

60th Medical Group (AMC), Travis AFB, CA
INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC)
FINAL REPORT SUMMARY

(Please type all information. Use additional pages if necessary.)

PROTOCOL #: FDG20180026A

DATE: 2 April 2019

PROTOCOL TITLE: Evaluation of Esmolol as an Adjunct to Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) In a Porcine (*Sus scrofa*) Model Of Non-Compressible Torso Hemorrhage.

PRINCIPAL INVESTIGATOR (PI) / TRAINING COORDINATOR (TC): Capt Carl Beyer

DEPARTMENT: SGSE

PHONE #: 941-223-8572

INITIAL APPROVAL DATE: 19 Jul 18

LAST TRIENNIAL REVISION DATE: N/A

FUNDING SOURCE: Air Force Surgeon General's Office

1. RECORD OF ANIMAL USAGE:

Animal Species:	Total # Approved	# Used this FY	Total # Used to Date
<i>Sus scrofa</i>	18	18	18

2. PROTOCOL TYPE / CHARACTERISTICS: (Check all applicable terms in **EACH** column)

- | | | |
|--|--|--|
| <input type="checkbox"/> Training: Live Animal | <input type="checkbox"/> Medical Readiness | <input type="checkbox"/> Prolonged Restraint |
| <input type="checkbox"/> Training: non-Live Animal | <input type="checkbox"/> Health Promotion | <input type="checkbox"/> Multiple Survival Surgery |
| <input type="checkbox"/> Research: Survival (chronic) | <input type="checkbox"/> Prevention | <input type="checkbox"/> Behavioral Study |
| <input checked="" type="checkbox"/> Research: non-Survival (acute) | <input type="checkbox"/> Utilization Mgt. | <input type="checkbox"/> Adjuvant Use |
| <input type="checkbox"/> Other () | <input checked="" type="checkbox"/> Other (Treatment) | <input type="checkbox"/> Biohazard |

3. PROTOCOL PAIN CATEGORY (USDA): (Check applicable) C D E

4. PROTOCOL STATUS:

***Request Protocol Closure:**

- Inactive, protocol never initiated
- Inactive, protocol initiated but has not/will not be completed
- Completed, all approved procedures/animal uses have been completed

5. Previous Amendments:

List all amendments made to the protocol. **IF none occurred, state NONE. Do not use N/A.**

For the Entire Study Chronologically

Amendment Number	Date of Approval	Summary of the Change
1	4 Sep 18	Personnel

6. **FUNDING STATUS:** Funding allocated: \$ 63,420.00

Funds remaining: \$ 0.00

7. **PROTOCOL PERSONNEL CHANGES:**

Have there been any personnel/staffing changes (PI/CI/AI/TC/Instructor) since the last IACUC approval of protocol, or annual review? Yes No

If yes, complete the following sections (Additions/Deletions). For additions, indicate whether or not the IACUC has approved this addition.

ADDITIONS: (Include Name, Protocol function - PI/CI/AI/TC/Instructor, IACUC approval - Yes/No)

<u>NAME</u>	<u>PROTOCOL FUNCTION</u>	<u>IACUC APPROVAL</u>

DELETIONS: (Include Name, Protocol function - PI/CI/AI/TC/Instructor, Effective date of deletion)

<u>NAME</u>	<u>PROTOCOL FUNCTION</u>	<u>DATE OF DELETION</u>

8. **PROBLEMS / ADVERSE EVENTS:** Identify any problems or adverse events that have affected study progress. Itemize adverse events that have led to unanticipated animal illness, distress, injury, or death; and indicate whether or not these events were reported to the IACUC.

None.

9. **REDUCTION, REFINEMENT, OR REPLACEMENT OF ANIMAL USE:**

REPLACEMENT (ALTERNATIVES): Since the last IACUC approval, have alternatives to animal use become available that could be substituted in this protocol without adversely affecting study or training objectives?

No.

REFINEMENT: Since the last IACUC approval, have any study refinements been implemented to reduce the degree of pain or distress experienced by study animals, or have animals of lower phylogenetic status or sentience been identified as potential study/training models in this protocol?

No.

REDUCTION: Since the last IACUC approval, have any methods been identified to reduce the number of live animals used in this protocol?

No.

10. **PUBLICATIONS / PRESENTATIONS:** The results of this experiment will be submitted for publication to the journal *Shock*.

11. **PROTOCOL OBJECTIVES:** The purpose of this protocol was to evaluate if esmolol infusion during resuscitative endovascular balloon occlusion of the aorta (REBOA) could mitigate cardiac injury induced by the high afterload and cardiac strain that occurs during aortic occlusion. This objective was met, and the results show that esmolol can mitigate this cardiac injury. This is a significant finding with the potential to improve outcomes for the severely injured warfighters that require REBOA for hemorrhage control.

12. PROTOCOL OUTCOME SUMMARY: (Please provide, in "ABSTRACT" format, a summary of the protocol objectives, materials and methods, results - include tables/figures, and conclusions/applications.)

Objectives: The purpose of this protocol was to evaluate if esmolol infusion during resuscitative endovascular balloon occlusion of the aorta (REBOA) could mitigate cardiac injury induced by the high afterload and cardiac strain that occurs during aortic occlusion.

Materials and methods: Swine were anesthetized and instrumented. The spleen was removed via a midline celiotomy. Hemorrhagic shock was induced via removal of 25% of the animals estimated blood volume over 30 minutes through the brachial arterial line. At the end of the hemorrhage period, the zone 1 balloon was inflated for 45 minutes; during the AO period, the esmolol infusion rate was titrated to maintain heart rate between 80 and 100 beats per minute in the intervention group. The esmolol infusion was discontinued at the beginning of balloon deflation. Shed blood was transfused to the animal over 20 minutes at T65. In both groups, the aortic balloon was deflated over 10 minutes. Animals were cared for with crystalloid boluses and norepinephrine until the end of the experiment.

Results: The mean esmolol dose over the 45 minutes of occlusion was $225.1 \pm 48.9 \mu\text{g}/\text{kg}$. There was no significant difference in the average heart rate during the hemorrhage phase (78 [71 - 92] and 92 [82 - 98], $p = 0.29$) or after balloon deflation (138 [151-159] and 152 [129 - 171], $p = 0.82$) between the control and esmolol groups, respectively. Heart rate was significantly higher in animals in the control group than in those in the esmolol group during aortic occlusion (193 [172 - 203] and 99 [87 - 108], respectively, $p < 0.001$). Serum troponin concentrations over time are presented in figure 1. There was a significant difference over time ($p=0.03$) and between groups (0.003). While there was no difference in serum troponin concentration over time in the esmolol group ($p=0.054$), it was significantly higher than baseline at T360 in the control group ($p=0.006$).

Conclusion: Esmolol reduced myocardial injury associated with REBOA in a porcine model of hemorrhagic shock. Future studies should investigate the prolonged use of esmolol in the resuscitation phase, in animals with persistent tachycardia.

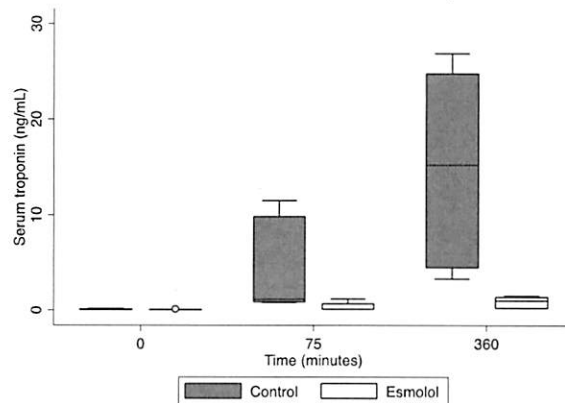


Figure 1



(PI / TC Signature)

6 May 2019
(Date)

Attachment 1

Defense Technical Information Center (DTIC) Abstract Submission

This abstract requires a brief (no more than 200 words) factual summary of the most significant information in the following format: Objectives, Methods, Results, and Conclusion.

Objectives: To evaluate if esmolol infusion during resuscitative endovascular balloon occlusion of the aorta (REBOA) could mitigate cardiac injury.

Methods: Swine were anesthetized and instrumented. Hemorrhagic shock was induced via removal of 25% of the animals estimated blood volume over 30 minutes. At the end of the hemorrhage period, the zone 1 balloon was inflated for 45 minutes; during the AO period, esmolol infusion rate was titrated to maintain heart rate between 80-100 beats per minute in the intervention group. The esmolol infusion was discontinued at the beginning of balloon deflation. Shed blood was transfused to the animal over 20 minutes at T65. In both groups, the aortic balloon was deflated over 10 minutes.

Results: Heart rate was significantly higher in the control group than in the esmolol group during aortic occlusion (193 [172 - 203] and 99 [87 - 108], respectively, $p < 0.001$). There was a significant difference in troponin concentrations over time ($p=0.03$) and between groups (0.003). There was no difference in serum troponin concentration over time in the esmolol group ($p=0.054$), it was significantly higher than baseline at T360 in the control group ($p=0.006$).

Conclusion: Esmolol reduced myocardial injury associated with REBOA.

Grant Number: There was no grant for this work.