic criteria.

reduced after oxygen therapy and rest. Treatments include bed rest, nasal cannula or oxygen mask, conventional drug therapy (including furosemide, aminophylline, prednisone, anisodamine, intravenous injection (1-2 times per day) and administration of appropriate narcotic and sedative drugs.

Stage II (medium): Diagnosis must take place after mild physical activity. Stage II patients will have difficulty breathing, chest pain, chest tightness, cough and spitting large amounts of white foam sputum. Unilateral or bilateral lower lung area will produce large amounts of moist rales. The breath rate will be over 25 times per minute. The heart rate will be over 110 beats per minute. Chest X-rays will show sheet cloudiness floc shadows over at least ½ the lung field. There will be a slightly higher hemogram. Stage II patients may also have severe headaches, chest tightness, nausea and vomiting of more than 10 times per day in frequency accompanied by deep lethargy and light coma, mental disorders or epileptic seizure, retinal artery spasm and papillary and retinal edema accompanied by spotted patchy hemorrhage, cerebrospinal fluid pressure of over 250 mm H_2O. These symptoms will be reduced but will not disappear after rest or oxygen treatment. Treatments include absolute bed rest, multi-channel oxygen supply (continuous oxygen mask or hyperbaric oxygen therapy), conventional drug therapy (intravenous injection of furosemide, dexamethasone, anisodamine, 0.25 g of aminophylline adding 40 ml injection of 10% intravenous glucose, intramuscular injection of promethazine or diphenhydramine as sedatives, 1-2 times per day).

Stage III (severe): Diagnosis must take place during the night while the patient is not supine. Stage III patients may pale, have a cold sweat on the forehead, extreme difficulty breathing, severe cough, spitting large amounts of white or slightly pink foam sputum. The patients' lungs may be full of large, medium and small bubbles and produce sounds like boiling water. The breath rate will be over 30 times per minute. The heart rate will be over 120 beats per minute, often accompanied by arrhythmia. Chest X-rays will show more than 1/2 the lung area of both lungs to be covered with central vector-type symmetrical cloudy shadows. Patients may also show severe headaches as precursors to vomiting of dozens of times per day in frequency, unconscious status, restlessness, urinary and fecal incontinence, positive pathological reflex, papillary and retinal edema, with exudation and large areas of flame-shaped hemorrhage, silver-filament arteries, a large degree of conjunctival edema, prominent eyeballs, unequal pupils, cerebrospinal fluid pressure over 300 mm H_2O and poor prognosis. Treatments include absolute bed rest, multi-channel oxygen supply, (endotracheal intubation or continuous positive pressure ventilation after incision) or application of early mechanical ventilation, drug therapy (intramuscular injection of dexamethasone followed by 10% glucose infusion with dexamethasone, 20% mannitol furosemide, vitamin C, 2-3 times per day and alternate use of energy medicine or energy mixture) and concurrent use of mild hypothermia therapy.

Stage IV (very severe): Diagnosis must take place on patients in near-death situations. Stage IV patients will look pale grey and have

weak breathing with auto-overflow of a large number of bubbles from the nose and mouth. Gurgling sounds will be audible over the lung area. Heartbeats will be weak and blood pressure will be reduced. This will often be accompanied by high altitude cerebral edema, heart dysfunction and secondary pulmonary infection alongside signs and symptoms are more severe than severe pulmonary edema. Chest X-rays will show cloudy shadows on unilateral or bilateral lung areas, an enlarged heart and significantly prominent pulmonary arteries. The hemogram will go up and down inconsistently. Severe cases may also involve pulmonary edema, heart dysfunction, systemic edema and secondary infection, hernia formation and other problems. Prognosis is very bad prognosis if timely rescue does not take place. Treatments include absolute bed rest, early mechanical ventilation strategies, drug treatment (administration of antibiotics early in treatment if infection is suspected; if complicated with high altitude pulmonary edema, after 1 intravenous injection of aminophylline, change to intravenous drip 2 times per day until pulmonary rales disappear; if complicated with heart failure, apply cardiac stimulation and increase the amount of diuretic dehydration; if complicated with cerebral edema taking head-down position, apply head cooling, implement hibernation therapy and increase the amount of diuretic dehydration; if combined with renal failure, correct water-electrolyte and acid-base imbalance as early as possible); use of mild hypothermia therapy in early treatment. The patient may be transferred to a lower altitude once his or her condition has become stable.

Comprehensive treatment program

The clinical rescue and treatment procedures for severe acute mountain sickness complicated by MODS should adhere to the following: multi-channel oxygen supply to ensure adequate oxygen inhalation; early mechanical ventilation; early dehydration or administration of diuretics to reduce intracranial pressure; early use of inhaled nitric oxide to reduce pulmonary artery pressure; early use of mild hypothermia therapy to reduce the amount of brain tissue oxygen consumption; early treatment of complications to prevent the occurrence of multiple organ failure.

Multi-channel oxygen supply: The fundamental cause of severe acute mountain sickness complicated by MODS is lack of oxygen, so inhaling oxygen may treatment this sickness at its cause. It is the most fundamental means of treating of severe altitude sickness. Administration of oxygen can increase the alveolar pressure and arterial partial pressure of oxygen (PaO_2), improve tissue hypoxia and relieve clinical symptoms. We use a multi-channel oxygen supply: 1) Inhalation of high flow oxygen delivery via nasal cannula or mask pressure (8-10 L/min) added with aerosol inhalation (15%-30% alcohol). 2) Positive pressure ventilation via breathing machine for cases of respiratory failure tracheostomy positive-pressure breathing machine oxygen supply should be administered if the patient's respiratory secretions are copious. 3) Hyperbaric oxygen therapy. Our study proved high-pressure oxygen treatment to be a reliable and effective way to improve the oxygen supply in patients with severe acute mountain sickness complicated by MODS so as to enhance the effectiveness and shorten the course of treatment. Hyperbaric oxygen therapy can lead to cerebral vasoconstriction and cerebral blood flow reduction, but brain oxygen pressure still remains higher than normal, thereby mitigating and relieving cerebral edema and reducing the symptoms of cerebral hypoxia. We observed nearly a hundred cases of acute mountain sickness complicated by MODS in patients undergoing conventional therapy plus hyperbaric oxygen and the cure rate was 100%. 4) Administration of venous oxygen. For some critically ill patients, in particular when other oxygen therapy is not ideal, oxygen can be administered intravenously by adding medical-grade pure oxygen to liquid for intravenous use, but attention must be paid to sterilization practices before any liquid is added. Our study has shown that venous oxygen can rapidly improve oxygen saturation, arterial partial pressure of oxygen (PaO_2) and tissue oxygen supply, thereby improving patient symptoms.

Diuretic dehydration: Diuretic dehydration can cause cerebral edema to subside, improve cerebral circulation, reduce intracranial pressure and improve oxygen diffusion among brain cells. The most common drugs are 20% mannitol, 50% glucose solution, furosemide, diamox dexamethasone and similar drugs.

Dexamethasone: Clinical observations suggest that dexamethasone is very effective with regard to reducing cerebral edema and lowering intracranial pressure, which may be related to its ability to stabilize the cell and lysosomal membranes, maintain the integrity of cerebral blood vessels, reduce the dilation of cerebral blood vessels, reduce cerebral vascular permeability, reduce blood flow, improve brain cell metabolism, improve the patients' mental state and promote the resumption of brain function. Dexamethasone treatment of high altitude cerebral edema rarely causes sodium and water retention or rebound phenomenon. Dexamethasone plus oxygen therapy works very well. Our observations show that the sooner the administration of dexamethasone, the better. The initial dose should be large—generally, the first dose is 10 mg via intravenous infusion—then gradually reduced over 8-10 days.

Mannitol: 20% mannitol induces hypertonic dehydration which can increase the osmotic pressure of blood, causing the water in brain tissue to transfer to the bloodstream, thereby eliminating cerebral edema. It can also expand blood vessels and increase renal blood flow, inhibiting ADH secretion. By this means, it has a strong diuretic and dehydration-inducing effect. On-site dosage is 20% mannitol 250 ml via rapid intravenous injection 2-4 times a day.

Furosemide/ethacrynic acid: Clinical observations suggest that the intravenous administration of 250 mg of furosemide with 10% glucose intravenously is equivalent to the effect of 250 ml 20% mannitol alone. Furosemide has a strong diuretic effect, can suppress the secretion of cerebrospinal fluid and significantly reduces cerebral edema. It is not for routine use but rather is better suited to high altitude cerebral edema complicated by pulmonary edema and heart failure. Earlier, some people used ethacrynic acid, but this it is no longer the norm due to ethacrynic acid's role in hearing damage. Hydrochlorothiazide or spironolactone is usually used instead.

Our approach to high altitude cerebral edema complicated by pulmonary edema is, while giving multi-channel oxygen, 0.25g of aminophylline can be administered, adding 40 ml of 10% glucose via intravenous injection. Meanwhile 10 mg of dexamethasone and 20 mg of furosemide should be administered by intravenous injection 1-2 times per day alongside 250 ml of 20% mannitol via rapid intravenous infusion if the condition is complicated by brain edema that occurs 2-4 times per day.

Aminophylline: Aminophylline, a classic bronchodilator, has been widely used in the treatment of high altitude pulmonary edema. The mechanism mainly involves expanding the bronchi, reducing hypoxic pulmonary hypertension, increasing diaphragmatic function, antagonism of lipid peroxidation and hypoxia-induced pulmonary vascular inflammation, strong cardiac and diuretic activity, clearing of mucus and elimination of the moist rales. The double-expansion role of aminophylline on the airway and vascular smooth muscle cannot

be attributed to general vasodilators in the treatment of high altitude pulmonary edema, giving aminophylline a unique benefit.

In addition, theophylline, nifedipine and nimodipine can also be used to reduce hypoxic pulmonary hypertension. In recent years it has been found that the non-selective, non-peptide endothelin receptor antagonist bosentan can also reduce pulmonary arterial pressure under resting conditions and significantly reduce the increase of hypoxic pulmonary artery pressure [42]. Furthermore, sildenafil and tatinafil, also studied in recent years, can relax pulmonary vascular smooth muscle, expand pulmonary arteries, decrease pulmonary artery pressure and improve both gas exchange and oxygen saturation.

Inhaled nitric oxide: On the basis of the conventional treatment, it has been concluded that inhalation of 0.001% (10×10^{6}) of nitric oxide (NO) for 30 minutes while changes in hemodynamics, oxygen saturation and front digital chest X-ray are observed and later compared to those taken before the treatment can produce an observable therapeutic effect. The results show that high altitude pulmonary edema patients with cerebral edema regained consciousness within 10 to 30 minutes of inhaling NO and were discharged in 1 to 3 days. Their hemodynamics changed from high-output and high-resistance to high-output and low-resistance after healing. These results indicate that inhaling NO has significant beneficial effects in the treatment of high altitude pulmonary edema complicated by high altitude cerebral edema. NO has small toxic side effects and requires only a short course of treatment. The mechanism for improvement of symptoms after inhalation of NO may be related to the decrease in pulmonary artery pressure that occurs upon inhalation of NO, improved pulmonary ventilation and function and increased blood oxygen saturation. NO also has second-messenger and neurotransmitter properties, is an effector molecule and can perform two-way adjustment to mediate and regulate a variety of physiological functions, thereby improving cerebral vascular tension and cerebral blood flow, reducing intracranial pressure and helping to restore consciousness.

Anisodamine (654-2) and energy mixture: Anisodamine (654-2) can expand capillaries, inhibit norepinephrine-induced microvascular contraction and improve the cerebral microcirculation. At the same time, it can reduce fibrinogen, increase fibrinolytic activity and inhibit micro-thrombosis. We observed that effect of treatment with dexamethasone with both anisodamine 654-2 and oxygen was superior to other treatments. Common use involves 10-20 mg of 654-2 and 4 mg of dexamethasone with 250 ml of 10% glucose via intravenous infusion 1-2 times per day.

Energy mixture: ATP can restore sodium pump function, promote the outflow of sodium, prevent cerebral edema, improve cerebral circulation, protect brain cells and promote functional recovery of the brain to some degree, but it must be used in conjunction with other measures.

Timely administration of mild hypothermia: In recent years, it was discovered that mild hypothermia therapy is not only suitable for patients with severe high altitude cerebral edema but is also safe for high altitude cerebral edema complicated by infection. Hypothermia can reduce cerebral blood flow, cerebral metabolic rate and intracranial pressure, thereby reducing the oxygen consumption of brain tissue, promoting recovery of damaged cells and eliminating brain edema. Best practice involves the use of an ice blanket and ice caps to bring the patient's temperature to 32-33°C. Other practices involve use ice bags plus hibernation drugs. We used mild hypothermia therapy in the treatment of dozens of patients with critical high-altitude illness. Even those with 7-day comas, the longest duration of any in our study, were successfully saved. The success rate is of this treatment is 100% and it is very safe. We expect that use of this treatment would also reduce national and personal economic loss.

Timely mechanical ventilation: For severe acute mountain sickness complicated by MODS patients, the key to reducing mortality is to accurately grasp the entry point for early diagnosis and treatment and to apply that treatment, including mechanical ventilation, early and effectively. We compared the effects of time and ventilation modes on mortality and found that applying traditional ventilation and a continuous positive airway pressure oxygen supply produced significantly higher mortality than the treatment developed by using high-altitude hypoxia as a starting point, the use of synchronous intermittent mandatory ventilation (SIMV) + PEEP mode, the early use mechanical ventilation, low tidal volume and low oxygen concentration. When comparing these 2 treatment models, we found that the mortality rate for the former model was 31.8% and the mortality rate for the latter treatment model was 16.5%. Practice has shown that implementation of ventilation early on in treatment can inhibit the development of inflammation and deterioration, enhance oxygen supply of tissues and organs, improve energy support and reduce mortality in a number of ways. We initially proved that when the patient has breathing difficulties, RR ≥ 30 times per minute, $Pa0_2$ ≤ 50 mmHg, or $Pa0_2/Pi0_2$ ≤ 150 mmHg or $Sa0_2$ ≤ 60 mmHg provided no relief of symptoms after 3 hours of continuous treatment. The indications for mechanical ventilation include a lack of improvement in and increasing severity of disease.

Timely continuous renal replacement therapy: Continuous renal replacement therapy (CRRT), also called continuous blood purification (CBP), is a type of blood purification technology developed in recent years. It clears the blood of metabolic wastes and so can also clear excess water from the body continuously and slowly, has little effect on hemodynamics, can maintain the stability of cardiovascular function and has been widely used in the rescue of a variety of critically ill patients in plains regions. However, it has not yet been applied to the treatment of severe acute mountain sickness. We used CRRT in adjuvant therapy for acute mountain sickness complicated with acute renal failure [43]. This resulted in the successful treatment of a number of patients with acute mountain sickness complicated by acute renal failure. The results showed early intervention with CRRT to be an important and effective adjuvant therapy for the treatment of severe acute mountain sickness, especially in patients whose conditions are complicated by MODS.

Prompt anti-inflammatory treatment: Administering Sivelestat Sodium or Ulinastatin (UTI) via intravenous infusion can inhibit neutrophil elastase activity significantly and reduce the degree of organ injury, thus protecting the organs. Another option is to give the patient an intravenous injection of the Chinese medicine aescinate. Clinical studies have proven that aescinate has significant anti-inflammatory, anti-edema and free-radical-scavenging effects and can restore normal capillary permeability, control inflammation and improve circulation etc. Aescin can inhibit phospholipase A_2, inhibit the release of precursors of inflammatory mediators and reduce tissue inflammation. It can also improve the level of prostaglandin in the tissue, particularly PGE_2, maintain vascular tension and reduce leakage. Aescin can significantly reduce the attachment to the wall and exudation of neutrophils under hypoxic conditions. It can also reduce the release of active oxygen, chemokines and proteases in the tissue, thus exhibiting anti-inflammatory and anti-edema functions. The study also found that giving ultrashort wave therapy early on in treatment, i.e. on the basis of conventional therapy, coupling with ultrashort wave therapy also significantly improved symptoms, increased SaO_2 and shortened

the disease course in patients with high altitude pulmonary edema complicated by MODS.

Care strategies: The success rate of treatment of severe acute mountain sickness complicated by MODS also depends on care strategies. Proper care can reduce further injury and prevent the occurrence of multiple organ failure. In nursing patients with severe acute mountain sickness complicated by MODS, we took the following points to heart: ① Select the appropriate form of oxygen therapy and ensure that it is working effectively; ② Choose the right wetting agent for the specific disease condition; ③ Avoid damage under high oxygen and re-hypoxic injury; ④ Make close observations of intake and output for evaluation of renal function; ⑤ Integrate treatment and care and avoid aggravating the disease; ⑥ Pay close attention to vital signs and to any changes in the patient's condition. Actively prevent multiple organ failure; ⑦ Improve the knowledge of nurses of high altitude disease complicated by MODS. Improve responsibility and make early assessment of the disease more practical, changing the nurse's role from waiting passively for the doctor's notice into nursing scientifically. Increase initiative and foresight in nursing, remembering that this can reduce and prevent complications.

Overall, treatment for severe acute mountain sickness complicated by MODS should strictly follow the mantra "timely, accurate and efficient," which refers to timely detection, accurate diagnosis and efficient treatment. Detection and treatment must be performed early, especially in high altitude areas. The proper type of treatment must be chosen and carried out as soon as possible and as quickly as possible so as to improve the cure rate and reduce mortality.

References

1. Zhang SF, Luo XH (2007) Acute High Altitude Reaction Syndrome and Systemic Inflammatory Response Syndrome. Zhongguo Yi Xue Ke Xue Yuan Xue Bao 29: 551-556.
2. Zhang SF, Wu TY (2007) Systemic inflammatory response syndrome and acute mountain sickness syndrome associated with research and thinking. Medical Journal of National Defending Forces in Northwest China. 282: 81-83.
3. Qiquan Z, Yongjun L, Hong L, Suzhi L, Xizhou Z, et al. (2010) Epidemiological study of mountain sickness complicated with multiple organ dysfunction syndrome on the Qinghai-Tibetan Plateau: Report of 103 cases. Scientific Research and Essays 5: 2506-2516.
4. Zhou QQ, Liu FY, Zheng BH, Gao YQ, Li SZ, et al. (2007) Analysis of 3 184 cases with acute mountain sickness complicated by multiple organ dysfunction syndrome. Chin Crit Care Med 19: 36-40.
5. Suzhi Li, Zheng B, Zhou Q (2006) An Analysis of Severe Acute High Altitude Disease Combined with Multiply Organs Disorder at High Altitude. Journal of High Altitude Medicine 16: 5-7.
6. Gao Wei,Zhang Shifan,Zhang Dehai, et al. (2004) Diagnostic criteria of MODS complicated from acute mountain sickness. Medical Journal of National Defending Forces in Northwest China 25: 7-9.
7. Zhang SF, Zhang DH, Gao W, Liu HP, Luo XH, et al. (2005) Multiple organ dysfunction scoring system: comparison and evaluation of correlation and accuracy of the three scoring systems in predicting the outcome of multiple organ dysfunction syndrome on highland. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue 17: 346-351.
8. Power CP, Wang JH, Manning B, Kell MR, Aherne NJ, et al. (2004) Bacterial lipoprotein delays apoptosis in human neutrophils through inhibition of caspase-3 activity: regulatory roles for CD14 and TLR-2. J Immunol 173: 5229-5237.
9. Mica L, Harter L, Trentz O, Keel M (2004) Endotoxin reduces CD95-induced neutrophil apoptosis by cIAP-2-mediated caspase-3 degradation. J Am Coll Surg 199: 595-602
10. Hirano T, Hirasawa H, Oda S, Shiga H, Nakanishi K, et al. (2004) Modulation of polymorphonuclear leukocyte apoptosis in the critically ill by removal of cytokines with continuous hemodiafiltration. Blood purification 22: 188-197
11. Zhang G, Gao Y, Liu F (2008) Rheological changes of leukocyte and expression of integrin CD18 in rats under hypoxia. Medical Journal of Chinese People's Liberation Army 33: 69-71
12. Takei M, Kobayashi M, Herndon DN, Pollard RB, Suzuki F (2006) Glycyrrhizin inhibits the manifestations of anti-inflammatory responses that appear in association with systemic inflammatory response syndrome (SIRS)-like reactions. Cytokine 35: 295-301
13. Ryugo M, Sawa Y, Takano H, Matsumiya G, Iwai S, et al. (2006) Effect of a polymorphonuclear elastase inhibitor (sivelestat sodium) on acute lung injury after cardiopulmonary bypass: findings of a double-blind randomized study. Surg Today 36: 321-326.
14. West MA, Koons A, Crandall M, Skinner R, Worley M, et al. (2007) Whole blood leukocyte mitogen activated protein kinases activation differentiates intensive care unit patients with systemic inflammatory response syndrome and sepsis. J Trauma 62: 805-811.
15. Martins JO, Ferracini M, Ravanelli N, Landgraf RG, Jancar S (2008) Insulin inhibits LPS-induced signaling pathways in alveolar macrophages. Cell Physiol Biochem 21: 297-304.
16. Zhou QQ, Liu FY, Zheng BH, Gao YQ, Li SZ, et al. (2007) The clinical significance of leucocytosis and increase in interleukin content in acute m ountain sickness complicated with multiple organ dysfunction syndrome. Chin Crit Care Med 19: 588-592
17. Zhang G, Deng X (2005) Neutrophils in role of pathogenesis of acute respiratory distress syndrome. Chinese Journal of Critical Care Medicine 25: 830-833.
18. Bailey DM, Kleger GR, Holzgraefe M, Ballmer PE, Bärtsch P (2004) Pathophysiological significance of peroxidative stress,neuronal damage and membrane permeability in acute mountain sickness, J Appl physiol 96: 1459-1463.
19. Hartmann G, Tschöp M, Fischer R, Bidlingmaier C, Riepl R, et al. (2000) High altitude increases circulating interleukin-6, interleukin-1 receptor antagonist and C-reactive protein. Cytokine 12: 246-252.
20. Takahashi H, Tsuda Y, Kobayashi M, Herndon DN, Suzuki F (2006) CCL2 as a trigger of manifestations of compensatory anti-inflammatory response syndrome in mice with severe systemic inflammatory response syndrome. J Leukoc Biol 79: 789-796.
21. Shao YM, Zhang LQ, Deng LH, Yao HG (2005) Clinical study on effects of ulinastatin on patients with systemic inflammatory response syndrome. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue 17: 228-230.
22. Larson DF, Horak K (2006) Macrophage migration inhibitory factor: controller of systemic Inflammation. Critical Care 10: 138.
23. O'Mahony DS, Liles WC, Altemeier WA, Dhanireddy S, Frevert CW, et al. (2006) Mechanical ventilation interacts with endotoxemia to induce extrapulmonary organ dysfunction Critical Care 10: 136.
24. Zhu Q, Qian X, Wang S, Yin T, Yang J, et al. (2006) A comparison of elderly and adult multiple organ dysfunction syndrome in the rat model. Exp Gerontol 41: 771-777.
25. Rupert JL, Monsalve MV, Kidd KK, Tan C, Hochachka PW, et al. (2003) Selective pressure has not acted against hypercoagulability alleles in high-altitude Amerindians. Ann Hum Genet 67: 426-432.
26. Jianhua C, Xizhou Z, Yong M (2001) Change of blood coagulation and fibrinolysis system of high altitude pulmonary edema. Chinese Journal of Critical Care Medicine 21: 479-480.
27. Jianhua C, Xizhou Z, Fuwen H (1999) Changes of hemorhheological properties and fibrinolytic system in patients with HAPE. Chinese Journal of Hemorheology 9: 239-242.
28. Kaur C, Singh J, Peng CM, Ling EA (2002) Upregulation of adrenocorticotrophic hormone in the corticotrophs and downregulation of surface receptors and antigens on the macrophages in the adenohypophysis following an exposure to high altitude. Neurosci Lett 318: 125-128.
29. Wu TY, Ding SQ, Liu JL, Jia JH, Dai RC, et al. (1991) Gastrointesinal mucosal lesion at high altitude. Jap J Mount Med 11: 55-58.
30. Recavarren AS, Ramirez RA, Gilman RH, Et al. (2005) Severe gastritis in Peruvian andes. Histopathology 46: 374-379.
31. Diebel LN, Liberati DM, Taub JS, Diglio CA, Brown WJ (2005) Intestinal epithelial cells modulate PMN activation and apoptosis following bacterial and hypoxic challenges. J Trauma 58: 1126-1133.

32. Yang DZ, Zhou QQ, Li SZ, Zheng BH, Gao YQ et al. (2009) Gastrointestinal dysfunction in acute severe mountain sickness and its relation with multiple organ dysfunction syndrome. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue 21: 95-98.

33. Zhou QQ, Yang DZ, Luo YJ, Li SZ, Liu FY, et al. (2011) Over Starvation Aggravate Intestinal Mucosal Injury and Promote Bacterial Translocation Under High-Altitude Hypoxic Environment Exposure. World J Gastroenterol 17:1584-1593.

34. Miki K, Unno N, Nagata T, Uchijima M, Konno H, et al. (2004) Butyrate suppresses hypoxia-inducible factor-1 activity in intestinal epithelial cells under hypoxic conditions. Shock 22: 446-452.

35. Hackett PH, Roach RC (2004) High altitude cerebral edema. High-Alt-Med-Biol 5: 136-146.

36. Yamagata K, Tagami M, Takenaga F, Yamori Y, Itoh S (2004) Hypoxia induced changes in tight junction permeability of brain capillary endothelial cell are associated with IL-1 beta and nitrc oxide .Neurobiology of Disease 17: 491-499.

37. Bailey DM, Kleger GR, Holzgraefe M, Ballmer PE, Bärtsch P (2004) Pathophysiological significance of peroxidative stress,neuronal damage and membrane permeability in acute mountain sickness, J Appl physiol 96: 1459-1464.

38. Felinski EA, Antonetti DA (2005) Glucocorticoid regulation of endothelial cell tight junction gene expression: novel treatments for diabetic retinopathy. Curr Eye Res 30: 949-957.

39. Velasco R, Cardona P, Ricart A, Martínez-Yélamos S (2008) Cerebral vasoreactivity in high-altitude cerebral edema. Neurologia 23: 65-68.

40. Bailey DM, Evans KA, James PE, McEneny J, Young IS, et al. (2009) Altered free radical metabolism in acute mountain sickness: implications for dynamic cerebral autoregulation and blood-brain barrier function. J Physiol 587: 73-85.

41. Qiquan Z, Shifan Z (2010) Early diagnosis and clinical treatment for severe acute mountain sickness with multiple organ dysfunction syndrome. Medical Journal of Chinese People's Liberation Army 35: 1183-1186.

42. Yongjun L, Qiquan Z, Yuqi G (2010) New drug for prevention and treatment of high altitude pulmonary edema. Medical Journal of Chinese People's Liberation Army 35: 1502-1503.

43. Wei Q, Yu TC, Hua MX, Xue HZ, Zi L, et al. (2009) Continuous renal replacement therapy in the treatment of severe acute mountain sickness. Ren Fail 31: 175-177.