Chinese Journal of Traumatology 19 (2016) 125–128

Contents lists available at ScienceDirect

Chinese Journal of Traumatology

journal homepage: http://www.elsevier.com/locate/CJTEE

Review article

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

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ARTICLE INFO

Article history:
Received 20 January 2016
Received in revised form
24 February 2016
Accepted 1 March 2016
Available online 18 March 2016

Keywords:
Blast injuries
Vascular endothelial cells
Blood brain barrier
Blood–air barrier

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.

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 data[3] indicate that the amount of human loss caused by explosive weapons has rised 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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Peer review under responsibility of Daping Hospital and the Research Institute of Surgery of the Third Military Medical University.

http://dx.doi.org/10.1016/j.cjtee.2016.03.001

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 al[7] 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 al[8] 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 experts[9] also deployed the research on blood brain barrier changes induced by explosive blast. They used ^{125}I 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.

Smith[3] 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