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20/08/2018	Presentation	08/20-23/2018

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6. AUTHOR(S) Lt Col Sams, Valerie G	**5d. PROJECT NUMBER** **5e. TASK NUMBER** **5f. WORK UNIT NUMBER**
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High mobility group box 1 protein increases after pulmonary contusion in a combat-relevant polytrauma model

Jae Hyek Choi, PhD, DVSc[1], Alexander Dixon, BS[1], Kyle Sieck, BS[1], Teryn Roberts, MS[1,2], George Harea, BS[1], Vitali Karaliou, MD[1], Daniel Wendorff, BS[1], Brendan Beely, RRT[1], Leopoldo Cancio, MD[3], Valerie Sams, MD[4], Andriy Batchinsky, MD[1,2]

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DISCLOSURES

The views presented here are the private views of the author(s) and are not to be construed as the official views or policies of the U.S. Air Force, the U.S. Department of Defense, or The Geneva Foundation.

The experiments reported herein were conducted according to the principles set forth in the National Institute of Health Publication No. 80-23, Guide for the Care and Use of Laboratory Animals and the Animal Welfare Act of 1966, as amended.

BACKGROUND

U.S. AIR FORCE

THE GENEVA FOUNDATION
The future of military medicine. Today

Thoracic injuries in US combat casualties: A 10-year review of Operation Enduring Freedom and Iraqi Freedom

Katherine M. Ivey, MD, Christopher E. White, MD, Timothy E. Wallum, MS, James K. Aden, PhD, Jeremy W. Cannon, MD, Kevin K. Chung, MD, Jeffrey D. McNeil, MD, Stephen M. Cohn, MD, *and* **Lorne H. Blackbourne, MD**

BACKGROUND: Mortality from thoracic injuries has declined significantly from 63% in the Civil War to 3% in Vietnam. We reviewed the injury patterns, procedures, blood products, and mortality of US soldiers sustaining a thoracic injury during Operation Enduring Freedom and Iraqi Freedom (OEF/OIF).

METHODS: Data on US soldiers with a thoracic injury during OEF/OIF from January 2003 to May 2011 was collected from the Joint Theater Trauma Registry. Coalition forces, civilians, and soldiers killed in action were excluded. Injuries and procedures were identified using DRG International Classification of Diseases 9th Rev. and Abbreviated Injury Scale (AIS) codes. Data are presented as mean (SD). Statistical analysis used χ^2 analysis and *t* test where appropriate.

RESULTS: Thoracic injuries occurred in 2,049 of 23,797 wounded US military personnel for a prevalence of 8.6%. Mean (SD) age was 26 (6.6) years, and mean (SD) chest AIS score was 2.9 (0.9). Penetrating trauma was the most common mechanism of injury (61.5%), and explosive devices were the most common cause of injury (61.9%). Of 6,030 thoracic injuries identified, pneumothorax and pulmonary contusions were most common (51.8% and 50.2%, respectively). Of 1,541 surgical procedures performed in theater, the most common was tube thoracostomy (47.1%). Most patients with penetrating fragmentation injuries (84%) were managed with tube thoracostomy as sole therapeutic intervention. The fresh frozen plasma to packed red blood cells ratio was 0.86. Overall mortality was 8.3%. Acute respiratory distress syndrome and inhalation injury were associated with mortality ($p < 0.006$).

CONCLUSION: Most penetrating fragmentation injuries can be managed with tube thoracostomy. Mortality of patients with chest injury in OEF/OIF is higher than in Korea and Vietnam. This most likely represents advances in prehospital care, personal protective equipment, and rapid transport that have resulted in more severely injured patients arriving alive to a medical facility. (*J Trauma Acute Care Surg.* 2012;73: S514 S519. Copyright © 2012 by Lippincott Williams & Wilkins)

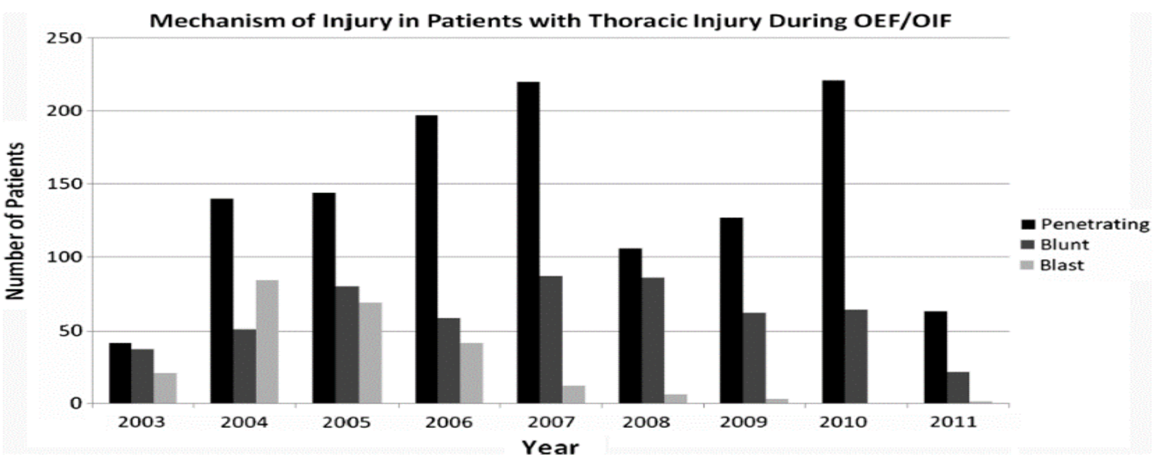


TABLE 1. Number of Thoracic Injuries and Percentage of Patients Sustaining That Injury

Injury	n (%)
Pneumothorax	1,061 (51.8)
Pulmonary contusion	1,028 (50.2)
Rib fractures	717 (35)
Hemothorax	615 (30)
Other chest injury	494 (24.1)
Open chest wound	264 (12.9)
Thoracic spine injury	299 (14.6)
Inhalation injury	295 (14.4)
Scapula fracture	219 (10.7)
Other major vessel injury	196 (9.6)
Lung laceration	190 (9.3)
Diaphragm	141 (6.9)
Clavicle fracture	109 (5.3)
Tracheal injury	55 (2.7)
Other heart injury	45 (2.2)
Sternal fracture	41 (2)
Heart laceration	33 (1.6)
Thoracic esophageal injury	31 (1.5)
Blast lung	28 (1.4)
Flail chest	26 (1.3)
Vena cava injury	13 (0.6)
Bronchus injury	12 (0.6)
Aortic injury	12 (0.6)

DOI: 10.1097/TA.0b013e3182754654

Thoracic trauma in Iraq and Afghanistan

Ryan Keneally, MD *and* **Dale Szpisjak, MD, MPH,** *Bethesda, Maryland*

BACKGROUND: Thoracic injuries are common among civilian trauma and have a high associated mortality. The use of body armor and exposure to different mechanisms of injury in combat setting could lead to different injury patterns and incidences from those found in peacetime.

METHODS: Thoracic trauma incidence rates and mortality risks were calculated from data extracted from the Joint Theatre Trauma Registry.

RESULTS: Among patients injured in military operations in Iraq and Afghanistan, 10.0% sustained thoracic injuries and had a mortality rate of 10.5%. Penetrating injuries were the most common mechanism of injury. The most common thoracic injury was pulmonary contusion. The highest mortality rate was in the subset of patients with thoracic vascular injuries or flail chest. The variables most strongly associated with mortality were number of units of blood transfused, admission base deficit, international normalization ratio, pH, Abbreviated Injury Scale scores for head and neck regions, and Injury Severity Score. Blunt injuries had the same mortality risk as penetrating injuries.

CONCLUSION: Combat-related thoracic trauma is common and associated with significant mortality in Iraq and Afghanistan. (*J Trauma Acute Care Surg*. 2013;74: 1292–1297. Copyright © 2013 by Lippincott Williams & Wilkins)

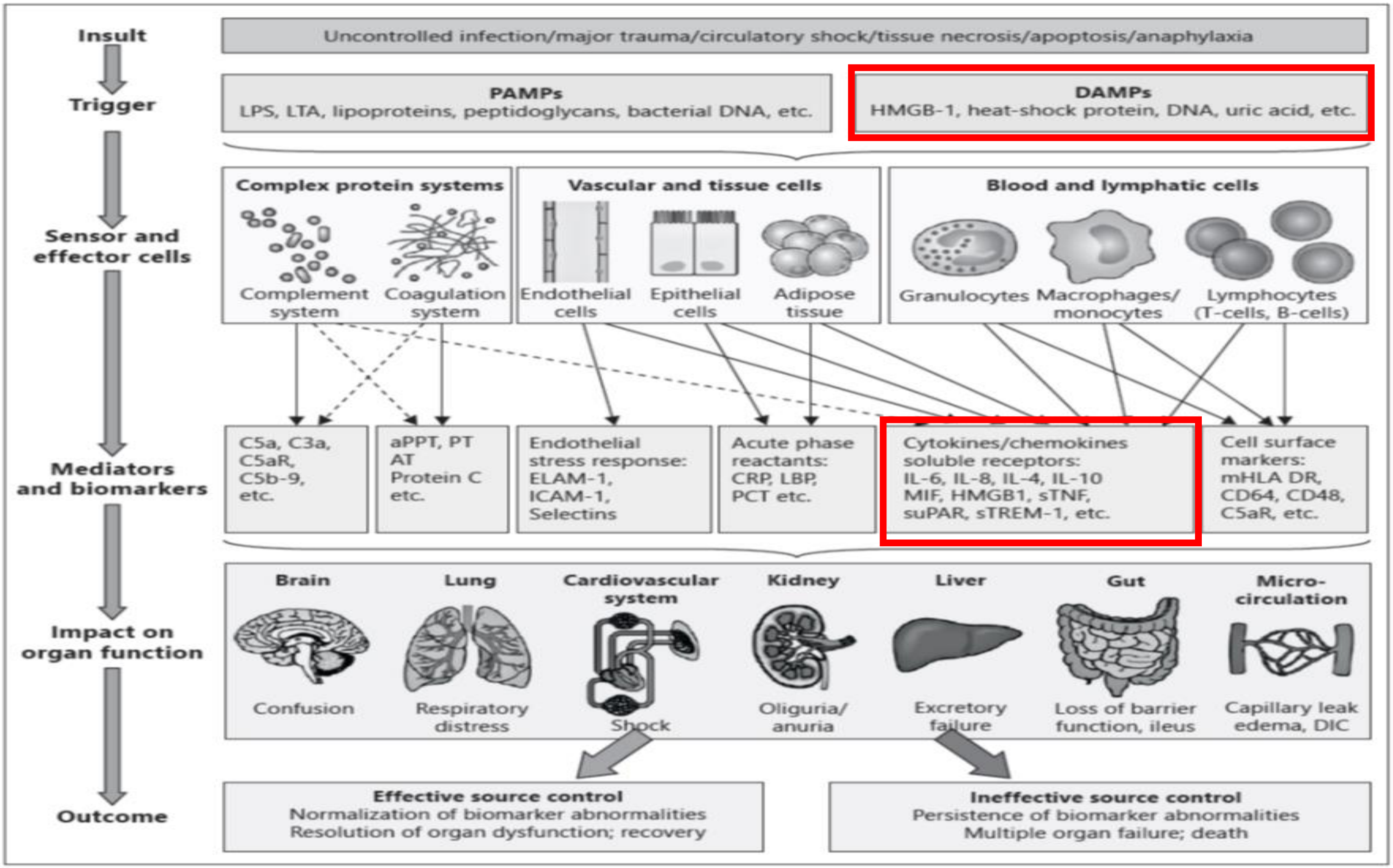
TABLE 1. Incidence and Mortality Rates

Diagnosis	Incidence in JTTR (%)	Incidence in Thoracic Trauma (%)	Mortality Rate (%)	OR for Mortality*	*p*
Contusions	4.68	46.36	7.00	0.434 (0.343–0.549)	<0.001
Lacerations	0.78	7.80	14.23	1.528 (1.065–2.192)	0.021
Pneumothorax	3.99	39.47	9.89	0.762 (0.606–0.958)	0.020
Hemothorax	1.70	16.78	14.62	1.301 (0.988–1.712)	0.061
Thoracic vascular injuries	0.38	3.74	19.86	2.049 (1.304–3.221)	0.002
Cardiac injury (all types)	0.24	2.49	13.26	1.584 (0.867–2.895)	0.135
Flail chest	0.27	2.70	19.90	0.444 (0.199–0.990)	0.047
Rib or sternal fractures	2.58	25.50	6.98	0.519 (0.390–0.689)	<0.001
All chest wall trauma	3.87	38.30	7.80	0.581 (0.456–0.739)	<0.001

*Independent variables included ISS, base excess, total units transfused, AIS head and neck, NATO status, pH less than 7.2, and international normalization ratio greater than or equal to 2. *p* value refers to OR.

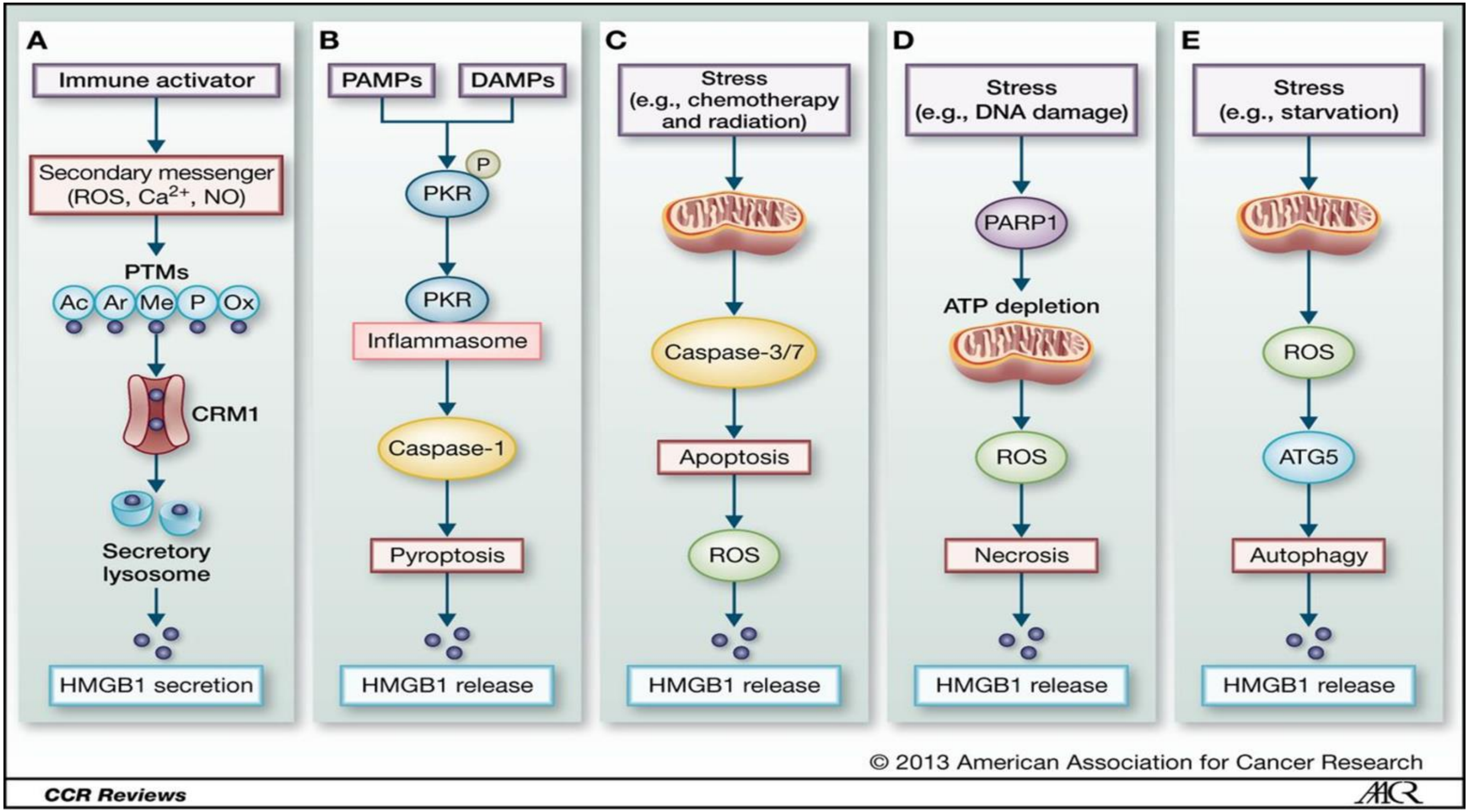
Incidence rates, percentage of patients with diagnosis; OR, odds ratio for mortality compared with all other patients with thoracic trauma (95% confidence interval).

DOI: 10.1097/TA.0b013e31828c467d



Clemens, *et al*. Reciprocal Risk of Acute Kidney Injury and Acute Respiratory Distress Syndrome in Critically Ill Burn Patients; *Crit Care Med, 2016.*

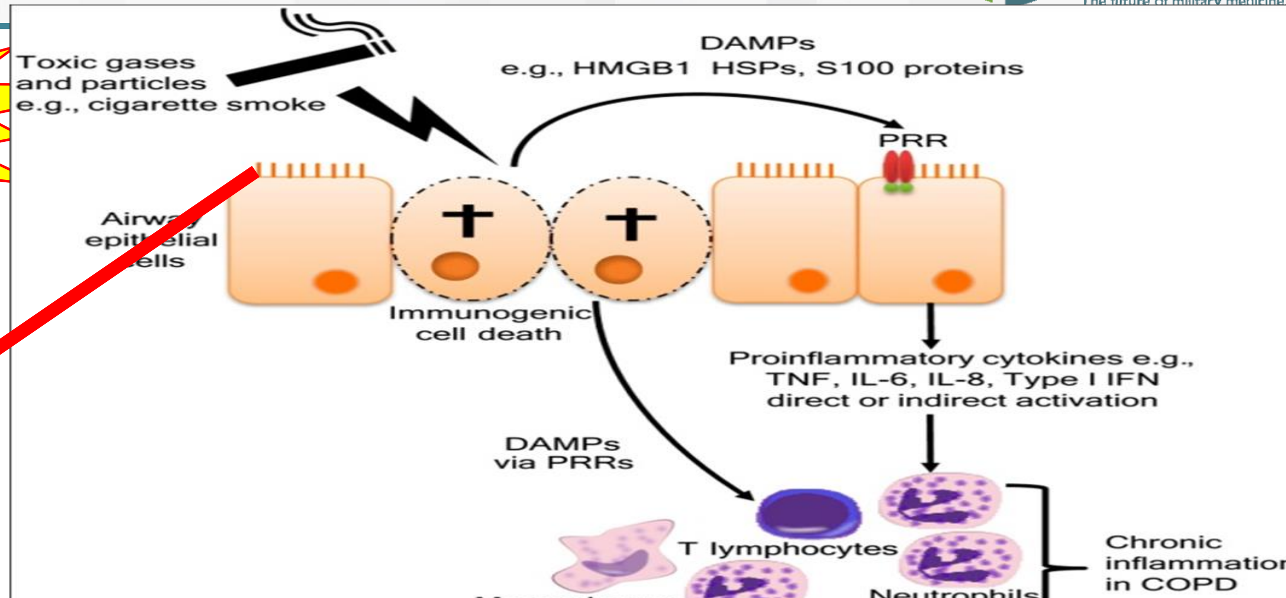
HMGB1



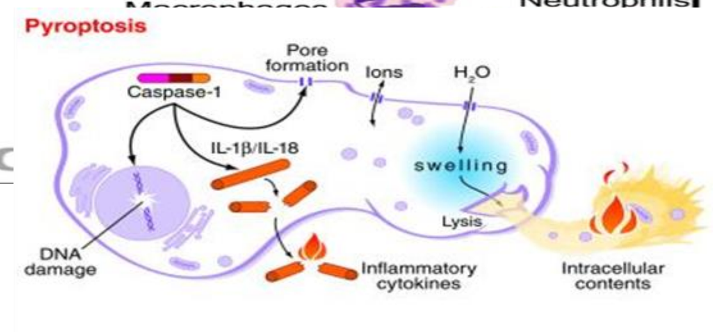
Immune activator | Pyrotosis | Apoptosis | Necrosis | Autophagy

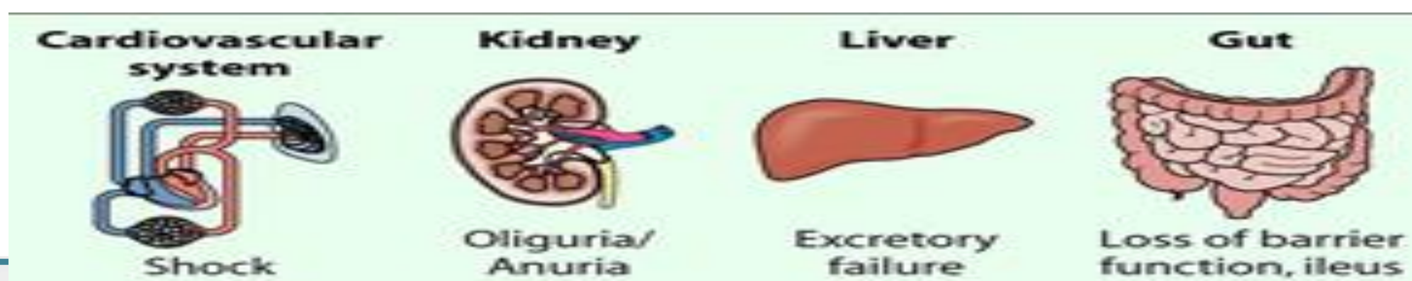
Possibility of DAMPs research for Multi Organ failure After traumatic injury such as Smoke inhalation

ARDS, MV, Traumatic injury



TLRs –> Pyroptosis, pro inflammation cytokines error





OBJECTIVE

- Develop a combat-relevant animal model of thoracic trauma with superimposed hemorrhagic shock, subsequent thoracotomy and unilateral hilar clamping.

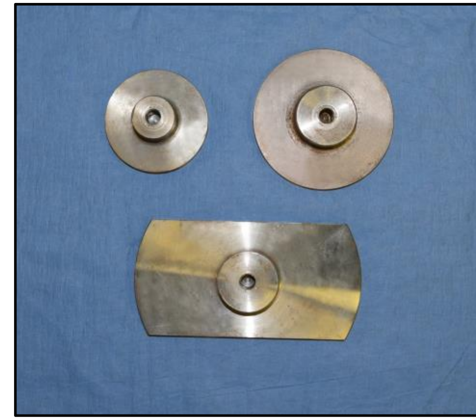
- We investigated expression of HMGB1 and plasma free hemoglobin (pfHb) in a combat-relevant polytrauma model consisting of pulmonary contusion (PC), hemorrhage, and resuscitation.

- We hypothesized that PC causes an increase in HMGB1 and pfHb concentration after injury.

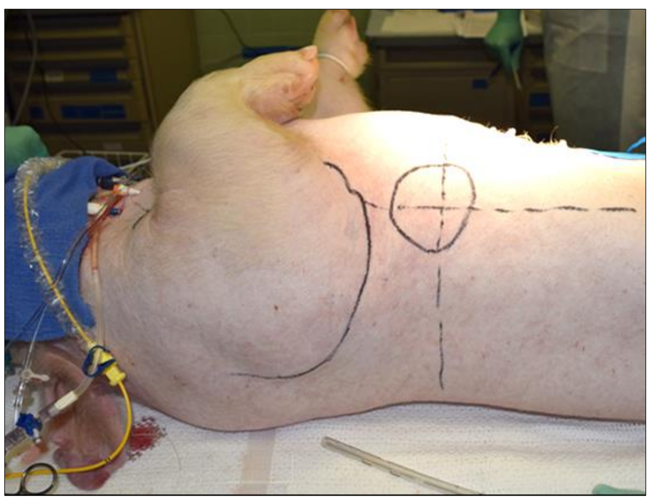
MATERIALS AND METHODS

Modified captive bolt stunners. (Model MKL, Karl Schermer, Packers Engineering, Omaha, NE)

Modified captive bolt stunner and charges (mild, moderate, severe).



Plates' sizes (70mm, 100mm, 80x100mm)

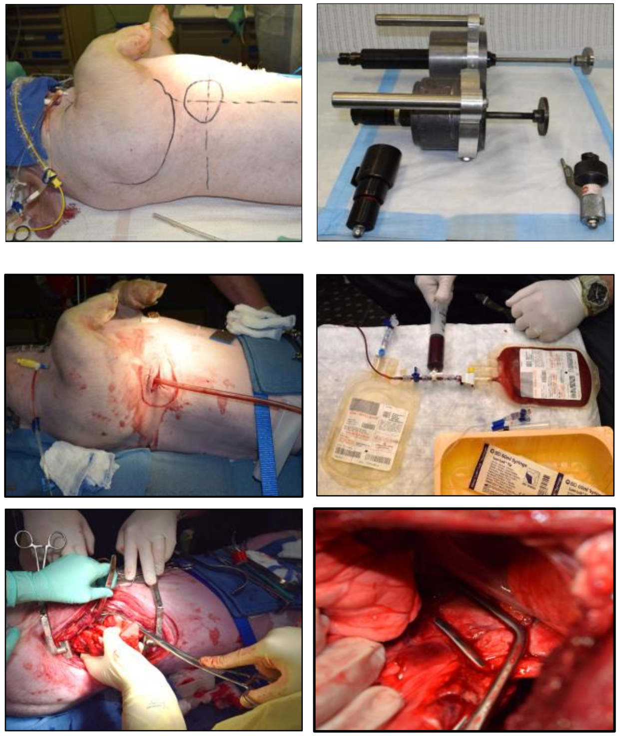


Site of pulmonary contusion.

- 10 female Yorkshire swine (52.6 ± 2 kg)
- Induction Isoflurane (0.5-5% in 100% O2)
- Foley catheter placement
- Vascular access: jugular veins, carotid artery, femoral vein and femoral artery
- TIVA: fentanyl, ketamine, midazolam and Propofol
- Continuous vital signs monitoring *(Monitor Dräger Infinity M450 & C700, Draeger, Inc., USA)*
- Tracheostomy (cuffed tube 8 mm ID)

MATERIALS AND METHODS

Combat-Relevant Model of Thoracic Trauma, Hemorrhage and Hilum Clamp



- Baseline
- Chest contusion (unilateral)
- Chest tube placement
- ~12 ml/kg blood loss over 12 min, with target MAP < 40
- Thoracotomy
- Hilum clamp
- Fluid resuscitation
- Blood transfusion
- ICU care and observation up to 24 hrs after injury

Time points:

- Baseline (BL)
- Post injury (PI)
- Post shock (PS)
- Post transfusion (PT)
- PI 3, 6,12, 18, 24h

MATERIALS AND METHODS

- Systemic HMGB1 concentration was measured in blood plasma using ELISA with standard HMGB1 kits.
- Plasma free Hb concentration was measured by 540nm wave length by Spectra Max i3 (Molecular Device, CA, USA) and transfer to mg/dL.
- Total plasma protein concentration was measured by Pierce™ BCA Protein Assay Kit protocol.
- Post mortem samples were fixed and analyzed for:
  - Injury severity diffused alveolar damage (DAD) scoring: Interstitial fibrosis (0-4), Alveolar space (0-4), Protein aggregate (0-4), Total tissue fibrosis (%), cumulative DAD score
  - Local expression of HMGB1/TLR4 in lung was evaluated using standard immunohistochemistry methods with antibodies to HMGB1, TLR4 (abcam, Cambridge, United Kingdom)

- One way ANOVA test and Kruskal-Wallis test with a Dunnett adjustment were used for statistical validation. Data represented as means ± SEM VS. Basline (*). significance when $p<0.05$

RESULTS

	BL	PC	Post Hem	Post Shock	Hilum clamp	Post Transf	12 Hours	24 Hours
Heart Rate	91± 6	105± 6	130± 14	135± 15	154± 23*	127± 13	127± 6	135± 14
MAP	94± 4	62± 4*	41± 4*	56± 4*	55± 5*	93± 10	67± 2*	64± 5*
CO Bolus	4.4± 0.3	3.8± 0.4	2.6± 0.4	3.2± 0.3	3.4± 0.3	4.8± 0.5	4.2± 0.0	4.0± 0.9
PAP	26± 1	30± 2	17± 4	19± 3	19± 5	36± 1	28± 1	30± 3
CVP	5± 2	6± 2	2± 2	3± 2	3± 3	10± 1	8± 2	10± 2
SpO2	97± 1	90± 2	86± 4	82± 4*	91± 4	92± 2	94± 2	92± 3
FiO2	21± 0	36± 11	54± 13	43± 9	56± 10	54± 13	31± 3	50± 13
VT	540± 22	536± 25	540± 22	540± 22	504± 26	474± 41	450± 33	396± 35
RR	13± 1	14± 1	11± 1	11± 1	13± 2	19± 4	19± 4	23± 2
PIP	22± 1	34± 1*	29± 1*	29± 2*	36± 2*	35± 2*	31± 2	33± 3
Pplat	20± 1	28± 1*	23± 1	23± 1	29± 1*	28± 1*	19± 5	29± 4
Pmean	10± 0	12± 0	11± 0	11± 0	13± 1*	15± 1*	14± 1	16± 2
P:F ratio	415± 13	207± 47*	176± 35*	205± 41*	248± 37*	302± 60*	369± 41	295± 78
Art pH	7.52± 0.02	7.49± 0.03	7.46± 0.03	7.37± 0.02*	7.31± 0.03*	7.23± 0.04*	7.34± 0.02*	7.39± 0.03*
Art pCO2	36.7± 1.4	37.8± 2.6	37.9± 2.5	43.1± 2.4	44.4± 3.3	47.4± 3.2	37.2± 2.7	35.5± 3.0
Art pO2	87.3± 2.6	56.4± 4.1	68.1± 9.9	69.4± 8.2	107.4± 14.2	133.1± 44.7	105.0± 10.3	102.6± 8.5
Art BE	6.5± 0.6	5.1± 1.1	3.1± 1.4	0.0± 1.3	-3.3± 2.4*	-6.5± 2.5*	-5.6± 1.8	-3.8± 1.6
Art HCO3	30.1± 0.5	28.9± 0.8	27.3± 1.2	25.3± 1.2	23.0± 2.1*	21.0± 2.1*	20.0± 1.7*	20.7± 1.5*
Art SO2 %	98± 0	91± 2	92± 2	92± 1	96± 1	92± 3	97± 1	96± 1
Art Lactate	0.84± 0.14	2.07± 0.62	3.81± 0.65	6.16± 0.91*	8.80± 1.55*	11.04± 1.62*	6.91± 1.31*	3.14± 1.06
Temp	35.3± 0.6	35.4± 0.8	35.7± 0.9	35.9± 1.0	36.2± 0.8	35.9± 0.6	39.0± 0.5*	39.5± 0.4*

Data presented as means ± SEM, statistics by Kruskal-Wallis test with a Dunnett adjustment, p-value < 0.05(*)

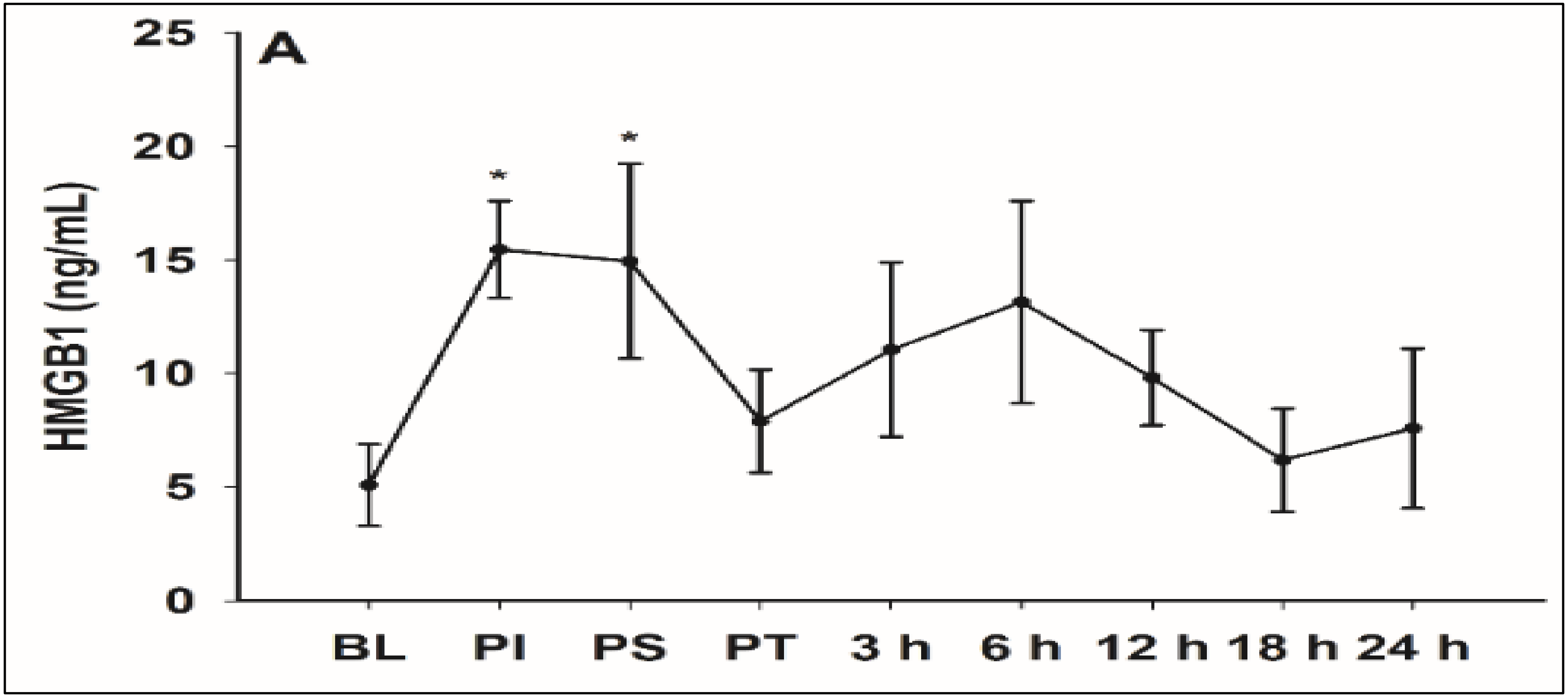


Figure 1. (A) Dramatic change systemic HMGB1 in unilateral pulmonary contusion (n=10, Data represented as means ± SEM VS. Basline (*). significance when $p<0.05$.

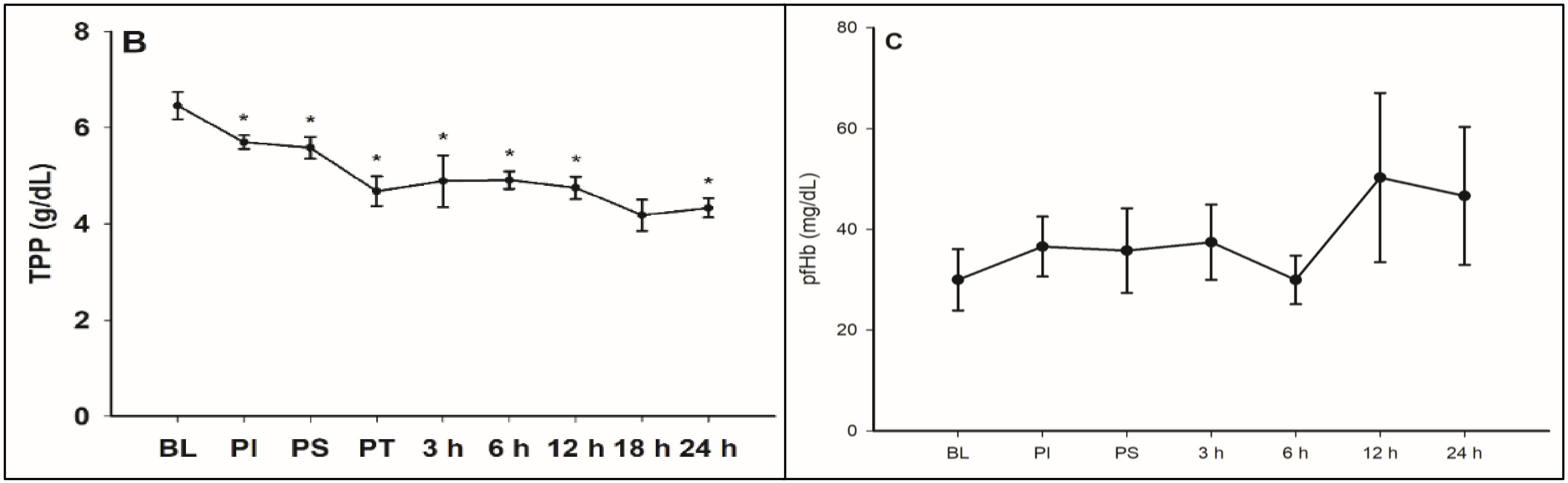
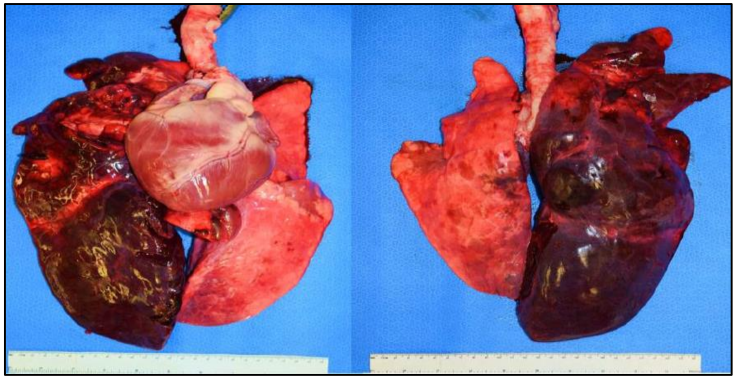


Figure 2. (B) Dramatic change total plasma protein concentration (TPP) and (C) plasma free hemoglobin (pfHb) in unilateral pulmonary contusion (n=10, Data represented as means ± SEM VS. Basline (*). significance when $p<0.05$.

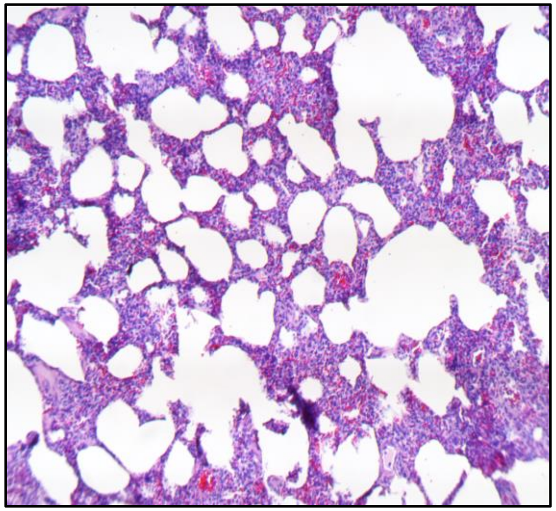
Gross pathology for pulmonary congestion and tissue edema

Macro-exam:
- Heavy wet lungs
- Congested lower lobes, hematomas
- Copious serosanguinous fluid or blood on sectioning



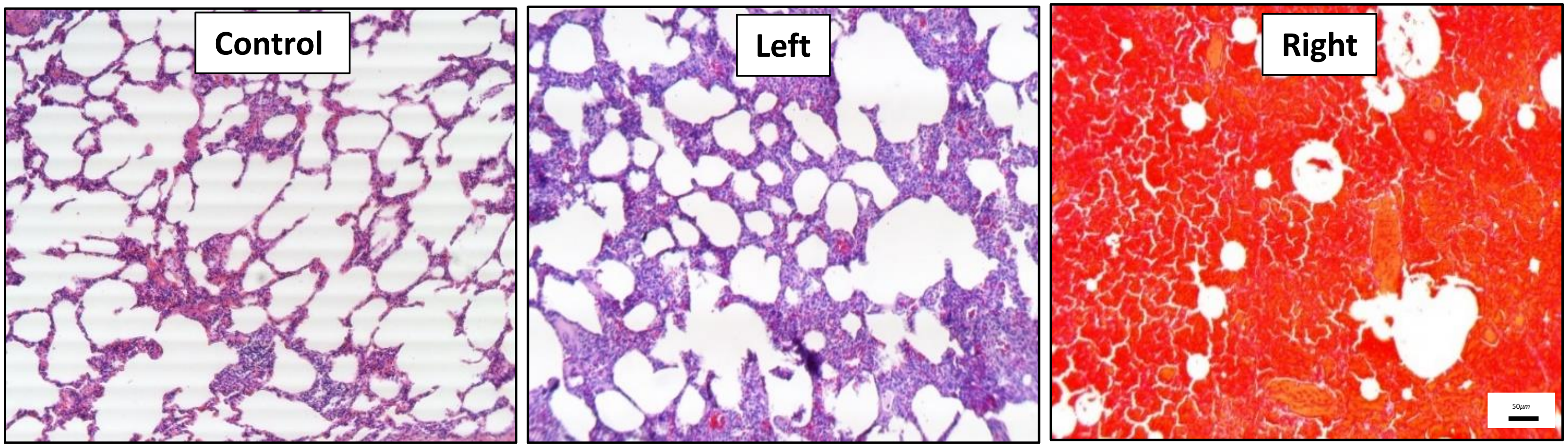
Frontal and dorsal appearance of lungs after hilum clamping from another 24 hour survivor.

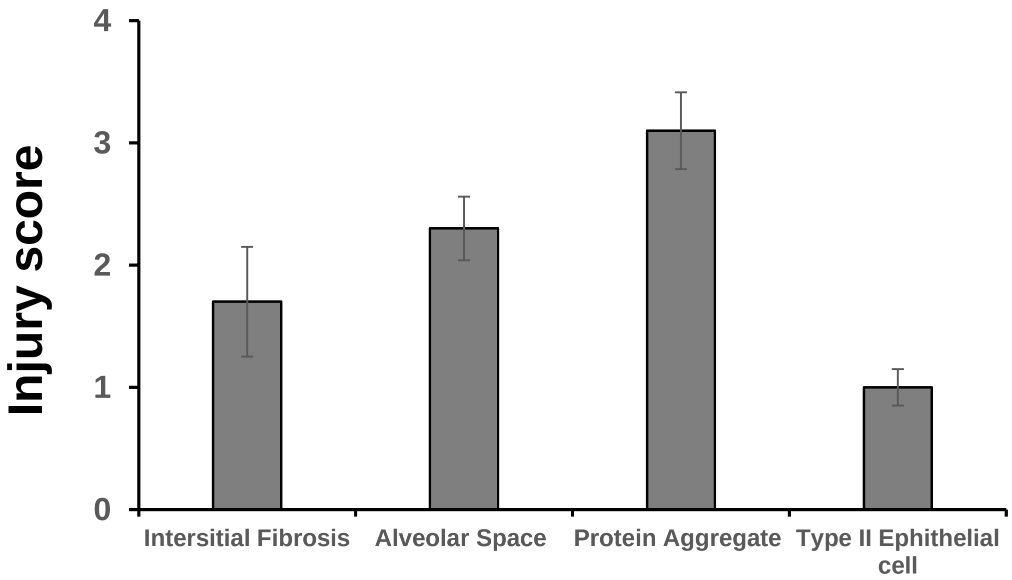
Microscopic examination:
- Dilated capillaries, dilated veins
- Transudate in the alveolar lumen
- Copious amount of RBCs in alveoli in some areas
- Signs of alveolar injury

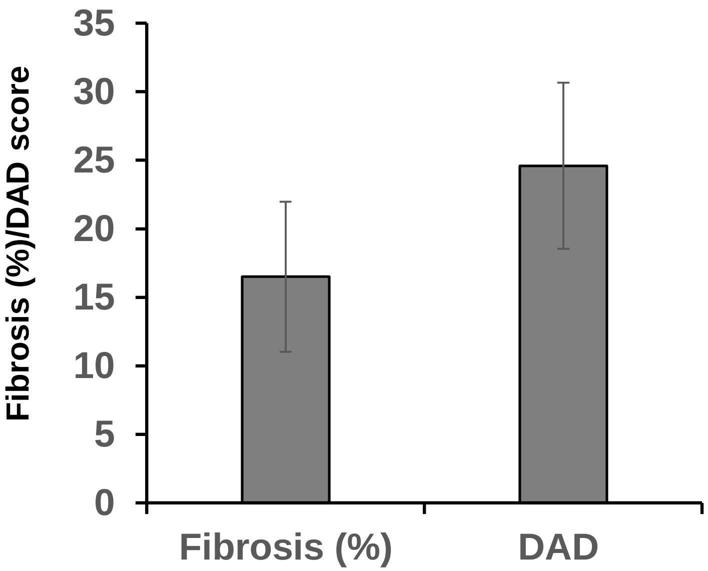


RESULTS

Histopathological DAD score in in unilateral pulmonary contusion

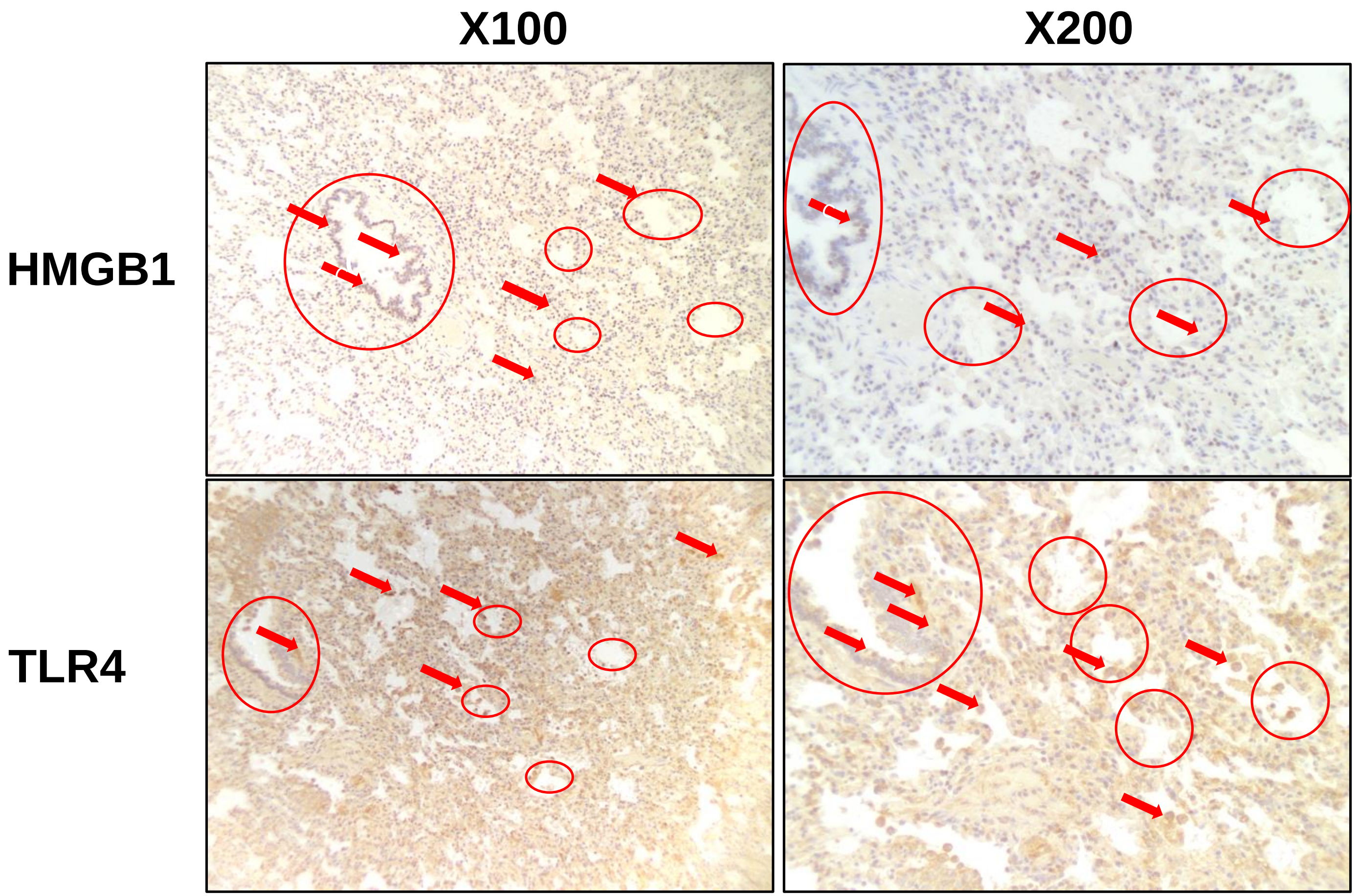






RESULTS

Localization of HMGB1 and TLR 4 in unilateral pulmonary contusion



HMGB1 – Endothelial layer of blood vessel, alveolar cells
TLR4 – Smooth muscle cells, alveolar cells.

RESULTS

- Mortality was 38% at 24 hr with mean survival time of 16.5± 3.6 hr
- HMGB1 concentration increased above BL levels (7.7 ± 2.4 ng/mL) at PS (14.8 ± 3.9 ng/mL, $p < 0.05$), 3 h PI (43.0 ± 29.4 ng/mL, $p < 0.05$), and 6 h PI (9.2 ± 3.1 ng/mL, $p < 0.05$)
- TPP concentration decreased at all timepoints following BL (6.3 ± 0.3 g/dL) at PS (5.6 ± 0.3), 3 h (5.3 ± 0.4), 6 h (4.9 ± 0.2), 12 h (4.9 ± 0.2), and 24 h (4.4 ± 0.2 mg/dL)
- pfHb concentration did not change.
- Tissue specific HMGB1 and TLR 4 was observed in the area of lung alveolar and pulmonary blood vessels.

RESULTS

Conclusion: PC led to a transient increase in HMGB1 levels and a sustained decrease in TPP. We conjecture that bedside assessment of DAMPs confirms injury and may provide a useful monitoring capability at point of care.