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TITLE: Gastroesophageal Resuscitative Occlusion of the Aorta (GROA)

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CONTRACTING ORGANIZATION: University of Michigan

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14. ABSTRACT
Natural Orifice Transluminal Endoscopic Surgery (NOTES) is an evolving surgical innovation, which allows for intra-cavitary surgeries to be performed with an endoscope passed through a natural orifice (mouth anus, vagina, urethra). It is the purpose of this proposal to leverage the concept of NOTES to develop a method of temporary aortic occlusion using an orally placed gastroesophageal device. This gastroesophageal resuscitative occlusion of the aorta (GROA) will be developed as a field bridge to more invasive and definitive means of control of non-compressible torso hemorrhage (NCTH) such as resuscitative endovascular balloon occlusion of the aorta (REBOA), angiography, and surgery.
Hypothesis: The anatomical relationship between the esophagus and stomach to the descending thoracic and abdominal aorta will allow complete mechanical occlusion of the aorta through the stomach that can prolong short-term survival of severe NCTH.
Specific Aims/Objectives:
1) Design and prototype GROA devices that can be orally placed into the stomach that mechanically produces complete occlusion of the aorta at or above the celiac artery and test the physiologic tolerance of GROA in comparison to REBOA in swine undergoing hemorrhage.
2) Test and compare GROA prototypes to REBOA for staunching severe NCTH in a large swine animal model of traumatic shock.
3) Demonstrate tandem use of GROA followed by REBOA as an example of point-of-care in field prolonged field care (PFC) and prolonged damage control resuscitation (pDCR) in a swine model of severe NCTH.
Experimental Approach: An iterative design and testing approach will be taken to develop a product, which leverages the anatomical relationship of the esophagus and stomach to the descending thoracic and abdominal aorta. A combination of thoracic and abdominal 3-D reconstructed computed tomography scans across a wide variety of patient types of body habitus (including warfighter phenotypes) will be used to inform the design characteristics of GROA, based on our previous approach using *morphomics* to map the 3-D vascular anatomy of over 2000 individuals in developing new REBOA systems. In-silico model and simulator testing will be used to understand actual tissue qualities and constraints on design characteristics and tolerances for device components including the development of balloons. A reliance on 3-D printing to produce prototypes will ensure rapid iterative development-refinement of GROA.
Preclinical testing using swine will also be used to test the effectiveness of the various GROA iterations to occlude the aorta in proximal Zone II at or above the celiac artery. Physiologic tolerance studies will be performed to understand potential complications and limitations compared to REBOA on hemorrhaged swine. GROA will also be compared to REBOA in a model of NCTH. Finally, tandem use of GROA to REBOA will be studied in experiments to simulate a potential PFC and pDCR situation. The latter will provide proof of feasibility of initial rapid stabilization using GROA followed by transition to the implementation of REBOA.

15. SUBJECT TERMS
Occlusion of the Aorta, Balloon, Stomach, Non-compressible hemorrhage, Resuscitation

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1. **INTRODUCTION:** Hemorrhage from potentially survivable injuries is believed to be responsible for more than 90% of military combat casualties and 40% of civilian trauma deaths. Treatment of non-compressible torso hemorrhage (NCTH) including deep pelvic hemorrhage continues to pose almost intractable challenges especially in the prehospital and PFC setting where almost 9 out of 10 deaths occur. REBOA technology is evolving and promising to offer a physiologic bridge to definitive surgery or other hemostatic techniques. The biggest challenge and contributor to complications regarding REBOA is likely to be the time interval and physiologic status of casualties between the time of initial injury and implementation of REBOA. It is the purpose of this proposal to leverage the concept of Natural Orifice Transluminal Endoscopic Surgery (NOTES) to develop a method of temporary aortic occlusion, similar to REBOA, using an orally placed gastroesophageal device. This gastroesophageal resuscitative occlusion of the aorta (GROA) will be developed as a field bridge to more invasive and definitive means of control of hemorrhage such as REBOA. The successful development of a minimally invasive alternative such as GROA could prove to be an effective temporary countermeasure for severe intra-abdominal and pelvic hemorrhage. Hypothesis: The anatomical relationship between the esophagus and stomach to the descending thoracic and abdominal aorta will allow complete mechanical occlusion of the aorta through the stomach that can prolong short-term survival of severe non-compressible abdominal hemorrhage.

   Specific Aims/Objectives:
   1) Design and prototype GROA devices that can be orally placed into the stomach that mechanically produce complete occlusion of the aorta at or above the celiac artery and test the physiologic tolerance of GROA in comparison to REBOA in severe hemorrhage in swine.
   2) Test and compare GROA prototypes to REBOA for staunching severe noncompressible abdominal hemorrhage in a large swine animal model of traumatic shock.
   3) Demonstrate tandem use of GROA followed by REBOA as an example of point-of-care in field pDCR and PFC in a swine model of severe hemorrhage.

2. **KEYWORDS:** Hemorrhage, REBOA, GROA, Swine, Shock, Resuscitation, NOTES, Aorta, Aortic occlusion, Stomach, PFC, pDCR

3. **ACCOMPLISHMENTS:**

   What were the major goals of the project?

   - **Major Task 1**: Design and prototype GROA devices that can be orally placed into the stomach that mechanically produces complete occlusion of the aorta at or above the celiac artery and test the physiologic tolerance of GROA in comparison to REBOA in swine undergoing hemorrhage.

     - **Subtask 1**: Local/Institutional IACUC approval (approved 6/6/2017)
     - **Subtask 2**: ACURO Approval (approved 8/9/2017)
     - **Subtask 3**: Obtain equipment, hire and train study personnel. (complete)
     - **Subtask 4**: Morphomics analysis and solid modeling of swine and human esophagus, stomach, aorta and surrounding structures from swine and human CT scans with development of first swine and human GROA prototypes with creation of in-silico and bench top esophageal-stomach-aorta model for testing: Months 2-12 (completed)

- **Subtask 5**: Swine testing of initial GROA prototypes on ability to occlude aorta followed by testing of physiologic tolerance of GROA compared to REBOA and control. 72 animals will be used total, 24 animals in each group: Months 4-16 (completed)

- **Milestone Targeted:** ACURO Approval (2-3 months) (Approved)
- **Milestone Targeted:** 2-3 GROA prototypes made (6-12 months) (completed)
- **Milestone Targeted:** Physiologic tolerance studies of GROA in comparison to REBOA (completed)
- **Milestone Targeted:** One or more peer reviewed publications (12 months) (completed)

- **Major Task 2:** Test and compare GROA prototypes to REBOA for staunching severe non-compressible abdominal hemorrhage in a large swine animal model of traumatic shock

  - **Subtask 1**: Continued refinement of both swine and human GROA prototypes: Months 12-24 (In progress ~ 90% complete)
  - **Subtask 2**: Testing of GROA prototypes in swine model of lethal abdominal hemorrhage comparing performance with REBOA and control. 30 animals will be used, 10 animals in each group. Months 16-24 in progress (75% complete)

  - **Milestone Targeted**: Complete comparison studies of GROA and REBOA in swine with severe noncompressible hemorrhagic shock. (24 months) (in progress 75% complete)
  - **Milestone Targeted**: One or more peer reviewed publications/year (In Progress; TBD upon on animal study completion)
  - **Milestone Targeted**: Use preliminary data to attract industry partner and/or begin considering small business spin off for technology transition plan (months 16-36)

- **Major Task 3:** Demonstrate tandem use of GROA followed by REBOA as an example of point-of-care in field prolonged damage control resuscitation (pDCR) and prolonged field care (PFC) in an animal model and severe non-compressible abdominal hemorrhage.

  - **Subtask 1:** Continued refinement of GROA prototypes: Months 24-36
  - **Subtask 2:** Testing of tandem use of GROA to REBOA: Months 24-36

  - **Milestone Targeted**: Successful demonstration of GROA to REBOA transition (48 months)
  - **Milestone Targeted**: Creation of final 1-2 human GROA prototypes suitable for consideration for human testing in follow-on studies. (48 months)
  - **Milestone Targeted**: One or more peer reviewed publications/year (48 months)
  - **Milestone Targeted**: Use refined data to continue to engage industry partner and/or launch small business spin off for technology transition plan (48 months)

What was accomplished under these goals?

- **Major Task 1**: Design and prototype GROA devices that can be orally placed into the stomach that mechanically produces complete occlusion of the aorta at or above the celiac artery and test the physiologic tolerance of GROA in comparison to REBOA in swine undergoing hemorrhage.

Prototype design progress

February 2020 – May 15, 2020:

- **Continued device development was performed during this reporting period.**
  Interplex medical continued manufacture of the most recent GROA balloon catheter devices. Figure 1 contains the most recent design specifications. The newest iteration of catheters contains the following design specifications:

    - Foremost, the device has been updated with a telescoping tip. This allows for the distal-most portion of the catheter, which previously extended beyond the balloon, to be retracted so that only the balloon portion of the catheter is in contact with the gastric mucosa only during deployment. This may decrease the likelihood of mucosal injury during application.
    - In addition to the newest tip design, we have also tested several new materials for the balloon in an attempt to reduce any gastric injury by allowing for the maximum amount of compliance while maintaining the structure necessary to occlude the aorta. We tested both a thinner and stiffer material but are unable to thermoform due to technical challenges. We have now improved the sealing process on the balloon material to reduce possibility of device failure.

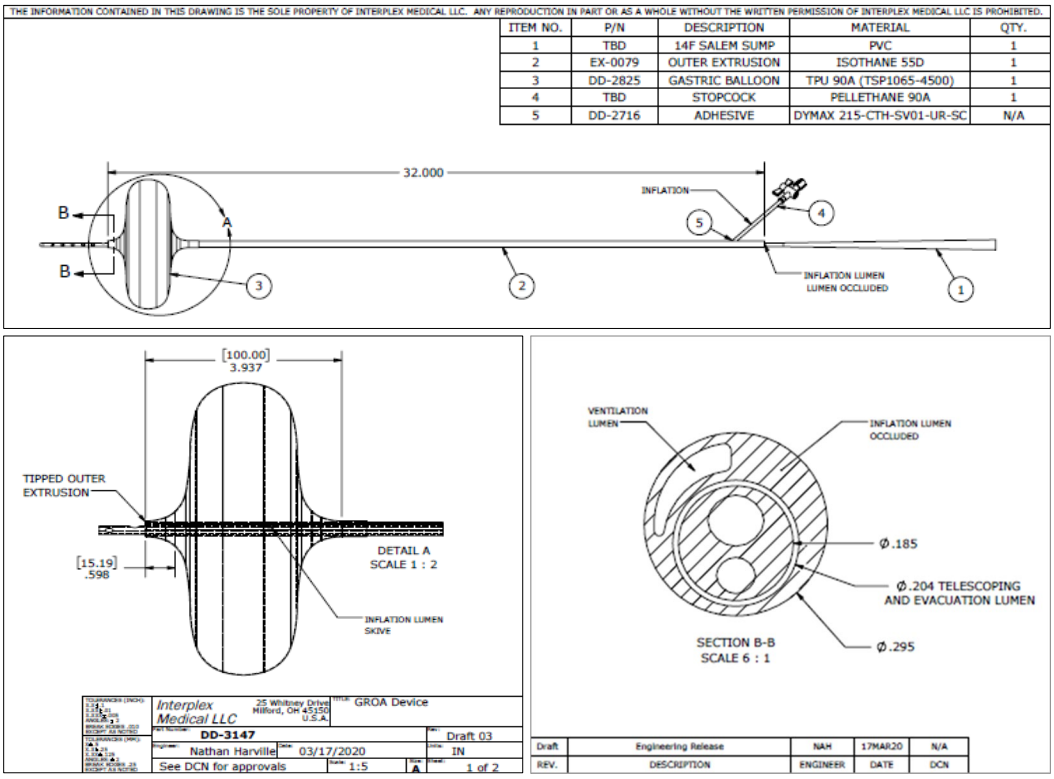


Figure 1. A). Schematic representation of latest device design B). Schematic of latest device design showing inner and outer extrusion for telescoping tip. C). Cross sectional view of the telescoping tip incorporated into the outer extrusion, and lumen specifications.

May 16, 2020 – August 15, 2020:

- **Device manufacture was completed by Interplex medical**

Interplex medical has completed device manufacturing and devices were delivered on June 6, 2020. Figure 2 contains images of the latest iteration device which contains the telescoping tip, updated lumen design and materials. The figure shows the device deflated, the device inflated with the sump tube in place, and the device inflated with the telescoping sump tube removed. The device is placed with the sump tube fully extended through the catheter to access the stomach and provide gastric ventilation. Once placed, the balloon can be inflated to initiate aortic occlusion. Once occlusion is achieved, the telescoping sump tip can be removed to reduce device surface contact with the stomach tissue which may mitigate gastric irritation and injury from device application.

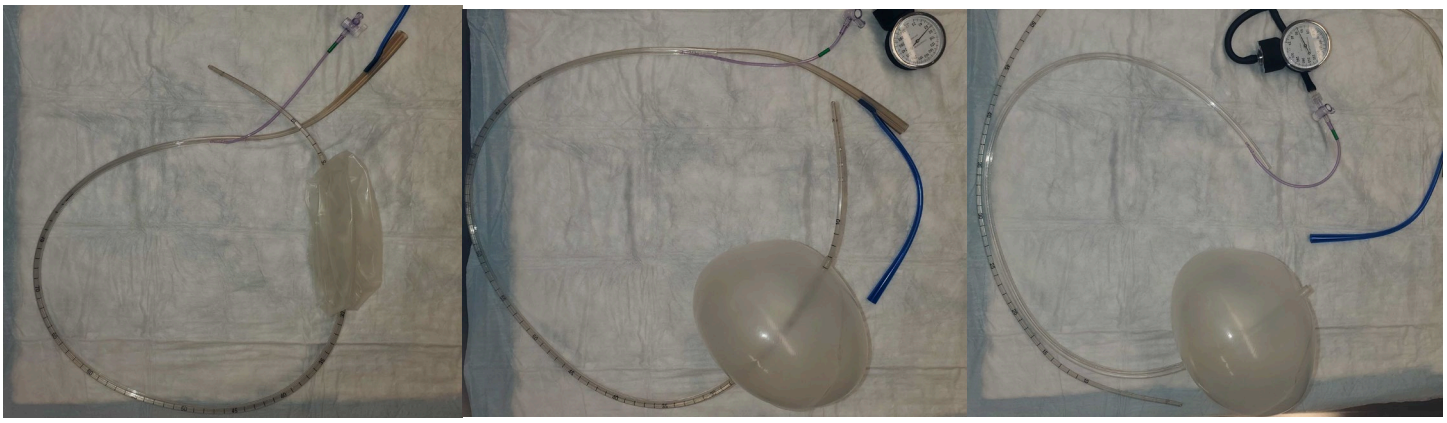


Figure 2. Latest iteration manufactured GROA catheter device with telescoping tip. The device is deflated with the tip fully extended for application (left). Once placed, the device is inflated with the tip in place (center), and once inflated the tip can be telescoped out of the stomach (right).

August 16, 2020 – November 10, 2020:

- **Additional device refinement has been accomplished on the abdominal plate assembly**:

Figure 3. External compression system with deployable storage box back-plate and abdominal plate with adjustable compression depth.

Figure 3 shows the external compression system. The system consists of a storage box which is deployable into a rigid back plate. This design features a quick-connect snap system, using the buckles and strips to easily connect the abdominal plate to the back plate to create adequate external pressure. These improvements enable the system to pack flatter while still allowing for rapid assembly and deployment. This design has been effectively tested in the animal studies for major task 1 and is being utilized for major task 2 as well. The abdominal plate and external pressure system have been refined based on observations in animal experiments. In the animal experiments for experiment 2, it was noted that in some cases, the balloon (when inflated in-vivo), would tend to (slightly) deflect laterally. Although it should be noted that despite this, aortic occlusion was still maintained. To limit this deflection and to

better hold the balloon in place during application, measurements of the abdomen curvature we taken and a new plate design was implemented which includes a curved abdominal contact surface, and a lateral extension of the inferior portion of the plate. These newest design aspects (figure 4) resulted in the production of a new prototype plate which serves the intention of discouraging lateral balloon migration by having a semi-lateral surfaces. Specific design changes from the previous abdominal plates include:

1) Curvature with radius of 240 mm is added in the *z*-axis of the abdominal plate.
2) Length of the plate in the *x*-axis is extended to 227.72 mm
3) Abdominal plate attachment base (located at the center of the plate) is kept flat and does not follow the curvature of the abdominal plate.

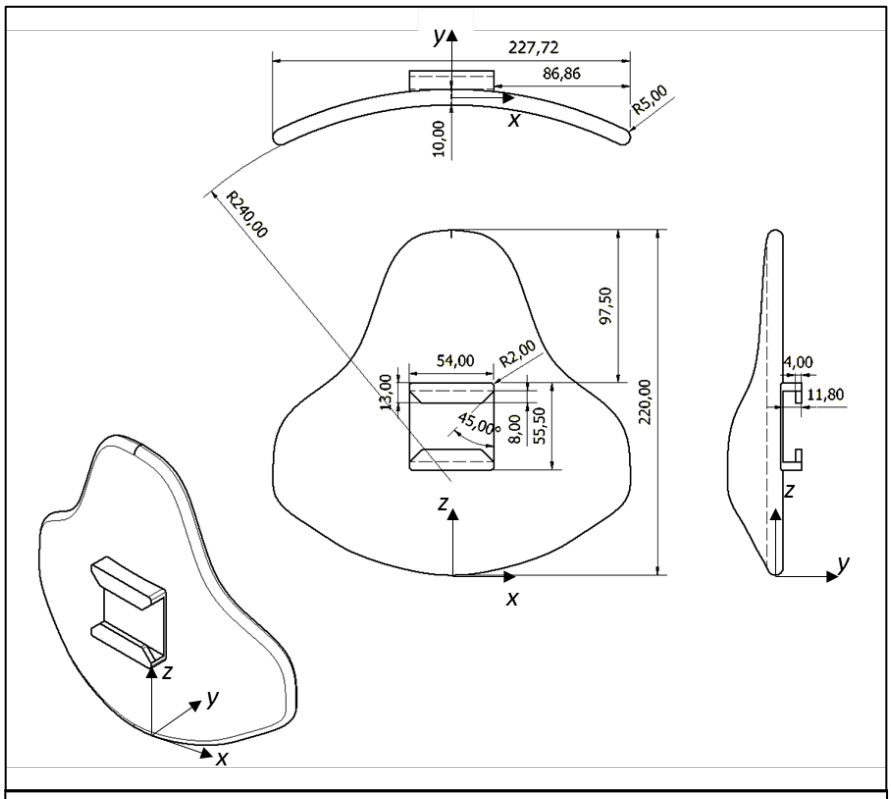


Figure 4. Schematic representation of latest abdominal plate design specifications.

The newest plate has been 3D printed using the design specifications above and the product is shown in figure 5 below. The plate has been function tested in the swine model of traumatic hemorrhage and has been founds effective at occluding the aorta and appears to better limit balloon migration as expected.

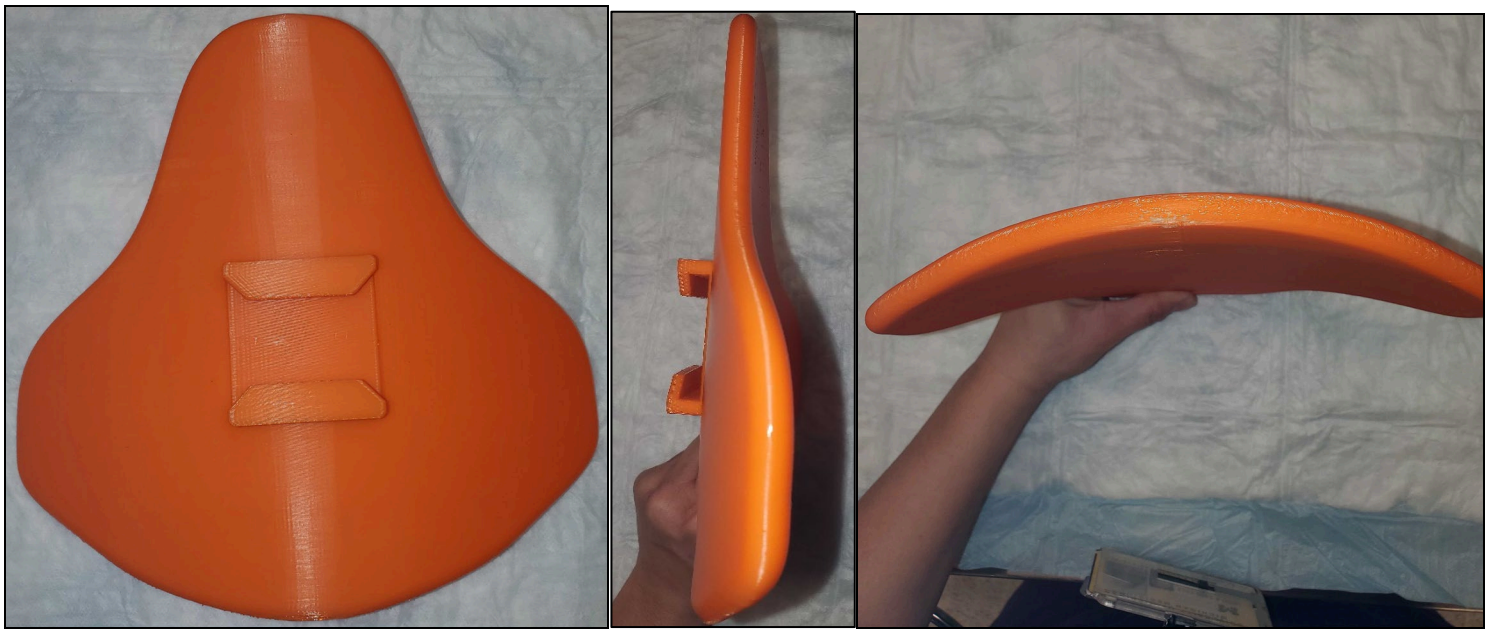


Figure 5. Latest iteration 3D printed abdominal plate featuring extended inferior base and curved z-axis to fit the abdominal curvature and provide greater device stability

Specific objectives

- **Subtask 1**: Local/Institutional IACUC approval (approved 6/6/2017)
- **Subtask 2**: ACURO Approval (approved 8/9/2017)
- **Subtask 3**: Obtain equipment, hire and train study personnel. (complete)
- **Subtask 4**: Morphomics analysis and solid modeling of swine and human esophagus, stomach, aorta and surrounding structures from swine and human CT scans with development of first swine and human GROA prototypes with creation of in-silico and bench top esophageal-stomach-aorta model for testing: Months 2-12 (completed)
- **Subtask 5**: Swine testing of initial GROA prototypes on ability to occlude aorta followed by testing of physiologic tolerance of GROA compared to REBOA and control. 72 animals will be used total, 24 animals in each group: Months 4-16 (complete)

Significant results

All work on major task 1 including all subtasks and milestones have been completed. All swine testing of initial GROA prototypes and testing of physiologic tolerance has been completed in this reporting period. This data has resulted in a peer reviewed scientific publication in the *Journal of Trauma and Acute Care Surgery* titled "***Gastroesophageal resuscitative occlusion of the aorta: Physiologic tolerance in a swine model of hemorrhagic shock***". Full Citation: *Tiba, Mohamad, MD, MS, McCracken, Brendan, et al. Gastroesophageal resuscitative occlusion of the aorta: Physiologic tolerance in a swine model of hemorrhagic shock. J. trauma acute care surg. 2020;89(6):1114-1123. doi:10.1097/TA.0000000000002867.*

Animals use Data:

a. Species: Sus Scrofa Domestica
b. Total animal number used this annual reporting period: 27
c. USDA pain category for all animals used: D

Animal data collected to date have been used to evaluate the ability of different iterations of GROA prototypes to occlude the aorta, and various measurements of physiological tolerance, as well as evaluate the ability of the device to stanch lethal noncompressible hemorrhage, while comparing to

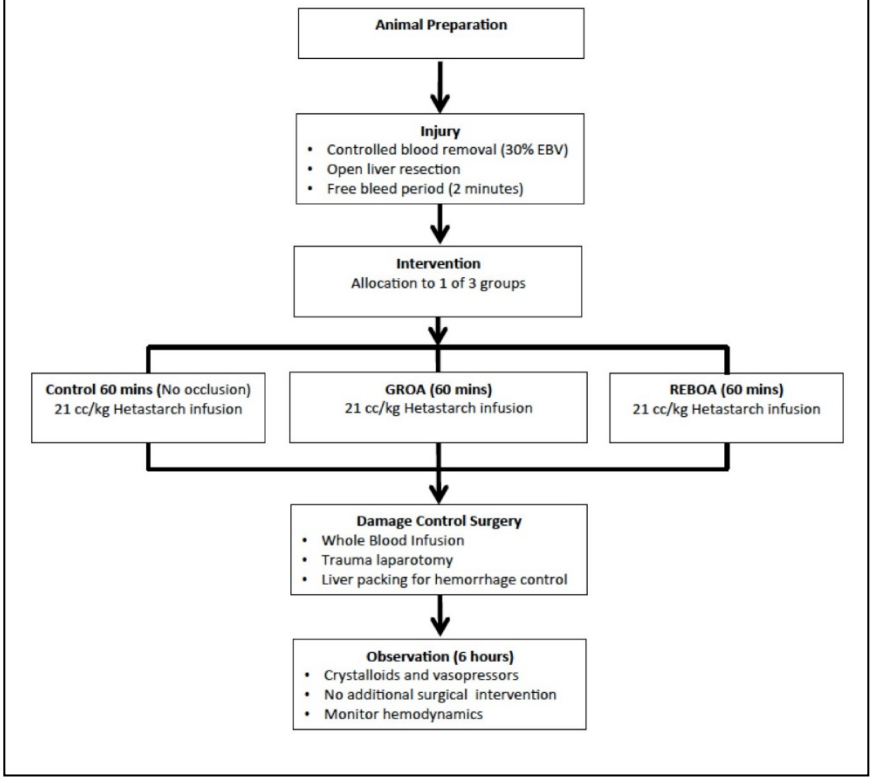
REBOA and controls.

- **Milestone Targeted:** ACURO Approval (2-3 months) (Approved)
- **Milestone Targeted:** 2-3 GROA prototypes made (6-12 months) (completed)
- **Milestone Targeted:** Physiologic tolerance studies of GROA in comparison to REBOA (completed)
- **Milestone Targeted:** One or more peer reviewed publications (12 months) (complete)

- **Major Task 2:** Test and compare GROA prototypes to REBOA for staunching severe non-compressible abdominal hemorrhage in a large swine animal model of traumatic shock
  - **Subtask 1**: Continued refinement of both swine and human GROA prototypes: Months 12-24 (in progress: 90% complete)
  - **Subtask 2**: Testing of GROA prototypes in swine model of lethal abdominal hemorrhage comparing performance with REBOA and control. 30 animals will be used, 10 animals in each group. Months 16-24 in progress (75% complete)

The majority of all project work this annual period pertains to major task 2, subtask 2. Significant work has been performed this reporting period on Aim 2: Experiment 2: *GROA Comparison with REBOA to control lethal noncompressible abdominal hemorrhage*.

Figure 6: Experiment 2: Design Comparing GROA to REBOA in NCTH.



Experimental design is shown in figure 6. Animals were anesthetized and instrumented as described in the aforementioned aim 1 publication. However, in these experiments a laparotomy was performed to allow for transection of the liver. The liver was marked along a planned transection plane 2 cm to the left of Cantile's line in order to provide a full thickness laceration of the left medial lobe which spans approximately 80% of the cranial-caudal plane. Through a catheter placed in the femoral artery, animals underwent controlled hemorrhage removing 30% of their estimated blood volume into CPDA blood bags over 20 minutes. Following blood removal, the liver was lacerated. Two minutes following the liver injury, intervention was implemented either by deployment of GROA, REBOA, or control (no intervention). Animals surviving 60 minutes of intervention were administered two units of the shed whole blood. At the same time the abdomen is opened and the liver is packed for hemostasis (damage control surgery). Supportive care in the form of additional crystalloid and vasopressors (norepinephrine, if needed) were be provided while the animals were monitored for an additional 4 hours.

Significant Findings & Results: Preliminary data for 23 animals across the three group are provided below. A Kaplan-Meier survival curve is presented as figure 7. All animals included in the GROA (8/8) and REBOA (7/7) groups survived the duration of the 60-minute intervention period while 7 of 8 controls died within 18 minutes of injury exposure consistent with previous literature using a similar lethal injury model. One control animal did however survive for the duration of

intervention and post-resuscitation periods. Airway pressures, carotid and femoral arterial blood pressures, heart rate, lactate, mixed venous oxygen saturation, and end tidal CO_2 data are provided in figures 8-11.

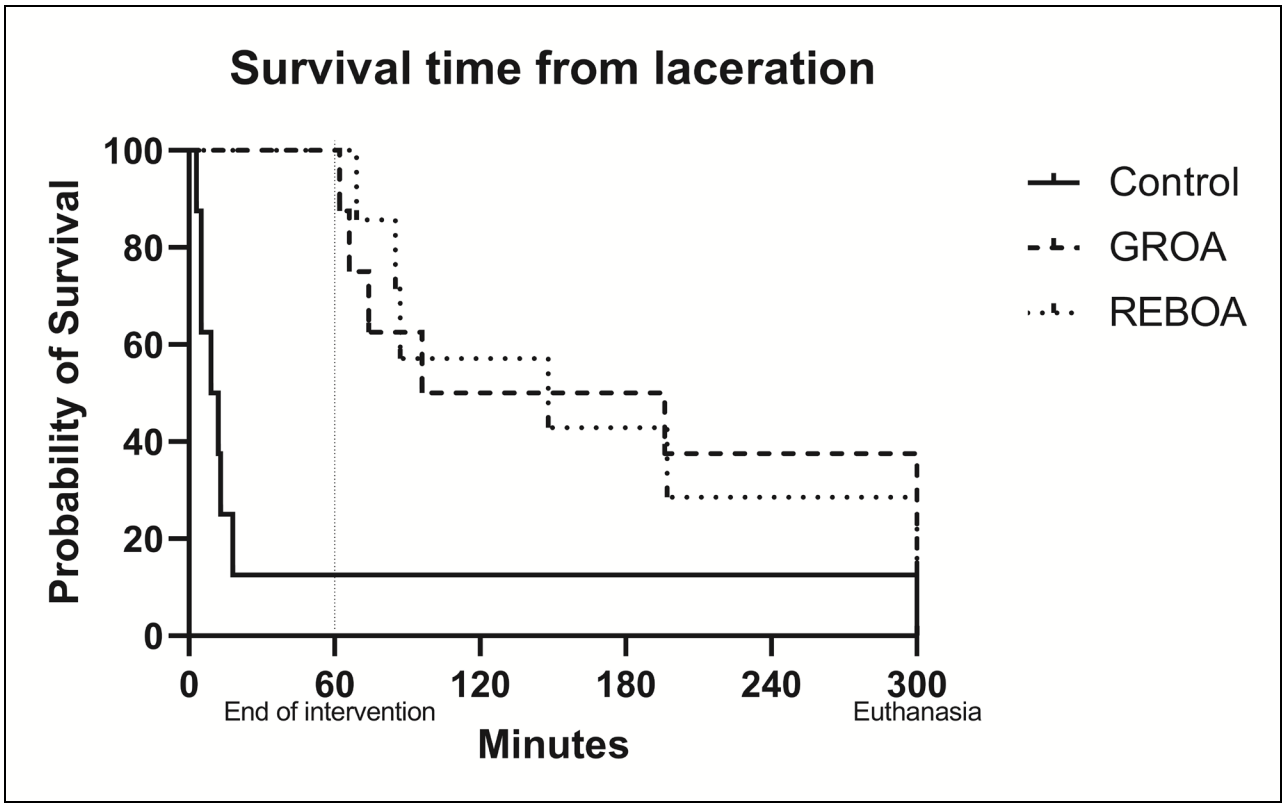


Figure 7. Kaplan-Meijer Survival curve showing the estimated probability of survival (y-axis) in minutes (x-axis) following liver laceration injury.

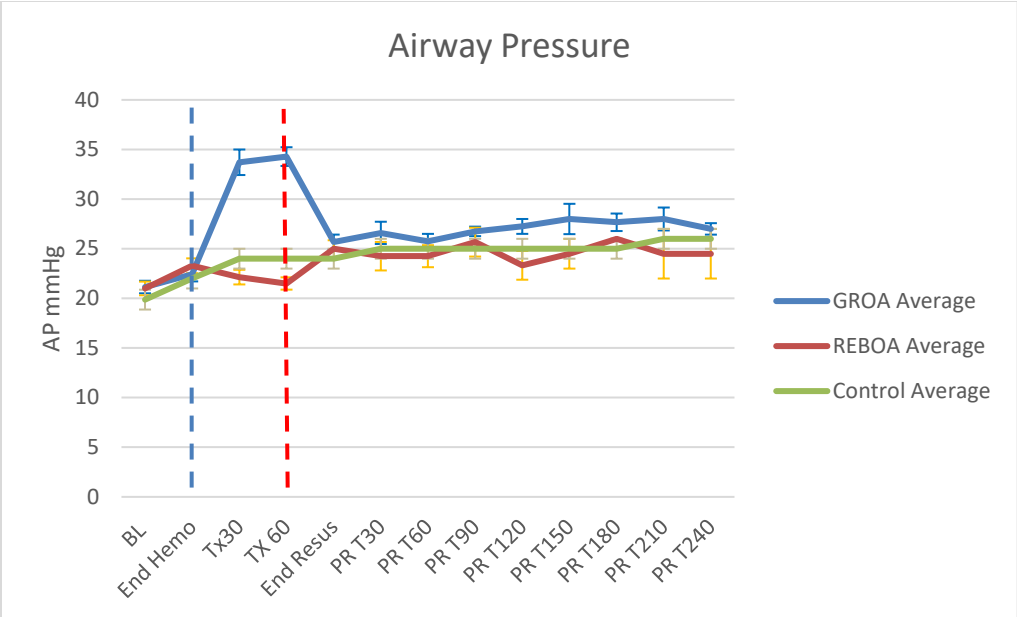


Figure 8 Airway Pressure. End hemo: end of controlled hemorrhage, tx30: thirty minutes after treatment randomization. Tx 60: end of intervention period. PR T; minutes post-resuscitation

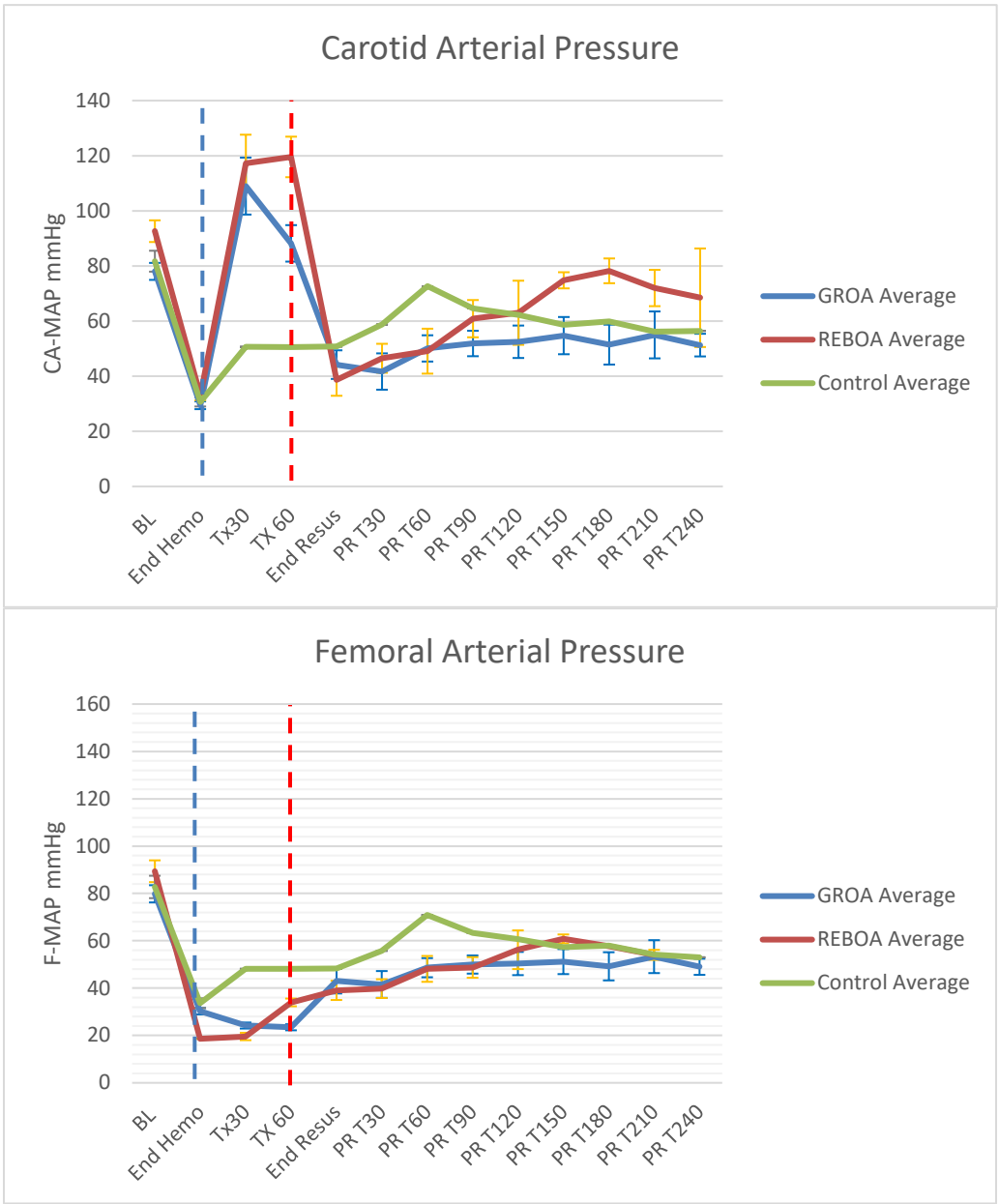


Figure 9 Carotid artery pressure (top) and Femoral artery pressure (bottom). End hemo: end of controlled hemorrhage, tx30: thirty minutes after treatment randomization. Tx 60: end of intervention period. PR T; minutes post-resuscitation

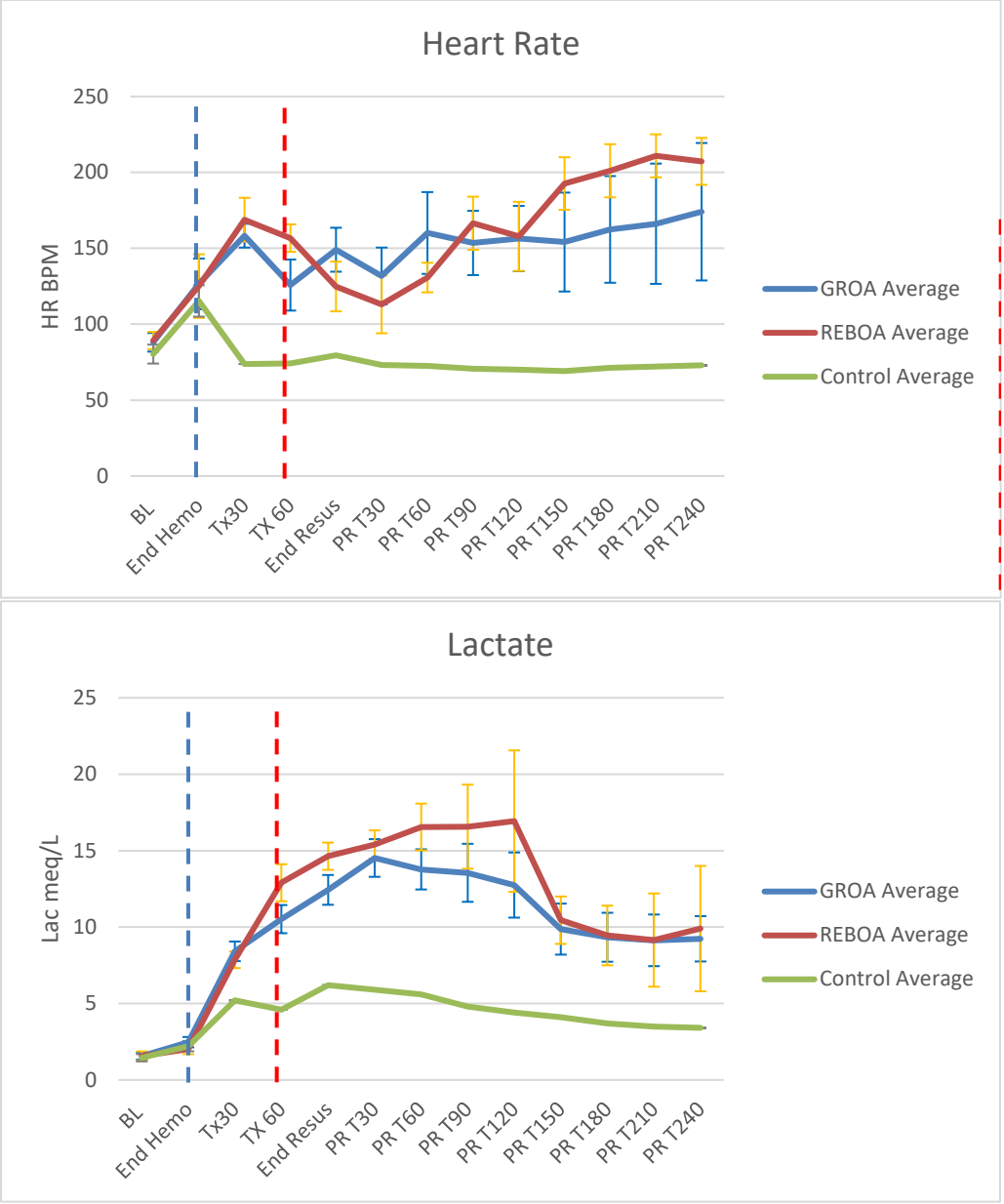


Figure 10. Heart rate (top) and Lactate levels (bottom). End hemo: end of controlled hemorrhage, tx30: thirty minutes after treatment randomization. Tx 60: end of intervention period. PR T; minutes post-resuscitation

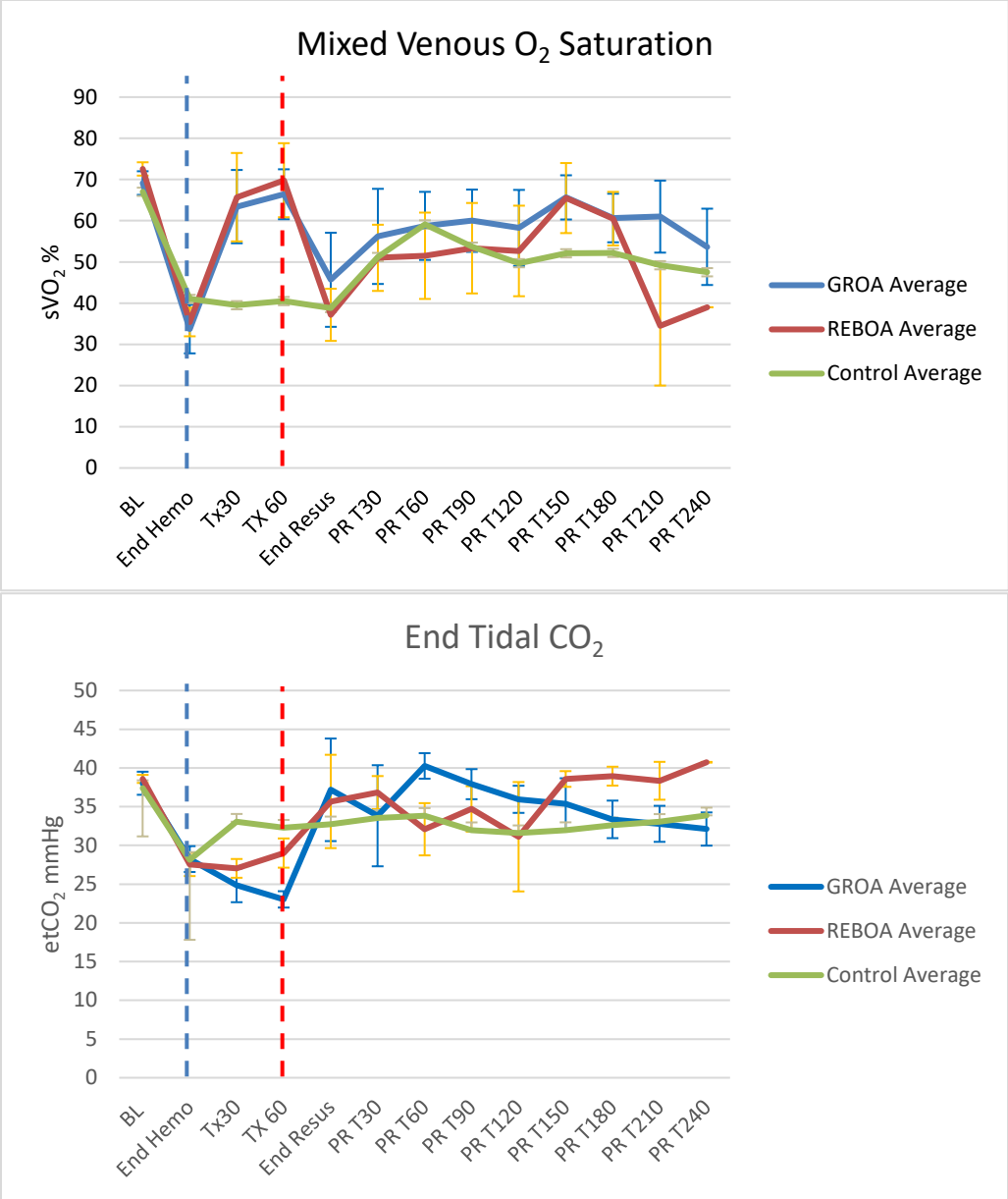


Figure 11. Mixed venous oxygen saturation (top) and End tidal CO_2 levels (bottom). End hemo: end of controlled hemorrhage, tx30: thirty minutes after treatment randomization. Tx 60: end of intervention period. PR T; minutes post-resuscitation

Tissue samples from the stomachs and aortas were collected for histopathological analysis by a blinded expert veterinarian pathologist. There was no evidence of injury in any aortic samples from any of the three groups. Examination of the stomach from the GROA samples revealed mild ischemic changes to the superficial mucosa, and mild serosal changes (fibrin, inflammatory cells) suggestive of mechanical irritation from the device. These findings are less severe than previous reports, and these improvements may be contributed to the refinement of the device. In the REBOA animal, gross changes in the stomach included moderate to severe diffuse reddening of the gastric mucosa however there was no histological evidence of stomach injury in the REBOA or control group. The full report is contained in the appendices.

Several animals used from this aim have been excluded due to technical issues or failures. Two animals were excluded due to gastric dilatation (bloating) during the experiment. Upon necropsy, the animals were found to have food contained in the stomach. In another separate animal, the liver laceration was found to be significantly smaller than in other animals and presumed to be inadequate and not a comparable injury. In

one additional animal there was a GROA device technical failure. Shortly after application of the device, the device began leaking air. Approximately 45 minutes into the intervention period the balloon ruptured. The experiment was terminated after device failure due to hemodynamic decompensation from the massive and instantaneous reperfusion. The engineering and device fabrication team is currently evaluating the failure. These animal's data are not provided in the data and figures presented above.

- **Milestone Targeted**: Complete comparison studies of GROA and REBOA in swine with severe noncompressible hemorrhagic shock. (24 months) (in progress 75% complete)
- **Milestone Targeted**: One or more peer reviewed publications/year (24 months) (In preparation)
- **Milestone Targeted**: Use preliminary data to attract industry partner and/or begin considering small business spin off for technology transition plan (months 16-36)

o **Major Task 3:** Demonstrate tandem use of GROA followed by REBOA as an example of point-of-care in field prolonged damage control resuscitation (pDCR) and prolonged field care (PFC) in an animal model and severe noncompressible abdominal hemorrhage.
  - **Subtask 1:** Continued refinement of GROA prototypes: Months 36-48
  - **Subtask 2:** Testing of tandem use of GROA to REBOA: Months 36-28

  - **Milestone Targeted**: Successful demonstration of GROA to REBOA transition (48 months)
  - **Milestone Targeted**: Creation of final 1-2 human GROA prototypes suitable for consideration for human testing in follow-on studies. (48 months)
  - **Milestone Targeted**: One or more peer reviewed publications/year (48 months)

  Milestone Targeted: Use refined data to continue to engage industry partner and/or launch small business spin off for technology transition plan (48 months)

What opportunities for training and professional development has the project provided?
Nothing to Report

How were the results disseminated to communities of interest?
A peer reviewed scientific manuscript has been published in the *Journal of Trauma and Acute Care Surgery.* The article is included as part of the appendices.
Full citation: *Tiba, Mohamad, MD, MS, McCracken, Brendan, et al. Gastroesophageal resuscitative occlusion of the aorta: Physiologic tolerance in a swine model of hemorrhagic shock. J. trauma acute care surg. 2020;89(6):1114-1123. doi:10.1097/TA.0000000000002867.*

An abstract was accepted for presentation at the 2020 Military Health System Research Symposium (MHSRS), Kissimmee, FL, However the conference was cancelled due to the Covid-19 pandemic. The accepted abstract is contained in the appendices.

What do you plan to do during the next reporting period to accomplish the goals?

- Work on Major task 2 is expected to be complete by the next reporting period. This includes the finalized manufactured prototype and external compression belt design iterations used for the animal studies. Non-compressible hemorrhage studies with comparison to REBOA are nearly complete for this task. One or more abstracts are planned to be submitted to the 2021 MHSRS and other national meetings. All data from the animal experiments are being processed for analysis and a draft manuscript is in progress for this task. Upon animal study completion the manuscript will be finalized and submitted to a medical journal for publication. Additional manuscript writing in an engineering scientific journal may be submitted as well

- Work on Major task 3 is expected to begin in the next reporting period. The aim of this task is to

test the ability of the GROA device to serve as a bridge to REBOA while staunching severe non-compressible abdominal hemorrhage in a large swine animal model of lethal traumatic shock. Prototyping focus will shift from swine applications and adaptation to human prototyping will be explored. Additional industry partners will be sought during this period.

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?

Early device iterations indicated the need for external pressure to be applied in order to prevent deflection of the balloon away from the aorta. The results lead to the development of the external compression system as an adjunct to the GROA prototype. This is actually believed to be advantageous as it may allow for partial occlusion using GROA similar to how "partial" REBOA is now being explored. This may also allow for safer deactivation of GROA in a more staged manner. Lastly, it may decrease the variation in performance if only a balloon is used.

What was the impact on other disciplines?

Nothing to report

What was the impact on technology transfer?

- Provisional patent application. GASTROESOPHEGEAL AORTIC OCCLUSION DEVICE AND METHOD. Application filed on August 19 2019. Application has not been published yet. We believe the new informed balloon design as well as the external pressure device components will lead to improved intellectual property protection making it more attractive for commercialization.
- A full patent application has been filed. It is a PCT patent application # PCT/US2020/046796 which allows entry into most countries, globally. Filing date: August 18, 2020. Publication is pending.
- Precision Trauma LLC, a new University of Michigan startup company, has taken an option to license GROA.

What was the impact on society beyond science and technology?

The short-term impact of this work is the successful development of prototypes capable of providing comparable Zone II aortic occlusive performance, physiologic tolerance, and survival in a large swine model of hemorrhage. This was followed by the recent pilot demonstration of the devices ability to staunch lethal uncontrolled hemorrhage. Potential for tandem use of GROA to REBOA mimicking a scenario for use of GROA in the field setting with replacement with REBOA in higher echelon care settings will also be explored. Knowledge gained through the use of animal and human morphomics and the iterative designs and manufacturing process will immediately inform future manufacturing, safety, and regulatory requirements should the device continue to compare favorably with REBOA in the preclinical studies. In addition, knowledge gained in the preclinical laboratory setting will greatly assist in understanding the physiologic and anatomical tolerances of the device. All information created will assist in moving the device more rapidly through a product development cycle and to prepare it for use in Phase I clinical trials.

The long-term impact of the proposed work is envisioned to be an FDA approved device suitable for the out-of- hospital setting in both the civilian and military setting as well as for Emergency Department/Trauma Center and various Military Role facility use. The work will be used to create a robust and easy to use device capable of staunching uncontrolled intrabdominal and/or pelvic bleeding for both the PFC and pDCR setting. GROA is anticipated to extend the life of the casualty in conjunction with other pDCR measures allowing the casualty to reach a higher echelon of care to provide more definitive hemorrhage control and resuscitation.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change
Nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them
As of March 18th 2020, the COVID-19 epidemic resulted in a temporary ramp-down of all non-critical University functions, which included any research which not directly related to COVID-19. Several employees were placed on temporary voluntary furlough effective May 30, 2020 (Colmenero, Greer) to conserve grant funds. As of June 4, 2020 some limited research activities have resumed under restrictions including social distancing and PPE use in laboratory spaces. As of June 26, 2020 our laboratory has obtained clearance to resume work. As of June 29, 2020 animal ordering and housing of swine is being allowed. As of July 20, 2020, density requirements have been increased which will allow for continuation of animal work and both furloughed staff members have been activated to resume work.
Detailed information regarding our university's research operations are available at https://www.research.umich.edu/covid-19/research-reengagement.
The State of Michigan and the University of Michigan mandated ramp-downs have resulted in unforeseen and uncontrollable circumstances that resulted in a prolonged lag for total data collection for this project. We have filed and been granted a no-cost extension to this project to mitigate the delay in testing. We do not anticipate any further problems or issues, and project to finish the work during the no-cost extension period.

Changes that had a significant impact on expenditures
Nothing to Report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects
Nothing to report

Significant changes in use or care of vertebrate animals
Nothing to report

Significant changes in use of biohazards and/or select agents
Nothing to report

6. PRODUCTS:

- **Publications, conference papers, and presentations**

- **Journal publications.**
  A peer reviewed scientific manuscript has been published in the *Journal of Trauma and Acute Care Surgery.* The article is included in the appendices.

  Full citation: *Tiba, Mohamad, MD, MS, McCracken, Brendan, et al. Gastroesophageal resuscitative occlusion of the aorta: Physiologic tolerance in a swine model of hemorrhagic shock. J. trauma acute care surg. 2020;89(6):1114-1123. doi:10.1097/TA.0000000000002867.*

- **Books or other non-periodical, one-time publications.** Nothing to report

- **Other publications, conference papers and presentations:**
  An abstract was submitted and accepted for presentation/publication at the 2020 MHSRS:

Abstract # MHSRS-20-01454 for Life Saving Interventions for Hemorrhage Control - Physiologic Tolerance of Gastroesophageal Resuscitative Occlusion of the Aorta (GROA) in a Swine Model of Hemorrhagic Shock. The abstract has been attached in the appendices.

- **Website(s) or other Internet site(s)**
  https://mcircc.umich.edu/groa?rq=GROA

- **Technologies or techniques**
  Nothing to report

- **Inventions, patent applications, and/or licenses**

  - Provisional patent application. GASTROESOPHEGEAL AORTIC OCCLUSION DEVICE AND METHOD. Application filed on August 19 2019. Application has not been published yet

  - A full patent application has been filed. It is a PCT patent application # PCT/US2020/046796 which allows entry into most countries, globally. Filing date: August 18, 2020. Publication is pending.

  - Precision Trauma LLC, a new University of Michigan startup company, has taken an option to license GROA.

- **Other Products**
  Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Kevin Ward, MD
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2
Contribution to Project:	Oversight of GROA development, data collection, and analysis
Funding Support:	

Name:	Albert Shih, PhD
Project Role:	Co-I
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Assisting in design of GROA, data collection, and analysis
Funding Support:	

Name:	Jonathan Eliason, MD
Project Role:	Co-I
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Surgical consultation for animal REBOA and GROA animal experiments.
Funding Support:	

Name:	Stewart Wang, MD
Project Role:	Co-I

Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Overseeing morphomics analysis for GROA dimension development
Funding Support:	

Name:	Mohamad Hakam Tiba, MD, MS
Project Role:	Co-I
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	3
Contribution to Project:	Oversight of data collection, animal experimentation and analysis
Funding Support:	

Name:	Denise M Poirier
Project Role:	Secretarial/administrative
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2
Contribution to Project:	Departmental administrative duties
Funding Support:	

Name:	Brendan McCracken, BS
Project Role:	Laboratory Assistant Director
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2
Contribution to Project:	Oversight and lab management, data collection, data analysis
Funding Support:	

Name:	Brandon Cummings, BS
Project Role:	Research Staff
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Data collection, signal processing and data analysis
Funding Support:	

Name:	Carmen Colmenero, BS
Project Role:	Research Staff
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	6
Contribution to Project:	Animal lab duties, data collection, data analysis
Funding Support:	

Name:	Danielle Leander, BS
Project Role:	Research Staff
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	4
Contribution to Project:	Animal lab duties, data collection, data analysis
Funding Support:	

Name:	Nicholas Greer, BS
Project Role:	Research Staff
Researcher Identifier (e.g. ORCID ID):	

Nearest person month worked:	5
Contribution to Project:	Animal lab duties, data collection, data analysis
Funding Support:	

Name:	Dian-Ru Li
Project Role:	Research Staff
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Device design: Technical design and Fabrication
Funding Support:	

Name:	Ketut Bagus Priambada Putra
Project Role:	Design Engineer
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	5
Contribution to Project:	Device design: Technical design and Fabrication
Funding Support:	

Name:	Brian Ross
Project Role:	Morphomics analysis
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	4
Contribution to Project:	Performed human morphomics analysis for GROA dimension needs
Funding Support:	

Name:	Edward Brown
Project Role:	Research Staff
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Morphomics analysis for GROA dimension development
Funding Support:	

Name:	Sven Holcombe Ph.D.
Project Role:	Research Staff
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2
Contribution to Project:	Morphomics analysis for GROA dimension development
Funding Support:	

Name:	Jonathan Motyka, MS
Project Role:	Research Staff
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Data collection, signal processing and data analysis
Funding Support:	

Name:	Miguel Lora
Project Role:	Research Staff
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	6
Contribution to Project:	Device design: Technical design and Fabrication

Funding Support:	

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
Nothing to report

What other organizations were involved as partners?
Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

QUAD CHARTS:

APPENDICES:

- PI biosketch
- Abstract # MHSRS-20-01454
- Histopathology Report
- Publication: *Gastroesophageal resuscitative occlusion of the aorta: Physiologic tolerance in a swine model of hemorrhagic shock.*
- Quad-Chart

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Ward, Kevin R

eRA COMMONS USER NAME (credential, e.g., agency login): KRWARD

POSITION TITLE: Professor Emergency Medicine and Biomedical Engineering, Executive Director: Michigan Center for Integrative Research in Critical Care

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Louisiana State University (Baton Rouge, LA)	B.S.	08/1985	Physiology-Zoology
Tulane University School of Medicine (New Orleans, LA)	M.D.	06/1989	Medicine
University of Pittsburgh (Pittsburgh, PA)	Residency	06/1992	Emergency Medicine Residency
The Ohio State University (Columbus, OH)	Fellowship	06/1994	Resuscitation Research Fellowship

A. Personal Statement

As a specialist in emergency medicine in treating the critically ill and injured, I have a great appreciation for the constant need to develop new collaborative approaches that produce the next best-in-class innovation for patients, their families and their health care providers. Emergency Medicine represents an ideal intersection clinical discipline to help develop and lead new clinical and research paradigms that impact the critically ill and injured. In this regard there is a tremendous unmet need to develop approaches in critical care team science that empower innovation allowing for the right care at the right time by the right individuals. I have lamented the lack of new technology that can be used to save lives with this approach. Integrative team science drawing from multiple medical, engineering, and information science disciplines became the new model for my approach, leading me to really understand what innovation was and how it should be executed. As Executive Director of the Michigan Center for Integrative Research in Critical Care (MCIRCC) and the architect and former Executive Director of a new Medical School-wide Innovation program called Fast Forward Medical Innovation, I have a solid track record in developing and leveraging multi and interdisciplinary teams of scientists to solve complex clinical problems in emergency, trauma, and critical care. I have successfully developed monitors for measuring tissue oxygenation, volume status, coagulation monitoring, redox monitoring, image and physiologic signal analysis, breath analysis and other physiologic parameters leading teams of engineers, basic scientists and clinicians bridging the translation gap. My expertise in the areas of innovation, emergency medicine, critical care, and interdisciplinary collaboration make me well suited to participate in efforts to develop new point of care technologies for, trauma, sepsis and other states of inflammation.

B. Positions and Honors

Positions and Employment

1994-1998: Senior Staff Physician and Physician Scientist Henry Ford Health System, Detroit, MI
1999-2003: Assistant Professor of Emergency Medicine and Director of Research VCU
2002-2010: Member VCU Office of Research Subjects Protection: Human Institutional Review Board:
2003-2008: Member U.S. Army Combat Casualty Care Program Task Area: Remote Triage
2004-2012: VCU Medical Site Director: Special Operations Combat Medic Training Program: U.S. Army Joint Special Operations Medical Training Center

2010-2012: Professor and Associate Chair: Department of Emergency Medicine: VCU
2004-2012: Director: VCU Reanimation Engineering Science Center (VCURES)
2010-12 Professor of Emergency Medicine and Physiology and Biochemistry
2012-Present: Professor, Department of Emergency Medicine: University of Michigan
2012-Present: Executive Director: Michigan Center for Integrative Research in Critical Care
2013-2018: Executive Director: Fast Forward Medical Innovation: University of Michigan Medical School
2013-2015: Oversight Committee: Coulter Translational Research Partnership
2017-Present Professor Biomedical Engineering: University of Michigan

Other Experience and Professional Memberships

1990-Present: Society of Critical Care Medicine;
1994-Present: Fellow and Founding Member America Academy of Emergency Medicine;
1994-present: Fellow American College of Emergency Physicians
2000- Present: Shock Society; Editorial Board: Resuscitation: Editorial Board: Shock. Manuscript reviewer for Annals of Emergency Medicine, Academic Emergency Medicine; American Journal of Emergency Medicine, Critical Care Medicine, Critical Care, Intensive Care Medicine, Executive Committee: Traumatic Hemostasis and Oxygenation Research (THOR) Network.

Selected Honors or Awards:

1992: Peter Safar Award for Excellence in Graduate Research: U of Pittsburgh
1992&94: Emergency Medicine Foundation Research Fellowship Award;
1996&97: Educator of the Year Award: Department Emergency Medicine, Henry Ford Hospital
1998: Henry Ford Health System New Clinical Investigator Award
2000: Society for Academic Emergency Medicine Young Investigator Award;
2003: Outstanding Achievement in Research VCU School of Medicine. .
2008: DoD Advanced Technologies Applications in Combat Casualty Care Award for Excellence
2010: VCU Innovator of the Year (Inventor of the Year) Award.
2012: Department of the Army Certificate for Patriotic Civilian Service
2013: Louisiana State University Alumni Hall of Distinction.
2017: Innovation and Commercialization Award: University of Michigan Medical School

C. Contribution to Science

1. Moving the Intensive Care Unit Far Forward: Death or survival from a sudden episode of critical illness and injury may be determined in minutes. Determining the severity of the critical state cannot be done with the physical exam and routine use of invasive monitoring has severe limitations. Being on the front lines of in the Emergency Department, I have led teams to develop noninvasive equivalents of technologies ranging from resonance Raman spectroscopy to impedance as a means to interrogate tissue and the cardiovascular system that is equivalent to invasive technologies used in the intensive care unit. These technologies are now being commercially transitioned and are entering trials for regulatory approval.

a. **Ward KR**, Tiba MH, Draucker GT, Proffitt EK, Barbee RW, Gunnerson KJ, Reynolds PS, Spiess BD: A novel noninvasive impedance-based technique for central venous pressure measurement. Shock 2010;33:269-273. PMID 19487978
b. Tiba MH, Draucker DT, Barbee RW, Terner J, Torres IF, Romfh P, Vakshoori D, **Ward KR**. Tissue oxygenation monitoring using resonance Raman spectroscopy during hemorrhage. J. Trauma and Acute Care Surg 2014;76:402-408. PMID 24378619
c. Tiba MH, Belmont B, Heung M, Theyyunni N, Huang RD, Fung CM, Pennington AJ, Cummings BC, Draucker GT, Shih AJ, **Ward KR**. Dynamic limb impedance and inferior vena cava ultrasound in patients undergoing hemodialysis**.** ASAIO J. 2016;62:463–469. PMID: 26919184
d. Tiba MH, McCraken B, Ansari S, Belle A, Cummings BC, Rajajee V, Patil PG, Alam HB, **Ward KR:** Novel noninvasive method of cerebrovascular blood volume assessment using brain bioimpedance. J Neurotrauma 2017: 15;34(22):3809-3096: PMID 28657491 .

2. Hemostasis, Coagulation, and Metabolic Monitoring: One of the greatest challenges in caring for the victim of trauma and shock is achieving hemostasis and controlling some of the overriding factors which

dictate the function of these integrated systems. Failure to approach the system as integrated has stunted our ability to develop new innovations, which may be lifesaving. New technologies require an understanding of a combination of materials science, biochemical function, and knowledge of the care process allowing for the development of new means to both monitor and treat. I have developed integrated teams which are developing new hemostatic materials, new insights into how the coagulation system functions, and new measures such as whole blood redox potential which may will provide critical insights in the metabolic drivers of coagulation and hemostasis.

a. White NJ, Wang Y, Fu X, Cardenas JC, Martin EJ, Brophy DF, Wade CE, Wang X, St John AE, Lim EB, Stern SA, **Ward KR**, López JA, Chung D. Post-translational modification of fibrinogen is associated with coagulopathy after traumatic injury Free Radic Biol Med. 2016 Apr 20;96:181-189 PMID: 27105953
b. Li Z, Li X, McCraken B, Shao Y, **Ward K**, Fu J: A Miniaturized Hemoretractometer for Blood Clot Retraction Testing. Small 2016 (Epub ahead of print). PMID 27248117.
c. Daniels RC, Jun H, Tiba MH, McCracken B, Herrera-Fierro P, Collinson M, **Ward KR**: Whole blood redox potential correlates with progressive accumulation of oxygen debt and acts as a marker of resuscitation in a swine hemorrhagic shock model. Shock 2018;49(3): 345-351. PMID 28658006
d. Li Y, **Ward KR**, Burns MA: Viscosity measurement using microfluidic droplet length. Anal Chem 2017 Apr 4;89(7):3996-400. PMID 28240541

3. <u>Medical Innovation, Entrepreneurship, Team Science, and Mentoring:</u> Sadly in the last 30 years, there has been very little innovation in Emergency and Critical Care Medicine resulting in new life-saving technologies. One of the reasons for this is a lack of inter and multidisciplinary collaboration especially outside the immediate scope of medicine. Creating such an approach requires a cultural shift and great patience since the language of disparate disciplines such as medicine, engineering and information science are significantly different. Innovation then becomes less about the ah-ha moment and increasingly more about a strategic and systematic approach to processes that allow for the rapid progression and iteration of the science that promotes a true solution. I have engaged in such approaches for the last 16 years at two large universities (Virginia Commonwealth University and now at the University of Michigan as the Executive Director of the Michigan Center for Integrative Research in Critical Care. At each of these institutions I developed critical care innovation programs In these programs I have had an opportunity to mentor over 60 students ranging from undergraduates and graduate students (MS and PhD) to post-doctoral, medical students, and residents. I have also mentored a great many junior faculty. A significant number of these mentoring relationships revolved around projects that intersected translational science, the development of intellectual property, and industry transition. The combination of the above experiences resulted in my appointment as the inaugural Executive Director of the University of Michigan Medical School's acclaimed Fast Forward Medical Innovation program. This program was developed to provide strategic innovation assets, which greatly expedite the movement of science into product development and commercialization. I am a serial innovator and entrepreneur in the field of critical care with over 60 issued and pending patents, 10 products licensed to industry, and 4 companies launched. My work has resulted in being awarded the Innovator of the Year at Virginia Commonwealth University, the University of Michigan Medical School and the Department of Defense for innovative work in hemostasis.
    a. Servoss JM, Chang C, Fay J, **Ward K**: The early tech development course: Experiential commercialization education for the medical academician. Acad Med 2017;92:506-510. PMID 28351064.
    b. Servoss JM, Chang C, Olson D, **Ward** KR, Mulholland MW, Cohen MC: The Surgery innovation & entrepreneurship development program (SIEDP): An experiential learning program for surgery faculty to ideate and implement innovations in healthcare. J Surg Educ. 2017; 75(4):935-941 PMID:28989009
    c. Servoss J, Chang C, Fay J, Lota KS, Mashour GA, **Ward** KR: *fast*PACE Train-the-Trainer*:* A scalable new educational program to accelerate training in biomedical innovation, entrepreneurship, and commercialization. Journal of Clinical and Translational Science 2017 Oct;1(5):271-277. PMID:29707247

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/kevinr..ward.1/bibliograpahy/48065982/public/?sort=date&direction= ascending

D. Research Support

Ongoing Research Support

1R21HL139156-01 Fan(PI)12/15/17-11/30/19
Sponsor:NIH
Rapid breath analysis for acute respiratory distress syndrome diagnostics
Description: Project to create and test a 3-D microgas chromatography unit to diagnose and track ARDS in humans
Role: Co-Investigator

NCAI-17-7-APP-UMICH Fan(PI)07/01/2017-06/30/2018
Sponsor: NIH/NCAI
Micro Gas Chromatography and Breathomics for Acute Point-of-Care Diagnostics of Acute Lung Injury
Description: The major goal of this award is to develop and refine a microgas chromatography device the diagnose and follow the trajectory of the acute respiratory distress syndrome.
Role: Co-Investigator

DM160299 Ward (PI) 01/30/18-12/30/21
Sponsor: DoD
Gastroesophageal Resuscitative Occlusion of the Aorta (GROA)
Description: This project will develop a minimally invasive device and method capable of occluding the descending aorta from the stomach for control of massive abdominal hemorrhage.
Role: Principal Investigator

DM160294 Ward (PI) 01/30/18-12/30/21
Sponsor DoD
Development and Testing of New Noninvasive Monitoring Tools for Prolonged Field Care Goal-Directed Therapy
Description: Project clinically test two novel noninvasive sensing technologies to test tissue oxygenation and circulatory volume in critically ill and injured patients.
Role: Principal Investigator

DM160225 Tiba/Ward (Co-PI)07/01/17-06/30/20
Sponsor: DoD
Novel Noninvasive Methods of Intracranial Pressure and Cerebrovascular Autoregulation Assessment: Seeing the Brain Through the Eyes
Description: This project will develop several noninvasive means to evaluate cerebral autoregulation and ICP using bioimpedance and ultrasound technologies.
Role: Co-Principal Investigator:

W81XWH-16-R-BAA1 BA150235: Najarian (PI) 03/01/17-02/26/20
Sponsor: DoD
Title: A Multimodal Integrative Platform for Continuous Monitoring and Decision Support during in Cardiac Patients
Description: This project will develop an innovative, real-time clinical decision support (DSS) platform, including Big Data analytic methods, novel algorithms, and software tools to integrate and analyze disparate sources of continuous and non-continuous patient data
Role: Co-investigator

RFA-HL-16-019: Neumar/Pinsky (PIs) 01/02/17-06/30/20
Sponsor: NIH
Career Development Program in Emergency Care Research (K12)

Description: This K12 provides training to produce the next generation of translational Emergency-Critical Care scholars with an emphasis on integrating biomedical engineering into their research.
Total Cost:
Role: Co-Investigator

Completed Relevant Research Support:

14-PAF03993 Ward (PI) 1/30/14-12/31/16
Sponsor: William Davidson
Foundation Title: Fast Forward
Medical Innovation
Description: This grant provides important funding to supplement the University of Michigan's new Fast Forward Medical Innovation initiative allowing investment in development of early stage technologies to accelerate their commercialization as well as develop important entrepreneurial educational initiatives Role: PI

14-PAF03993 Ward(PI) 1/30/14-12/31/16
Sponsor: William Davidson
Foundation Title: Fast Forward
Medical Innovation
Description: This grant provides important funding to supplement the University of Michigan's new FastForward Medical Innovation initiative allowing investment in development of early stage technologies to accelerate their commercialization as well as develop important educational initiatives around entrepreneurialism.
Role: PI

15-PAF03360 Ward/Tiba (PI) 1/30/15-7/30/15
Sponsor: Baxter Healthcare Corporation
Title: Comparison of Respiratory Induced Limb Bioimpedance with Inferior Vena Cava Diameter Changes to Assess Intravascular Volume
Description: This grant will assess the ability of limb impedance as an accurate surrogate of functional intravascular volume in the management of dialysis and critical care patients.
Role: PI

W81XW H-1120089 Ward (PI) 01/10/11-01/09/13
Sponsor: Department of Defense: US Army Medical Research and Materiel Command Title: Defining Platelet Function During Polytrauma.
Description: This project will characterize longitudinal platelet function in human victims of polytrauma Role: PI

ONR N000140710526 Ward (PI) 01/29/07-01/10/2014
Sponsor: Department of Defense: Office of Naval Research
Title: Novel Acute Rescue Strategies using Non-pulmonary Oxygenation
Description: This project explores the creation of special compounds and delivery methods that provide tissue oxygenation via nonpulmonary routes.
Role: PI

NSF 0969062 Pidapart i (PI) 08/10-07/13
Sponsor: National Science Foundation
Title: Multiscale Study of the Respiratory Airway Mechanics for Cellular Inflammation
Description: This study utilizes several advanced computation techniques to model multiple levels of acute lung injury.
Total Cost:

Role: Co-PI

H92239-09-003 Ward (PI) 09/09-09/12
Sponsor: Department of Defense: U.S. Army
Title: Preceptor Support Servces at VCU for Joint Special Operations Combat Medic/Special Forces
Course Description: This is a contract to provide clinical training to Special Operations Combat Medics prior to deployment
Role: PI

Abstract: # MHSRS-20-01454

Physiologic Tolerance of Gastroesophageal Resuscitative Occlusion of the Aorta (GROA) in a Swine Model of Hemorrhagic Shock.

Brendan M. McCracken[1,2], Mohamad Hakam Tiba[1,2], Carmen I. Colmenero[1,2], Jeffery S. Plott[2,4], Danielle C. Leander[1,2], Nicholas L. Greer[1,2], Stewart Wang[2,3], Albert Shih[2,4], Jonathan Eliason[2,5], and Kevin R. Ward[1,2,3]
1. Emergency Medicine, 2. Michigan Center for Integrative Research in Critical Care (MCIRCC) 3. Biomedical Engineering, 4. Mechanical Engineering 5. Department of Surgery

Introduction: Hemorrhage continues to be the leading cause of preventable death due to trauma. Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) has recently been characterized and shown to be an effective counter measure against non-compressible torso hemorrhage, however this technique is limited in its application outside of trauma centers or in the pre-hospital environment. Aortic occlusion may be achieved less-invasively by a novel device and technique designated Gastroesophageal Resuscitative Occlusion of the Aorta (GROA). In this study, we aimed to characterize the physiological tolerance and hemodynamic effects of a prototype GROA device and compare it to REBOA and controls in a model of severe hemorrhagic shock and resuscitation. We hypothesized that aortic occlusion using the GROA device would produce a similar physiological response to REBOA.

Methods: Male Yorkshire swine (n=46) were anesthetized and surgically instrumented for data collection. A 35% controlled arterial hemorrhage was performed. Animals were assigned to 30, 60 or 90-minute interventions of GROA, REBOA, or control. Upon completion of the intervention period occlusion devices were deactivated and autologous whole blood and crystalloid fluid resuscitation was initiated. Animals were monitored for four hours following resuscitation and euthanized at the end of the monitoring period.

Results: All animals in all groups survived the duration of their intervention periods. Survival through resuscitation phase in GROA, REBOA and control groups were similar in the 30 and 60-minute intervention groups. The 90-minute intervention groups exhibited deleterious effects upon device deactivation and reperfusion; no REBOA animals survived and only 2 GROA animals survived. MAP in GROA and REBOA animals increased to average(sd) of 98(32.55) mmHg and 122(24.79) mmHg, respectively following intervention. Lactate was elevated across all GROA and REBOA groups relative to controls during and following intervention but cleared in the 30 and 60-minute groups. Airway pressure in the all GROA intervention groups was elevated to 31(3.1) cmH2O but returned to baseline following deactivation. Post-mortem histological examination of the gastric mucosa revealed mild to moderate inflammation across the GROA groups.

Conclusion: In this study, the hemodynamic effects and physiological tolerance of GROA were similar to REBOA. The GROA device was capable of achieving full, high zone-II aortic occlusion and may be able to serve as an effective method of temporary aortic impingement, capable of staunching life threatening non-compressible torso hemorrhage.

Learning Objective 1: Describe the unmet need for field-deployable and early phase treatment strategies of non-compressible torso hemorrhage.
Learning Objective 2: Discuss the concept of aortic occlusion as a treatment strategy for non-compressible torso hemorrhage, and current strategies of aortic occlusion such as REBOA and surgical hemostasis.
Learning Objective 3: Analyze the physiological tolerance of gastroesophageal resuscitative occlusion of the aorta (GROA) compared to REBOA as treatment strategy for non-compressible torso hemorrhage.

University of Michigan
Medical School

Request Date: 1/21/2021
Pathologist: MJH
Returned Date: 1/22/2021

HISTOPATHOLOGY REPORT

ULAM In Vivo Animal Core
North Campus Research Complex
2800 Plymouth Road B36/G157
Ann Arbor, MI 48109-0614
Lab: (734) 647-0654
Email: ULAM-IVAC@umich.edu

Case number: 21M010
Date of necropsy: NA
Species: SUS
PI: Ward/Tiba
Contact: Colmenero

History
Samples of stomach and aorta from three pigs (20201216, 20200915, and 20200827) were submitted for gross and histopathologic examination.

RESULTS (Gross examination)
20200827-GROA: There was multifocal reddening along the serosal surface of the greater curvature of the stomach, involving the fundus and portions of the cardia.
20200915-REBOA: Moderate to severe, diffuse reddening of the mucosa was observed.
20201216-Control: No gross lesions observed.

RESULTS (Histopathology)
20200827-GROA: In sections of fundus, there was diffuse expansion of the superficial mucosa with edema, with multifocal zones of superficial mucosal necrosis associated with underlying degeneration of the deeper mucosal layers. Along the serosal surface of the fundus, there was a moderate inflammatory infiltrate composed predominantly of neutrophils and eosinophils admixed with fibrin. The adjacent submucosa was moderately expanded with edema and scattered inflammatory cells, often arranged perivascularly. Sections of cardia were similarly affected with submucosal edema and inflammation, and focal superficial mucosal necrosis, and the mucosa was expanded by a moderate mixed inflammatory infiltrate of lymphocytes, macrophages, and neutrophils. There were no significant changes in sections of pylorus or aorta.
20200915-REBOA: No significant lesions observed in the stomach or aorta.
20201216-Control: No significant lesions observed in the stomach or aorta.

DISCUSSION:
The purpose of this evaluation was to evaluate the submitted stomach and aortic samples grossly and histologically for evidence of pathology. The only significant findings were in animal 20200827, which were characterized by multifocal necrosis of the superficial mucosa, submucosal edema, and inflammatory infiltrates throughout, including along the serosal surface. The necrosis observed was suggestive of an ischemic change, but was fairly mild; the underlying mucosa appeared disrupted, with individualization of cells and significant submucosal edema and evidence of reactive vasculature associated with neutrophils and eosinophils. The serosal changes (fibrin, inflammatory cells) suggest irritation or injury of this site, possibly from local manipulation or abdominal surgical procedure. The other samples did not show significant evidence of injury.

Pathologist: Mark J. Hoenerhoff, DVM, PhD, DACVP

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This report is intended for rapid communication of histopathology results to the submitting researcher. If portions of this report are subsequently utilized in a publication or presentation, please communicate this to the pathologist so that the draft may be reviewed to ensure a narrative appropriate to the particular forum.

Gastroesophageal resuscitative occlusion of the aorta: Physiologic tolerance in a swine model of hemorrhagic shock

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BACKGROUND: Resuscitative endovascular balloon occlusion of the aorta (REBOA) has been shown to be effective for management of noncompressible torso hemorrhage. However, this technique requires arterial cannulation, which can be time-consuming and not amendable to placement in austere environments. We present a novel, less invasive aortic occlusion device and technique designated gastroesophageal resuscitative occlusion of the aorta (GROA). In this study, we aimed to characterize the physiological tolerance and hemodynamic effects of a prototype GROA device in a model of severe hemorrhagic shock and resuscitation and compare with REBOA.

METHODS: Swine (N = 47) were surgically instrumented for data collection. A 35% controlled arterial hemorrhage was followed by randomizing animals to 30-minute, 60-minute, or 90-minute interventions of GROA, REBOA, or control. Following intervention, devices were deactivated, and animals received whole blood and crystalloid resuscitation. Animals were monitored for an additional 4 hours.

RESULTS: All animals except one GROA 90-minute application survived the duration of their intervention periods. Survival through resuscitation phase in GROA, REBOA, and control groups was similar in the 30-minute and 60-minute groups. The 90-minute occlusion groups exhibited deleterious effects upon device deactivation and reperfusion with two GROA animals surviving and no REBOA animals surviving. Mean (SD) arterial pressure in GROA and REBOA animals increased across all groups to 98 (31.50) mm Hg and 122 (24.79) mm Hg, respectively, following intervention. Lactate was elevated across all GROA and REBOA groups relative to controls during intervention but cleared by 4 hours in the 30-minute and 60-minute groups. Postmortem histological examination of the gastric mucosa revealed mild to moderate inflammation across all GROA groups.

CONCLUSION: In this study, the hemodynamic effects and physiological tolerance of GROA was similar to REBOA. The GROA device was capable of achieving high zone II full aortic occlusion and may be able to serve as an effective method of aortic impingement. (*J Trauma Acute Care Surg.* 2020;89: 1114–1123.

KEY WORDS: Shock; noncompressible hemorrhage; aorta; resuscitation; swine.

Hemorrhage is responsible for more than 90% of all potentially survivable military combat casualties and up to 40% of civilian trauma deaths.[1–3] Despite recent advancements in the treatment of extremity and junctional hemorrhage,[4–7] treatment of noncompressible torso hemorrhage (NCTH) including deep pelvic hemorrhage continues to pose serious challenges. These challenges are exacerbated in the prehospital and prolonged field care settings where almost 9 of 10 hemorrhage-related deaths occur.[2,8] Casualties with significant NCTH who manage to reach a first echelon of care often present in extremis with no physiologic reserve where immediate resuscitative thoracotomy and aortic cross-clamping are used but for which poor outcomes exists.[9] These dire outcomes for patients with NCTH highlight the urgent need to further explore options for rapid control of hemorrhage in prehospital and field care environments.

Aortic occlusion is an effective temporary countermeasure against NCTH[8]; however, many implementation barriers exist for its timely application. Beyond thoracotomy with aortic cross-clamping, resuscitative endovascular balloon occlusion of the aorta (REBOA) is the only currently available method for such occlusion.[10] Since its emergence, the implementation of REBOA is gaining popularity[11–15]; however, its deployment to field or point of injury care may be logistically problematic. Current standards require REBOA to be implemented by or in conjunction with acute care surgeons,[16] and vascular access can be time-consuming and requires surgical or ultrasound guided placement. In far-forward treatment scenarios, surgical capabilities may be limited, and portable imaging equipment may not be available. These challenges continue to be a barrier to the use of aortic occlusion for NCTH in austere environments (including civilian prehospital use), necessitating the exploration of alternatives.

The close anatomical relationship of the distal esophagus, proximal stomach, descending aorta, and thoracic vertebrae suggests that the aorta may be impinged and occluded between the posterior stomach and anterior thoracic vertebrae by a device inserted into the stomach. We term this approach gastroesophageal resuscitative occlusion of the aorta (GROA) and developed a prototype device and approach using GROA to produce

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a zone II aortic occlusion[17] (celiac trunk to the most caudal renal artery).

This feasibility study evaluated a prototype GROA device for its ability to achieve high zone II aortic occlusion in a swine model of hemorrhagic shock, characterized the physiological effects and tolerance of the device during 30 minutes, 60 minutes, and 90 minutes of occlusion, and compared it with REBOA and controls.

MATERIALS AND METHODS

This study adhered to the principles stated in the *Guide for the Care and Use of Laboratory Animals*[18] and was approved by the Institutional Animal Care and Use Committee, and Animal Care and Use Review Office of the United States Army Medical Research and Development Command.

Device Description

The GROA device (Fig. 1) consists of four components: a gastroesophageal tube, a balloon, an air pump/pressure gauge assembly, and an external compression system. The gastroesophageal tube includes three lumens for suction and evacuation of gastric contents, air vent to avoid vacuum/pneumatic tension in the stomach, and balloon inflation and deflation. The balloon inflates to an ellipsoid shape with a diameter of approximately 17 cm reaching a total volume of approximately 1,600 cm^3 when fully inflated, which is less than an adult stomach volume capacity of 2,000 cm^3 to 4,000 cm^3, providing the structure necessary to occlude the aorta when downward external pressure is applied to the epigastric area. The dimensions of the balloon and tube were based on morphomic analysis of human adult abdominal and chest CT scans in a manner similar to that used to develop recent REBOA technology.[19] The air pump/pressure gauge assembly allows for controlled balloon inflation/deflation and visual feedback on the pressure of the balloon. The external compression system consists of a back plate and an abdominal plate. When activated, this system prevents lateral and anterior deflection of the balloon, keeping the balloon over the aorta. The back plate serves as an anchor for the abdominal plate, which is secured in place by nylon straps. The system can be adjusted to apply controlled posterior-directed pressure. The system is constructed to prevent the application of circumferential pressure around the abdomen as would occur with the use of products such as the abdominal aortic junctional tourniquet.

Preparation

Male Yorkshire-mix swine were fasted overnight with ad libitum access to water. Anesthesia was induced with a combination of tiletamine/zolazepam (4–6 mg/kg) and xylazine (2 mg/kg) followed by 1% to 2% isoflurane delivered in 30% to 40% O_2 for the duration of the experiment. Animals were intubated using a 7.5-mm endotracheal tube and ventilated with a tidal volume of 7 to 8 mL/kg. Respiratory rate was adjusted to achieve an end-tidal CO_2 ($PetCO_2$) between 35 mm Hg and 45 mm Hg. Temperature was maintained between 37.0°C and 39.0°C during instrumentation using a temperature blanket (Blanketrol; Sub-Zero Medical, Cincinnati, OH). Electrocardiogram was monitored using a standard three-lead configuration (SurgiVet Advisor; Smiths Medical, Dublin, OH).

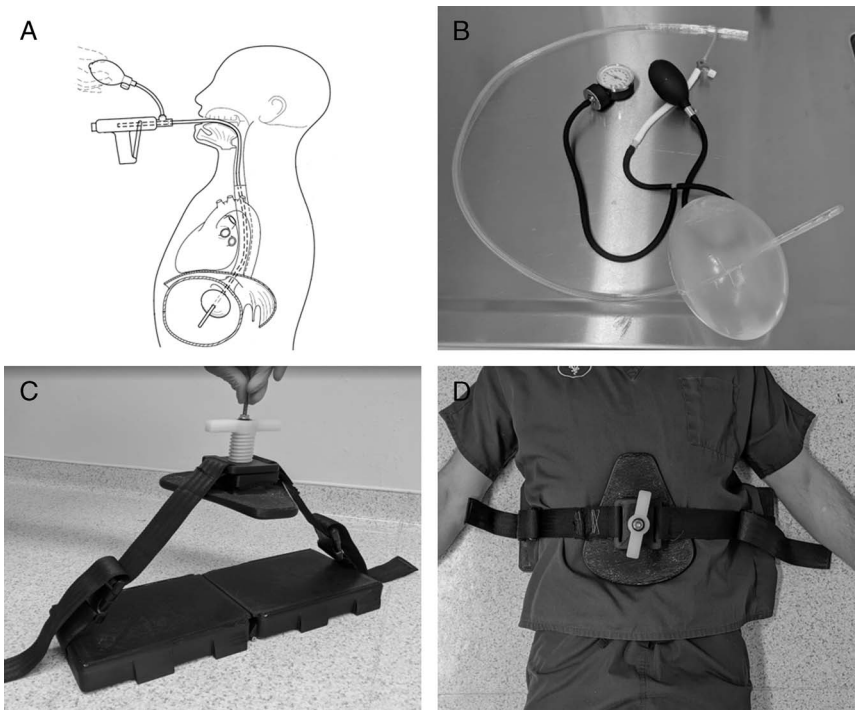

Figure 1. (*A*) Schematic view of GROA device inserted into stomach through the esophagus and inflated. (*B*) The GROA prototype device composed of a gastroesophageal tube, a balloon (inflated), and an air pump/pressure gauge assembly. (*C*) External compression system including back plate, abdominal plate, and tourniquet. (*D*) Anterior view of external compression system applied to a person.

Instrumentation

The right carotid artery was cannulated for measurements of mean arterial pressure (MAP) and collection of blood samples. The left and right external jugulars were cannulated for blood and fluid resuscitation, and for placement of a pulmonary artery catheter (CCOmbo V, 8 F; Edwards Lifesciences, Irvine, CA) for monitoring central venous pressure (CVP) and pulmonary artery pressure (PAP). The right femoral artery was cannulated with a 9-F introducer (Arrow; Teleflex, Morrisville, NC) for controlled arterial hemorrhage and REBOA access; the left was cannulated for measurement of femoral arterial pressure. ER-REBOA catheters (Prytime Medical, Boerne, TX) or GROA devices were placed (but not activated) at the conclusion of instrumentation, and baseline measurements and blood samples were obtained.

Study Design

Device effectiveness and physiologic tolerance were tested by adapting the model described by Markov et al.[20] Animals were randomly assigned REBOA, GROA, or no intervention (control), as well as an intervention duration of 30 minutes, 60 minutes, or 90 minutes (Supplemental Digital Content 1, Supplementary Fig. 1, http://links.lww.com/TA/B731). A 30-minute hemorrhage period was initiated where approximately 35% total blood volume was removed representing class III and IV shock, mimicking an out-of-hospital preintervention period. A total of 17.5% estimated blood volume was removed in 7 minutes and 17.5% over the following 13 minutes. The rate was then reduced to 0.15 mL/kg per minute for 10 minutes to maintain hypotension and minimize hemodynamic compensation. Shed blood was collected in citrate phosphate dextrose bags (Fenwal Inc., Lake Zurich, IL), and 2 U (900 mL) was saved for resuscitation.

Intervention (30 Minutes, 60 Minutes, or 90 Minutes)

Immediately following hemorrhage, interventions were deployed. In the control groups, there was no intervention, and animals were observed for the duration of the assigned intervention period (30–90 minutes). In the REBOA groups, the balloon was inflated using 5 to 7 mL of saline. In the GROA groups, the balloon was inflated with air to a pressure of 60 to 80 mm Hg (approximate volume of 1600 cm^3). Controlled external pressure was applied using the abdominal plate assembly until aortic occlusion was achieved. Occlusion in GROA and REBOA groups was verified by loss of femoral artery waveform. Example occlusion data are shown in Figure 4. After aortic occlusion, animals were monitored for the duration of their intervention periods.

Resuscitation

Resuscitation was initiated following the intervention phase similar to that described by Markov et al.[20] Resuscitation included shed blood transfusion (900 mL), followed by intravenous lactated Ringer's solution infusion. Intravenous calcium chloride (100 mg/mL Ca^{2+}) was administered to maintain Ca^{2+} levels 1.0 mmol/L to 1.3 mmol/L. In the control groups, whole blood resuscitation was initiated at the end of the intervention period. In the aortic occlusion groups, whole blood administration started 10-minutes before the end of the intervention period to raise MAP and mitigate acute hemodynamic decompensation associated with reperfusion injury. At the end of intervention for the aortic occlusion groups, devices were slowly released over an average period of 7 minutes to 10 minutes. Blood pressure was titrated to a target MAP of >60 mm Hg using intravenous lactated Ringer's supplemented by administration of norepinephrine (4 mg) in 5% dextrose in NaCl 0.9% (500 mL), titrated to effect. Postresuscitation monitoring and data collection continued for 4 hours while blood samples were collected at designated points. All animals were euthanized with potassium chloride under isoflurane at the completion of the monitoring period.

Data Collection

Measurements of MAP, femoral arterial pressure, CVP, PAP, peak airway pressure, heart rate, temperature, mixed venous oxygen saturation (SvO_2), $PetCO_2$, and ECG were recorded continuously (MP160; Biopac Systems Inc., Goleta, CA). Arterial and mixed venous blood gases were analyzed every 30 minutes (ABL800flex; Radiometer America Inc., Brea, CA). Complete blood count (Vetscan HM5; Abaxis, Inc., Union City, CA) and thromboelastography (TEG 5000; Haemonetics Corp., Braintree, MA) samples were obtained at the end of hemorrhage period, end of intervention, end of resuscitation, and every 2 hours thereafter. Comprehensive diagnostic chemistry profiles (VetScan; Abaxis Inc., Union City, CA) were sampled at baseline and end of experiment for all groups. Following euthanasia, stomach and aortic samples were harvested for histological analysis by a blinded veterinary pathologist.

Statistical Analysis

Descriptive statistics are presented as means and SDs. Repeated measures analysis of variance repeated measures analysis of variance, one-way analysis of variance with Tukey's correction for multiple comparisons, and *t* test were used as applicable. A level of significance was considered at $\alpha = 0.05$. Data were analyzed using MATLAB R2017a (The MathWorks, Inc., Natick, MA) and PRISM 8 (GraphPad Software, San Diego, CA).

RESULTS

Forty-eight animals were used in this study. One animal was excluded because of early death during hemorrhage after removal of 20% of blood volume. Baseline characteristics of remaining 47 animals are outlined in Table 1.

Survival

All animals except one GROA 90-minute application survived the duration of their intervention periods. The overall survival for each group is described in Table 2. For animals that died following intervention, survival time ranged from 2 minutes to 32 minutes following resuscitation.

Mean Arterial Pressure

Mean arterial pressure data for all groups are presented in Figure 2. All animals showed a significant reduction in MAP from baseline with an average (SD) of 85.2 (11.50) mm Hg down to 35.0 (5.41) mm Hg ($p < 0.0001$) following the controlled hemorrhage with no intergroup differences at baseline or end of hemorrhage. Full aortic occlusion was achieved in all animals in both the GROA and REBOA groups, indicated by the loss of pulsatile waveform in the femoral artery. All

TABLE 1. Baseline Hemodynamic Characteristics and Hemorrhage Volume by Group

	30-min Intervention			60-min Intervention			90-min Intervention		
	Control	GROA	REBOA	Control	GROA	REBOA	Control	GROA	REBOA
n	6	5	5	5	5	5	5	6	5
Weight, kg	53 (1.7)	54 (1.1)	49 (5.8)	51 (2.9)	53 (3.6)	53 (2.3)	52 (3.9)	56 (5.9)	49 (4.8)
Hemorrhage volume, %	35 (2.0)	34 (3.0)	35 (1.0)	35 (2.0)	35 (3.0)	35 (3.0)	39 (4.7)	35 (1.4)	40 (7.1)
MAP, mm Hg	80 (7.5)	84 (7.6)	88 (8.1)	97 (9.4)	81 (10.4)	86 (10.5)	82 (15.4)	81 (16.1)	85 (12.5)
Heart rate, bpm	85 (9.2)	84 (11.6)	92 (0.7)	103 (28.7)	85 (2.3)	77 (4.4)	102 (28.1)	90 (9.7)	82 (4.7)
Temperature, °C	36.9 (0.71)	37.2 (0.47)	37.2 (0.44)	37.0 (0.61)	37.7 (0.79)	37.3 (0.43)	36.8 (0.69)	37.5 (0.42)*	36.5 (0.37)
Lactate, mEq/L	1.3 (0.31)	1.3 (0.57)	1.4 (0.64)	1.8 (0.80)	1.4 (0.67)	2.7 (1.46)	2.5 (1.19)	1.8 (0.75)	1.6 (0.52)
$SmvO_2$, %	70.6 (7.39)	69.1 (7.10)	69.6 (5.56)	69.4 (8.07)	71.0 (5.71)	70.7 (5.77)	75.9 (6.78)	68.9 (7.44)	71.9 (4.59)
$PetCO_2$, mm Hg	38.0 (2.22)	38.0 (2.87)	37.8 (1.72)	41.5 (5.15)	38.9 (2.04)	39.8 (2.67)	40.6 (4.64)	39.4 (1.99)	36.6 (8.67)

Data are presented as averages (SD). Statistical significance was set at $\alpha < 0.05$.
*Denotes statistically significant difference between GROA and REBOA.
bpm, Beats per minute; $SmvO_2$, mixed venous oxygen saturation (%); $PetCO_2$, end-tidal CO_2 (mm Hg).

REBOA and GROA animals experienced a considerable increase in MAP relative to controls during intervention. Mean arterial pressure in GROA and REBOA animals increased to 98 (31.50) mm Hg and 122 (24.79) mm Hg, respectively, 15 minutes into the intervention period. At the end of intervention period, MAP ranged from 61 mm Hg to 90 mm Hg in the GROA groups and 76 mm Hg to 120 mm Hg in the REBOA groups. Animals that survived 4 hours postresuscitation, on average, maintained MAP more than 60 mm Hg with the exception of the two surviving GROA 90-minute occlusion animals where MAP averaged 53 mm Hg.

Lactate

Arterial lactate levels are presented in Figure 2. In all GROA and REBOA groups, lactate increased relative to controls gaining statistical significance by 30 minutes of intervention to 7.4 (1.8) mEq/L, 7.1 (1.6) mEq/L, and 4.1 (1.8) mEq/L, respectively ($p = <0.0001$). There was no significant difference between GROA and REBOA groups. Lactate levels peaked in all surviving intervention groups 30-minute postresuscitation to levels of 8.1 (1.43) mEq/L REBOA-30, 9.5 (2.37) mEq/L GROA-30, 12.7 (1.49) mEq/L REBOA-60, 10.6 (4.66) mEq/L GROA-60, and 18 (2) mEq/L GROA-90. The REBOA 90-minute group lactate peaked during resuscitation to 10.7 (2.62) mEq/L. There were no significant differences in lactate between GROA and REBOA groups during the postresuscitation monitoring period. Lactate levels decreased in all REBOA and GROA groups following device deactivation and resuscitation, with the GROA 30-minute and 60-minute groups losing significance compared with baseline by 4 hours postresuscitation. Lactate remained significantly increased in the GROA 90-minute group when compared with the control 90-minute group: 15.7 (4.7) mEq/L and 3.2 (1.80) mEq/L ($p = 0.0024$).

Mixed Venous Oxygen Saturation

SvO_2 is presented in Figure 3. SvO_2 increased following occlusion in both GROA and REBOA groups relative to controls at 30 minutes, to levels of 60.6% (22.90%) and 81.5% (15.31%), versus 42.4% (15.45%), respectively ($p < 0.05$). SvO_2 in the GROA group was significantly lower than in the REBOA group ($p = 0.0078$) at the same period. At 60 minutes of occlusion, SvO_2 in the GROA and control groups was similar: 50.6% (15.88%) versus 50.6% (16.68%), respectively, while REBOA remained significantly increased: 71.0% (21.27%) ($p < 0.05$). No significant differences between GROA, REBOA, or control groups were observed at 90 minutes of intervention. SvO_2 returned and was maintained near baseline levels following resuscitation in all groups except the 90-minute REBOA group in which no animals survived.

End Tidal CO_2

$PetCO_2$ decreased in both GROA and REBOA groups relative to controls following at 30 minutes of occlusion to levels of 25.1 (6.88) mm Hg and 30.3(4.59) mm Hg, versus 37.2(4.41) mm Hg, respectively ($p < 0.05$). $PetCO_2$ in the GROA groups was significantly lower than the REBOA groups ($p = 0.028$) at the same period. This decrease maintained significance for the duration of the intervention periods and then returned to near baseline levels following device deactivation and resuscitation in the 30-minute and 60-minute intervention groups. $PetCO_2$ remained depressed in the two surviving GROA 90-minute animals 31.7 (1.68) mm Hg ($p = 0.0233$) (Fig. 3). Similarly, mean $PaCO_2$ was decreased in the intervention groups relative to controls; however, $PaCO_2$ in GROA and REBOA groups were not different during intervention (Table 2).

Resuscitation Requirements

Crystalloid fluid and norepinephrine requirements during the resuscitation and monitoring period are presented in Table 2. There were no statistical differences in the volume of crystalloids used in the 30-minute and 60-minute intervention groups. The GROA 90-minute group required more crystalloids than the control group, 23.36 (3.84) mL/kg per hour and 7.20 (7.83) mL/kg per hour, respectively ($p = 0.035$). Similarly, there were no statistical differences between norepinephrine administered in the 30-minute and 60-minute intervention groups; however, there was a difference between the GROA 90-minute groups and the control group, 6.53 (9.829) μg/kg per hour and 0.01 (0.017) μg/kg per hour, respectively ($p = 0.0021$).

TABLE 2. Survival Ratios, Resuscitation Requirements, and Organ Function Metrics Reported by Group and Time Point

	30-min Intervention			60-min Intervention			90-min Intervention		
	Control	**GROA**	**REBOA**	**Control**	**GROA**	**REBOA**	**Control**	**GROA**	**REBOA**
Survival									
Ratio	3:6	4:5	5:5	5:5	5:5	4:5	5:5	2:6	0:5
Resuscitation									
Crystalloids: LR									
mL/kg/h	6.1 (1.97)	5.5 (1.14)	3.9 (2.53)	4.5 (2.57)	7.4 (6.62)	5.8 (3.08)	7.2 (7.83)	23.4 (3.84)*	—
Norepinephrine									
mcg/kg/h	0.01 (0.036)	0.39 (0.587)	0.04 (–)	—	2.57 (3.40)	0.85 (1.054)	0.01 (0.017)	6.53 (9.829)*	—
Metrics									
pH									
Baseline	7.42 (0.023)	7.40 (0.019)	7.49 (0.084)	7.38 (0.038)	7.39 (0.036)	7.38 (0.069)	7.45 (0.056)	7.39 (0.051)	7.46 (0.023)
End int	7.42 (0.058)	7.40 (0.070)	7.41 (0.046)	7.35 (0.025)	7.33 (0.075)	7.3 (0.044)	7.38 (0.027)	7.32 (0.080)	7.37 (0.076)
End exp	7.44 (0.046)	7.41 (0.015)	7.44 (0.033)	7.41 (0.022)	7.37 (0.028)	7.37 (0.059)	7.45 (0.013)	7.20 (0.119)*	—
Hb, g/dL									
Baseline	9.3 (1.39)	9.2 (1.57)	10.0 (0.76)	9.7 (1.37)	9.3 (0.29)	9.4 (1.77)	11.0 (0.72)	9.3 (0.66)	10.4 (0.40)
End int	9.1 (1.21)	9.2 (1.80)	10.5 (0.56)	9.6 (1.51)	9.6 (1.15)	9.7 (1.71)	10.8 (1.47)	8.9 (0.86)	10.4 (1.10)
End exp	9.3 (2.11)	9.1 (1.99)	10.2 (1.61)	9.7 (1.71)	10.3 (1.35)	10.9 (2.11)	10.4 (1.16)	10.3 (1.70)	—
PLT, 10^9/L									
Baseline	252 (138.6)	320 (76.7)	231 (108.0)	312 (114.3)	297 (92.7)	245 (104.7)	272 (78.6)	340 (72.0)	282 (67.3)
End int	354 (86.6)	300 (56.6)	283 (73.2)	297 (116.8)	260 (96.6)	220 (86.2)	287 (16.1)	318 (57.0)	217 (80.4)
End exp	266 (67.1)	310 (74.6)	236 (79.5)	242 (101.0)	232 (106.5)	182 (79.6)	243 (66.3)	174 (127.9)*	—
K^+, mmol/L									
Baseline	3.8 (0.17)	3.7 (0.23)	3.5 (0.20)	3.5 (0.21)	3.7 (0.27)	3.6 (0.12)	3.6 (0.22)	3.8 (0.53)	3.6 (0.27)
End int	4.5 (0.4)	4.8 (0.62)	4.2 (0.38)	3.9 (0.56)	4.5 (0.54)	4.4 (0.42)	4.3 (0.43)	4.0 (0.47)	4.3 (0.36)
End exp	4.2 (0.15)	4.5 (0.45)	4.4 (0.27)	4.4 (0.15)	5.3 (0.93)	4.9 (0.66)	4.9 (0.57)	6.5 (2.12)	—
Ca^{++}, mmol/L									
Baseline	1.25 (0.077)	1.29 (0.076)	1.17 (0.082)	1.21 (0.069)	1.31 (0.052)	1.22 (0.047)	1.26 (0.068)	1.28 (0.072)	1.31 (0.088)
End int	1.22 (0.080)	1.25 (0.065)	1.19 (0.078)	1.21 (0.071)	1.20 (0.091)	1.18 (0.043)	1.21 (0.085)	1.22 (0.063)	1.21 (0.136)
End exp	1.33 (0.078)	1.26 (0.079)	1.14 (0.115)	1.18 (0.046)	1.27 (0.073)*†	1.13 (0.051)	1.23 (0.135)	1.17 (0.007)	—
PaO_2/FiO_2									
Baseline	463 (55.1)	477 (10.3)	497 (36.7)	412 (133.8)	383 (114.3)	458 (41.2)	443 (57.3)	422 (97.7)	473 (61.9)
End int	452 (23.7)	454 (173.8)	538 (44.8)	411 (56.3)	456 (63.4)	546 (31.3)**†	444 (39.0)	382 (145.1)	518 (109.5)
End exp	439 (31.3)	372 (104.4)	434 (37.5)	408 (57.8)	400 (84.4)	447 (100.5)	383 (23.2)	336 (152.6)	—
$PaCO_2$, mm Hg									
Baseline	38 (1.5)	40 (2.1)	37 (1.3)	41 (4.5)	40 (4.1)	41 (4.3)	41 (4.1)	37 (5.7)	40 (3.4)
End int	34 (5.1)	26 (4.4)*	31 (3.3)	43 (2.7)	30 (9.5)*	30 (1.4)**	39 (5.8)	20 (2.7)*	27 (3.7)**
End exp	39 (2.0)	37 (10.0)	39 (1.5)	41 (3.4)	40 (2.6)	40 (1.6)	42 (1.7)	32 (17.3)	—
PaO_2, mm Hg									
Baseline	151 (14.8)	163 (16.5)	152 (9.8)	141 (44.3)	139 (44.6)	167 (33.5)	144 (26.8)	140 (41.0)	156 (28.1)
End int	146 (28.3)	150 (51.3)	161 (11.1)	149 (15.6)	172 (16.6)	196 (42.0)	139 (14.4)	138 (49.0)	175 (37.2)
End exp	131 (17.9)	142 (12.2)	130 (17.9)	147 (16.0)	152 (36.7)	159 (14.0)	120 (9.7)	152 (73.5)	—
AP, cmH_2O									
Baseline	20 (0.8)	22 (2.8)	21 (1.4)	22 (3.1)	24 (2.1)	21 (3.0)	22 (4.4)	23 (1.6)	20 (1.5)
End int	20 (0.9)	30 (4.6)*†	21 (1.2)	23 (2.1)	30 (2.9)*†	21 (1.9)	22 (3.6)	31 (2.5)*†	23 (1.8)
End exp	20 (0.9)	21 (2.3)	20 (1.0)	23 (1.2)	25 (3.2)	22 (2.1)	21 (3.8)	26 (1.4)	—
BUN, mg/dL									
Baseline	5 (1.2)	6 (0.8)	5 (1.5)	5 (1.4)	8 (2.0)	6 (1.3)	6 (1.5)	5 (1.0)	6 (1.8)
End exp	10 (1.1)	9 (1.0)	9 (1.1)	9 (1.8)	11 (1.5)	10 (1.7)	11 (2.7)	8 (1.4)	—
CRE, mg/dL									
Baseline	1.3 (0.17)	1.2 (0081)	1.3 (0.22)	1.2 (0.10)	1.4 (0.18)	1.3 (0.19)	1.4 (0.24)	1.1 (0.08)	1.1 (0.31)
End exp	1.5 (0.05)	1.5 (0.23)	1.6 (0.08)	1.5 (0.27)	2.3 (0.47)*	2.3 (0.38)**	1.7 (0.37)	2.3 (0.14)	—

Continued next page

TABLE 2. *(Continued)*

	30-min Intervention			60-min Intervention			90-min Intervention		
	Control	GROA	REBOA	Control	GROA	REBOA	Control	GROA	REBOA
ALT, U/L									
Baseline	41 (6.2)	48 (4.7)	42 (9.2)	40 (8.1)	42 (4.6)	45 (10.4)	50 (10.5)	46 (4.1)	45 (8.9)
End exp	37 (9.8)	48 (6.0)	42 (6.6)	38 (5.0)	47 (10.2)	50 (2.2)**	51 (14.8)	64 (21.9)	—
TBIL, mg/dL									
Baseline	0.2 (0.04)	0.2 (0.07)	0.2 (0.00)	0.2 (0.00)	0.2 (0.00)	0.2 (0.04)	0.2 (0.05)	0.2 (0.04)	0.2 (0.05)
End exp	0.2 (0.05)	0.2 (0.05)	0.2 (0.04)	0.2 (0.08)	0.2 (0.08)	0.3 (0.05)	0.2 (0.04)	0.2 (0.04)	—

Data are presented as averages (SD). One-way ANOVA using Tukey's correction for multiple comparisons was used for intergroup analysis. Statistical significance was set at $\alpha < 0.05$.
*Denotes statistically significant difference between GROA and control.
**Denotes statistically significant difference between REBOA and control.
†Denotes statistically significant difference between GROA and REBOA.
ANOVA, analysis of variance; Hb, hemoglobin; PLT, platelets; K^+, potassium; Ca^{++}, calcium; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; $PaCO_2$, partial pressure of carbon dioxide; AP, airway pressure; BUN, blood urea nitrogen; CRE, creatinine; ALT, alanine aminotransferase; TBIL, total bilirubin; End int, end of intervention period; End exp, end of experiment; LR, lactated ringer's.

Organ Function

Parameters for renal and hepatic function are presented in Table 2. Chemistry profiles indicated a statistically significant increase in creatinine levels in the GROA and REBOA relative to controls after 60 minutes of occlusion reaching levels of 2.3 (0.47), 2.3 (0.38), and 1.5 (0.27) mg/dL, respectively. A similar increase in the GROA 90-minute group, 2.3 (0.14) mg/dL, was observed but did not achieve statistical significance. Thromboelastography analysis revealed no clinically relevant changes in reaction time (R), clot formation kinetics (K and α), measures of clot firmness (maximum amplitude [MA] or time to MA), or lysis (LY30), suggesting no evidence of coagulopathy between groups.

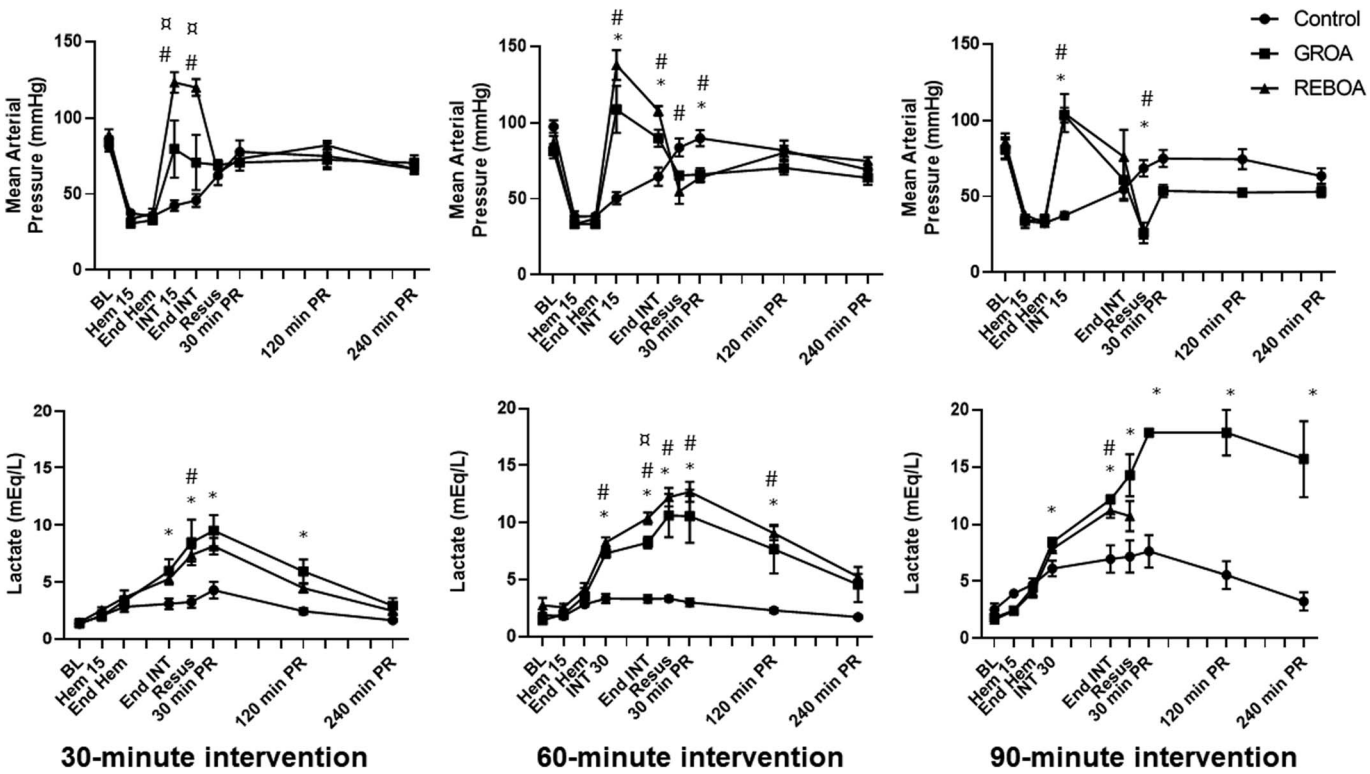

Figure 2. Average and standard error of MAP of the carotid artery and arterial lactate concentration for 30-minute, 60-minute, and 90-minute interventions. *Denotes statistically significant difference from GROA and control. #Denotes statistically significant difference from REBOA and control. ¤Denotes statistically significant difference from GROA and REBOA. BL, baseline; Hem 15, 15 minutes into hemorrhage; End Hem, end of hemorrhage; INT 15, 15 minutes into intervention; INT 30, 30 minutes into intervention; End INT, end of intervention; Resus, resuscitation; PR, postresuscitation.

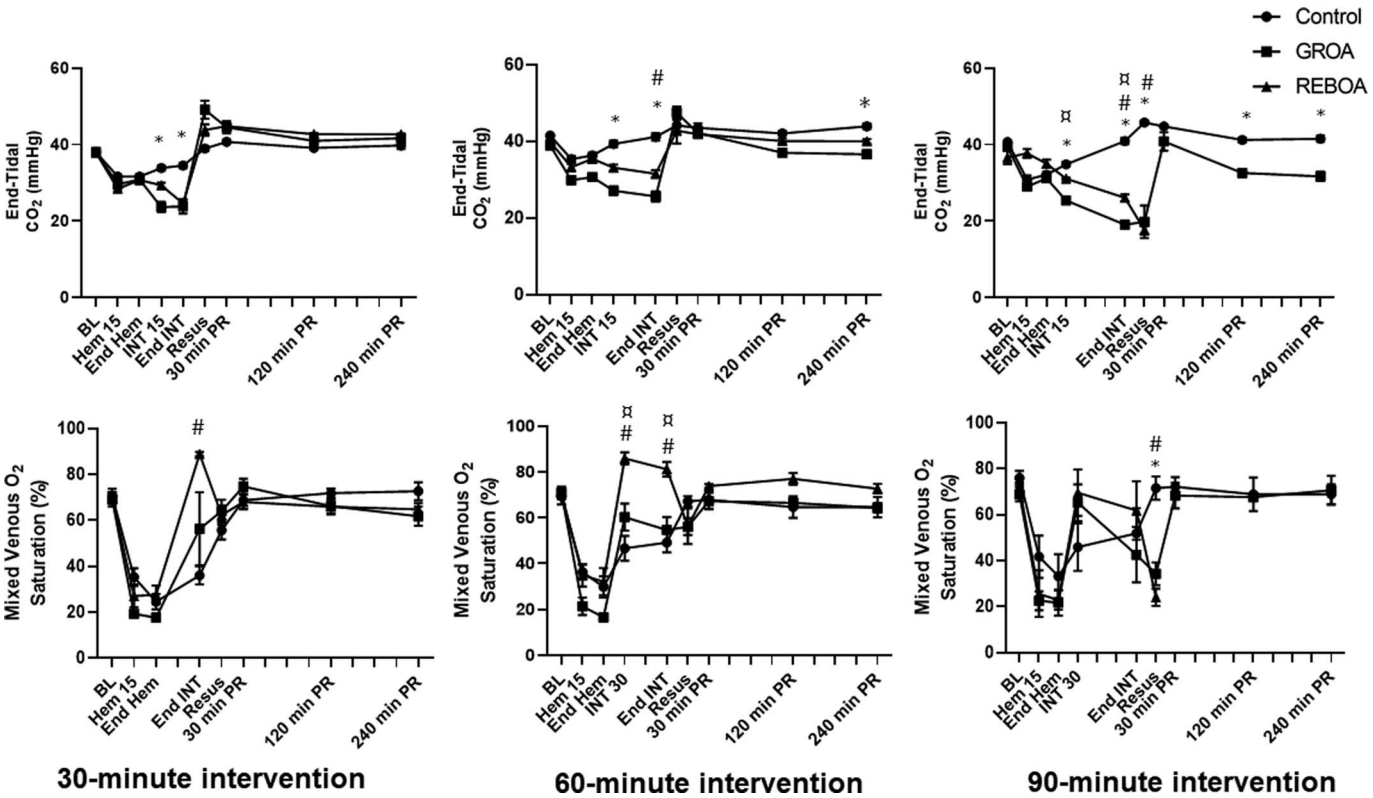

Figure 3. Average and standard error of end-tidal CO_2 ($PetCO_2$) and mixed venous oxygen saturation ($SmvO_2$), for 30-minute, 60-minute, and 90-minute interventions. *Denotes statistically significant difference from GROA and control. #Denotes statistically significant difference from REBOA and control. ¤Denotes statistically significant difference from GROA and REBOA. BL, baseline; Hem 15, 15 minutes into hemorrhage; End Hem, end of hemorrhage; INT 15, 15 minutes into intervention; INT 30, 30 minutes into intervention; End INT, end of intervention; Resus, resuscitation; PR, postresuscitation.

Airway, Central Venous, and PAPs

Animals receiving GROA intervention showed a significant increase in peak airway pressures relative to REBOA and control groups (31 [3.1] cmH_2O, 22.7 [2.7] cmH_2O, and 22.4 [2.9] cmH_2O, respectively) during intervention ($p < 0.0001$). Intergroup airway pressure data are presented in Table 2. The airway pressure was elevated immediately following the GROA device application period and was maintained until device

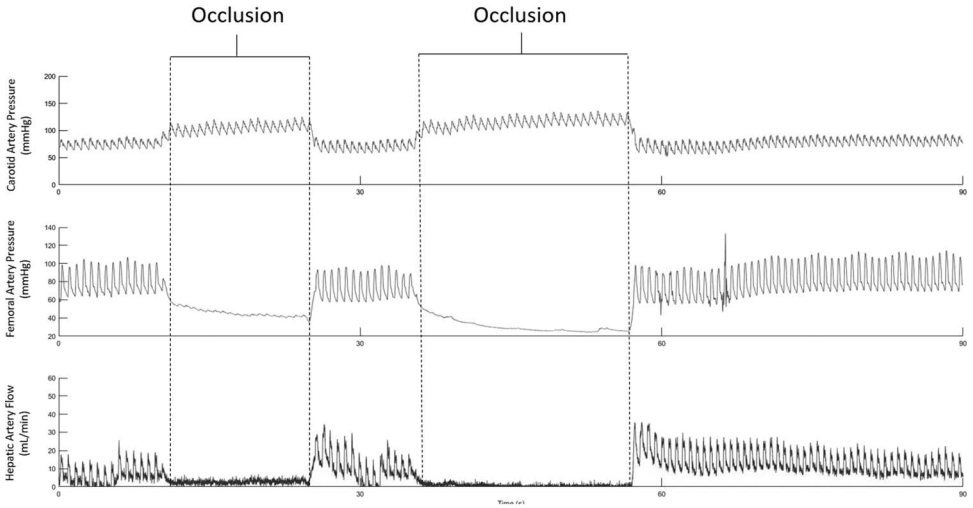

Figure 4. The GROA device's effect on carotid artery pressure (mm Hg), femoral artery pressure (mm Hg), and hepatic artery flow (mL/min). Noted are the increases in carotid pressure and the cessation of pulsatile flow in both the femoral artery and hepatic artery during device inflation, verifying zone II aortic occlusion.

deactivation with a range of 25 to 39 cmH_2O across all animals. Airway pressures returned to baseline following device deactivation and maintained throughout the postresuscitation monitoring period. Airway pressure data are available in Supplemental Digital Content 2 (Supplementary Fig. 2, http://links.lww.com/TA/B732). Central venous and PAPs changes during hemorrhage, intervention period, and resuscitation showed no differences between the three groups at any of the intervention periods (30 minutes, 60 minutes, and 90 minutes) (Supplemental Digital Content 3, Supplementary Fig. 3, http://links.lww.com/TA/B733).

Histology

Histological examination of the stomach tissues of animals receiving the GROA intervention showed evidence of localized mild to moderate inflammation (gastritis) of the fundus and cardia with occasional areas of hemorrhage within the superficial mucosa. Mild to moderate disruption of the superficial glandular mucosal architecture, with disassociation and single cell degeneration of glandular epithelial cells, was noted with multifocal loss of glandular epithelium consistent with mild ischemic injury. Within the stromal supporting tissue, scattered inflammatory cells including mononuclear cells and neutrophils were noted. Animals receiving the REBOA intervention were also found to have mild ischemic injury of the gastric mucosa but to a lesser extent compared with animals undergoing intervention with GROA. There was no evidence of gross or histological lesions in the control group. Aortic histology for both GROA and REBOA animals demonstrated that there was minimal to mild patchy disruption of elastin layers, and multifocal single cell vacuolation, fragmentation, nuclear pyknosis, and shrinkage with hypereosinophilia.

DISCUSSION

Similar to REBOA, the GROA device is envisioned to be applied in cases of NCTH of the abdomen or pelvis as a bridge to definitive surgical hemostasis. However, the main motivation in its development was to allow for rapid aortic occlusion for the management of NCTH in more austere conditions such as civilian prehospital or role 1 combat casualty care settings, or in hospital non–trauma center settings where surgical resources may be delayed. The purpose of the current study was to evaluate the feasibility of the device to achieve aortic occlusion and test the physiological tolerance of the application of the device. The GROA device was found to be effective at achieving and maintaining high zone II aortic occlusion for a period of up to 90 minutes. In a previous unpublished pilot study (n = 4), the zone of aortic occlusion was verified by the cessation of flow in the common hepatic artery indicating that GROA occlusion occurs either directly over or superior to the celiac trunk (Fig. 4). While it is possible, we do not believe that there is a direct mechanical occlusion of the superior mesenteric artery (SMA) or renal arteries based on balloon dimensions.

The survival rate between REBOA and GROA for all intervention durations was similar except that no REBOA animals survived resuscitation after 90 minutes of complete aortic occlusion. With only two animals surviving the 4-hour resuscitation period after 90 minutes of GROA, our study suggest that 90 minutes of complete aortic occlusion is possible but not well tolerated. We were thus not able to duplicate the level of REBOA tolerance reported by Markov et al.[20] The overall survival rate between REBOA and GROA intervention in the 30-minute and 60-minute occlusion groups suggest that the overall tolerance of the GROA device may be equal to the already well-characterized physiological tolerance of REBOA for those occlusion times.[20–23]

The hemodynamic effects of GROA appear to be similar to those produced by REBOA. Overall, increased MAP and SvO_2 suggest increased central redistribution of blood flow and potentially increased perfusion of brain and heart consistent with previous REBOA studies.[24,25] Lactate was also increased in all GROA groups during occlusion and peaked following reperfusion; however, these observations are again similar to REBOA and consistent with previous studies. Lactate burden created by both methods of aortic occlusion were able to be alleviated in the 30-minute and 60-minute intervention groups by adequate resuscitation. As expected, lactate levels were highest in the 90-minute occlusion GROA group during the reperfusion period but could not be compared with 90-minute REBOA animals since no animals in this group survived resuscitation.

The largest limitation to aortic occlusion by REBOA may be the time interval between injury and implementation of treatment. In a study using prehospital REBOA for cardiac arrest, Brede et al.[26] found a mean (SD) of 45.6 (6.3) minutes and a range of 34 to 57 minutes from the time of dispatch to the time of occlusion. In addition, the largest rate limiting step to implementation of prehospital REBOA might be failure to cannulate the femoral artery.[16,27] In another study using prehospital REBOA for pelvic trauma, only 15 of 21 cannulation attempts were successful.[28] Gastroesophageal resuscitative occlusion of the aorta holds application advantages over REBOA that could considerably reduce time to occlusion. The less-invasive GROA device does not require surgical intervention or imaging techniques, such as fluoroscopy or sonography, and is easily applied with minimal training. Gastroesophageal resuscitative occlusion of the aorta device application in this study was successful in all animals and deployed within 2 minutes. Since the device used in this study was designed using human morphomics data, it is envisioned to translate to humans in a clinical environment. The application is similar to insertion of a nasogastric or Sengstaken-Blakemore tube in regards to length of insertion, confirmation of placement, and application of traction to secure its position. Given the similar tolerance to REBOA, these attributes may favor an initial approach using GROA as a first line tool in damage-control resuscitation or as an adjunct therapy to advanced techniques such as REBOA or definitive surgical hemostasis.

The current form of the GROA device causes mild to moderate gastric mucosal injury, which we believe is mainly due to contact pressure injury from balloon, although the REBOA animals demonstrated (lesser) mucosal injury likely from ischemia-reperfusion injury. However, the full extent of this injury will require longer survival studies to allow mucosal ischemia injuries to mature for complete quantification. We are currently working with alternative materials to lessen pressure injury and strategies for adjusting the external pressure plate before balloon inflation. Increased airway pressure appears to be a result of the GROA balloon contacting the diaphragm during ventilation; however, the pressure remains below the

40 cmH_2O threshold associated with increased risk of injury,[29] and blood gas analysis verified no change in PaO_2 or PaO_2/FiO_2 during the intervention and recovery period, indicating adequate ventilation. Furthermore, neither CVP or PAP was significantly different between the groups, indicating that, if compression of the inferior vena cava (IVC) by GROA occurs, decreases on cardiac preload from inferior vena cava impingement versus reductions in venous return from aortic occlusion did not affect outcomes.

As expected, animals undergoing aortic occlusion for longer than 30 minutes, regardless of method, developed evidence of mild renal injury as noted by increases in creatinine at the end of the 4-hour resuscitation period.[30] No evidence of liver injury as measured by liver enzymes or bilirubin was noted.

This study has several limitations. The study only evaluated the acute physiology and tolerance of GROA during hemorrhagic shock. Unlike Markov et al.,[20] we terminated the study 4 hours postresuscitation and did not examine tissues from other organ systems for damage. Hence, we cannot speak to organ damage that could arise during a prolonged recovery phase. Long-term studies that include survival are needed to further investigate the long-term effects of GROA. This feasibility study is underpowered to detect a discrete difference in a primary outcome or enable us to support superiority or noninferiority; however, we believe that the N of this study is large enough to give a certain confidence as to the feasibility of the device. The initial prototype we developed is preliminary and needs further refinement aimed at minimizing injury to the stomach and to ensure its correct placement in chaotic environments. Unlike REBOA where suggested inflation volumes of the balloon result in complete occlusion and the ability to monitor arterial blood pressure proximal to the occlusion via the REBOA catheter, GROA will require adjunctive monitoring methods to ensure occlusion such as photoplethysmography of the toe to confirm lack of pulsatile blood flow. However, initial noninvasive blood pressure monitoring and upper extremity pulse quality could serve as initial indicators of improved hemostasis and perfusion. We will note that in our pilot studies we were able to produce partial occlusion (partial GROA) guided by femoral artery blood pressure similar to partial REBOA, which is being studied to reduce the ischemia produced by total occlusion.[21,31–33] Partial GROA is produced by decreasing the pressure that the abdominal plate applies to the epigastric area (Supplemental Digital Content 4, Supplementary Fig. 4, http://links.lww.com/TA/B734). This study also only evaluated the device's effects following a controlled arterial hemorrhage. However, the degree of this hemorrhage resulted in a state of significant hypotension that would have been an indication for REBOA use if definitive surgical hemostasis would be delayed. Additional hemostasis studies involving uncontrolled organ and/or vascular injury are indicated to further explore the device's capabilities and limitations.

CONCLUSIONS

In this study, GROA was effective in creating zone II aortic occlusion and may therefore be capable of temporarily staunching severe NCTH and improving survival. Based on hemodynamics, survival rate, and acute phase organ response data, the physiological tolerance of GROA appears similar to REBOA. This study warrants ongoing evaluation of the efficacy of GROA to staunch uncontrolled hemorrhage. Gastroesophageal resuscitative occlusion of the aorta may serve as a fast, effective, and short-term method of achieving hemostasis until definitive surgical interventions may be performed.

AUTHORSHIP

M.H.T., B.M.M., and K.R.W. contributed in the literature search, study design, data collection, data analysis, data interpretation, writing, and critical revisions. C.I.C., D.C.L., and N.L.G. contributed in the data collection, data analysis, data interpretation, and some writing. J.S.P., A.J.S., S.C.W., and J.L.E. contributed in the study design, data interpretation, and critical revisions.

ACKNOWLEDGMENTS

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DISCLOSURE

K.R.W., and J.S.P. have intellectual property associated with the device used in this study assigned to the University of Michigan. The GROA device has been licensed from the University of Michigan by Precision Trauma LLC. K.R.W. and J.S.P. have equity in the company. The remaining authors declared no conflicts of interest. This work is supported in full by a grant from the United States Department of Defense (contract number, W81XWH-18-1-0033).

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Gastroesophageal Resuscitative Occlusion of the Aorta (GROA)

DM160299 Prolonged Field Care Research Award

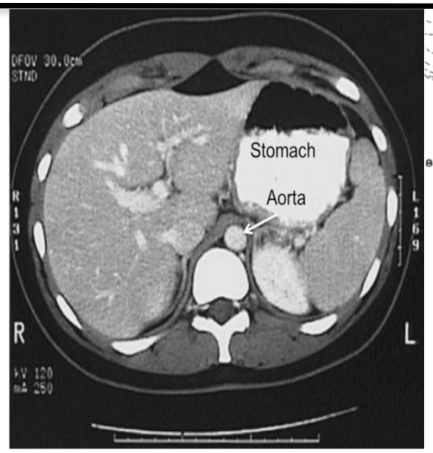
PI: Kevin Ward, MD **Org:** University of Michigan **Award Amount:** $2,995,616

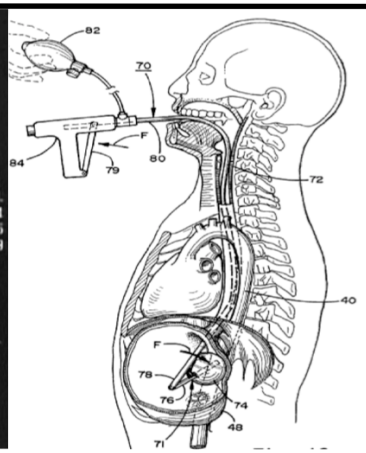
Study/Product Aim(s)

- Design and prototype GROA device(s) that can be inserted into the stomach to allow occlusion of the aorta and test the physiologic tolerance of the device and compare to REBOA in severe hemorrhage in swine.
- Test and compare GROA prototypes to REBOA for staunching severe noncompressible abdominal hemorrhage in a large swine animal model of traumatic shock.
- Demonstrate tandem use of GROA followed by REBOA as an example of near point-of-care in field pDCR and PFC in animals.

Approach

We will use a rapid iterative design approach based on 3-D morphomic reconstruction of human CT scans coupled with 3-D printing and tissue testing to develop GROA prototypes for testing in large animal models of noncompressible abdominal hemorrhage with and without tandem use of REBOA. Designs will be developed for warfighter anatomy.





Using iterative design based on morphomics and 3-D printing, develop and test GROA in large animals as a bridge to REBOA and other techniques

Timeline and Cost

Activities	CY18	CY19	CY20/21
Morphomic 3-D design and 3-D prototyping with initial animal studies			
Animal studies of GROA in hemorrhage and physiologic tolerance studies			
Tandem use studies of GROA to REBOA			
Refinement of human factors and GROA design for future clinical studies			
Estimated Budget ($K)	$988,148	$995,137	$1,012,331

Goals/Milestones

CY18 – Morphomic, 3-D printing, and animal study work flows

☑ Human morphomics analysis and 3-D printing-prototyping

☑ Initial animal studies in test physiologic tolerance compared to REBOA

CY19 Goals – Continued iterative design and animal studies

☑ Continue animal physiologic tolerance studies

☑ Begin animal studies in noncompressible hemorrhage compared to REBOA continued through 2020

CY20/21 Goals – Additional Preclinical and Human Factors Testing

☐ Complete noncompressible hemorrhage compared to REBOA studies

☐ Iterative design and study as necessary

☐ Tandem use studies of GROA to REBOA

☐ Refinement of human GROA design for future clinical studies

Comments/Challenges/Issues/Concerns

- COVID-19 has slowed project progress
- A no cost extension has been granted trough 2021 to offset delays

Budget Expenditure to Date: $2,410,155