

Pulmonary microvascular dysfunction and pathological changes induced by blast injury in a rabbit model

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ABSTRACT

BACKGROUND: Vascular leakage has been proven to play a critical role in the incidence and development of explosive pulmonary barotrauma. Quantitatively investigated in the present study was the severity of vascular leakage in a gradient blast injury series, as well as ultrastructural evidence relating to pulmonary vascular leakage.

METHODS: One hundred adult male New Zealand white rabbits were randomly divided into 5 groups according to distance from the detonator (10 cm, 15 cm, 20 cm, 30 cm, and sham control). Value of pulmonary vascular leakage was monitored by a radioactive ¹²⁵I-albumin labeling method. Pathological changes caused by the blast wave were examined under light and electron microscopes.

RESULTS: Transcapillary escape rate of ¹²⁵I-albumin and residual radioactivity in both lungs increased significantly at the distances of 10 cm, 15 cm, and 20 cm, suggesting increased severity of vascular leakage in these groups. Ultrastructural observation showed swelling of pulmonary capillary endothelial cells and widened gap between endothelial cells in the 10-cm and 15-cm groups.

CONCLUSION: Primary blast wave can result in pulmonary capillary blood leakage. Blast wave can cause swelling of pulmonary capillary endothelial cells and widened gap between endothelial cells, which may be responsible for pulmonary vascular leakage.

Keywords: Blast injury; permeability; pulmonary dysfunction; vascular leakage.

INTRODUCTION

Blast injuries are a series of minor, major, or lethal traumas that may lead to dysfunctions in pulmonary, gastrointestinal, and auditory systems.^[1-5] In the past, the majority of blast injuries were sustained during military conflict, or industrial or mining accidents. However, explosions in different kinds of

terrorist attacks have become the leading cause of blast injuries. It has been reported that blast injuries sustained during terrorist attacks increased 4-fold from 1999 to 2006, worldwide.^[6] Therefore, investigations into the mechanism of blast injury are imperative, as they may aid in exploring solutions for blast injury patients.

Pulmonary barotrauma is one of the most critical injuries in civilian or military blast settings. It has been shown that pathological characteristics of explosive pulmonary barotrauma include alveolar hemorrhage, interstitial edema, and alveolar septa rupture. Such pathological changes are always lethal, due to impairment of gas exchange capacity.^[2-4,6] Thus far, several contributing factors for pulmonary blast injury have been identified, including direct tissue damage, progressive vascular leakage, and inflammatory changes. In particular, vascular leakage has been shown to play a critical role in the incidence and development of explosive pulmonary barotraumas.^[7-12] Although the existence and significance of vascular leakage in pulmonary blast injury has been confirmed, there has been insufficient quantitative investigation into pulmonary vascular leakage. In addition, ultrastructural evidence of pulmonary vascular leakage has not been identified. Therefore, the pri-

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mary aim of the present study was to quantitatively investigate the severity of vascular leakage in a gradient blast wave series. The secondary aim was to explore ultrastructural evidence of pulmonary vascular leakage.

MATERIALS AND METHODS

Animal Model of Blast Injury

One hundred adult male New Zealand White rabbits weighing from 2.0 to 2.5 kg were provided by the Experimental Animal Center of the Third Medical University. All experimental protocols were approved by the Institutional Animal Care and Research Advisory Committee, and were performed in accordance with the National Institutes of Health Guidelines for Animal Use and Care. The animals were randomly divided into 5 groups (n=20), including 1 group that served as sham control. Each animal was anesthetized by intravenous injection of 3.0% pentobarbital-sodium at a dose of 30 mg/kg, and received an intravenous injection of 2 mg/kg carprofen to prevent pain. A 10-cm×10-cm region of the surface of the xiphoid process was shaved, and the rabbit was fixed on a specially designed plate, lying on the right side to prevent movement in response to blast impact. Electrocardiogram (ECG) was recorded with a CardiMax FX-7202 electrocardiograph (Fukuda Denshi Co. Ltd., Tokyo, Japan), with a vertical calibration of 10 mm/mV, and a horizontal paper speed of 25 mm/second. Printouts were made prior to detonation and every 10 min after detonation, or as necessary. The blast wave was generated by detonator containing 0.9 g trimethylene trinitramine (RDX) and 0.4 g diazodinitrophenol (DDNP; No. 845 Factory, Chongqing, China). The detonator was placed at the same horizontal level as the thoracoabdominal midline of the animal, pointed at the surface of the xiphoid process. In order to achieve the gradient blast injury, the detonator was set at 10 cm, 15 cm, 20 cm and 30 cm from the animals. In each group, 5 rabbits were distributed for histological observation, while the others were subjected to permeability measurement. The animals of the control group underwent the same protocols, with the exception of detonation. Certain necessary emergency treatments were conducted following detonation, such as chest compressions and methods to ensure that the respiratory tract was unobstructed.

Determination of Blast Wave

Following anesthetization by pentobarbital-sodium, each animal was placed on a specially designed wooden desk, with left forelimb secured tightly to expose the chest and abdomen. The detonator was placed vertically at the series of distances (10 cm, 15 cm, 20 cm and 30 cm), in alignment with the xiphoid process. A SK-902 piezoelectricity pressure sensor (Jili Electron Machine Factory, Yangzhou, China) was attached to the right chest. The sensor was connected to a SK6882 charge amplifier (Jili Electron Machine Factory, Yangzhou, China). Real-time signal was recorded

and processed by a HP54501A data-recording oscillograph (Hewlett-Packard Inc., Palo Alto, CA, USA) during detonation. Characteristic parameters of blast wave included peak pressure, duration of positive pressure, and the time of pressure-to-peak.

Pulmonary Microvascular Permeability

Severity of vascular leakage in a series of blast injuries was monitored by a radioactive ¹²⁵I-albumin labeling method. After induction of anesthesia, blood samples (3 ml) of each animal were drawn into vacutainer tubes containing ethylene diamine tetraacetic acid (EDTA) through the right jugular vein of the rabbits. Each blood sample was centrifuged at 10,000 r/min for 10 min, hematocrit (HCT) value was determined using a ZJ2000 blood cell analyzer (Shounuote Scientific Instrument, Inc., Jiangxi, China), and ¹²⁵I-albumin (20 μCi/kg) was administered through the internal jugular vein. After 5 minutes, 1 ml of blood from animals in each group (n=15) was obtained to measure radioactivity (counts/minute, min⁻¹). Thirty minutes after detonation, the process was repeated. While blood was released from the femoral artery, 500 ml 0.9% sodium solution was injected into the internal jugular vein. Thereafter, each rabbit was sacrificed to acquire value of radioactivity in both lungs. On the assumption that total red cell volume would be constant throughout the experiment, the transcapillary escape rate of total ¹²⁵I-albumin (R_1) and the rate of residual-radioactivity (R_2) in both lungs were acquired using the following equations:

$$R_1 = (1 - (Hct_1 \times r_2) / (Hct_2 \times r_1) - r_4 / r_1) \times 100\% \quad (1)$$

$$R_2 = r_3 / (W_t \times r_2) \times 100\% \quad (2)$$

The symbol r_t stands for total radioactivity before injury, r_1 for radioactivity per ml blood before injury, r_2 for radioactivity per ml blood after injury, r_3 for residual radioactivity of lung tissue after injury, r_4 for radioactivity of blood drawn from the femoral artery, W_t for the weight of tissue, HCT_1 for HCT before injury, and HCT_2 for HCT after injury.

Histological Study

Following 30 minutes of observation, the animals were sacrificed via overdose of pentobarbital until ECG became isoelectric. Lung tissue specimens of 25 rabbits (n=5 in each group, 5 groups) were immediately fixed in 2.5% glutaraldehyde. The specimens were dehydrated in an ascending grade of ethanol, cleared in xylene, and embedded in paraffin wax. Serial sections of 5-mm thickness were obtained using rotatory microtome. Deparaffinized sections were routinely stained with haematoxylin and eosin (HE). Photomicrographs of each slide were obtained using digital research photographic microscope (IX50; Olympus Co., Ltd., Tokyo, Japan).

Ultrastructural Observation

Ultrastructural alterations were investigated with electron microscopy. Harvested lung samples were post-fixed by 1%

osmium tetroxide in 0.1-M sodium cacodylate buffer (pH 7.3) for 1 hour at room temperature. They were then dehydrated in ethanol and embedded in resin. Ultra-thin sections of lung samples were prepared and stained with uranyl acetate and lead citrate. They were then examined under a transmission electron microscope (TECNAI 10; Philips Healthcare, Inc., Eindhoven, Netherlands). Morphometric evaluation was conducted by an examiner who had not been informed of the experiment's design.

Statistical Analysis

Values are expressed as mean±SD. Following test for normalcy of distribution, data were analyzed with one-way analysis of variance (ANOVA) using the SPSS software package (version 13.0; SPSS Inc., Chicago, IL, USA). When significant overall difference among groups was determined, Tukey's post hoc test was used to perform pairwise comparison, and $p < 0.05$ was considered statistically significant.

RESULTS

Distance Decay of Blast Wave in Air

The distance decay of the blast wave was recorded by pressure sensor. Data regarding distances from the detonator are displayed in Table 1. Pressure peak of blast wave and time required for pressure rise both decreased as the distance to the detonator increased, while the duration of positive pressure increased.

Blast Wave Increased Pulmonary Microvascular Permeability

Transcapillary escape rate of ^{125}I -albumin was measured to

evaluate the severity of vascular leakage by calculating the variation of total radioactivity in blood. It was shown that the transcapillary escape rate of ^{125}I -albumin significantly increased after injury at the distances of 10 cm, 15 cm, and 20 cm, suggesting an increase of vascular leakage in these groups ($p < 0.05$, Table 2). Little influence on the transcapillary escape rate of ^{125}I -albumin was found in rabbits at the distance of 30 cm ($p > 0.05$, Table 2). In particular, the transcapillary escape rate of ^{125}I -albumin at the distance of 10 cm was significantly higher than rates at the distances of 15 cm, 20 cm, and 30 cm. This outcome demonstrated that higher intensity of blast wave can result in more severe vascular leakage ($p < 0.05$, Table 2).

Residual radioactivity in both lungs was measured to reflect the amount of ^{125}I -albumin leaking into the interstitial space through the damaged microvessel in the lung. The data showed that residual radioactivity significantly increased following injury at the distances of 10 cm, 15 cm, and 20 cm, suggesting an increased amount of vascular leakage in these groups ($p < 0.05$, Table 2).

Animal Experiment and Pathology Results

All animals survived the 30-minute observation period. Body surface of injured animals suffered burn and subcutaneous hemorrhage without penetrability trauma, while foliated hemorrhage was observed in the lungs. Representative photographs of HE-stained sections are shown in Fig. 1. Observed in the 10-cm group were alveolar and interstitial hemorrhage, pulmonary interstitial edema, multifocal alveolar septum fracture, focal bullae formation, and necrosis or loss of pulmonary capillary endothelial cell in lumen (Fig. 1b, c). In the 15-cm group, red blood cells were found in the alveolar lumen, and the edema of the alveolar epithelial cell

Table 1. Blast wave pressure at various distances from the detonator in air (Mean±SD)

Distance (cm)	n	Peak pressure (kPa)	Duration of positive pressure (μs)	Pressure rise time (μs)
10	15	1108.30±173.75	121±14	24.0±7.5
15	15	381.50±46.64	152±61	22.0±4.7
20	15	175.43±22.34	170±24	18.0±4.3
30	15	68.50±13.57	209±53	12.0±3.6

Table 2. Change of rate of escaped and retained ^{125}I -albumin radiation in lung tissue after trauma caused by explosive blast at various distances from explosive center (Mean±SD, n=15)

Group	Rate of ^{125}I -albumin escaped (%)	Remained radiation (counts/min/g)	
		Left lung	Right lung
Control	26.43±7.49	4080.58±971.64	4628.11±409.82
10 cm	41.79±6.69**	7496.94±729.48**	6189.36±583.80**
15 cm	39.58±8.40**	5579.31±719.32**	6173.80±744.81**

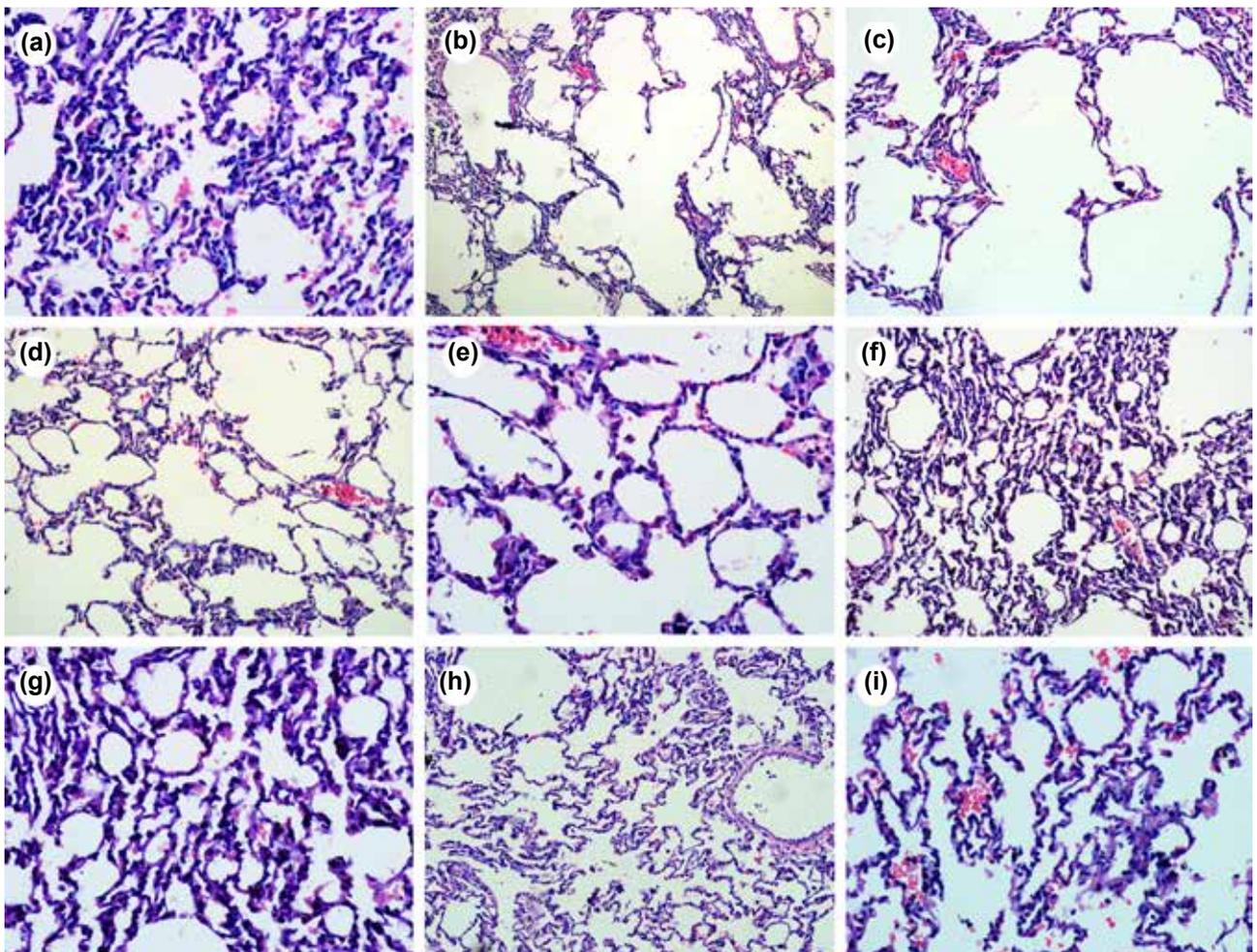


Figure 1. Representative HE micrographs of impaired lungs in normal group (a) and in blast injury groups at 10 cm (b, c), 15 cm (d, e), 20 cm (f, g), and 30 cm (h, i). Original magnifications: 100×(a, b, d, f, h); 200×(c, e, g, i).

and alveolar-interstitial. Focal fracture of the alveolar septum, interstitial capillary congestion, and lymphocyte infiltration were also noted (Fig. 1d, e). In the 20-cm group, red blood cells were found in the alveolar lumen, and alveolar epithelial cell edema and spotty necrosis were also noted (Fig. 1f, g). In the 30-cm group, only scattered red blood cells were found in the alveolar lumen (Fig. 1f, h).

Ultrastructural Evidence of Impaired Pulmonary Permeability

Following blast injury, ultrastructural changes were found with transmission electron microscopy. In the 10-cm group, it was observed that pulmonary microvascular endothelial cells were generally swollen (Fig. 2b). Necrosis was also found in some endothelial cells (Fig. 2c). In the 15-cm group, the gap between pulmonary microvascular endothelial cells was significantly widened (Fig. 2d). Red blood cells had escaped through the alveolar wall, and pulmonary capillary endothelial cell swelling was noted (Fig. 2e). Neutrophils were incarcerated in the endovascular system (Fig. 2f). In the 20-cm group, pulmonary capillary endothelial cell swelling was noted (Fig.

2g,h). In the 30-cm group, no obvious ultrastructural change was observed (Fig. 2i).

DISCUSSION

Quantitatively investigated in the present study was the severity of vascular leakage in a series of gradient blast injuries. In addition, ultrastructural evidence relating to pulmonary vascular leakage was explored. It was found that blood condensed following blast injury. The amount of vascular leakage decreased as the distance to the explosion center increased. In addition, the pulmonary capillary endothelial cells swelled, died, or were lost, and the gap between pulmonary microvascular endothelial cells widened. These phenomena may be responsible, at least in part, for the increased amount of pulmonary vascular leakage after blast injury.

Blast wave was generated by detonator containing RDX and DDNP, which are widely used in the improvised explosive devices of terrorist attacks.^[1,6,12] The detonators were placed at a series of distances (10 cm, 15 cm, 20 cm, and 30 cm) to generate waves of varying intensity. It was found that peak pres-

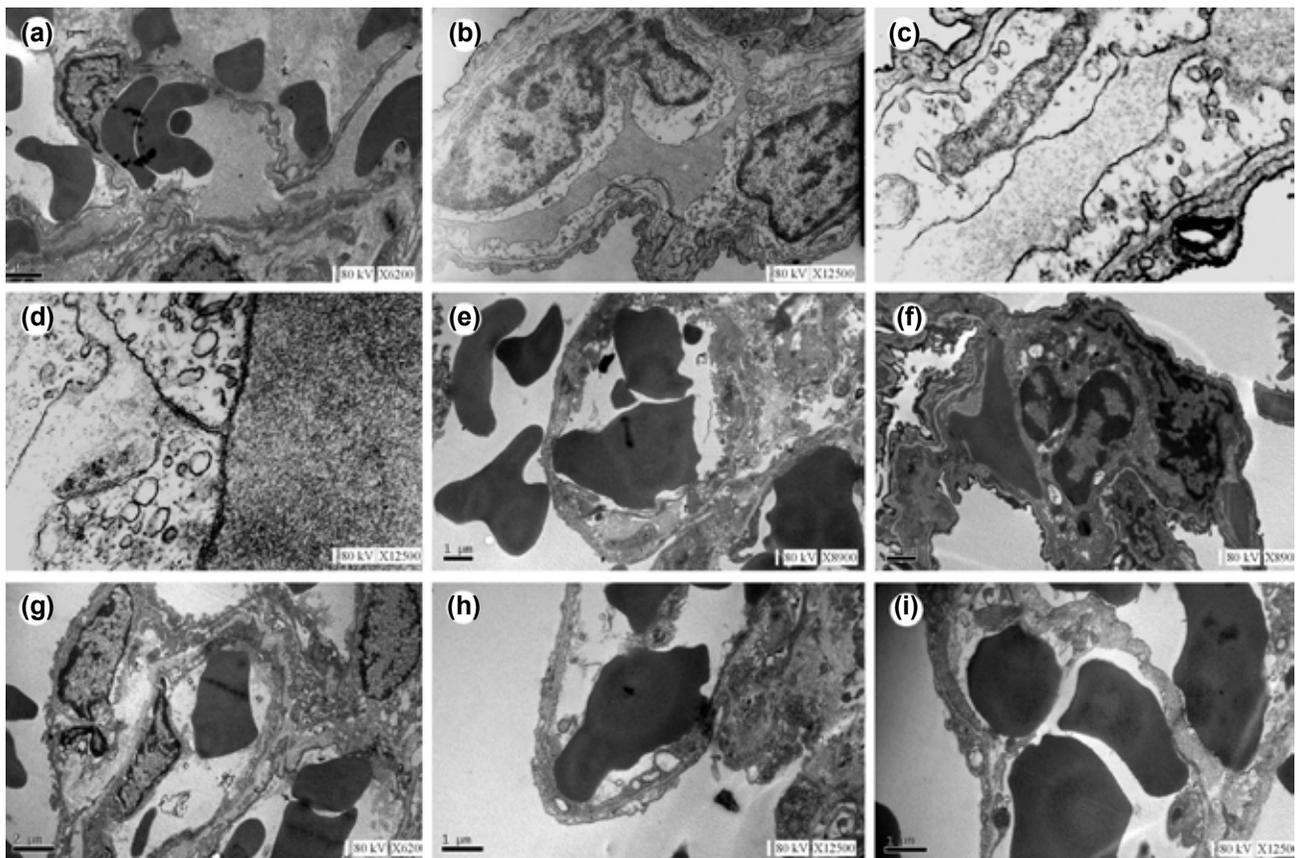


Figure 2. Representative ultrastructural appearances of impaired lungs in normal group (a) and in blast injury groups at 10 cm (b, c), 15 cm (d–f), 20 cm (g, h), and 30 cm (i). a: normal lung; b: swelling of pulmonary microvascular endothelial cells with nuclear swelling; c: necrosis of pulmonary microvascular endothelial cells; d: significantly widened gaps between pulmonary microvascular endothelial cells; e: red blood cells escaped through the alveolar wall; f: swelling observed in the pulmonary capillary endothelial cells and neutrophils incarcerated in the endovascular system; g and h: pulmonary capillary endothelial cell swelling; i: no cell swelling was observed.

sure decreased as distance increased, while duration of positive pressure and time required for pressure rise remained relatively constant. This observation was in accordance with findings of previous studies^[2,11,13,14] and matched the characteristics of blast wave transmission in air.

Blast wave caused plasma loss in the pulmonary endothelium, which was monitored by the radioactive ¹²⁵I-albumin labeling method. It was found that a blast wave of higher intensity resulted in greater pulmonary vascular leakage. Such a finding was evidenced by higher rates of ¹²⁵I-albumin escape and greater residual radioactivity in the lungs of rabbits in the 10-cm and 15-cm groups. The extent of pulmonary vascular leakage was highly correlated with damage to pulmonary endothelial cells. Under a relatively low pressure (such as that of the 20-cm group), pulmonary capillary endothelial cells were somewhat swollen, but the gap between endothelial cells was not affected. However, under higher pressures (such as those of the 10-cm and 15-cm groups), the gap between pulmonary capillary endothelial cells widened, and more severe damage was observed. It was clear that blast waves had destroyed pulmonary capillary endothelial cells, and that cells had widened, resulting in vascular leakage.

The pulmonary endothelium participates in the exchange of water and solute between the blood and the interstitium. In normal conditions, a small amount of fluid is filtered across the endothelial monolayer and drained by the lymphatic system. Fluid filtration is limited by endothelium continuity, with multiple connections between the cells called tight and adherens junctions.^[15,16] Thus, water and solute flux is strictly regulated, occurring passively between endothelial cells, termed the paracellular pathway, and driven by the hydrostatic pressure gradient between intravascular and perivascular space.^[16–18] Albumin and other macromolecules are actively transported through endothelial cells by an elaborate vesicle system known as the transcellular pathway.^[16,19–21] In the present study, swollen pulmonary capillary endothelium and widened gap between endothelial cells were observed following injury. Water and solute may easily leak out of the capillary vessel through the widened gap, a reverse result of blood condensation. Therefore, the widened gap and swollen endothelial cells that resulted from the blast wave may be the ultrastructural basis for the increased severity of vascular leakage and blood condensation. Vascular leakage was a significant cause of pulmonary edema.

It was found that the gap between the pulmonary microvascular endothelial cells widened significantly, and that red blood cells had escaped through the alveolar wall, a significant cause of pulmonary hemorrhage. Blast overpressure simultaneously exerts compressive forces on the extravascular fluid, driving it into the alveolar space and causing pulmonary edema and alveolar hemorrhage.^[22] It has been demonstrated in animal studies that edema and hemorrhage increase lung weight and correlate with blast peak pressure and mortality.^[23] Therefore, it is very necessary to manage pulmonary edema and hemorrhage. It has also been demonstrated that administration of hemostatic nanoparticles led to significant improvement in short-term survival, and that no complications were observed.^[24]

Blast injury often leads to severe systemic inflammatory response and multiple organ dysfunction. Acute lung injury (ALI) and its most severe extreme, acute respiratory distress syndrome (ARDS) refer to increased permeability in pulmonary edema caused by a variety of pulmonary or systemic insults.^[25] TNF- α and IL-6 are involved in the pathogenesis and development of ARDS in blast injury.^[26] Haemoxygenase-I activated by hemin was reported to increase survival in rats with blast lung, possibly involving an anti-inflammatory mechanism,^[27] while administration of antioxidant N-acetylcysteine amide was shown to facilitate lung recovery from inflammatory damage, protection that could be vital in situations of more severe blunt lung trauma with progression to ALI/ARDS.^[28] In a clinical scenario, studies have shown improved outcome of severe sepsis/systemic inflammatory response with the use of activated protein C, steroid replacement, and aggressive control of blood glucose following blast injury.^[29]

ALI and ARDS are usually accompanied by hypoxemia and the need for mechanical ventilation. The risk of air embolism from positive pressure ventilation has led to a variety of methods of ventilation, such as limited peak inspiratory pressure with permissive hypercapnia, intermittent mechanical ventilation, and high-frequency ventilation, to varying degrees of success.^[30] Pneumothorax as a result of lung rupture is the chief reason for early death and dysfunction of the circulatory system, and is also an important cause of early death.^[26] Endotracheal intubation should be instituted to maintain the artificial ventilation required in cases of pulmonary blast injury. It is worth noting that positive pressure from mechanical ventilation may cause rapid increase in pneumothorax size by inducing lung tissue disruption and increasing air leakage into the pleural space.^[31]

In conclusion, it was demonstrated in the present study that primary blast wave can result in blood condensation and increase in pulmonary microvascular permeability. In addition, not only can blast wave cause pulmonary capillary endothelial cell swelling, but it can also widen the gap between endothelial cells, which may cause increasing severity of pulmonary vascular leakage and blood condensation. The present find-

ings provide novel histological evidence of pulmonary blast injury, which may aid in better understanding of the mechanism of this critical disease.

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Conflict of interest: None declared.

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DENEYSEL ÇALIŞMA - ÖZET

Bir tavşan modelinde blast travmasıyla indüktlenen pulmoner mikrovasküler disfonksiyon ve patolojik değişiklikler

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AMAÇ: Eksplosif pulmoner barotravmada vasküler kaçığın kritik bir rol oynadığı kanıtlanmıştır. Bu çalışmada vasküler kaçığın bir giderek artan şiddet derecesindeki blast travması serisinde şiddet derecesiyle pulmoner vasküler kaçığa ilişkili altyapısal kanıtlar kantitatif olarak araştırıldı.

GEREÇ VE YÖNTEM: Yüz adet erkek beyaz Yeni Zelanda tavşan detonatörden uzaklıklarına göre beş gruba randomize edildi (10 cm, 15 cm, 20 cm, 30 cm ve plasebo kontrol). Pulmoner vasküler kaçığın miktarı radyoaktif 125I-albümin etiketleme yöntemiyle izlendi. Blast dalgasının neden olduğu patolojik değişiklikler ışık ve elektron mikroskopuyla incelendi.

BULGULAR: 125I-albüminin kapillerlerden kaçış hızı ve her iki akciğerde rezidüel radyoaktivite detonatörden 10, 15 ve 20 cm mesafede anlamlı derecede artmış olması bu gruplarda şiddetli derecede vasküler kaçığın olduğunu düşündürmektedir. Ultrastrüktürel gözlem 10 ve 15 cm'lik gruplarda akciğer kapillerlerinde ödem ve endotel hücreleri arasındaki mesafenin açıldığını gösterdi.

TARTIŞMA: Primer blast dalgası akciğer kapillerlerinden kan sızıntısına neden olabilmektedir. Blast dalgası akciğer kapillerlerinin endotel hücrelerinin şişmesine neden olabilmekte, endotel hücrelerinin arasındaki mesafenin artması pulmoner vasküler kaçaktan sorumlu olabilmektedir.

Anahtar sözcükler: Blast travması; permeabilite; pulmoner disfonksiyon; vasküler kaçık.

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