

The Current Opinions of Capillary Leak Syndrome

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Received 25 February 2015; accepted 6 March 2015; published 13 March 2015

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Abstract

Capillary Leak Syndrome (CLS) in patients with severe course of disease is more and more common, and the clinical manifestations of CLS include systemic edema, hypoproteinemia, effective circulating blood volume reduction and hemoconcentration. The common pathogenies are sepsis, severe trauma, cardiopulmonary bypass and so on. Clinically, CLS is usually divided into leakage period and recovery period, with different pathophysiologic process, clinical manifestation and treatment in different period respectively. Although there are more treatments, they are not effective treatment measures. There have been so many studies about improvement of endothelial function, macromolecular colloid liquid applications, and continuous blood purification treatment. Systematic understanding of the pathological mechanism, clinical manifestations and staging, diagnosis and treatment of the CLS has a guiding value.

Keywords

Capillary Leak Syndrome, Pathogenesis, Treatment, Continuous Blood Purification

1. Introduction

Capillary Leak Syndrome (CLS) is a syndrome of hypoproteinemia, hypovolemic shock, acute renal ischemia in clinical manifestations and the main reasons are the cell injury of capillary endothelial, increased vascular permeability, and a large number of plasma proteins leaking into the tissues of small molecule clearance. [1]. Patients in CLS will be with progressive systemic edema, hypoproteinemia, weight gain, blood concentration rapidly and be multiple organ failure in serious condition.

Diagnostic criteria of CLS [2]: 1) Central venous pressure (CVP) decreases (<5 cm H₂O); 2) No obvious decline of red blood cell specific volume(HCT); 3) Significant reduction of serum albumin (<25 g/L); 4) Progressive generalized edema, weight gain or with the chest, pericardial and peritoneal effusion; 5) Oxygenation index

decreased and X-ray showed exudative changes in interstitial pulmonary. Exclusion criteria: Critically ill patients are after fluid recover and confirmed by cardiac, hepatic, nephrogenic edema, neurogenic pulmonary edema, hemorrhagic and septic shock [3].

Critically ill patients with CLS will influence their prognosis. So incidence, risk factors and the impact on function of the important organs of CLS will get more and more concern by critical medicine physicians. According to reports [4], the main risk factors of CLS are serious infections and surgery in ICU together with SIRS. But critically ill patients' condition in ICU is complex. There are many CLS risk factors and prognosis influence factors. It will be good for physicians to guard against these factors, decrease CLS incidence and mortality and improve CLS patients' prognosis by full understanding of CLS.

2. Cause and Pathogenesis

According to internal and external osmotic pressure vessel changes, water and electrolytes can access to the tissue space freely through the capillary barrier and the plasma protein and other ingredients cannot be under normal physiological conditions. Body can cause series of CLS clinical manifestations in the pathological state, for example, severe trauma, sepsis, the operation after cardiopulmonary bypass (particularly in infants and young children) and reperfusion injury, snakebite, acute lung injury or acute respiratory distress syndrome, burns, toxic effects of drugs (recombinant IL-2 and docetaxel) and so on will cause increased capillary permeability by exuding materials of molecular weight less than 20×10^3 Da and even molecular weight of 90×10^3 Da in serious condition [5].

2.1. Serious Infection or Trauma

These pathogenic factors can cause systemic inflammatory response syndrome by excessive activation of mononuclear macrophage system and release of inflammatory mediator. Under the function of inflammatory mediator, endothelial cell and capillary walls damage, cell junction separation and cracks appear, capillary transport channel diameter and vascular permeability increase, small protein in the blood leaks into the interstitial space by causing the interstitial colloid osmotic pressure, interstitial edema, such as body height of edema, ascites and pleural fluids and the effective circulating blood volume decrease. Interstitial pulmonary edema leads to hypoxemia, tissue hypoxia increases cell damage and then causing MODS [6].

2.2. The Operation after Cardiopulmonary Bypass

In the operation of cardiopulmonary bypass, systemic inflammatory response can be caused by the blood surface contact with the pump pipe, non-physiological perfusion, surgical trauma, ischemia reperfusion injury, and changes in body temperature [7]. The inflammation caused by cardiopulmonary bypass is related to perioperative capillary leak. Liu *et al.* [8] found independent factors of CLS were infection cycle time, type of cardiac malformation, the lowest temperature of operation, age and so on by analysis of 310 cases of congenital heart disease by the operation after cardiopulmonary bypass clinical data of patients.

2.3. Mechanical Ventilation

Positive pressure mechanical ventilation itself can cause or worsen lung injury. Slutsky [9] indicated that the mechanical ventilation induced lung injury can demonstrate diffuse alveolar injury (alveolar epithelial and endothelial damage) induced by the gas leakage (*i.e.* stress injury) and non-cardiac source pulmonary edema.

2.4. Drug Toxicity

Using of certain anticancer drugs, especially recombinant human interleukin (interleukin 2, IL-2) therapy, overdose will occur CLS [10] and after injection of interferon 1β in patients with multiple sclerosis also can cause CLS. With the increasing use of granulocyte colony-stimulating factor treatment in hematologic cancer and use of arsenic trioxide treatment for recurrence of acute promyelocytic leukemia, the side effects about CLS were increased [11].

2.5. Inflammatory Mediators

Oberholzer *et al.* [12] showed that TNF, IL-1, IL-8 and so on can accelerate the occurrence of CLS. Assier's research shows that rat NK cells involve in the pathological process of CLS [13]. Chihara *et al.* [5] found that CLS

patients had increased leukotriene B4 and this might be related to increased vascular permeability, plasma extravasation and others. Rafi found that IL-2 could enhance the cytotoxic T lymphocyte activity, increase fas ligand and perforin, Lymphocyte-activated killer cells and endothelial cells in close contact and start the autolysis to endothelial cell damage. Railan *et al.* [14] proposed that nitric oxide could lead to vascular endothelial cell injury and increase capillary permeability.

3. Clinical Manifestations

CLS can be divided into capillary leakage stage and recovery stage.

3.1. Capillary Leakage Stage

3.1.1. Respiratory System

With the increased pulmonary capillary permeability, plasma proteins and other small molecules ooze from the vascular permeability to pulmonary interstitial rapidly, pulmonary effusion changes and leads to hypoxemia. Patients in serious condition will be in pulmonary edema [15] and pleural effusion.

3.1.2. Circulatory System

Small proteins of plasma leaks to extravascular, plasma colloid osmotic pressure decreases, effective circulating blood volume reduces and then decreased blood pressure may occur. Pericardial effusion as well as cardiac tamponade [16] will format by pericardial effusion increasing and furthermore venous will reduce.

3.1.3. Digestive System

Large amount of liquid leaks from the capillary wall and will cause ascites under abdominal wall, gastrointestinal wall and peritoneal edema, then anorexia, nausea, vomiting, abdominal distension, and luminal expansion. Pancreatic tissue edema and trypsin penetrates into the abdominal cavity will make damage increased. Liver cell congestion, edema, degeneration and other pathological changes will impair liver function and acute liver injury appears.

3.1.4. Urinary System

The formation of massive proteinuria will make the plasma colloid osmotic pressure decreased and tissue edema [17] increased further by increased glomerular filtration membrane permeability and plasma protein leakage of small molecules. Low blood volume makes the kidneys perfusion less efficient and also increases the acute kidney injury.

3.1.5. Nervous System

Brain capillary permeability increases, a large number of white matter intercellular fluid accumulates (extracellular space expansion) and is rich in protein, glial elements around gray matter blood vessels and neurons swells (glial cell edema), brain size and weight increase, gyrus is wide and flat, sulci becomes narrow, ventricles reduce and the performance of intracranial hypertension appears. Severe cerebral edema can cause herniation [18].

3.1.6. Mucocutaneous Disorders

Increased capillary permeability makes small proteins in plasma penetrate into tissue space. And then decreasing of plasma colloid osmotic pressure, increased interstitial fluid colloid osmotic pressure, serious edema of systemic mucocutaneous, conjunctival edema, increasing tears overflow in plasma samples and pain of limbs muscle show.

3.2. Convalescence

In the recovery stage of CLS, there are two ways for interstitial fluid to reflux. When it reabsorbs from the venous capillaries and drains into the right atrium through lymphatic, gradually capillary permeability returns normally and blood volume tends to restore. Leakage of plasma proteins to the organization cannot return to capillaries and the colloid osmotic pressure in tissue fluid is still high because of normal capillary permeability. Edema in patients will hardly disappear with normal serum albumin levels and sometimes may last longer. If continuing to offer a lot of fluid at this time, acute pulmonary edema, alveolar atrophy, gas diffusion barriers, increased arterial and venous blood shunt and decreased arterial partial pressure of oxygen will become. Rapid in-

creasing in cardiac preload will induce acute left ventricular failure easily and lead to repeated illness. Some studies have shown [19] that the happened pulmonary edema in recovery is more than that in acute leakage. Therefore, giving rehydration therapy should be in the premise of hemodynamic monitoring if condition is permitted.

4. Treatment

Currently, there are many researches about CLS therapy with no specific treatment. The following treatment is in favor of shortening the duration of capillary leakage and improving the successful rescue rate except for active treatment and removal of the primary disease inducing predisposing factors.

4.1. Drug Treatment

Tahirkhel *et al.* reported that terbutaline and aminophylline were effective drugs to prevent occurrence of CLS. Terbutaline (β agonist) and aminophylline (phosphodiesterase inhibitor) can loose endothelial cells and improve capillary permeability. In addition, terbutaline has anti-inflammatory effect and can adjust the production of cytokines. Zhang *et al.* [20] discovered that patients lacked of C4A genes added C4A gene-rich plasma before surgery and it was able to reduce the incidence of CLS after CPB.

4.2. Fluid Therapy

The key point of fluid therapy in CLS is maintaining the effective circulating blood volume and avoiding shock. For a long time, liquid crystal or colloid treatment is controversial to CLS patients [21]. With patients' large capillary permeability and small molecular weight of liquid crystals, most of them can leak into the interstitial space and then systemic edema increases after infusion. So we should limit the volume of liquid crystals and avoid interstitial edema and cell swelling caused by excessive liquid crystals in the premise of ensuring the effective circulating blood volume. We need to prevent increased pulmonary edema, cardiac, thoracic and abdominal cavity effusion and added organ damage. Colloid hydroxyethyl starch as the generation of plasma in the traditional product is still the effective and available drug in clinical for CLS treatment. Tian *et al.* [22] thought that the newest plasma substitutes were hydroxyethyl starch of 130×10^3 Da and 200×10^3 Da molecular weight, polygeline of $(27.5 - 39.5) \times 10^3$ Da molecular weight and so on. In theory, they may have better expansion effect. When blood volume is restored, we use diuretics to reduce swelling of tissues and organs. In the leakage of the CLS, the human serum albumin can leak from capillaries, redistribute after entering into body and influence plasma colloid osmotic pressure in short time. Now we promote to use generation of plasma including new macromolecular plasma substitutes and don't advocate adding FFP and/or human serum albumin for emergency treatment of CLS. At the recovery time, fluid intake should be strictly limited and increased diuresis with normal capillary permeability gradually returning and intravascular volume increasing.

4.3. Improving Capillary Permeability

4.3.1. Glucocorticoid

It can widely inhibit inflammatory reaction and decrease capillary permeability. In the acute phase, using small doses of hormones can control the inflammatory mediated vascular endothelial injury effectively and reduce the clinical symptoms. It should not be used as a preventive treatment because of the side effects of steroid restrictions.

4.3.2. Increasing the Amount of EPC

It can promote injury repair and regeneration of capillaries [23]. Animal experiments showed [24] that increasing the gene expression of vascular endothelial growth factor can specifically increase the concentration of EPC in peripheral blood and promote EPC mobilization and repair of vascular endothelial. Erythropoietin can promote EPC proliferation and differentiation [25]. EPO treatment can increase the number of EPC in peripheral blood and is positively correlated with concentration of erythropoietin.

4.3.3. Histamine Dihydrochloride

It can protect IL-2 induced rat model of CLS by dose-dependent and reduce the CLS severity and mortality [26]. Comparing with 42% survival rate of the control group, the dose of histamine dihydrochloride are 0.47, 4.7, 47.0 mg/kg and the model mouse survival rates are 56%, 75% and 81%. It can reduce the IL-2-induced lung injury, decrease pulmonary edema (lung wet and dry ratio reduce up to 62%) and pulmonary capillary leakage deter-

minated by Evans blue dye.

4.3.4. Interferon- β

Studies have shown that [27] pretreatment of Interferon- β (IFN- β), CD73's new type inducer could significantly improve the barrier function of animals after intestinal ischemia-reperfusion pulmonary vascular. Interferon- β can almost completely inhibit capillary leakage after ischemia in reperfusion period obviously. Interferon- β can induce CD73 expression of pulmonary vascular endothelial cells in cultured human and reduce capillary leakage meanwhile. So it is expected to be used in clinical treatment of CLS.

4.4. Respiratory Support

In the leakage of CLS, for a large number of fluid in capillaries leaks to interstitial lung with making lung compliance, increased airway resistance, decreased ventilatory function and severe hypoxemia may occur. Mechanical ventilation improves lung compliance and ventilation or perfusion ratio, decreases airway resistance, improves oxygenation and reduces pulmonary effusion by increasing positive end expiratory pressure. Mechanical ventilation can effectively increase the oxygen supply of tissues and organs and has great help in improving body environment and treatment of primary disease [28].

4.5. Continuous Blood Purification

CBP treatment can enhance clearance of inflammatory mediators, improve pulmonary gas exchange, keep hemodynamics stable control of azotemia, reduce fluid overloading because of entering macromolecular synthetic colloids, be convenient for nutrition support, improve oxygen metabolism or tissue perfusion in patients [29], control SIRS symptoms, prevent the development of the disease to the MOD and improve the survival rate in critically ill patients. It also can make rapid absorption and removal of endotoxin in blood, correct acidosis and improve the body's homeostasis. Meanwhile, CBP has a protective effect on vascular endothelial function [30]. CBP also can improve coagulation dysfunction *in vivo* because of heparin. It can reduce blood coagulation cascade [31] and play a role in the treatment CLS.

5. Conclusion

Currently, there is no specific prevention and treatment for critically ill patients in CLS. We should restore blood volume as soon as possible, improve hypoxemia and capillary permeability and reduce the degree of capillary leakage at the same time of active treatment of primary disease. With the pathogenesis deepening research of CLS and the comprehensive application of various prevention methods, the incidence of CLS will reduce, the survival rate will increase and patients' prognosis will improve.

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