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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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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 intraabdominal 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.

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

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 IRB approval
    - **Subtask 2**: ACURO Approval
    - **Subtask 3**: Obtain equipment, hire and train study personnel.
    - **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
    - **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

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

o **Major Task 2:** Test and compare GROA prototypes to REBOA for staunching severe noncompressible 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
- **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
-
- **Milestone Targeted**: Complete comparison studies of GROA and REBOA in swine with severe noncompressible hemorrhagic shock. (24 months)
- **Milestone Targeted**: One or more peer reviewed publications/year (24 months)
- **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 24-36
- **Subtask 2:** Testing of tandem use of GROA to REBOA: Months 24-36

- **Milestone Targeted**: Successful demonstration of GROA to REBOA transition (36 months)
- **Milestone Targeted**: Creation of final 1-2 human GROA prototypes suitable for consideration for human testing in follow-on studies. (36 months)
- **Milestone Targeted**: One or more peer reviewed publications/year (36 months)
- **Milestone Targeted**: Use refined data to continue to engage industry partner and/or launch small business spin off for technology transition plan (36 months)

- **What was accomplished under these goals?**

Major activities

1. **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

   May – August 2018
   We have tested numerous balloon prototypes to find the optimal balance between vessel occlusion, ease of insertion, and strength. In general, a larger and stronger balloon will make aorta occlusion easier, but at the cost of more difficult insertion.
   The first hypothesis we tested was whether a balloon on its own could provide enough pressure on the aorta to stop blood flow. To test the feasibility of this we used a stiff nylon balloon with

either a metal rod (minimizing beam deflection to maximize the force or the aorta) and a medium stiffness tube (easier insertion) coupled to a stiff, nylon balloon (Fig 1.)

After testing, we found that having a stiffer rod to minimize balloon deflection had little to no improvement on the balloon's ability to occlude the aorta. In both instances external pressure was required.

Moving to a medium stiffness insertion tube, we then explored several different balloon geometries to see if we could better focus pressure on the aorta, making occlusion easier (example shown in Figs. 2 & 3). While we could achieve occlusion with these balloon designs coupled with external pressure, we found that the nylon material began to degrade after ~30 minutes in the stomach. Over time the nylon absorbed the moisture in the stomach and became very soft, causing premature balloon failure.

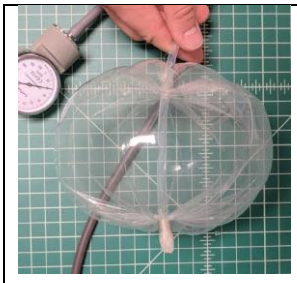


Fig. 1

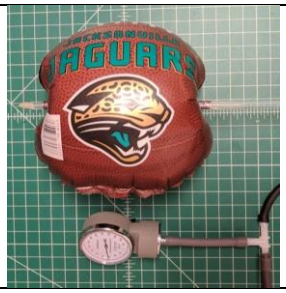


Fig. 2

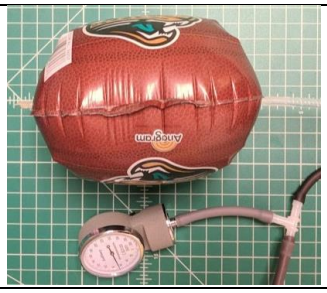


Fig. 3

We then explored a new balloon material, fluorinated ethylene propylene (FEP), which is heat-sealable (important for hand-made prototype production) like nylon but with much higher chemical resistance properties. The first design was ~8" in diameter and 3" in width. We also coupled this with an external pressure device to provide controllable, directed, and sustained external pressure (Figs 4-6). This combination performed well, allowing for "hands-off" aorta occlusion without material degradation, even after 2 hours in the stomach. However, the dimension of the balloon made it somewhat difficult to pass into the stomach.

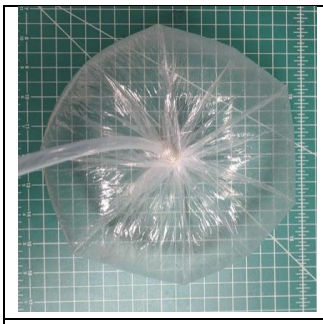


Fig. 4

Fig. 5

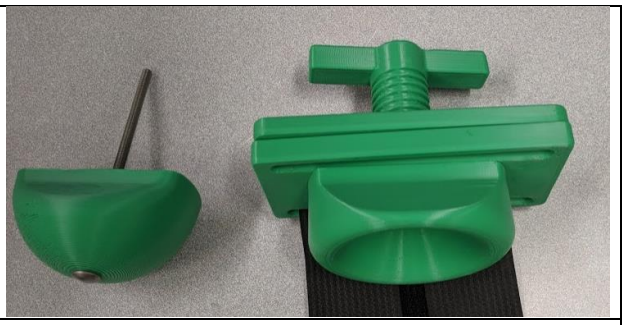


Fig. 6

The latest design utilized the same FEP material but with slightly smaller dimensions (~6" diameter & 2" width) to make it easier to position in the stomach, Fig 7. We are then coupling that with an anatomically designed pressure plate to provide even more stable, directed pressure to the abdomen, Fig 8.

Fig. 7

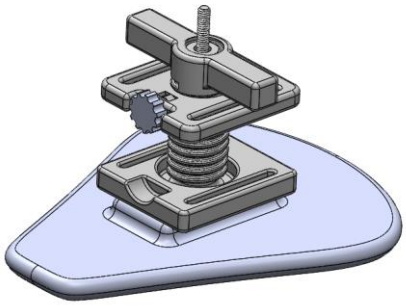


Fig. 8

September – November 2018

From September through November 2018 we built upon the initial success of the previous designs to further optimize the GROA system.

Balloon Tip Optimization: In previous testing we identified difficulty inserting the balloon down into the stomach. The balloon catheter would typically reach the entrance of the stomach but not penetrate past the esophageal sphincter and into the stomach without significant force. This led to significant trauma and esophageal perforation in some cases. To make insertion easier and less traumatic, we explored three different new tip styles (Figs. 9-11).

Fig. 9

Fig. 10

Fig. 11

The design of Fig. 9 has a rounded tip with the goal of making it easier to pass through the esophageal sphincter. This design provided marginal improvement, however the inflexibility of the tip precluded the device from easily passing through the bend at the base of the esophagus and into the stomach.

In the design of Fig. 10, a 1” flexible and tapered tube was incorporated on the tip of the balloon catheter. This further improved insertion but still required the use of an inner stylet to create enough thrust force to pass the balloon into the stomach.

The design of Fig. 11 uses a 2.5” long flexible tip with the same properties as the commonly used Salem Sump tube (designed for stomach content pumping). With this device the GROA balloon can now be inserted into the stomach with minimal thrust force, no significant trauma, and no longer requires an internal stylet.

External Pressure Optimization: Another critical aspect we improved upon was the external pressure device. In previous tests, we used a specially designed tourniquet to provide external pressure. While this was enough to occlude the descending aorta in combination with the balloon catheter, it caused an unacceptable increase in airway pressures from ~ 20 cmH20 without the device up to ~50 cmH20 with the device applied. To mitigate this, we re-designed the tourniquet strapping so the straps don’t wrap circumferentially around the torso (Figs. 12-14). With this design change, the peak airway pressure dropped from ~50 cmH20 to an acceptable 20-30 cmH20 with GROA applied. Further improvements will be made to this device to ensure the external pressure is secure even during transportation while simultaneously reducing peak airway pressures.

Fig. 12

Fig. 13

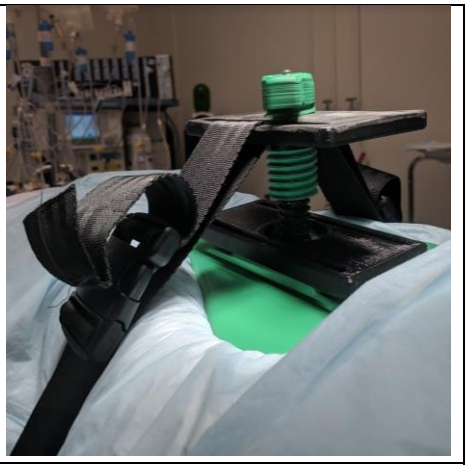


Fig. 14

Commercially Manufacturable Balloon Design: Now that we have achieved the concept freeze stage, work has begun to source a manufacturer who can produce balloon catheters to our specifications using industry standard manufacturing techniques. A manufacturer, Interplex Medical, has been identified for this task. As such, we prepared engineering drawings (partially shown in Fig. 15) along with the design verification matrix which final devices will be tested against as part of the FDA submission process.

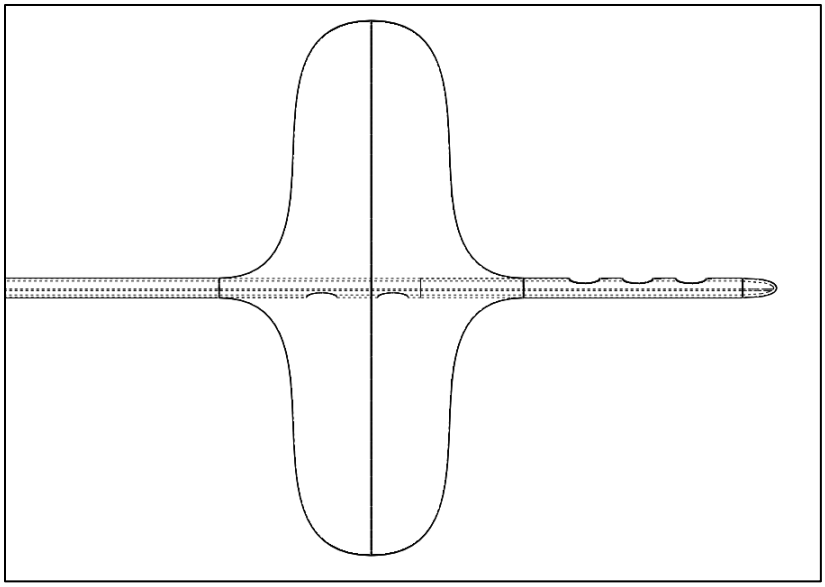


Fig 15

November 2018 – January 2019

GROA Balloon & Catheter: We began working with Interplex Medical to ensure the GROA balloon and catheter tubing is designed for mass manufacturing. This involved the development of our design specifications and engineering drawings. The current status of the design verification matrix is shown in Table 1. While this document will continue to evolve over time, it provides a framework of current known requirements based on our device testing. Once we receive the devices from Interplex, the validation work will begin.

Table 1: Design Verification Matrix - GROA Catheter System

Date: 12/11/2018 Revision Level: 4

Design Inputs and User Requirements	Design Outputs	Requirement Rationale	Verification Document(s) Showing Evidence of Conformance (Output = Input)	O = I (Y/N)
1.0 User Requirements (Product Features)				
1.1 System Requirements				

The system shall navigate to the target location. Catheter balloon able to pass through the mouth, down the esophagus, past the esophageal sphincter, and into the entrance of the stomach.	Distal tip of catheter shaft shall have a durometer hardness between X-Y, a length of between 70-80mm, and a blunt end which prevents perforations, and a smooth finish. The remaining catheter shaft shall have a durometer hardness between H-I, a length of between 900-1100mm, and a smooth finish. The maximum OD of the collapsed balloon on the catheter lumen shall be no greater than Zmm.	*Using the Salem Sump tube as a predicate for required flexibility to enter into the stomach. Prototype testing on pigs used to determine maximum allowable device OD.*		
The system shall allow for simultaneous balloon inflation, stomach content evacuation, and stomach pressure equalization to ambient pressure.	*Catheter tube contains at least three lumens. Balloon inflation lumen has cross sectional area of at least 4mm^2, evacuation lumen cross sectional area of at least 7mm^2, equalization lumen has a cross sectional lumen of at least 4mm^2.*	*Using the Salem Sump tube as a predicate for stomach content evacuation.*		
System shall occlude descending aorta when deployed	*Balloon can be inflated with ambient air to at least 160 mmHg under anatomic compression (50% compression from parallel plate (external pressure) onto a 2.5" diameter dowel (spine)) in less than 30 seconds.*			
System must be "hands-free" after deployment	*Aorta must remain occluded when system is deployed even without an operator for at least 2 hours.*			
System shall be resistant to internal and external fluid contact	*Device materials capable of contacting bodily fluids, including stomach acid, without deterioration, softening, or stretching*			
System shall allow for balloon collapse to ease insertion and removal.	*Balloon can be collapsed via hand-held vacuum in under 30 seconds*			
System shall indicate when desired internal pressure is achieved	*System includes a pressure gauge coupled to balloon pressure.*			

System shall remain stable in transport	*Catheter balloon and external pressure subsystems shall remain in position during transport such that no change in occlusion is created*			
1.2 Catheter Balloon Subsystem Requirements				
Catheter balloon shall not break during insertion	*Material has sufficient tear resistance to resist breaking if scratched by tooth*			
Catheter balloon shall not leak	*Must maintain a pressure of at least 160mmHg for at least 2 hours in uncompressed and anatomically compressed scenario*			
Catheter balloon must collapse down to aid insertion ease	*Collapsed diameter must be less than or equal to X mm.*			
Catheter balloon shall minimize damage	*Balloon material must have smooth surface finish with no sharp edges*			
Catheter balloon shall not degrade in-vivo	*Catheter shall be corrosion resistant to biological fluids and medication [X]*			
Catheter balloon shall not break during operation	*Able to withstand compression force of X without leak, able to withstand tensile pull of Y N without leak or relative movement between the catheter balloon and shaft.*			
Catheter balloon shall be suitable size when inflated	*Balloon dimensions shall be ~6" OD x 2" wide when inflated to 60 mmHg.*			
Catheter balloon tubing shall not break/kink	*Tubing resists breaking/kinking under compression load of at least X N.*	*cannot kink/break during device insertion, use, or removal*		
1.3 Inflation Subsystem Requirements				
Pump shall be capable of both inflation and vacuum	*Pump can inflate and deflate catheter balloon in under 30 seconds*			
Pump shall be able to couple and decouple to catheter balloon system	*Pump can be sealably coupled and decoupled in under 10 seconds.*			

Pump shall be not leak	*Must maintain a pressure of at least 160mmHg for at least 2 hours*			
Pump shall not break during operation	*Capable of at least 500 pumping cycles. Able to withstand tensile pull of X N without leak.*			
1.4 External Pressure Subsystem Requirements				
External pressure shall be applied over a sufficient area	*External pressure plate covers an area of approximately X mm^2*			
External pressure shall be applied rapidly	*External pressure can be fully deployed in under 30 seconds*			
External pressure shall not cause excessive airway pressure	*External pressure subsystem shall minimize circumferential pressure on abdomen. Airway pressures shall increase no more than X inH2O*			
External pressure shall minimize internal organ damage	*Pressure plate shall be anatomically shaped such that pressure is directed toward the balloon location and minimized in other areas.* *Pressure shall be continuously adjustable such that the pressure can be titrated so that only the minimum required pressure for occlusion in used.*			
Must be portable	*Device shall weigh less than X lbs and shall take up no more space than X x Y x Z when stored*			
2.0 Biocompatibility and Environmental				
Materials used shall be biocompatible.	*Rated for short term internal and external bodily contact*			
3.0 Use and Human Factors				
Device can be set on a suitable surface.				

Device can be manipulated and placed using typical intubation techniques				
Device prevents common misuse scenarios.				
4.0 Specific Quality, Reliability and Durability				
TBD.				
5.0 Potential Customer/Patient Risk				
Documented in dFMEA.				
6.0 Serviceability				
None.				
7.0 Sterilization				
TBD				
8.0 Aesthetics				
None.				
9.0 Statutory and Regulatory Requirements				
TBD.				
10.0 Product Acceptance Criteria				
TBD.				
11.0 Safety and Proper Use Characteristics:				
TBD.				
12.0 Other				
Not Applicable.				

With these design specifications, we produced an engineering drawing and provided that to Interplex Medical as shown in Figure 16.

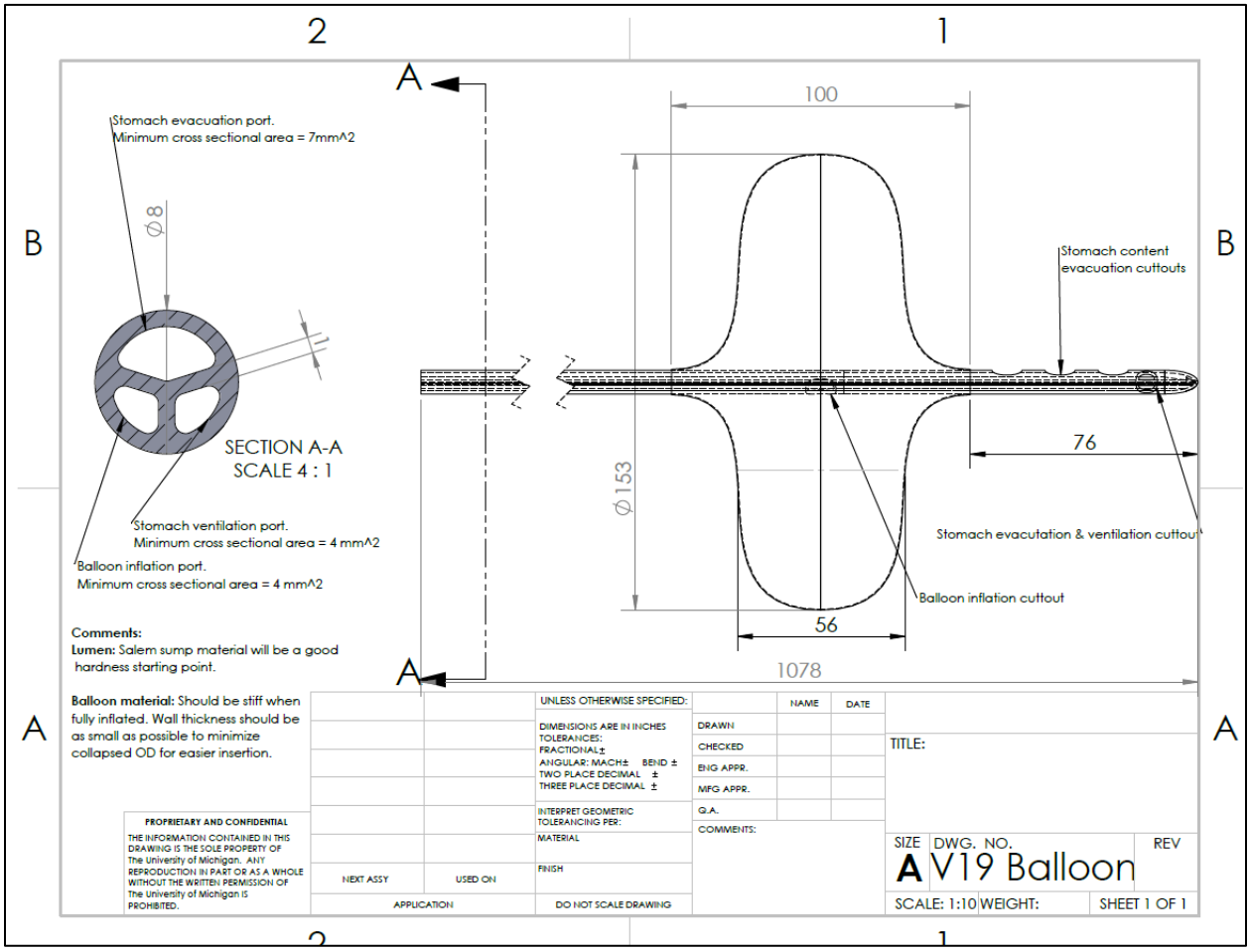


Fig. 16

With this engineering drawing and design specifications, Interplex has kicked off the custom extrusion needed to produce the triple lumen tubing (one lumen for balloon inflation, one lumen for stomach content evacuation, and one lumen for stomach venting to atmosphere) and the custom tooling needed to mold the GROA balloon shape. We expect to receive the first batch of completed GROA balloons from Interplex by the end of March 2019. Once prototypes are received, we will continue device testing and validation

2. **Specific objectives**
   - **Subtask 1**: Local/Institutional IRB 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, Work in progress.

SUBMITTED TO AND APPROVED BY:

Protocol [HRPO Assigned Number]: DM160299

Title: GROA: Review of Computed Tomography (CT) Scans

Target required for clinical significance: 10000

Target approved for clinical significance: 99999999

IRBMED Approved 2/1/2018

HRPO Approved 3/26/2018

3. Significant results

Initial Morphomic analysis:

In order to optimize the balloon design to also work in human, the science of morphomics was utilized. The figures below (fig 17-19) give an idea of where the aorta is positioned in relation to the inferior aspect of the vertebral body of T10 in 1641 war fighter aged subjects. The center of the vertebral body in the axial plane is used as the origin in all figures. After determining the position of the gastro-esophageal junction of 95 of these subjects we can say with reasonable confidence that the inferior aspect of the vertebral body of T10 is the z-axis location that we'll be using to reference the GE junction due to it's being the most proximal vertebral point.

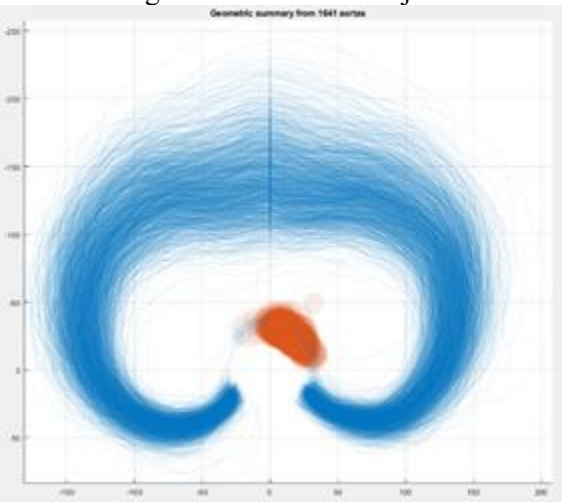


Fig 17. The blue lines represent the outer border of the abdominal cavities. To better visualize the aortas the vertebral bodies have been removed from the image but their position can be easily inferred.

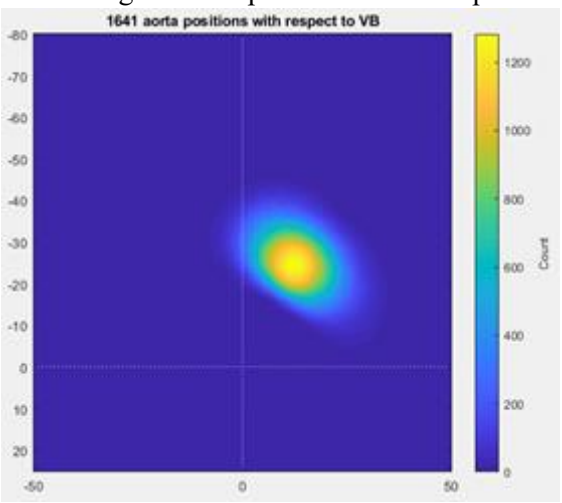


Fig 18. Radial relationship to center of vertebral body

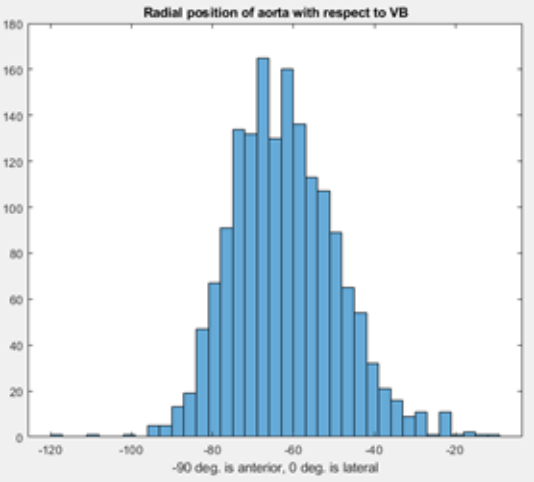


Fig 19.

Work in progress includes evaluation of the location of the gastroesophageal junction and most superior aspect of the stomach to better characterize its position in this population.
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, work in progress

Animals use Data:
a. Species: Sus Scrofa Domestica
b. Total animal number used: 11
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, verify the area of occlusion, and various measurements of physiological tolerance.
All animals received the same surgical instrumentation for evaluation of:
● Invasive ascending aortic blood pressure (MAP)
● Invasive Descending aortic blood pressure (Femoral artery)
● Continuous cardiac output
● Pulmonary artery pressure
● Central venous pressure
● Inferior vena cava pressure
● Hepatic artery flowometry

1- Carotid artery cannulation: for measurement of arterial blood pressure and arterial blood gases, hemoglobin, lactate levels and other chemistry and hematology panels.
2- Femoral artery cannulations: for measurement of arterial blood pressure, and controlled arterial hemorrhage.

3-Femoral vein cannulation: The vein will be dissected from surrounding tissues and cannulated for pressure measurements from the vena cava and provide additional IV access for resuscitation methods.

4- Cannulation of the external jugular veins: for placement of an oximetric thermodilution pulmonary artery catheter for continuous measurement of mixed venous hemoglobin oxygen saturation, cardiac output, central venous pressure (CVP), pulmonary artery pressure (PAP), and core temperature. This cannulation site will also allow for provision of intravenous anesthesia, and delivery of resuscitation fluids.
5- Laparotomy: placement of a hepatic artery flow probe for continuous measurement of organ specific blood flow.
We have used 7 animals to test preliminary GROA prototypes and their ability to be applied into and withdrawn from the stomach while also gathering preliminary physiological data on the devices ability to occlude the aorta and general tolerance during inflation, deflation, insertion and removal. The device has been uniformly successful at occluding the aorta when external pressure is being applied in addition to inflation. We've found in addition to successfully occluding the aorta, pulsatile flow through the hepatic artery is lost during device inflation confirming a low zone 1 occlusion (fig 20)

Technical limitations: Concomitant partial occlusion of the inferior vena cava has been noted in addition to occlusion of the aorta. The implications for this in life threatening abdominal hemorrhage is unclear. Other physiologic measures such as SvO2, lactate, etc. do not appear to be different from those during traditional REBOA use. However, we believe the new balloon design as well as changes in the external belt/pressure device will limit or minimize IVC occlusion. Recent iteration of the belt design has reduced airway pressure to more acceptable levels, (20-30 cm H_20)

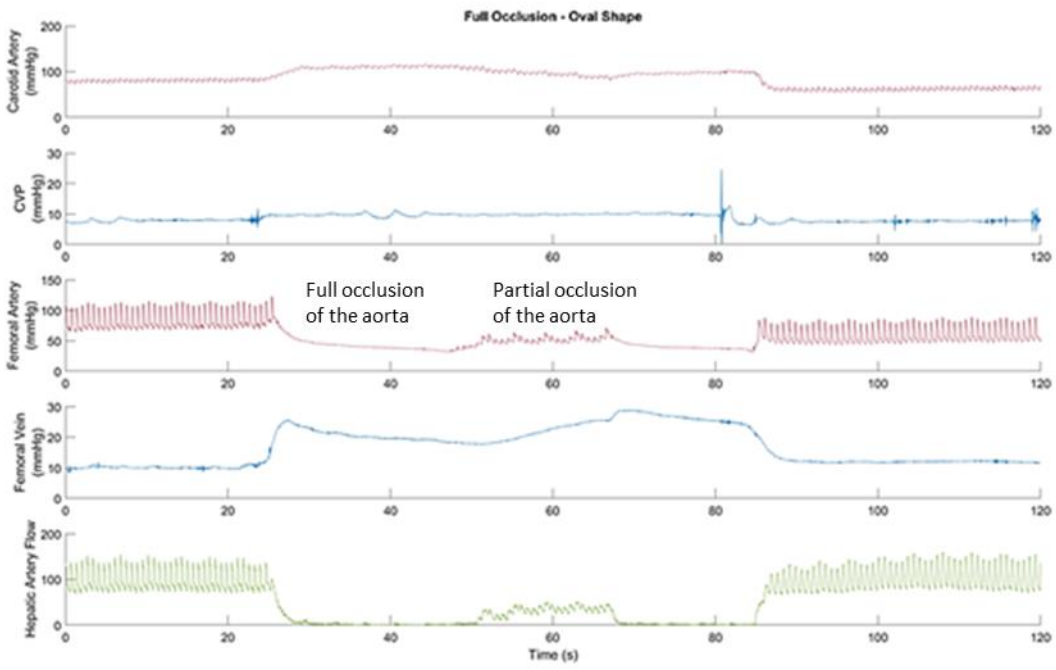


Fig 20. The physiologic effects of full, partial, and again full occlusion of the aorta during GROA device balloon inflation, while applying external pressure to the abdomen. The femoral arterial pressure loses all pulsatility during full occlusion (25-45 seconds). During partial occlusion (45-65 seconds) the mean and pulse pressures are reduced. Hepatic artery flow follows a similar pattern. During full occlusion flow is lost, followed by a reduced mean and pulsatile flow during the partial occlusion period. The hepatic artery flow reduction indicates the GROA device's ability to be effective for high zone 2 hemorrhage control.

In addition to initial application testing, 4 experiments have been run to refine the Experiment 1 hemorrhage model followed by 60 minutes of GROA aortic occlusion during hemorrhagic shock to evaluate physiological tolerance.

Experiment 1: Initial Occlusion and Physiologic Tolerance Testing
Animals were instrumented as described above. Once instrumented and baseline measures were obtained, animals were subjected to a controlled arterial hemorrhage of approximately 40% of their estimated blood volume (based on total estimated blood volume of 65 cc/kg) over 30-60 minutes by computer controlled peristaltic pump. Blood was collected into a blood collection bag primed with citrate phosphate dextrose solution.

Following hemorrhage, GROA device was deployed through the oral cavity and into the stomach. The balloon was inflated for 60 minutes of aortic occlusion (Fig. 21). Occlusion was verified by loss of femoral arterial pulse and hepatic artery flow.

At the conclusion of treatment time, an initial bolus of shed whole blood was infused prior to deactivation of GROA to attempt to avoid precipitous cardiovascular collapse. All remaining blood was reinfused following device deactivation (500mL). Calcium chloride was administered IV during blood administration to prevent hypocalcemia. Up to 2 liters of Ringer's lactate was infused IV following blood to attempt to maintain a mean arterial pressure of 60 mmHg. Animals were monitored for up to 1 hour following resuscitation. Laboratory samples were collected at various time points during the experiment for hematology, chemistry, blood gas, lactate, and coagulation analyses. Surviving animals were euthanized at 1 hour after resuscitation and stomachs were harvested post mortem for histological analysis.

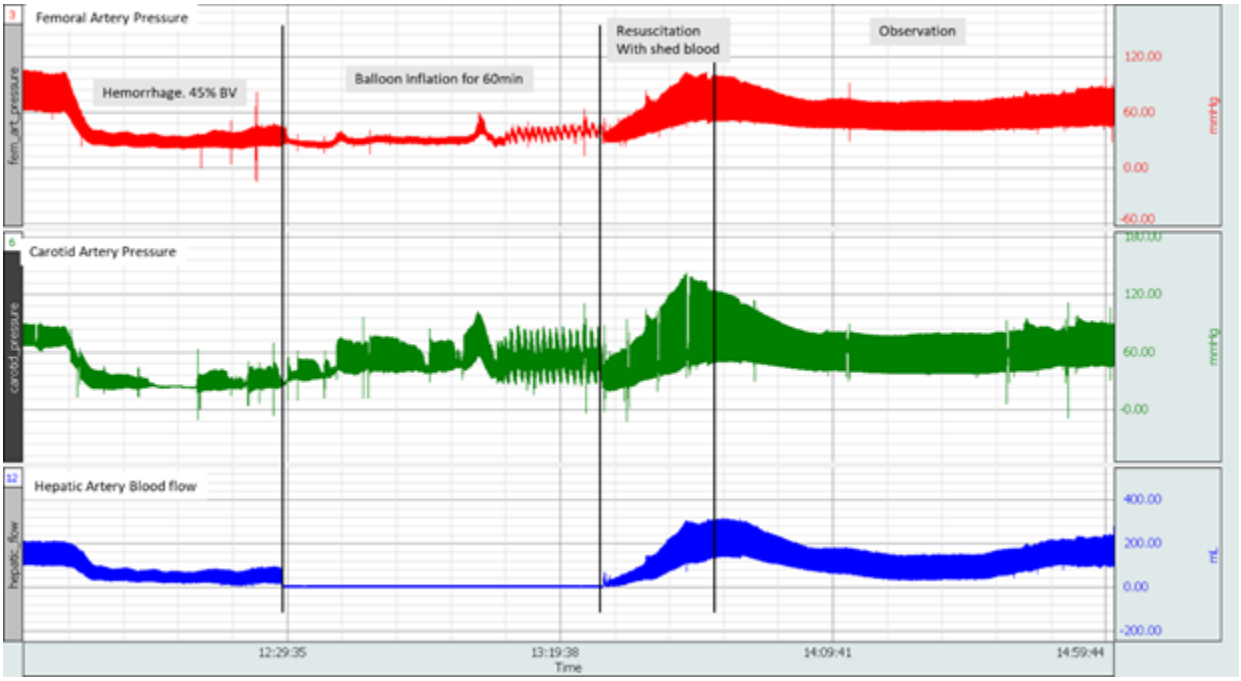


Fig 21. The above graph shows the physiologic effects of a sample 60min tolerance testing. Animal was hemorrhaged to a lactate of 5meq/dL then GROA balloon inflation, and external pressure applied to the abdomen. The femoral arterial pressure loses all pulsatility during full occlusion. Hepatic artery flow is lost during inflation as

well. After 60min, balloon was deflated and animal resuscitated with shed blood. Animal was monitored for 60 additional minutes with mean arterial pressure maintained ~65mmHg.

Technical limitations: 2 animals receiving GROA treatment for 60 minutes survived during the period of GROA activation. However, during release (balloon deflation), animals experienced hemodynamic collapse. Methods to explore belt release and balloon deflation at a slow controlled rate are being explored in additional to altering resuscitation during GROA induced aortic occlusion. These same challenges have been reported when using REBOA in animals and humans. We are deferring additional GROA experiments until we receive the manufactured balloon prototypes (described above).

Initial histology testing of the stomach tissue showed evidence of localized mild to moderate inflammation (gastritis) of the fundus and cardia that we believe will be mitigated with refinement of balloon material and configuration. Histology will be repeated and updated as experiments continue. See histology report in appendices

4. Other achievements and milestones

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

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

B. How were the results disseminated to communities of interest?
Nothing to Report

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

- Work on Major task 1 will be continued and expected to be complete by the next annual reporting period. This includes finalizing the manufactured and tolerance testing of the device prototype, and continuing to refine the external compression belt design iterations and efficient deployment strategies. Morphomics analysis to better understand the anatomy of the gastroesophageal junction will be continued, as well as in-silico modeling of swine and human subjects for further prototype development. Animal tolerance testing will be resumed and completed using manufactured prototypes upon their receipt. One or more abstracts are planned to be submitted to MHSRS and other national meetings. We also aim to begin manuscript writing in both medical and engineering scientific journals for publication within the next reporting period.
- Work on Major task 2 will begin upon completion of initial animal tolerance testing. Here we will move on to testing and comparing GROA prototypes to REBOA for staunching severe noncompressible abdominal hemorrhage in a large swine animal model of traumatic shock. Swine prototypes will continue to be refined, and human prototyping will be started upon completion of the morphomics analyses. Additional industry partners will be sought during this period.

IMPACT:

A. **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 belt (tourniquet) 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.

B. **What was the impact on other disciplines?**
Nothing to Report

C. **What was the impact on technology transfer?**
Invention disclosure on file with the University of Michigan Office of Technology Transfer. Disclosure Title: Gastroesophageal Resuscitative Occlusion of the Aorta (GROA) Disclosure Date: Sep 26, 2018 OTT Ref. No.: 2019-106. See attached disclosure in appendices. 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.

D. **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 will be followed by demonstrating the 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. 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 prove to compare favorably with REBOA in the preclinical laboratory setting. 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.

CHANGES/PROBLEMS:

A. **Changes in approach and reasons for change**
Nothing to Report

B. **Actual or anticipated problems or delays and actions or plans to resolve them**
Waiting on the device design iterations and manufacturing of GROA prototypes has caused a brief delay in animal tolerance testing as outlined in Major Task 1. Expected delivery of manufactured prototypes in March will allow for the continuation, and then acceleration of animal tolerance

experiments should resolve the delay. We believe this temporary delay in order to obtain the new prototypes will allow the best use of animals and other resources.

C. **Changes that had a significant impact on expenditures**
Nothing to Report

D. **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents:**
Nothing to Report

E. **Significant changes in use or care of human subjects:**
None to report

F. **Significant changes in use or care of vertebrate animals:**
None to report

G. **Significant changes in use of biohazards and/or select agents:**
None to report

PRODUCTS:

A. Publications, conference papers, and presentations
1. **Journal publications.** Nothing to Report
2. **Books or other non-periodical, one-time publications.** Nothing to Report
3. **Other publications, conference papers, and presentations.** Nothing to Report
4. **Website(s) or other Internet site(s).** Nothing to Report

B. Technologies or techniques.
Nothing to Report

C. Inventions, patent applications, and/or licenses
Invention disclosure: Gastroesophageal Resuscitative Occlusion of the Aorta (GROA) Disclosure Date: Sep 26, 2018 OTT Ref. No.: 2019-106. See appendices

D. Other Products
Nothing to Report

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

A. 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
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
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
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:	2
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:	4
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:	2
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:	Chandler Rygalski, 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:	Daniel Taylor, MA
Project Role:	Data Engineer
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	3
Contribution to Project:	Signal processing, data storage and analysis
Funding Support:	

Name:	Mark Salamango, PhD
Project Role:	Data Engineer
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Signal processing, data storage and analysis
Funding Support:	

Name:	Jeffery Plott, PhD
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:	Lei Chen
Project Role:	Design Engineer
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	3
Contribution to Project:	Analysis, design and fabrication of the GROA devices for animal lab studies
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:	Morphomics analysis
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	3
Contribution to Project:	Collection, vetting and analysis of morphomic data.
Funding Support:	

B. 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

C. What other organizations were involved as partners?
Nothing to Report

SPECIAL REPORTING REQUIREMENTS

- **COLLABORATIVE AWARDS:**
  Nothing to Report

- **QUAD CHARTS:**
- QuadChart is included with this report
-
- **APPENDICES:**
  - Histology report
  - Invention disclosure
  - PI biosketch

Gastroesophageal Resuscitative Occlusion of the Aorta (GROA)

DM160299 Prolonged Field Care Research Award

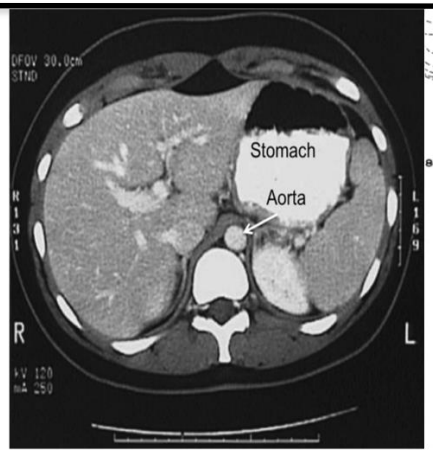
PI: Kevin Ward, MD **Org:** University of Michigan **Award Amount:** $2,995,616

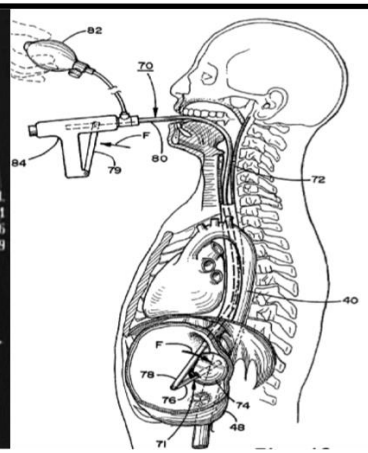
Study/Product Aim(s)

- Design and prototype GROA device(s) that can be into the stomach to allow occlusion of the aorta and test the physiologic tolerance of the device 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 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
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 Goal – 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

✓Animal studies in noncompressible hemorrhage compared to REBOA

✓Iterative design and study as necessary

CY20 Goal – Additional Preclinical and Human Factors Testing

✓Tandem use studies of GROA to REBOA

✓Refinement of human factors and GROA design for future clinical studies

Comments/Challenges/Issues/Concerns

✓None at this time.

Budget Expenditure to Date: $782,234

In Vivo Animal Core (IVAC)
North Campus Research Complex
2800 Plymouth Road B36/G157
Ann Arbor, MI 48109-0614
Lab: (734) 647-0654 **Fax: (734) 936-3235**
Email: ULAM-IVAClab@umich.edu **Web Site: http://med.umich.edu/ulam/services/pathology.html**

Request Date: 7/26/18
Pathologist: MJH
Returned Date: 8/28/18

Case number: 18M053
Species: SUS
PI: Tiba
Contact: Carmen Colmenero

History

An intact pig stomach was submitted in formalin for pathology evaluation. The stomach was immersion fixed in formalin, and the esophagus and duodenum were tied off with surgical tape. The lumen of the stomach was not infused with formalin. Sections were requested from multiple sections of the cardia, fundus, pylorus, and body of the stomach for histopathology.

RESULTS (descriptive)

Grossly, the mucosal surface of the stomach was unremarkable. There were multifocal areas of mild mucosal sloughing due to autolysis. Histologically, there was mild autolysis of the surface epithelium, with sloughing and loss of superficial mucosa. Sections of pylorus and stomach body were histologically unremarkable. In sections of fundus, there was mild expansion of the submucosa with edema and a mild to moderate inflammatory infiltrate composed predominantly of clusters of eosinophils, macrophages, and fewer lymphocytes, which extended multifocally into the associated deep mucosal lamina propria. Milder but similar inflammatory cell infiltrates were observed in sections of cardia. There was prominent gastrointestinal associated lymphoid tissue (GALT) in sections of fundus and cardia, with evidence of central lymphocytolysis and the presence of tingible body macrophages. However, the extent of autolysis made the interpretation of GALT hyperplasia difficult. Direct damage to the mucosal surface, either mucosal or squamous, was not observed in sections examined.

Morphologic diagnosis: Gastritis, eosinophilic to mixed, mild to moderate, locally extensive, with possible GALT hyperplasia.

DISCUSSION:

The purpose of this evaluation was to evaluate multiple areas of the submitted stomach for evidence of tissue damage. There were locally extensive inflammatory changes in sections of cardia and predominantly fundus, associated with tissue edema, suggesting a local reaction to stimulus in these areas. A cause for these inflammatory cell infiltrates was not observed histologically, but local irritation due to an ingested substance or other inflammatory stimulus may produce such a lesion. The large number of eosinophils in the inflammatory population is not unusual for a pig, as this is a common finding often in mixed inflammatory infiltrates, and without a corresponding control animal, is difficult to determine the biologic relevance of the inflammatory reaction in this animal, because random foci of inflammation may actually represent background lesions in unmanipulated pigs. More information regarding the experimental manipulation and endpoints may be helpful to better understand the relevance of this lesion to the goals of the study. There was no evidence of direct damage to the mucosa of the stomach otherwise.

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

August 28th, 2018

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.

TECH TRANSFER
UNIVERSITY OF MICHIGAN

Invention Disclosure – CONFIDENTIAL

Please see the last page of this document for detailed instructions for completion and submission of the University of Michigan Invention Disclosure form.

Disclosure Date: September 26, 2018

Title: Gastroesophageal Resuscitative Occlusion of the Aorta (GROA)

Description:

The GROA device is a tube with deployable balloon that is a designed to limit catastrophic abdominal or pelvic hemorrhage from trauma or other causes. The device is designed to be placed into the stomach from the oral cavity. Once placed, the balloon is inflated just below the gastro-esophageal juncture. An external adjustable belt is placed around the abdomen and is designed to apply external pressure to the epigastric area of the patient. This pressure causes the gastric balloon to be displaced posteriorly resulting in compression of the aorta between the posterior wall of the stomach and the anterior body of the thoracic vertebral body. The external pressure applied by the belt and/or balloon inflation can be adjusted to partially occlude the aorta as well.

Endovascular balloon occlusion has been used over decades for torso hemorrhage control and has recently been commercialized as Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) https://prytimemedical.com/ New patents were filed (by the University of Michigan) to cover catheter designs, etc. However, REBOA requires insertion of the catheter into the femoral artery and is not suitable for field use. GROA overcomes these challenges by allowing occlusion via rapid insertion of the device into the stomach from the oral cavity.

GROA can also be used as an adjunct to cardiopulmonary resuscitation during cardiac arrest as a means to increase coronary and cerebral perfusion pressure.

The GROA device/technique has been previously described through a series of patents by Dr. Kevin Ward while at Ohio State University in the mid 1990's and early 2000's. These patents are provided.

The GROA concept was proposed at that time to the Dept of Defense (DoD) but was not embraced. However, given the war on terror and the increase use of prolonged field care by the military, the DoD is now very interested in the technology and approach and awarded the Michigan Center for Integrative Research in Critical Care (MCIRCC) a 3 million dollar grant to develop GROA.

A close examination of the prior art will need to be performed in conjunction with the inventors to determine if new IP can be developed that enhanced the chance of the GROA technology to be moved forward and commercialized.

Additional materials are provided including grants, updated design information, and previously applied patents.

Date of First Public Disclosure: See accompanying patents and grant.

Circumstances of Public Disclosure:

Researchers:

Researchers Name	Organization & Department	Email and Contact Info	Contribution %
Kevin Ward	UM Dept Emerg Med	keward@umich.edu	80
Jeffery Plott	UM Dept Mechanical Engineering	plottjs@umich.edu	20

Funding: *(include all sources of funding which supported this work, including federal, corporate/industry, foundations, departmental, startup, etc.)*

Organization	UM PAF or PGN	Grant or Award Number
Department of Defense	16-PAF08148	W81XWH-18-1-0005

Additional Questions:

1. Are any publications or other public disclosures planned for this discovery?
   If Yes, please provide anticipated date(s) and additional details:

Abstract submissions to national meetings are anticipated in the next 6-12 months

2. Is this work funded by Wireless Integrated MEMS Center (WIMS)?

No

3. Do any researchers have either a WOC (Without Compensation) or DAP (Dual Appointment Personnel) appointment with the VA (Veterans Administration)?
   If Yes, please provide the names of those with VA appointment:

No

4. Do any researchers have any appointment with HHMI (Howard Hughes Medical Institute)?
   If Yes, please provide the names of those with HHMI appointment:

No

5. Is this work covered by any MTA, or have you received materials or data from another party?
   If Yes, please provide additional details:

No

6. Have you entered into any contracts with third parties related to this matter (e.g. consulting agreements, other agreements you have signed personally)?
   If Yes, please provide additional details:
No

7. Are any non-UM collaborators involved in this work who are not included in the Researcher Information section of this submission?
   If yes, please provide name, organization and email address for each:

No

8. Are you aware of any potential licensees for this discovery?
If so, please provide additional details:

Prytime Medical: https://prytimemedical.com/
Zoll Medical Inc
Combat Medical Inc

9. Please describe the closest known product/technology:

Resuscitative Endovascular Occlusion of the Aorta (REBOA). A version of this (ER-REBOA) was patented by Dr. Jonathan Elliason of the UM and licensed to Prytime Medical.

Abdominal Aortic Tourniquet: https://www.chinookmed.com/05246/abdominal-aortic-junctional-tourniquet-aajt.html This device compresses the aorta externally but aortic compression occurs at a lower level (zone) that can be achieved with either REBOA or GROA.

Please provide any additional details, attachments and supplemental information related to this disclosure, as necessary.

Instructions for University of Michigan Invention Disclosure

Disclosure Date – Please provide the date on which you are submitting this new disclosure form.

Title – Enter a brief title for your disclosure. This title should be generic and should not include any confidential information, acronyms or trademarks.

Description – Provide a brief summary and general description of the invention, idea or discovery that you are reporting to our office. Please provide a detailed technical description of your work by including supporting documents with your submission.

First Public Disclosure – Please enter the exact date (mm/dd/yyyy) of the first public disclosure of this work, or any portion thereof. Public disclosures impact patent protection options, funding compliance, etc. and will need to be discussed. If no public disclosure has yet occurred, please leave this field blank. Planned or potential public disclosures will be covered in a later field.

Circumstances of Disclosure – Please provide details of the public disclosure (i.e. format, content, location, audience) and include a copy of the publication, poster, presentation, etc. with your submission. If no public disclosure has yet occurred, please leave this field blank.

Researchers – Please provide enter information regarding all individuals who participated in the conception or development of elements of this invention, **including those not at the University of Michigan**. For each UM contributors, please include, at a minimum, their UM department and @umich.edu email address. For each Non-UM contributor, please include, at a minimum, the name of their company, organization or institution, and a current email address. **NOTE: This is not an indication of who the inventors are. Inventorship is a legal determination that will be made if a patent application is drafted and claims are written.**

Please indicate the contribution % for each contributor. The % Contribution should indicate your assessment of each individual's relative contribution to the concepts of this invention and must equal **a total of 100%**.
NOTE: License revenues, if any, will be distributed according to University Policy.

Funding – Please provide information for all funding sources which supported this work, including external sources, department and/or discretionary funds. This information is required in order to satisfy obligations and compliance efforts to federal funding agencies, industry partners or other sponsors. For all funding sources, please provide the name of the sponsor (i.e. funding agency, foundation, company, institution, department, etc.), the UM PAF or PGN, and the grant or award number, if known. If no funding information is provided, additional verification will be required before the disclosure submission is accepted.

Additional Questions – Please answer all additional questions before submitting your disclosure. Please provide details, including exact dates if known, for all planned public disclosures, publications, manuscript submissions, etc.

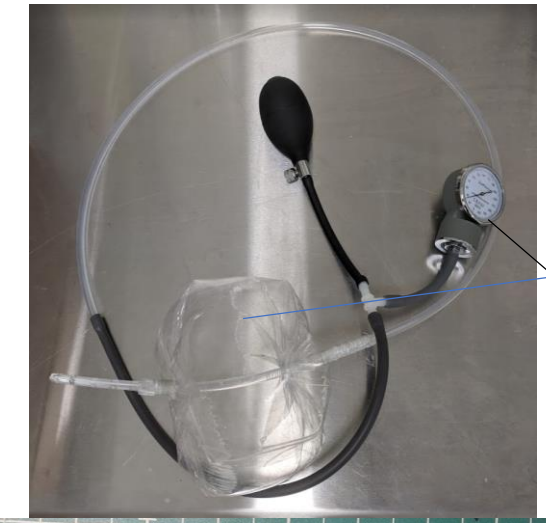
Submission and Attachments – Please email your completed disclosure form, along with all relevant documents and supplemental material, including, but not limited to, a complete technical description of the invention, draft manuscripts, figures, drawings, posters, presentations, etc., to OTT at techtransfer@umich.edu.

Questions? – If you have questions or problems with the form, please email OTT at techtransfer@umich.edu or call 734-763-0614. You may also visit: https://techtransfer.umich.edu.

The information contained in a disclosure submission to OTT is confidential and should not be disclosed to persons outside the University or to persons not requiring access to this information.

Method of use:

The system consists of a catheter balloon which is placed down the esophagus and into the entrance of the stomach. A tourniquet with anatomical pressure plate is placed around the abdomen and tightened. The catheter balloon is then inflated until the desired occlusion of the descending aorta is achieved.

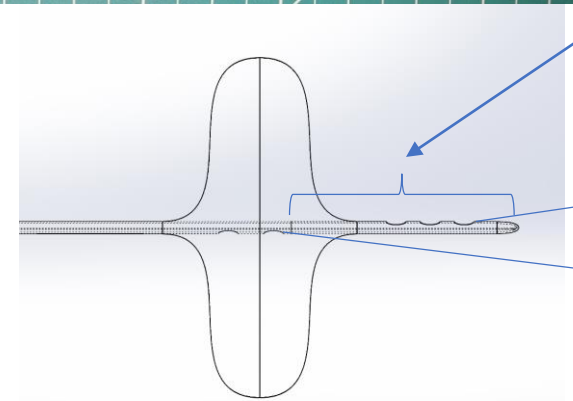


The balloon material is ideally thin (~<0.005”) with high tensile modulus so that it can act as a flexible yet rigid body when pressed against the aorta.

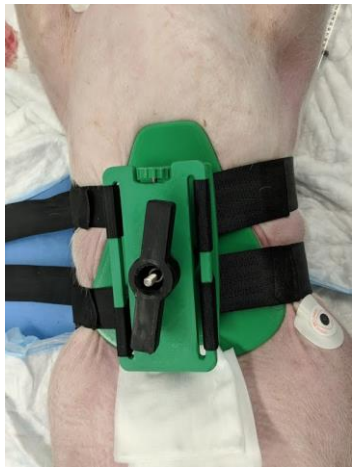
The balloon can be inflated with fluid (preferably ambient air) using a hand pump. It can have a gauge to indicate pressure. Can also have sensors to detect pulsatile flow.

The balloon can also be attached to a vacuum pump to help remove air and make insertion/removal easier

Catheter balloon can include a multi-durometer lumen. Preferably, the tip has high flexibility (low durometer material ~10-70A shore hardness) and a blunt end. This helps to prevent perforation and also helps the device navigate through the esophageal sphincter and into the entrance of the stomach. Since the balloon is so large, the flexible portion of the catheter can optionally extend into the area where the balloon is secured to the tubing to help the balloon bend and direct its way past the esophageal sphincter and into the stomach. The other part of the tube can be of higher durometer to help make it easier to push the balloon into the stomach. A sheath can also be placed over the balloon and removed/dissolved/broken once the balloon in in position and ready for inflation.



Can have one or more lumen(s) to allow for separate balloon inflation and stomach content evacuation



External pressure is required to give the balloon an opposing force since high force is required to occlude the descending aorta.

The pressure plate is designed to press on the abdomen while minimizing the restriction on the rib cage/lungs. Since we want the balloon to stay as high up in the stomach as possible to occlude the descending aorta as high as possible, the pressure plate can also include features that hinder the balloon’s ability to float out of the idea position in the body.

To adjust the tourniquet pressure, we are using a modification of the invention in patent US20180193030A1.

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 new high fidelity complex large animal models of critical illness and injury, 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 approaches and technologies for complex critical illness and injury disease processes.

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
2019-Present Lieutenant Colonel U.S. Army Reserves Medical Corps

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. Medical Innovation, Entrepreneurship, Team Science, and Mentoring: 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

NSF: 1837985 Dersken (PI) 09/01/18-08/30/21
Sponsor: National Science Foundation
Algorithms for Tensor-Based Modeling of Large Scale Structured Data
Description: The major goal of this project is to apply tensor based modeling to large scale heterogenous data to develop predictive algorithms using sepsis as a target.
Role: Co-Investigator

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
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: $358,129
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