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Review article

Damage of vascular endothelial barrier induced by explosive blast and its clinical significance

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ABSTRACT

In recent years, injuries induced by explosive blast have got more and more attention owing to weapon development and frequent terrorist activities. Tear, bleeding and edema of tissues and organs are the main manifestations of blast shock wave damage. Vascular endothelial barrier is the main defense of tissues and organs' integrity. This article aims to discuss possible mechanisms of endothelial barrier damage induced by explosive blast and main manifestations of blood brain barrier, blood–air barrier, and intestinal vascular barrier impairments. In addition, the main regulatory factors of vascular permeability are also summarized so as to provide theoretical basis for prevention and cure of vascular endothelial barrier damage resulting from explosive blast.

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Explosive weapons are the most commonly used lethal weapons in modern warfare. Recent studies^{1,2} show that injuries caused by explosive weapons are on the rise both in wartime and peacetime. Previous war survey data³ indicate that the amount of human loss caused by explosive weapons has risen to the first place instead of the second place in the First World War. During the Gulf War, the proportion of explosive weapon injury reached over 80%. Therefore, the prevention and cure of explosive weapon injury have become the focus of modern war trauma studies.

Among many killing factors of explosive weapons, explosive blast remains to be the main cause of injury. Explosive blast can lead to the damage of vital organs such as the head, chest and abdomen. Bleeding and edema of tissues are main pathological changes, while the pathophysiological basis of bleeding and edema in the tissues is the damage to vascular endothelial barrier. Thus, it is essential to know the mechanism of vascular endothelial barrier damage induced by explosive blast for the prevention and cure of explosive weapon injury.

Possible mechanisms of endothelial barrier damage induced by explosive blast

The possible mechanisms of endothelial barrier damage induced by explosive blast include primary physical factors and secondary neurohumor factors.^{4–6}

The primary physical factors mainly stem from overpressure generated during the explosion process and negative pressure. When overpressure acts on body surface, compression of the abdominal wall makes the abdominal pressure increased. As overpressure oppresses the diaphragm, blood from the upper chamber suddenly flows into the heart and lungs, leading to a rapid increase of blood volume. On the other side, compression of the chest wall reduces the chest wall's volume and the intrapleural pressure rises sharply. Following overpressure, the thorax expands due to the tractive effect. The rapid compression and expansion result in a series of hemodynamic changes in the pleural cavity and generate vascular endothelial injury. Besides, when pressure waves act on the body, liquid components in the body will not be compressed; whereas gas components will be compressed obviously. Then the negative pressure after overpressure can increase gas volume. The continuous compression and expansion of the alveoli and other gas-bearing tissues will lead to “implosion effect”, causing tear and bleeding of the alveolar wall and pulmonary capillaries. Moreover, pressure differences play an important role in the mechanism of lung damage caused by explosive blast. After

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explosive blast, the pressures of both pulmonary liquid components (vessel) and gas components (alveoli) increase, but the pressure of liquid components rises more, thus forming a large pressure difference between them, which can result in microvascular rupture and damage of vascular endothelial barrier.

As a physical stimulus, explosive blast can trigger generalized neuroendocrine response, and a variety of secondary neurohumoral factors can mediate vascular endothelial damage effect. It can cause stress response when any stressor acts on the body, and a series of neuroendocrine response occur in the hypothalamus-pituitary-sympathoadrenal system. A large number of experimental studies and clinical data have indicated that pulmonary edema and pulmonary hemorrhage occur due to explosion injury and other severe traumas. Meanwhile, the sympathetic neurotransmitters in blood such as adrenaline, norepinephrine, catecholamine and so on will be greatly increased. Therefore, it is believed that vascular endothelial damage is related with the mediating effect of sympathetic neurotransmitters. It has been reported recently that application of excitatory amino acid receptor agonists can reproduce pulmonary edema, while the application of excitatory amino acid receptor blockers can ease the damage of respiratory distress syndrome, which suggests that excitatory amino acids can mediate lung injury. Furthermore, the studies show the protein content increased in pulmonary edema fluid after lung injury and suggest that the occurrence of pulmonary edema should be attributed to the increased vascular permeability induced by sympathetic neurotransmitters' mediation. In the process of pulmonary edema, it is generally acknowledged that $\alpha 1$ receptor has mediated the increase of pulmonary microvascular permeability. When $\alpha 1$ receptor in pulmonary vasculature combines with agonist, on one side, it leads to pulmonary vasoconstriction which causes the rise of pulmonary vascular fluid static pressure and vascular filtration pressure. On the other side, the concentration of Ca^{2+} in pulmonary vascular endothelial cells increases, and the action on contractile component of cytoskeleton can make cells contract and intercellular space increase. Meanwhile, cell membranes are damaged and endothelial cells become loose and falling off, which results in the increase of pulmonary microvascular permeability.

Damage of blood brain barrier induced by explosive blast

Many American soldiers who retired from wars in Iraq and Afghanistan suffer from mild traumatic brain injury (mTBI), with main manifestations of cognitive impairments, memory disorders, depression, anxiety and diffused white matter injury, and explosive blast are considered as the main cause of injury. Moreover, explosive attacks resulting from constant terrorist activities around the world in recent years have brought extensive attention to brain injury induced by explosive blast. Shetty et al⁷ hold that the main reason for brain injury induced by explosive blast is dysfunction and damage of blood brain barrier. The explosive blast with an overpressure of 123 kPa can lead free radicals to generate secretion of enzyme, increase of oxidative stress, loss of tight junction protein, edema formation and increased leakage of blood brain barrier. While 145–323 kPa explosive blast can result in acute rupture of cerebral blood vessels and damage of blood brain barrier. According to studies on pathogenetic mechanisms of brain injury induced by explosive blast, the damage of blood brain barrier is an important cause of injury. Yeoh et al⁸ applied shock waves with an overpressure of 145 kPa, 232 kPa, 323 kPa to rats respectively, and observed the extravascular exudation of immunoglobulin IgG through a quantitative analytical method of immunohistochemistry immediately and 24–48 h after injury. It is indicated that primary blast waves can lead to generalized blood brain barrier

damage, whose range of damage is positively correlated with overpressure values of explosive blast but not correlated with occurrence time.

Wang and other Chinese experts⁹ also deployed the research on blood brain barrier changes induced by explosive blast. They used ¹²⁵I to label serum albumin and observed microvascular permeability changes in different organs of the rabbit after explosive blast. The results showed that when 1.3 g TNT point explosion sources exploded, the overpressure peak value of explosive blast was 1108 kPa with a distance of 10 cm from explosion center (the distance between explosion sources and the rabbit head was 60 cm), and the residual radioactivity in brain tissues (radioactivity of per gram tissue compared to radioactivity of per ml blood $\times 100$) rose to 3.07 from the normal 1.69, with a rising range of 81%.

Blood brain barrier is the structure that can selectively allow some substance to pass through the blood and brain, and its permeability is closely related with the degeneration, injury and inflammation of the central nervous system. Studies have indicated that blood brain barrier damage plays a critical role in the development of vascular dementia. With effects of matrix metalloproteinases, tumor necrosis factor, nitric oxide and other factors, the structure and function of blood brain barrier can be changed, which makes it one of the important pathological changes of vascular dementia.

Damage of blood–air barrier induced by explosive blast

Pulmonary edema is one of the main pathologic manifestations of blast shock wave injury and it has great significance in the occurrence of severe complications such as respiratory failure after explosive shock wave injury. And the change of pulmonary microvascular endothelial cell permeability is the first step of pulmonary edema. The disruption of alveolar epithelial cell junctions is usually the reason for permeability changes. The junctions of alveoli epithelial cell permeability are relatively tighter than those of endothelial cells. Pulmonary interstitial edema usually occurs before alveolar edema. In order to understand the mechanism of pulmonary edema, it is meaningful to study the changes of pulmonary microvascular endothelial cell permeability.

Smith³ concluded the cases of accompanying medical institutions' treatment to the wounded when British armed forces performed military missions overseas. From 2003 to 2009, a total of 1678 blast injury cases were treated. Among them, there were 113 cases of pulmonary blast injury, accounting for 6.7%. A great number of researches have shown that shock waves can lead to the injury of pulmonary microvascular endothelial cells. Two hours after explosive blast, it can be seen that the medium aorta is removed in a few case, the smooth muscle of the tube wall is dispersed, and most of arterioles are highly contracted and even closed. There are bleeding and edema around some blood vessels. Electron microscope observation shows that the capillary endothelium is generally segmental swelling, mainly occurring in the thick cytoplasm. Occasionally, degenerative endothelial cells intrude into the capillary lumen. Edema also occurs in blood capillary pericyte and interstitial cells owing to the increase of permeability.

Pulmonary edema and hemorrhage always occur simultaneously. Mild pulmonary edema only manifests as an increase of lung weight and lung water content, which still remains at a high level in 24 h after injury. A shallow red edema area with clear borders can be seen around bleeding areas after 24–48 h, with a distended appearance and foamed liquid in the section. Under the microscope, the pulmonary capillary congestion is obvious, and there is much light red edema fluid and a few red blood cells in the

alveolar cavity, some of which appear as hyaline membranes close to the inner walls of cells.¹⁰

Jin et al¹¹ in our institute have also observed the integral value changes of vascular endothelial cell labeled factor vWF content in plasma and vWF content in pulmonary microvascular endothelial cells affected by explosive blast. And the results show that vWF content in plasma is gradually increased, while vWF content in pulmonary microvascular endothelial cells is gradually decreased, and thus there is a significant negative correlation between them. It also indicates that explosive blast may lead to generalized damage to pulmonary vascular endothelial cells.

Damage of intestinal vascular barrier induced by explosive blast

Abdominal hollow organ is also an important target organ affected by explosive blast. Many intestinal gas–liquid interfaces are inclined to produce the implosive effect and inertial effect by explosive blast, and these kinds of effects are easy to spread widely in the intestinal tracts. The intestinal tract is one of the organs that are most sensitive to shock wave damage in the body. At the same time, intestinal mucosa is the most abundant part of capillaries, whose barrier is also the most vulnerable after injury. As the intestinal mucosa is the first affected part and most sensitive to ischemia and hypoxia, a lot of bacteria and toxins in the intestinal tracts are prone to produce bacterial and toxin translocation, causing systematic reactions.

Wani et al¹² have conducted a statistical analysis on 154 cases of primary blast injury, among which, there are 149 cases of exploratory laparotomy accounting for 96.75%. Through exploratory laparotomy, it is found that explosive blast has an extensive damage to abdominal organs, including the large intestine, small intestine, liver, spleen, kidney, stomach, duodenum, gallbladder, bladder, appendix, mesentery, peritoneum, caecum, omentum, etc. There are 54 patients suffering from damage in more than 1 organ, accounting for 35.06%. Among all injury types, intestinal perforation is the most commonly seen, with 58 cases accounting for 37.66%; small intestine perforation is more common than others in intestinal perforation, with a total of 48 cases (31.16%). There are 26 cases of hematoma in the duodenum, mesentery, peritoneum, caecum and omentum, which shows that explosive blast has a wide range of vascular damage to abdominal organs.

Nie et al¹³ observed malondialdehyde (MDA) content in serum and intestinal tissues and dynamic changes of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activity after injury through a simulation of rats' abdominal blast injury induced by the explosion in cabin. The results indicate that MDA content in serum and intestinal tissues is increase till the peak value after 24 h, and activity values of SOD and GSH-Px are slightly increased. These manifestations show that the oxidative stress produced after abdominal blast injury can lead to damage of intestinal barrier.

Regulation of vascular endothelial barrier damage

As stated above, the vascular endothelial barrier damage is not only related to direct damage from explosive blast, but also related to endothelial regulatory factors. Knowledge of endothelial regulatory factors of vascular endothelial barrier after explosive blast is helpful to define the biological damage mechanism of explosive blast and enhance the repairing level of vascular endothelial barrier damage. The regulatory factors which can affect endothelial permeability are quite sophisticated. So far, dozens of factors have been found including tumor necrosis factor, interleukin, endothelin, vascular endothelial growth factor and endothelial cell permeability factor.

Platelet activating factor (PAF)

PAF is a kind of highly efficient lipid inflammatory mediator. It may have a direct effect on endothelial cells, or an indirect effect generated by activating leukocyte and inducing other mediators to release.¹⁴ Bussolino et al¹⁵ used PAF to deal with endothelial monolayer and found that PAF could quickly induce endothelial cells to contract and become rounded (in ten minutes), presented in a walk-like way, then intercellular junctions disappeared and permeability of cell monolayer to ¹²⁵I albumin increased. PAF receptor antagonists could block these changes, and the morphology and barrier of endothelial cells return to normal after removal of PAF. In addition, Björk et al¹⁶ also reported that PAF can increase microvascular permeability by affecting endothelium–granulocyte interaction in microvascular beds.

Thrombin

Thrombin is often used to study the active medium of endothelial monolayer permeability. Garcia,¹⁷ Killackey,¹⁸ Minnear¹⁹ et al used thrombin to deal with endothelial cell monolayer. The cells had no traumatic changes but fissures were formed between cells and permeability was increased. The permeability returned to normal after removal of thrombin. Therefore, it is recently believed that endothelial cells can actively regulate the permeability.²⁰

5-HT

The effect of 5-HT on endothelial monolayer morphology is consistent with albumin permeability changes, and the effect can be blocked by 5-HT antagonists. 5-HT acts on the receptors of endothelial cell membrane surface, which causes intracellular Ca²⁺ to be increased, cytoskeletal microfilament aggregated, and intercellular junctions closer. 5-HT can also be directly combined with actin to stabilize microfilament structures.²¹

TNF

TNF can increase vascular endothelial permeability by changing extracellular matrix. After bovine pulmonary microvascular endothelial cells are incubated for 24 h with 10⁴ μ/ml TNF, the permeability of monolayer endothelial cells to ¹²⁵I albumin is increased to 2–3 times. While endothelial cells are treated by TNF, an increase in the expression of 96 KD gelatinase is induced. It exists in the matrix of endothelial cells and has the effect of increasing endothelial permeability.²²

Endothelin (ET) and nitric oxide (NO)

ET and NO are bioactive peptides and respectively contract and expand blood vessels, and they can increase vascular permeability. The mechanism of NO leading to an increased vascular permeability is to activate guanosine cyclase and increase the cGMP content in endothelial cells. While cGMP promotes contraction of endothelial cells, protein contraction or conformational change of cytoskeletal protein, the enlarged intercellular space can increase the vascular permeability. On one side, ET can increase vascular permeability through the change of hemodynamics, and the capillary pressure increases as ET contracts blood vessels; on the other side, ET can stimulate endothelial cells to produce NO and make permeability of endothelial cells increased.²³

Neutrophil leukocyte

Normal neutrophil leukocyte can reduce filtration fraction (KF) of the monolayer endothelial cell liquid to make the osmotic reflection coefficient (σ) increased. After adhesion of neutrophil leukocyte in pathological state (such as burn) and vascular endothelial cell granules, the permeability of microvessel to macromolecules and micromolecules is significantly increased. Adhesion molecules CD116/CD18 on McAb closed neutrophil leukocyte membrane can reduce the effect of neutrophil leukocytes on endothelial cell permeability, which indicates that the effects of neutrophil leukocyte on endothelial cell permeability is produced through adhesion molecules CD116/CD18 on the membrane.²⁴

Endothelial cell adhesion molecules

The intermediate connection between endothelial cells is mainly produced by adhesion molecules or adhesion proteins on the endothelial cell membranes. Therefore, the changes of endothelial cell adhesion molecules may affect the changes of endothelial permeability. There are three families of adhesion molecules involved in the linking structures of endothelial cells, which are mainly integrin family, calcium dependent adhesion family and immunoglobulin family.²⁵

To sum up, vascular endothelial cells are a layer of flat cells, covered on the inner surface of blood vessels. Vascular endothelial cells take part in many functional regulations, such as vasomotion, vascular endothelial permeability barrier, anti-coagulation, body metabolism and immunoregulation, etc. Among them, the barrier function is the main function. They constitute the interface between blood and tissue, and regulate the exchange between blood and tissue fluid. It is important to maintain normal cardiovascular function.

Pulmonary edema and brain edema are the main clinical manifestations after explosive blast injury. The damage of vascular endothelial barrier is its pathological basis. Therefore, the regulation of vascular endothelial permeability is very important for saving casualties with blast injury.

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