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A Novel Rat Model of Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA)-Induced Acute Kidney Injury

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Introduction

Non-compressible torso hemorrhage (NCTH) accounts for over 80% of potentially preventable battlefield mortalities (1,2). To temporarily control active hemorrhage and stabilize the casualty, resuscitative endovascular balloon occlusion of the aorta (REBOA) is utilized to extend the survival window for transport and definitive care. However, prolonged REBOA use leads to severe complications, including ischemia-reperfusion injury (IRI) and acute kidney injury (AKI) (3).

The kidneys are especially vulnerable during IRI due to their high metabolic demand and sensitivity to hypoxia (4,5). Current treatment for REBOA-induced organ damage, including AKI, is dependent on supportive care strategies, as pharmacological therapies to mitigate organ damage remain limited.

Developing a reproducible and reliable small animal model to evaluate REBOA induced IRI and AKI is critically needed to study and validate novel therapeutics.

Objective

- Develop a combat relevant small animal model of REBOA in rats;
- Optimize the duration of aortic occlusion required to consistently induce AKI and associated biomarkers of organ dysfunction.

Methods

Sprague-Dawley (SD) rats weighing 400-600g were anesthetized with isoflurane and given analgesics (buprenorphine, sc). Catheters were placed into the carotid and tail artery for blood pressure measurement and femoral vein for drug/vehicle infusion. A 2F Fogarty balloon catheter was introduced via femoral artery and positioned between the renal pedicle and the diaphragm. The balloon was inflated with saline for 40 min (Figure 1 & 2). Mean arterial pressure (MAP) and heart rate (HR) were measured through the experiment. Blood samples were collected at baseline (BL) and 0h, 0.5h, 1h, 3h and 6h post REBOA balloon deflation.

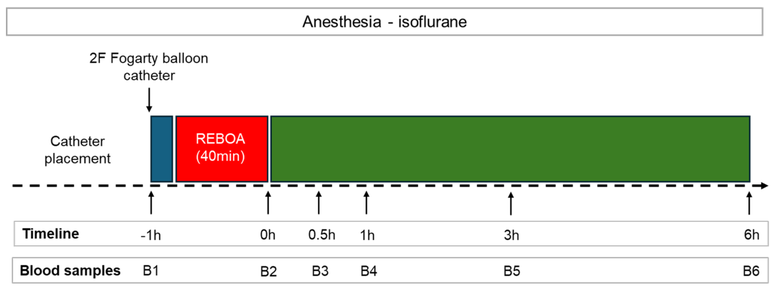

Figure 1. Experimental design of REBOA-induced AKI. Rats were subjected to 40 minutes of REBOA occlusion, followed by deflation, auto-resuscitation, and 6 hours of monitoring. Blood samples were collected at baseline (BL) and at 0, 0.5, 1, 3, and 6 hours post- REBOA deflation.

Results

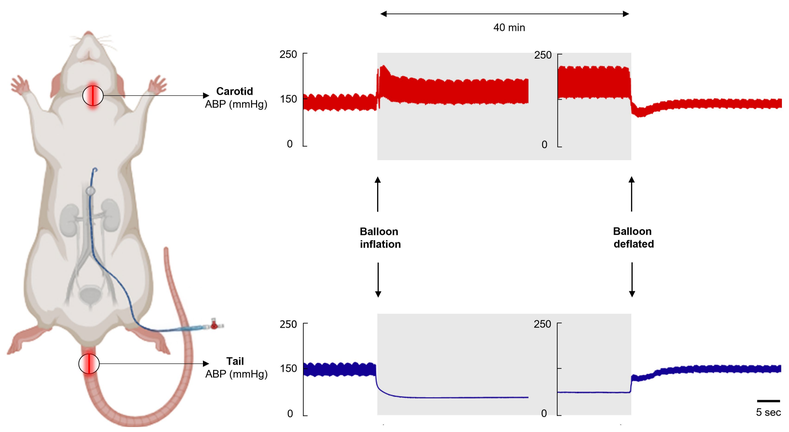

Figure 2. Rat REBOA model. Arterial blood pressure (ABP) was measured both proximal (upper level) and distal to the REBOA balloon, which was positioned in Zone I (between the diaphragm and the renal pedicle/vessels). Upon balloon inflation, carotid blood pressure increased as a physiological response to abdominal aortic occlusion and subsequent ventricular overload. Conversely, distal ABP decreased immediately following inflation, reflecting the occlusion of blood flow to the lower body. Following 40 minutes of REBOA, the balloon was deflated, and tail artery ABP returned to baseline.

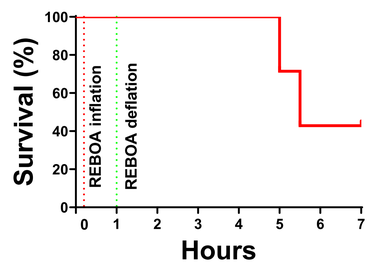

Figure 3. Mortality rate on rat REBOA model. 40 minutes aortic occlusion led to 57% of mortality (4 out of 7) within 6 hours after REBOA deflation.

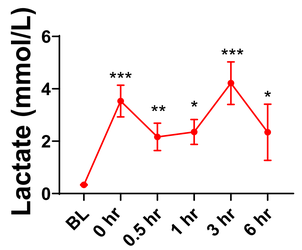

Figure 4. Lactate increased post REBOA. Lactate levels significantly increased after REBOA and remain increased up to 6 hours after balloon deflation (n=4-7). Data are presented as mean ± SEM. Mann-Whitney tests. *p<0.05, **p<0.01, ***p<0.001.

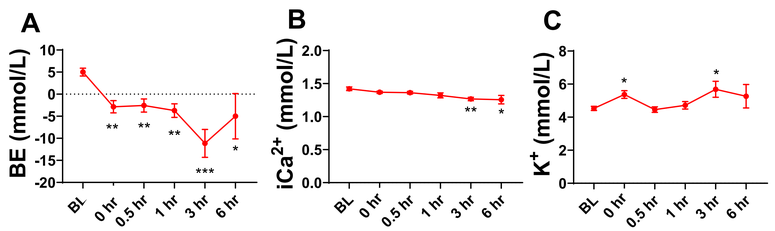

Figure 5. REBOA rat model chemistry profiles. Base Excess (BE), iCA2+ and K+ were quantified in the plasma using iSTAT (n=4-7). (A) BE significantly decreased after balloon deflation up to 6h. (B) iCA2+ significantly decreased after 3 hours and (C) K+ significantly increased post REBOA deflation and at 3h post REBOA deflation. Data are presented as mean ± SEM. Statistical analyses were performed by Mann-Whitney tests. *p<0.05, **p<0.01, ***p<0.001.

Results

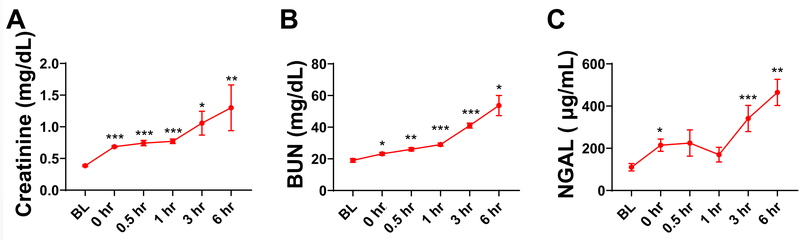

Figure 6. Sustained aortic occlusion via REBOA resulted in renal dysfunction in rats. Creatinine and Blood Urea Nitrogen (BUN) were quantified using iSTAT and plasma Neutrophil Gelatinase-Associated Lipocalin (NGAL) were analyzed with ELISA (n=4-7). (A) Creatinine, (B) BUN and (C) NGAL significantly increased after balloon deflation. Data are presented as mean ± SEM. Mann-Whitney tests. *p<0.05, **p<0.01, ***p<0.001.

Conclusion

A 40-minute Zone I REBOA occlusion produced reproducible ischemia-reperfusion injury characterized by severe metabolic derangement, acute kidney injury, and substantial early mortality.

This model provides a platform for preclinical testing of therapeutics targeting REBOA-associated organ injury. Ongoing studies are evaluating improving oxygen delivery and HMGB1-targeted therapies using this platform

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Statement:
Research was conducted in compliance with the Animal Welfare Act, the implementing Animal Welfare Regulations, and the principles of the Guide for Care and Use of Laboratory Animals. The Institutional Animal Care and Use Committee approved all research conducted in this study. The facility where this research was conducted is fully accredited by AAALAC International.

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