Development of an Animal Model for Burn-Blast Combined Injury and Cardiopulmonary System Changes in the Early Shock Stage

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Abstract The purposes of this study were to establish an animal model for burn-blast combined injury research and elaborate cardiopulmonary system changes in the early shock stage. In this study, royal demolition explosive or RDX (hexagon, ring trimethylene nitramine) was used as an explosive source, and the injury conditions of the canine test subjects at various distances to the explosion (30, 50, and 70 cm) were observed by gross anatomy and pathology to determine a larger animal model of moderate blast injury. The canines were then subjected to a 35 % total body surface area (TBSA) full-thickness flame injury using napalm, which completed the development of a burn-blast combined injury model. Based on this model, the hemodynamic changes and arterial blood gas analysis after the burn-blast combined injury were measured to identify the cardiopulmonary system characteristics. In this research, RDX explosion and flame injury were used to develop a severe burn-blast injury animal model that was stable, close to reality, and easily controllable. The hemodynamic and arterial blood gas changes in the canine subjects after burn-blast injury changed distinctly from the burn and blast injuries. Blood pressure and cardiac output fluctuated, and the preload was significantly reduced, whereas the afterload significantly increased. Meanwhile, the oxygen saturation (SO₂) decreased markedly with carbon dioxide partial pressure (PCO₂), and lactic acid (Lac) rose, and oxygen partial pressure (PO₂) reduced. These changes suggested that immediate

clinical treatment is important during burn-blast injury both to stabilize cardiac function and supply blood volume and to reduce the vascular permeability, thereby preventing acute pneumonedema or other complications.

Keywords Animal model · Burn · Blast · Burn-blast combined injury

Introduction

With the development of high-technology weaponry, the morbidity of combined injuries sustained in local wars and terrorist attacks has increased rapidly [1, 2]. The detonation of an explosive generates shock wave and heat, causing burn-blast combined injury and aggravating the wound by the interaction of blast and burns [3–5]. Several animal models have been developed in early research [6], but no mature model has been established because of various model limitations [7]. Beagle dogs were chosen in the development of a stabilized, controllable, and repeatable animal model that can imitate the actual site of the burn-blast combined injury using explosion and napalm burns. Based on this model, the hemodynamic changes in the early shock stage were investigated.

Materials and Methods

Animals

The study protocol was approved by the Animal Use and Care Committee of the First Affiliated Hospital of the People Liberation Army General Hospital, Beijing, China and adhered to the Institutes of Health Guide for the Care and Use

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of Laboratory Animals. Forty-three pure-bred adult beagle dogs (weight 10.13 ± 0.54 kg, body length 73.32 ± 2.12 cm; Marshall Co. Beijing) were acclimatized in our animal house for 1 week prior to the surgical operations.

Preexperiment Preparation

The dogs were fasted for 12 h prior to the operations. They were then anesthetized with ketamine (8 mg/kg, intramuscular injection) and shaved. An incision was made into their neck to take out the right external jugular vein and right external carotid artery. Under aseptic conditions, an indwelling double-lumen catheter (Pulsion, Germany) was placed in the right external jugular vein, and a pulse-induced contour cardiac output (PiCCO) arterial catheter (Pulsion, Germany) was placed in the right external carotid artery. All animals were fed with ordinary dog food after regaining consciousness and were allowed to recuperate for 2 days prior to burn injury [8].

Injury Program

Blast Injury

Royal demolition explosive (RDX, hexagon, ring trimethylene nitramine) was used as an explosive source (height 2 cm; diameter 1.5 cm; dose 5 g). A #8 electric detonator (diameter 0.5 cm and length 4 cm) with a copper sheet was ignited using an electric device. The explosive source was fixed close to the top of the detonator, which was attached on the supporting base. The detonator was folded with a heavy metal to prevent the ejection of the copper sheet, and the explosive source was kept exposed above the electric detonator.

Three beagles were anesthetized with propofol (4 mg/kg, intramuscularly (i.m.)). The canines were set in a standing position and fixed to three supporting structures around the explosive source with limbs hanging. The heart and the explosive source were maintained at the same level. The left chest was positioned to face to the explosive source. The distances between the chest wall of each canine and the explosive source were 30, 50, and 70 cm.

Burn Injury

A previously established 35 % total body surface area (TBSA) full-thickness burned animal beagle model was used in this experiment [9]. After the canines were anesthetized with propofol (4 mg/kg, i.m.), the limbs and head were fixed. The back and limbs were exposed. After smearing 3 % gelatinized gasoline (Changhua Chemical Industry, Beijing, China) on the scrape of the back and limbs, ignition followed for 30 s before the fire was put out using wet cotton.

Burn-Blast Combined Injury

A burn-blast combined injury model was established including blast injury caused by explosion and then immediately followed by burns caused by gelatinized gasoline flame.

Grouping

Three beagles were randomly chosen as blast models at different distances to the explosive source (30, 50, and 70 cm), in order to develop an animal model for severe burn-blast combined injury.

The other 40 beagles were randomly divided into four groups comprising ten canines per group according to the different injuries sustained. The four groups were the sham group (no injury), burn group (35 %TBSA full-thickness severe burn injury), blast group (midrange blast injury caused by RDX explosion at a distance of 50 cm), and combined group (35 % TBSA full-thickness severe burn injury + midrange blast injury caused by RDX explosion at a distance of 50 cm).

Injury Scoring

The air superpressure peaks were measured at parallel the height of the RDX and the explosive source at 30, 50, and 70 cm, respectively, using pressure sensors (113A21 ICP, PCB, USA) and a long-time/transient recorder (Odyssey, Nicolet, USA). Three canines were sacrificed by phlebotomy 30 min after injury. The gross anatomy of vital organs was observed, including the heart, liver, spleen, lung, and kidney, among others. A piece of tissue in the left lung was then cutoff, fixed by formalin, stained with hematoxylin and eosin (HE), and observed by light microscopy (Fig. 1).

Fig. 1 Schematic diagram of the burn-blast combined injury experiments

Resuscitation

Fluid resuscitation using lactated Ringer's injection was started 0.5 h after injury. The total fluid used was 4 ml/(kg × 1 % TBSA) in 24 h, where half was infused in the early 8 h and the other half after 16 h [10]. All canines were sacrificed by phlebotomy 24 h after injury (Fig. 2).

Hemodynamics Measurements

The hemodynamic parameters, namely, the mean arterial pressure (MAP), cardiac index (CI), intrathoracic blood volume index (ITBI), systemic vascular resistance index (SVRI), cardiac function index (CFI), and extravascular lung water index (ELWI), were assessed with pulse-induced contour cardiac output (PiCCO, Pulsion, Germany) using the thermal dilution

method prior to the burn injury experiment at 30 min, as well as at 2, 4, 8, 12, 18, and 24 h after injury [11–13].

Arterial Blood Gas Analysis

Arterial blood samples were taken to determine the levels of power of hydrogen (pH), oxygen partial pressure (PO₂), carbon dioxide partial pressure (PCO₂), oxygen saturation (SO₂), and lactic acid (Lac).

Statistical Analysis

The data were analyzed using SPSS 13.0 for Windows and expressed as mean ± SD. The differences between the groups were determined using a two-factor analysis of variance and the Student-Newman-Keuls test (SNK). *P* < 0.05 was considered statistically significant.

Fig. 2 Measurement of the pressure peaks at the various distances tested. The pressure peak at 30 cm near the 5 g RDX explosive was 122.224 kPa, whereas it was 99.2875 kPa at 50 cm, and 94.0798 kPa at 70 cm

Fig. 3 Gross anatomy and pathological changes (HE×100) in the lungs of canines after the explosion of 5 g RDX. *30 cm* the volume of various organs showed remarkable swelling, including tensile envelopes on the liver and spleen. The color became dull red, ecchymoses were present, and the parenchyma of the organs was ruptured. The envelope of the lung was tensile, the color became pink, and ecchymoses and rib pressure trace bleeding can be found in the lung parenchyma. The interalveolar septum became widely significant, the alveolar spaces were narrow, and the pulmonary alveoli underwent diffuse fusion. Diffuse acute

inflammatory cells infiltrated the interstitial tissue. The capillary became extensively hemorrhagic. *50 cm* the volume of various organs showed a little intumescencia. Three ecchymoses can be seen in the lungs and liver, and the lungs became pink. The interalveolar septum became swollen. Diffuse acute inflammatory cells had infiltrated the interstitial tissue. The capillary became hemorrhagic. *70 cm* the volume of some organs showed a little intumescencia, and no ecchymosis can be seen in the organs. The interalveolar septum became partially swollen. Some inflammatory cells had infiltrated in the interstitial tissue

Results

Animal Model Establishment

Overpressure Measurements

The strength of the shock wave decreased from the center of the explosion to the surrounding area after the measurement. The air superpressure peaks were 122.224 kPa at 30 cm and 94 kPa at 70 cm from the center of the explosion (Fig. 2).

Injury Judgment

Gross Anatomy The splanchnocoele of the canines was unclosed, and the heart, liver, spleen, lung, kidney, and other vital organs were revealed through a thoracoabdominal midline incision. The canine 30-cm away from the explosion was seriously wounded. Edema and hyperemia of the organs, as well as several ecchymoses and ruptures in the liver, left lung, and spleen, were observed. A hypodermic gore by rib pressure trace in the left lung was also identified. The canine 50-cm away from the explosion was wounded moderately, showing three ecchymoses in the liver and left lung. The canine 70-cm away from the explosion was wounded slightly, showing no signs of bleeding (Fig. 3).

Pathology Under light microscopy, the lung of the canine 30-cm away from the explosion showed evident infiltration by inflammatory cells and erythrocytes, with most of the pulmonary alveoli broken and converted into bullae. Some pulmonary alveoli were also broken, and infiltration of several inflammatory cells and erythrocytes were found in the lung of the canine 50-cm away from the explosion. However, the pulmonary alveoli were not broken, and only some inflammatory cells were found in the lung of the canine 70-cm away from the explosion (Fig. 3).

Based on the gross anatomy and pathology findings, RDX explosion caused several ecchymoses in the liver and lung of the canine 50-cm away from the explosion. No signs of organ rupture was found, which is indicative of a midrange blast injury. A severe burn-blast combined injury model was established using blast injury immediately followed by 35 % TBSA III° burns using gelatinized gasoline flame [14].

Hemodynamics

The duration of the experiment was 24 h, with 100 % dog survival. The changes in the hemodynamic indices of the canines in the combined group differed with that of the burn and blast groups. The MAP in the combined group of canines decreased remarkably after injury and then increased at 8 h after injury. The CI in the combined group also decreased

initially and then began to increase after 6 h, similar to that in the burn group. However, the preload in the combined group decreased after injury and began to rise after 4 h, whereas the afterload in the group rose after injury and decreased after 4 h, which is similar to that in the burn group. Furthermore, the CFI of the canines in the combined group declined continuously, which is lower than those in the blast and burn groups. Finally, the ELWI in the combined group rose continuously after the injury and was higher than that in the burn group (Fig. 4).

Arterial Blood Gas Analysis

The changes in the arterial blood gas indices of the canines in the combined group also differed with those of the burn and blast groups. The blood gas analysis showed acidosis in the combined group of canines after injury. The PCO_2 increased and the PO_2 decreased in the combined group, which were different in the other three groups. So the SO_2 decreased in the combined group, lower than that in other groups markedly. Furthermore, the Lac in the three injury groups all increased after injury obviously. In the three groups, Lac was highest in the combined group (Table 1).

Discussion

With the development of modern weapons, injuries resulting from explosions have correspondingly ranged from simple burns, trauma, blast, and radiational injury to combined injuries caused simultaneously or successively by two or more injury factors, thus inflicting more serious damage on the body [15]. The combined effect of several factors was reflected at different levels: the whole body, tissues and organs, cells, and submicroscopic and molecular structures. The effects were also reflected in important pathophysiological processes. In many cases, the compounded effect of the combined injury was “mutually aggravating,” which can contribute to the difficulty of curing the wound [16].

Burn-blast combined injury is one of the common injuries both during war and peacetime. Even in local military conflicts, explosives are used as the main offensive weapon and are often accompanied by burning, which contributes to the increased morbidity of burn-blast combined injury [4, 17, 18]. About 35,000 cases were attributed to explosions during the war in Iraq and Afghanistan [19]. Meanwhile, the numerous terrorist acts worldwide, especially suicide bomb attacks, have resulted in more than 200,000 explosion-related deaths [20]. Previous studies had confirmed that the mortality of burn-blast combined injury patients was significantly higher than that of burn or blast injury patients. Burn-blast combined injury damages multiple organs and organ systems, such as the central nervous system regulatory function, respiratory

system, circulatory system, liver, and metabolic systems. Burn-blast combined injury even induces sepsis and multi-functional organ failure [21].

The summary of the clinical treatment of severe burn-blast combined injury shows that the characteristics of patients after severe burn-blast combined injury included serious illness, multiple organ damage, blood coagulation, immune function disorder, and so on. Except for scrape burns, the heart, liver, lung, pancreas, and blood coagulation function showed varying degrees of dysfunction in the early stage after injury and continued for a long time. The lungs were the most seriously injured. As shown by flexible bronchofiberscope examination, the tracheal mucosa became congested and edema occurred. Chest X-rays showed that the density of the left or both lungs increased, along with increased markings, ground-glass changes, and even bullae [5]. The clinical symptoms of early disseminated intravascular coagulation (DIC) appeared during patient hospitalization, and the protamine vice agglutination test showed positive in some patients. Monocyte human leukocyte antigen DR (HLA-DR) expression was significantly lower. Previous studies confirmed that the incidence of shock after burn-blast combined injury was extremely high, for example, 100 % for the extremely severe burn-blast combined injury, 80 % for severe injury, and 30 % for moderate injury. Severe infection appeared earlier, as well. Blood cultures of these patients tested positive 2.2 days post-injury, which showed that generalized infection appeared during the shock stage. The positive blood culture rates in patients with extremely severe and severe burn-blast combined injuries were 75 and 50 %, respectively [22].

The previous study by the authors on burn-blast combined injury showed that two injuries affected the animal model successively. In the year 1993, Zhu PF reported the establishment of the burn-blast combined injury animal model using biological microwave tubes and napalm flame. The advantages of this previous model were localization, accuracy, repeatability, and controllability [23–25], but the effect of the shock wave was limited to the local organs of the body. Therefore, the model cannot actually simulate the explosion situation during wartime and peacetime. However, the model used in the present study was closer to the actual situation, and the degree of the explosions could be controlled. This characteristic allows the development of different blast injuries by adjusting the distance between the explosion and the animals. In the present study, all six severe burn-blast combined injury canines showed decreased blood pressure, accelerated heart rate, shallow and fast breathing, and other symptoms of shock. Fluid resuscitation restored these symptoms to normal. Therefore, the present animal model can be used as a good research platform on the mechanisms of fluid resuscitation during burn-blast combined injury shock.

The compound effects of burn and blast injuries caused differences between the cardiopulmonary system changes of

Fig. 4 The hemodynamic changes of the canines in the four groups after injury ($n=10$). * $P < 0.05$, compared with that of the combined group; ** $P < 0.01$, compared with that of the combined group. **a** The MAP changes. The MAP of the canines in the combined groups reduced rapidly after 2 h and then returned, which was lower than those of the other groups. **b** CI changes. The CI of the canines in the burn and combined groups decreased rapidly. Then it returned 4 h after injury. However, the CI in the combined group was lower than that in the other groups after 12 h post-injury. **c** ITBI changes. The ITBI values of the canines in the burn and combined injury groups were reduced rapidly and returned after post-injury. However, ITBI increased continuously in the blast group. The ITBI in the burn and combined groups were lower than those in the blast and sham groups. **d** SVRI changes. The SVRI of the canines in the burn

and combined groups increased rapidly and returned after 4 h post-injury. In addition, the SVRI in the combined group was higher than that in the other groups 4 h post-injury. However, SVRI was stable in the blast group. **e** CFI changes. The CFI of canines in the burn group decreased rapidly and returned to baseline values 4 h after injury. However, CFI initially increased before decreasing in the combined group 4 h after injury and was lower compared with those of the other groups 12 h after injury. **f** ELWI changes. The ELWI of the canines in the burn, blast, and combined groups rapidly increased after injury and were all higher than that in the sham group. Eight hours after the injury, the ELWI decreased in the burn and blast groups but increased continuously in the combined injury group

the burn-blast combined injury and those after burn or blast injury.

First, heart damage was caused by overpressure after the blast injury, for example, endocardial and epicardial punctate

Table 1 The variation of arterial blood gas analysis ($n=10$)

Variables	Post-injury (h)						
	0	2	4	8	12	18	24
pH							
Sham group	7.41±0.03	7.42±0.05*	7.42±0.03*	7.43±0.02*	7.44±0.02*	7.42±0.01*	7.44±0.02*
Burn group	7.38±0.05	7.40±0.05*	7.43±0.03*	7.47±0.07*	7.46±0.06*	7.42±0.08*	7.43±0.04*
Blast group	7.40±0.01	7.33±0.04*	7.31±0.05*	7.33±0.02*	7.35±0.06*	7.34±0.03	7.35±0.02
Combined group	7.39±0.02	7.30±0.05	7.27±0.03	7.29±0.07	7.30±0.07	7.37±0.04	7.32±0.01
PO₂ (mmHg)							
Sham group	39.2±2.3	35.4±3.1*	37.1±2.2*	36.8±2.4*	39.2±2.8*	38.5±2.8	37.4±3.5
Burn group	37.9±4.8	32.3±2.2*	30.1±4.6*	39.2±2.3*	39.2±2.3	39.2±2.3	39.2±2.3*
Blast group	36.9±3.2	41.0±2.5	43.2±2.3*	45.8±1.5*	37.2±3.1*	37.7±2.6	36.1±3.8
Combined group	37.8±3.1	43.3±4.1	47.5±2.2	52.5±1.7	41.8±3.4	36.7±1.4	34.5±2.3
PCO₂ (mmHg)							
Sham group	87.3±2.8	89.1±3.1*	87.7±1.8*	89.6±3.0*	91.7±2.6*	90.1±2.5*	88.6±3.5*
Burn group	88.3±4.2	102.1±3.9*	106.1±5.3*	105.7±3.5*	102.9±5.0*	107.6±2.4*	100.8±1.5*
Blast group	93.8±3.5	84.2±2.0	78.0±3.6	75.4±1.7*	74.1±2.1*	76.8±2.7*	77.0±3.8*
Combined group	92.0±2.3	80.3±3.5	77.2±3.9	72.6±4.1	71.6±4.4	72.4±2.2	71.2±3.3
SO₂ (%)							
Sham group	98.1±2.2	99.3±1.2*	98.4±0.8*	98.8±0.6*	98.1±1.4*	97.8±1.8*	98.5±1.0*
Burn group	97.9±1.5	97.5±0.9*	97.4±1.4*	97.1±1.7*	96.3±1.8*	97.8±1.1*	98.1±1.4*
Blast group	98.5±1.3	92.5±2.0*	88.4±2.7*	83.2±0.8*	85.3±3.1*	90.2±2.2*	92.6±1.7*
Combined group	98.0±1.1	88.9±2.7	80.4±2.2	74.6±3.1	79.7±2.8	80.1±3.3	78.2±2.5
Lac (mmol/L)							
Sham group	1.86±0.31	1.81±0.32*	1.96±0.46*	2.14±0.27*	2.03±0.19*	2.01±0.22*	2.08±0.31*
Burn group	2.23±0.37	3.46±0.25*	4.75±0.18*	5.61±0.39*	3.12±0.22*	2.79±0.20*	2.88±0.17
Blast group	2.05±0.37	3.10±0.19*	3.65±0.20*	4.11±0.37*	3.37±0.28*	2.99±0.12	2.74±0.23*
Combined group	2.06±0.48	4.09±0.28*	6.75±0.75*	7.81±0.73*	5.53±0.65*	3.35±0.44*	3.02±0.31*

* $P<0.05$, compared with compared with combined group

bleeding, myocardial degeneration and necrosis, and even fragmentation of the myocardium [26]. However, in the present study, the CI showed a tendency of a decrease first and followed by an increase, which was not same as that after burn injury. The decompensation resulted in a decreased cardiac output with the aggravation of injuries and gradually restored to normal after fluid resuscitation. At 24 h after injury, the CI of canines in the burn and blast injury groups recovered to normal values, but the values continued to decline in the burn-blast combined injury group, which indicated an occult cardiac injury sustained from the combined injury.

Second, the preload in the burn-blast combined injury group declined immediately after the injury, which was the same as that in the burn injury group. These results showed that the blood volume in both the burn injury and burn-blast combined injury groups declined rapidly, thus prompting the need for fluid resuscitation. In the present study, the preload did not return to its preinjury level 24 h after injury even with the administration of intravenous lactated Ringer's solution in accordance with the Parkland formula. The afterload on the

burn-blast combined injury increased after the injury and then decreased after resuscitation, which was the same as that in the burn injury group. The systemic microvascular function was not significantly changed in the early stage of the blast injury, except for the microvascular changes in the lungs.

The lungs showed the most severe damage after the blast injury [1, 27, 28]. In the burn-blast combined injury group, the lungs were also severely damaged. Pathological observation showed that a large number of neutrophils aggregated immediately after injury. The integrity of the alveolar wall was destroyed, part of the alveoli was ruptured, and a small amount of red blood exuded from the blood vessels. Meanwhile, hemodynamic monitoring showed the EVWI increased continuously after the burn-blast combined injury despite fluid resuscitation. This finding indicated acute pulmonary edema occurred in the early stage of the burn-blast combined injury and then continued to increase. The blood gas analysis showed acidosis and hypoxemia with low PO₂ and high PCO₂ after combined injury.

However, the burn-blast combined injury animal model in this research has yet to be further improved. Firstly, the patients with moderate blast injury and a 35 % TBSA burn had a high to nearly complete survival in shock stage, so more serious burn-blast combined injury were required for further research. Secondly, the changes of burn-blast combined injury were observed only for 24 h after injury, and the variation of tissue ischemia and hypoxia (such as oxygen transmission capacity, oxygen consumption, and MDA) were not detected. These all need to be observed in the next experiments.

Conclusion

In summary, a workable, stable, and repeatable severe burn-blast combined injury large animal model was established using RDX explosives and napalm flame burns. This model can be used as basis in the pathogenesis of burn-blast combined injury and intervention on basic research. The cardiopulmonary system change observed was distinctive. Nevertheless, the mechanisms and preventive measures for burn-blast combined injury need further investigation in the future.

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