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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 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 (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 (in progress 80% complete)

- **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) (in progress 80% 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 75% 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 (10% complete)

  - **Milestone Targeted**: Complete comparison studies of GROA and REBOA in swine with severe noncompressible hemorrhagic shock. (24 months) (in progress 10% complete)
  - **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)

- **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 (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 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 2019 – May 2019:

- **Received and tested the first batch of balloon samples by Interplex.**
  During this time, we received our first balloon samples produced by Interplex Medical (identified manufacturer in 2018 based on our design requirements). As seen in Fig. 1, the old prototype balloon is shown on the left while the newly manufactured balloon from Interplex is on the right. Upon evaluating the sample, we were encouraged by the inflated shape and much more compact deflated form factor when compared to our prototype balloons. This leads us to believe the balloon performance will exceed that of our hand-made prototypes. The new balloons also proved to be durable and leak free in benchtop testing. Even though the balloons arrived, there was a delay in the catheter extrusion manufacturing so we have not yet been able to test the new balloon design in a live animal. We expect to receive complete GROA devices by mid-May and plan to test in pigs shortly thereafter.

Fig. 1 Prototype comparison: hand-molded balloon (left) vs. Interplex manufactured balloon (right).

May 2019 – Aug 2019:

- **Received and tested the first and second batches of complete GROA prototypes.**
  During this quarter, we received our first complete GROA device samples produced by Interplex Medical. These prototypes included a custom triple lumen catheter extrusion and urethane balloon of various hardness and thicknesses affixed to the catheter, shown in Fig. 2. Multiple balloon hardness and thicknesses were selected based on prior prototyping work to evaluate and optimize the tradeoff between balloon strength and ease of placement. Based on our testing, we determined that the softer balloon material (Shore 90A, 0.0055” thick) could easily pass through the esophagus and into the stomach. However, due to the soft and thin nature of the balloon material, it could not withstand the necessary pressures needed to achieve aortic occlusion without experiencing some permanent deformation. Conversely, the harder balloon material (Shore 55D, 0.0045” thick), was not compliant enough when molded into balloon shape to easily fit down the esophagus. Interplex also experienced manufacturing issues and failed to fully sealing the

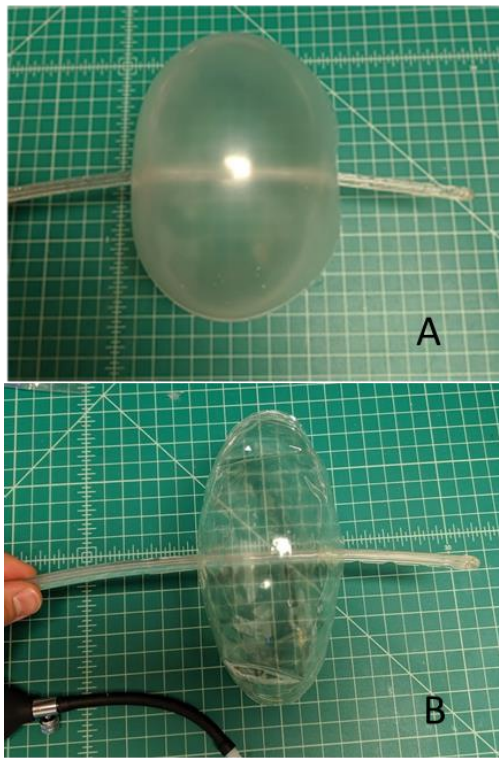

Fig. 2 Interplex Medical manufactured GROA device: (a) soft balloon material (90A, 0.0055” thick) and (b) hard balloon material (55D, 0.0045” thick)

harder balloon material onto the custom catheter due to low compliance.

With this first round balloon testing complete, we decided to have Interplex Medical produce a second batch of GROA prototypes using a slightly thicker version of the soft balloon material (Shore 90A, 0.01" thick). The design thinking behind this second batch of balloons was that by utilizing the same soft material as the balloon version which easily passed into the stomach, but with a slightly increased thickness, we could preserve the ease of insertion while giving the balloon enough strength to withstand the high pressures required for aortic occlusion. We received this new GROA design in late July. Images of the complete GROA device in both inflated and deflated conditions are shown in Fig. 3.

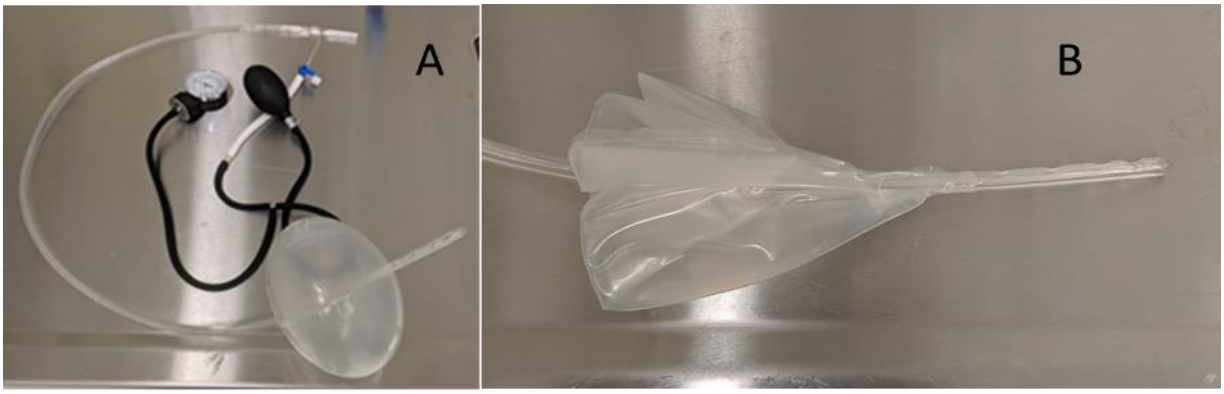

Fig. 3 Second round of Interplex Medical manufactured GROA device with soft balloon material and increased thickness (90A, 0.01" thick): (a) fully inflated device and (b) deflated device.

Since this new device passed benchtop evaluation, we then moved to testing it out in a live animal experiment. The device performed well and was able to be successfully inserted, inflated to sufficient pressure to cause aortic occlusion, and maintain structural integrity over a period of 30 to 90 minutes for the whole test. Figure 3 shows this second round GROA prototype after completion of the live animal testing. No degradation of the device was observed making us confident that we have the correct combination of geometrical design and material properties. The next steps include producing additional prototypes of this design to ensure they can be manufactured reliably and continue to perform in live animal experiments.

- **Continued optimization of external pressure storage/back-plate system**
  While the previous external pressure system was able to successfully create sufficient downward force on the abdomen without being overly restrictive to breathing, we continued to iterate the design focusing on reducing the weight and volume of the system along with its ease-of-use. As part of that effort, we tested a variety of different abdominal plate sizes to discover the minimum required geometry for the GROA application. We also modified the back plate which can easily provide a flat surface to support the subject's abdominal site. Furthermore, the quick-connect snap features, using the buckles and strips, were added as a fixation method to easily connect the abdominal plate to the back plate during use. Figure 4 shows the use of the refined system to create

Fig. 4 Eternal pressure system with reduced weight, volume, and quick-connect snap system.

adequate external pressure. These improvements enable the system to pack flatter while still allowing for rapid assembly and deployment. Consequently, the storage box size was also able to be reduced. This new system was successfully tested in a live animal experiment. Next steps include continued testing of this new design along with a more rigorous human factors analysis to ensure it meets the needs of all the potential end users of the device.

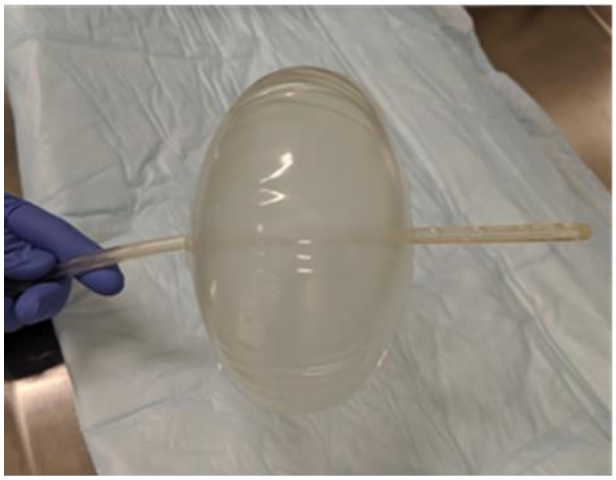

Fig. 5 The second round Interplex Medical manufactured GROA device with soft balloon material and increased thickness (90A, 0.01" thick) after successful live pig study. No device degradation or damage was observed.

- **Received and tested additional GROA device prototypes**
  During this quarter, we continued working with Interplex to order more GROA devices (Fig. 5) to test the manufactured reliability and device performance in live animal experiments.

- **Optimization of balloon catheter design and delivery procedure**
  While the GROA device was able to create the aortic occlusion, we continued to iterate the device design focusing on mitigating the stomach damage caused by the catheter tip during delivery. Inspired by the telescope configuration, we developed the new balloon catheter design allowing the combination use with the existing stomach tube. The existing stomach tubes, specifically Salem Sump, have demonstrated to enable an easy and safe delivery process. In the envisioned procedure, the stomach tube will be deployed first as a guidewire, and then the GROA balloon catheter (coaxially installed onto the stomach tube) will follow the deployed tube to the desired anatomic position. Such new configure can reduce the resistance during the GROA balloon insertion and the collateral damage due to the force required to push the balloon into the stomach. We are currently working with Interplex on this design change and manufacturability evaluation. Next steps include producing this new balloon design and testing using the live animals to ensure the delivery procedure can be improved and stomach damage will be reduced.

- **Optimization of external pressure storage/back-plate system**
  In the recent tests of the previous external pressure system, we found that the strips used to connect the abdominal plate to the back plate gradually slipped out from the buckles over time, causing the external pressure to drop. This was due to the reaction force created by the applied pressure which pulled the strips and loosened the connection between the strips and buckles. Such phenomenon then required additional effort to re-adjust the strip length

Fig. 6 Refined eternal pressure system offering steady external pressure.

periodically to maintain the desired pressure, which potentially introduce the variations and human errors during the experiments. Therefore, we continued to refine the system design focusing on eliminating such issue and steadily maintaining the applied external pressure. Figure 6 shows the refined system prototype. We modified the buckle features to ensure the connection between the strips and buckles will be maintained regardless the magnitude and direction of the reaction force from the applied pressure. In the latest animal test, we have demonstrated this new external system design to offer steady external pressure and ease of use. This improves the system reliability and avoids additional labor efforts. Next steps include continued testing of this new design along with a more human factors analysis to ensure it meets desired performance and the needs of all the potential end users of the device.

Specific objectives

- **Subtask 1**: Local/Institutional IRB approval (approved 6/6/2017)
- **Subtask 2**: ACURO Approval (approved 8/9/2017)
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Significant results

Swine testing of initial GROA prototypes and testing of physiologic tolerance is near completion. Animals use Data:

a. Species: Sus Scrofa Domestica
b. Total animal number used this period: 50
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

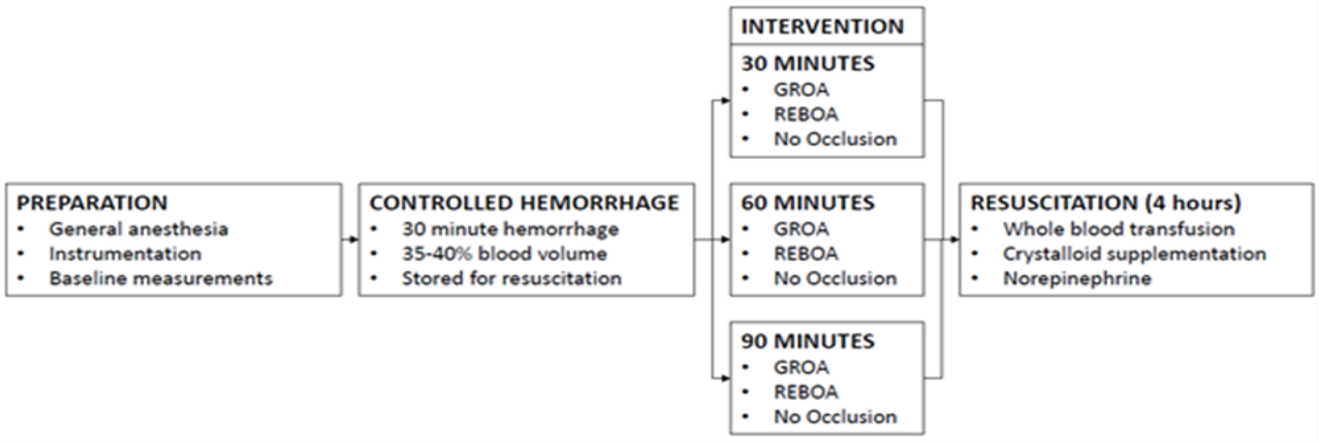


Figure 7: Experiment 1) Flow chart of experimental procedures and intervention groups.

(Experiment 1). Forty-six male Yorkshire mix swine have been used to evaluate physiologic tolerance. Animals were randomly designated to one of nine intervention groups prior to anesthesia. Animals were

assigned an intervention REBOA, GROA, or no intervention (control), as well as an intervention duration of 30, 60, or 90 minutes (figure 7).

Instrumentation. The right carotid artery was cannulated for measurements of mean arterial pressure (MAP) and collection of blood samples. The left external jugular was cannulated for delivery of resuscitation. The right external jugular was cannulated with a pulmonary artery thermodilution catheter. The right common femoral artery was cannulated with a 9F introducer for controlled arterial hemorrhage and REBOA access while the left was cannulated for measurement of femoral arterial pressure (FAP). According to experimental designation, ER-REBOA catheters or GROA devices were placed at the conclusion of instrumentation and baseline physiologic measurements and laboratory samples were obtained.

Hemorrhage. A 30-minute controlled hemorrhage period was initiated where approximately 35% total blood volume was removed. Two units of shed blood were collected in citrate phosphate dextrose bags and saved for resuscitation.

Interventions (30, 60 or 90 minutes). Immediately following hemorrhage, prescribed interventions were deployed. In the control groups, there was no intervention and animals were observed for the duration of the assigned treatment period. Occlusion in GROA and REBOA groups was verified by loss of pulsatility in the femoral artery waveform. After device deployment and aortic occlusion was verified, animals were observed for the duration of their intervention periods.

Resuscitation. Resuscitation for all groups included whole blood transfusion using the two units of shed blood, followed by IV crystalloid (Lactated Ringer's) solution infusion. At the end of treatment period for the aortic occlusion groups, the devices were slowly released to reestablish aortic flow. Post resuscitation monitoring and data collection continued for 4 hours while laboratory samples were collected at designated points. All animals were euthanized with potassium chloride under isoflurane at the completion of the monitoring period. Following euthanasia, stomach and aortic samples were harvested for histological analysis by a blinded veterinary pathologist.

Significant Findings & Results: Baseline characteristics of all animals included in the study are outlined in table 1. All animals included in the study survived the duration of their intervention periods.

	30-Minute Intervention			60-Minute Intervention			90-Minute Intervention		
	Control	GROA	REBOA	Control	GROA	REBOA	Control	GROA	REBOA
N	6	5	5	5	5	5	5	5	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(6.4)	49(4.8)
Hemorrhage (%)	35(2.0)	34(3.0)	35(1.0)	35(2.0)	35(3.0)	35(3.0)	39(4.7)	35(1.5)	40(7.1)
MAP (mmHg)	80.8(7.50)	84.3(7.60)	88.9(8.07)	97.5(9.42)	81.3(10.41)	86.6(10.52)	82.0(15.43)	81.8(17.83)	85.8(12.59)
Heart Rate (BPM)	85.2(9.20)	84.4(11.68)	92.1(0.76)	103.9(28.71)	85.4(2.37)	77.3(4.44)	102.2(28.16)	91.5(10.39)	82.6(4.78)
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)	37.4(0.47)[¤]	36.5(0.37)
pH	7.42(0.023)	7.40(0.019)	7.49(0.085)[¤]	7.38(0.038)	7.39(0.036)	7.38(0.069)	7.45(0.056)	7.38(0.051)	7.46(0.023)
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)	2.7(1.84)	1.6(0.52)
SvO_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)	68.7(8.31)	71.9(4.59)
$PetCO_2$ (mmHg)	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)	39.6(2.09)	36.6(8.67)

Table 1. Baseline hemodynamic characteristics. Data is presented as average (standard deviation). 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. MAP = Carotid mean arterial pressure. SvO_2 = Mixed venous oxygen saturation. $PetCO_2$ = Pressure of end tidal CO_2.

Mean Arterial Pressure(MAP) and lactate data for all groups are presented in figure 8. All animals showed a significant reduction in MAP from baseline an average(SD) of 85.4(11.55) mmHg to 34.9(5.35) mmHg p<0.0001. MAP in GROA and REBOA animals increased to 98(32.55) mmHg and 122(24.79) mmHg respectively 15 minutes into the intervention period. At the end of intervention period, MAP ranged from 61-90mmHg in the GROA groups and 76–120 mmHg in the REBOA groups. Animals which survived 4 hours post resuscitation, on average maintained MAP above 60mmHg following device deactivation with the exception of the two surviving GROA 90-minutute occlusion animals where MAP averaged at 53 mmHg.

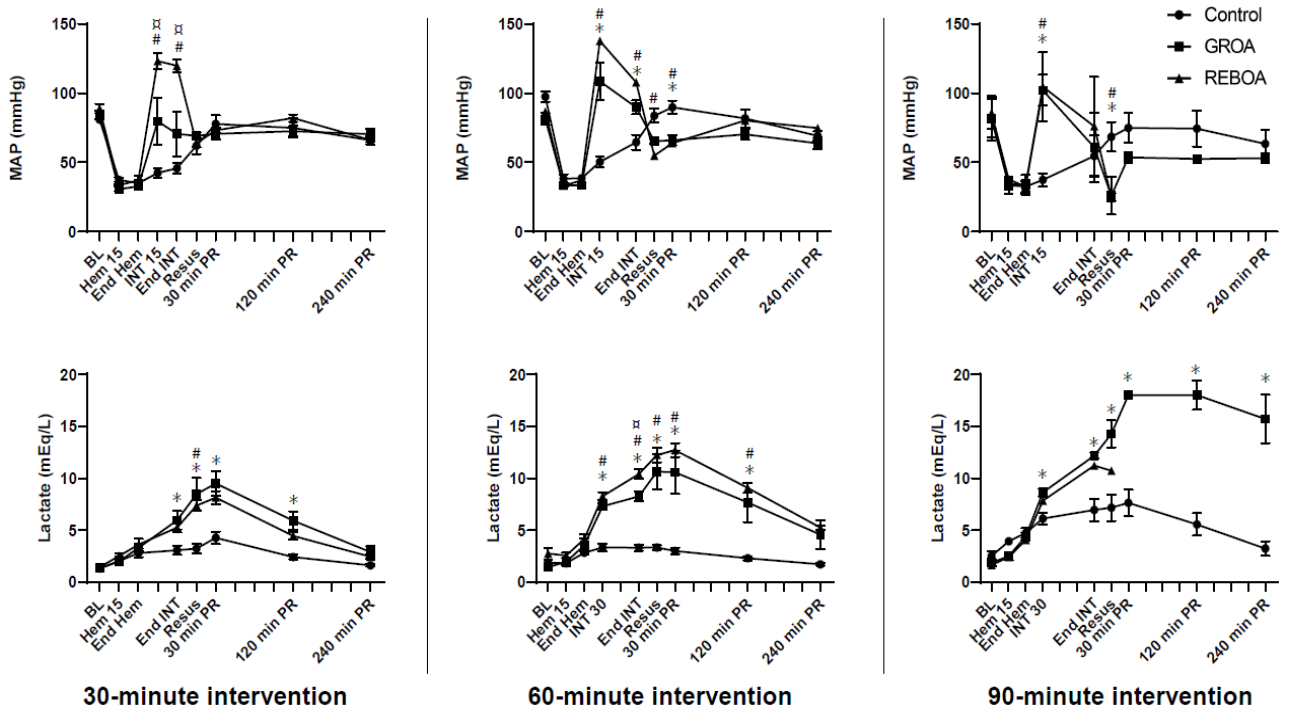


Figure 8: Average and standard error of mean arterial pressure (MAP) of the carotid artery and arterial lactate concentration for 30, 60, and 90-minute interventions. BL, baseline; Hem 15, 15 minutes into hemorrhage, End Hem, End of hemorrhage; INT 15, 15 minutes into intervention; End INT, End of intervention; Resus, Resuscitaion; PR, Post Resuscitation.
* Denotes statistically significant difference from GROA and control, # Denotes statistically significant difference from REBOA and control, ¤ Denotes statistically significant difference from GROA and REBOA

In all GROA and REBOA groups, lactate increased relative to controls and gaining statistical significance by 30 minutes of intervention to 7.3(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. There were no significant differences in lactate between GROA and REBOA groups during the post resuscitation monitoring period. Lactate levels decreased in all REBOA and GROA groups following device deactivation and resuscitation.

Data for mixed venous oxygen saturation (SvO_2)and end tidal CO_2 are presented in figure 9. SvO_2 increased in both GROA and REBOA groups relative to controls at 30 minutes of occlusion to levels of 59.7(23.38)% and 81.5(15.31)%, vs 42.4(15.45)%, respectively p<0.05. SvO_2 in the GROA group was significantly lower than in the REBOA group p=0.0063 at the same time period.

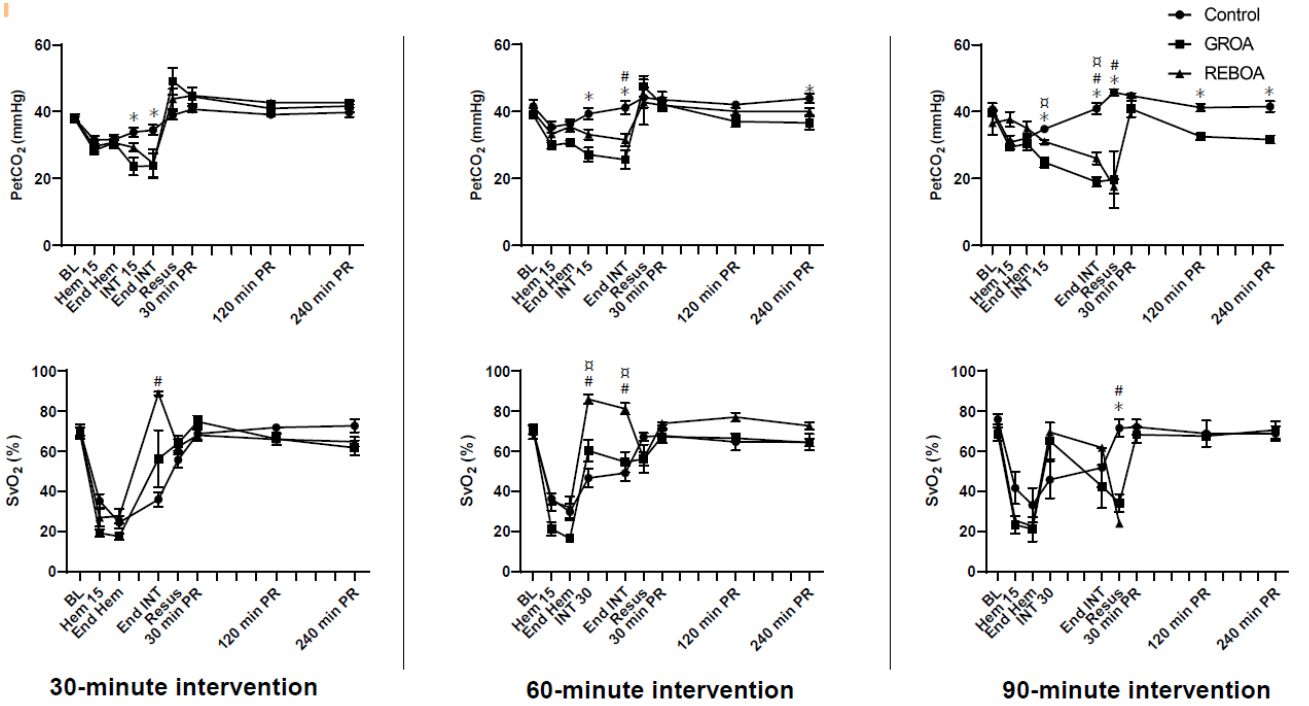


Figure 9: Average and standard error of end tidal CO_2 ($PetCO_2$) and mixed venous oxygen saturation (SvO_2), for 30, 60, and 90-minute interventions. BL, baseline; Hem 15, 15 minutes into hemorrhage, End Hem, End of hemorrhage; INT 15, 15 minutes into intervention; End INT, End of intervention; Resus, Resuscitaion; PR, Post Resuscitation.
* Denotes statistically significant difference from GROA and control, # Denotes statistically significant difference from REBOA and control, ¤ Denotes statistically significant difference from GROA and REBOA

SvO_2 was observed to return and was maintained near baseline levels following resuscitation in all groups. $PetCO_2$ decreased in both GROA and REBOA groups relative to controls following at 30 minutes of occlusion to levels of 24.9(7.07) mmHg and 30.3(4.59) mmHg, vs 37.2(4.41) mmHg, respectively $p<0.05$. $PetCO_2$ returned to near baseline levels following device deactivation and resuscitation in the 30 and 60-minute intervention groups.

Data for survival, resuscitation requirements, airway pressure, and end organ function are presented in table 2. 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 ($p<0.0001$). However this pressure does not exceed safe tolerance levels and returned to baseline following device deactivation.

		30-Minute Intervention			60 Minute Intervention			90 Minute Intervention		
		Control	GROA	REBOA	Control	GROA	REBOA	Control	GROA	REBOA
Survival to end-exp	*Ratio*	3:6	4:5	5:5	5:5	5:5	4:5	5:5	2:5	0:5
Resuscitation										
Lactated Ringer's	*mL*	1336(444.5)	1200(270.8)	750(452.4)	918(543.8)	1640(1527.4)	1250(655.7)	1455(1578.6)	4837(53.0)*	-
Norepinephrine	*mcg*	23.0(47.38)	85.6(124.50)	2.0(4.47)	0	571.1(764.11)	180.4(221.45)	2.4(3.57)	1088.1(1731.87)*	
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)	7.38(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)	9.4(0.56)	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(1.69)	-
PLT(10^3/L)	Baseline	252(138.6)	320(76.7)	231(108.0)	312(114.3)	297(92.7)	245(104.7)	272(78.6)	316(48.1)	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(0.58)	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)	1.27(0.079)	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(mmHg)	Baseline	151(14.8)	163(16.5)	152(9.8)	141(44.3)	139(44.6)	167(33.5)	144(26.8)	133(42.3)	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)	-
Airway Pressure (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(1.3)	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(0.9)	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(0.08)	1.3(0.22)	1.2(0.10)	1.4(0.18)	1.3(0.19)	1.4(0.24)	1.3(0.47)	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)	-
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(4.0)	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)	-
ALP(U/L)	*Baseline*	119(28.7)	105(18.1)	126(15.9)	112(25.9)	76(6.5)	107(14.8)	114(26.3)	124(39.2)	126(27.6)
	End-exp	122(41.6)	112(15.0)	125(13.9)	106(29.6)	131(69.6)	185(33.5)	118(33.2)	342(168.2)*	-
ALB(U/L)	*Baseline*	3.0(1.22)	3.2(0.13)	3.3(0.28)	3.3(0.22)	3.0(0.33)	3.4(0.12)	3.0(0.47)	3.4(0.19)	3.2(0.30)
	End-exp	2.9(0.60)	2.9(0.05)	3.0(0.18)	2.8(0.19)	2.4(0.33)*¤	3.0(0.11)	2.6(0.53)	1.8(0.84)	-

Table 2) Data is presented as average (standard deviation). 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. Hb, Hemoglobin; PLT, Platelets; K^+, Potassium; Ca^{++}, Calcium; PaO_2, partial pressure of arterial oxygen; BUN, blood urea nitrogen; CRE, creatinine; ALT, alanine aminotransferase; ALP, alkaline phosphatase; ALB, albumin; End-Int, End of intervention period; End-exp, End of experiment.

Technical limitations: Two animals were excluded from the study due to technical issues; one died at 9 minutes into the controlled hemorrhage after removal of 20% of blood volume, and another died during intervention phase of sudden cardiac arrest which appeared unrelated to device application. Repeated histology testing of the stomach tissues 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 continue to be further explored as experiments continue. See histology reports in appendices

- **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 (80% completed)

- **Milestone Targeted:** One or more peer reviewed publications (12 months) (in progress 80% 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 75% 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 (10% complete)

Work began this reporting period on Experiment 2: GROA Comparison with REBOA to Control Lethal Hemorrhage. 3 animals have been used, one in each group GROA, REBOA, and Control as a pilot to the study. Animals were anesthetized and instrumented as described earlier. However, 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 an approximately 80% amputation of the left lateral lobe of the liver and 40% of the left medial liver lobe. Animals underwent removal of 30% of their estimated blood volume over 20 minutes through the catheter placed in their femoral artery. Following blood removal, the liver was sharply transected and the abdomen closed. 2 minutes following injury intervention was performed as GROA, REBOA, or control (no intervention). Animals surviving 60 minutes were administered the whole blood that was initially taken at the same time the abdomen is opened and packed for hemostasis (damage control surgery). Supportive care in the form of additional crystalloid were be provided while the animals were monitored for an additional 2 hours.
Significant Findings & Results: Preliminary data for MAP and lactate are provided in figure (10). The control animal met endpoints of exsanguination 42 minutes following injury consistent with previous literature using a similar model. Both animals receiving REBOA and GROA survived the intervention period and subsequent resuscitation efforts.

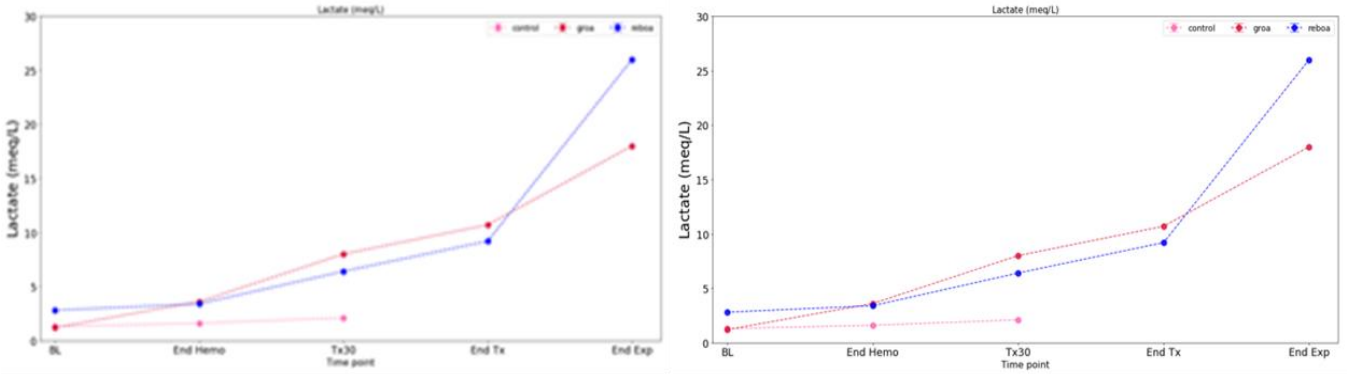


Figure 10: Mean arterial pressure (left) and Lactate (right) from preliminary experiments comparing GROA to REBOA and Controls for the ability to staunch hemorrhage in a lethal model. N=3. 1/group.

- **Milestone Targeted**: Complete comparison studies of GROA and REBOA in swine with severe noncompressible hemorrhagic shock. (24 months) (in progress 10% complete)
- **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)

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

How were the results disseminated to communities of interest?
An abstract and poster containing data from this project was presented in part at the August 2019 Military Health System Research Symposium (MHSRS), Kissimee, FL. Abstract # MHSRS-19-01529 and poster presentation received an award for excellence: honorable mention. The abstract and poster and award are provided in the appendices.

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

- Work on Major task 1 will is nearly complete and expected to be complete by the next reporting period. This includes finalizing the manufactured prototype and continuing to refine the external compression belt design iterations. Animal tolerance testing is nearly complete for this task. One or more abstracts are planned to be submitted to MHSRS and other national meetings. A draft manuscript containing the data presented in this report has been completed and is being edited prior to submission to a medical journal. Additional manuscript writing in an engineering scientific journal may be completed for publication within the next reporting period.

- Work on Major task 2 has begun and will continue. Here we move on to testing and comparing GROA prototypes to REBOA for staunching severe non-compressible abdominal hemorrhage in a large swine animal model of lethal traumatic shock. Swine prototypes will continue to be refined, and human prototyping will be explored. Additional industry partners will be sought during this period.

- Work on Major task 3 will begin within the next reporting period. Devices will continue to be prototyped and refined for adaption to humans. Testing of GROA as a bridge to REBOA will be explored as

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 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.

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. In addition, we are currently in the process of creating a start-up (Precision Trauma LLC) with plans to license the GROA technology.

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
Waiting on the device manufacturing of GROA prototypes has caused delays in animal tolerance testing as outlined in Major Task 1, and subsequently slowed the initiation of studies outlined in Major task 2. Delivery of additional manufactured prototypes is expected and will allow the completion of major task 1 and 2. The team will continue preclinical studies at an accelerated pace to minimize or

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

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.** Nothing to report

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

- **Other publications, conference papers and presentations:**
  An abstract and poster containing data from this project was presented in part at the August 2019 Military Health System Research Symposium (MHSRS), Kissimee, FL. Abstract # MHSRS-19-01529 and poster presentation received an award for excellence: honorable mention. See appendices for abstract, poster, and award.

- **Website(s) or other Internet site(s)**
  Nothing to report

- **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

- **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
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:	12
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:	1
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:	5
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:	8
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:	3
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:	Jeffery Plott, PhD
Project Role:	Design Engineer
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	11
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:	Anne Weitzel BS
Project Role:	Research Staff
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Animal lab duties, data collection and data analysis
Funding Support:	

Name:	Sven Holcombe Ph.D.
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:	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:	9
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-19-01529
- Poster # MHSRS-19-01529
- Award for Excellence: MHSRS-19-01529

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: $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

Gastroesophageal Resuscitative Occlusion of the Aorta (GROA)

Brendan McCracken, BS[1,2], Mohamad Hakam Tiba, MD, MS[1,2], Jeffrey Plott, PhD[2,3], Carmen Colmenero, BS[1,2], Danielle Leander, BS[1,2], Anne Marie Weitzel, BS[1,2], Brandon Cummings, BS[1,2], Albert Shih, PhD[2,3,5], Stewart Wang, MD[2,4], Jonathan Eliason, MD[2,4], Kevin Ward, MD[1,2,5]

[1] Department of Emergency Medicine, University of Michigan

[2] Michigan Center for Integrative research in Critical Care, MCIRCC

[3] Department of Mechanical Engineering, University of Michigan

[4] Department of Surgery, University of Michigan

[5] Department of Biomedical Engineering, University of Michigan

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 abdominal and pelvic hemorrhage continues to pose almost intractable challenges especially in the prehospital and field care setting. Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) has shown promise as an effective bridge to surgical hemostasis; however, field application and time to application from the initial injury present logistical challenges that could limit effectiveness and widespread use of REBOA in austere environments. Due to the anatomical position of the stomach and the aorta it may be feasible to occlude the aorta, similar to REBOA, via gastroesophageal placement a balloon catheter into the stomach. This concept is termed Gastroesophageal Resuscitative Occlusion of the Aorta (GROA). In this study, we aim to prototype and test a novel GROA device capable of effectively occluding the aorta through the stomach to provide short-term hemostasis for NCTH.

Hypothesis: The anatomical relationship between the esophagus, stomach, and vertebral bodies 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.

Methods: Male Yorkshire swine (51.3(3.4) kg) were anesthetized and surgically instrumented for advanced hemodynamic monitoring and controlled arterial hemorrhage. Various GROA prototype iterations were developed, combining gastroesophageal balloon catheters and external pressure belts, and tested for their ability to be inserted and removed from the stomach, and ease of application. Measurements were evaluated to detect the ability of the devices to occlude the descending aorta, stop femoral pulsatile pressure, and hepatic artery flow. Animals were subjected to controlled arterial hemorrhage of 40% blood volume. The low pressure shock state was maintained for 30 minutes, followed by use of the GROA device or REBOA catheter for 60 minutes. Following the device application period, whole blood and crystalloid fluid resuscitation was initiated followed by deactivation of the device (GROA or REBOA). Animals were monitored for 60 minutes post resuscitation. Upon completion of data collection, animals were euthanized. Post-mortem histological analysis was performed on stomach tissues directly in contact with the GROA device.

Results: A total of 6 animals (4 GROA and 2 REBOA) were utilized. Testing confirmed the feasibility of application and removal of the GROA device. Aortic occlusion by GROA was achieved in all preliminary tests with the addition of external abdominal pressure. Aortic occlusion was verified by loss of femoral

artery pulse pressure. Hepatic artery flow was decreased from 131(12) to 0(0) mL/min. GROA application during hemorrhagic shock increased proximal aortic pressure from 33(8) to 59(11) mmHg compared to REBOA 29(O) to 65(11) mmHg. Peak lactate levels between GROA and REBOA animals were not different 11.2(1.8) vs 11.4(0.3) meq/L respectively. Histological analysis of stomach tissue after GROA application showed evidence of localized mild to moderate inflammation (gastritis) of the fundus and cardia.

Conclusion: In these early studies, the GROA method appears to be effective at high zone 2 occlusion of the aorta in a swine model of hemorrhagic shock and may therefore be capable of temporarily staunching severe NCTH. In initial testing, the hemodynamic response produced by GROA activation is similar to the effects of REBOA. This study is ongoing to further evaluate the efficacy and physiological tolerance of GROA. GROA may serve as a fast, effective, and short term method of achieving hemostasis until definitive surgical interventions may be performed.

Learning Objective 1: Describe the unmet need for field-deployable 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 use of gastroesophageal resuscitative occlusion of the aorta (GROA) and how it relates to REBOA (hemodynamic effects) as treatment of non-compressible torso hemorrhage

Gastroesophageal Resuscitative Occlusion of the Aorta (GROA)

Brendan McCracken, BS[1,2]; Mohamad Hakam Tiba, MD, MS[1,2]; Jeffery Plott PhD[2,3]; Carmen Colmenero, BS[1,2]; Danielle C. Leander, BS[1,2]; Anne Marie Weitzel, BS[1,2] Brandon Cummings, BS[1,2]; Albert Shih, PhD[2,3,5]; Stewart Wang, MD[2,4]; Jonathan Eliason, MD[2,4]; Kevin Ward, MD[1,2,5]

Departments of: [1]Emergency Medicine, [2]Michigan Center for Integrative Research in Critical Care, [3]Department of Mechanical Engineering, University of Michigan, [4]Department of Surgery, University of Michigan, [5]Department of Biomedical Engineering, University of Michigan

University of Michigan, Ann Arbor, Michigan

CENTER FOR INTEGRATIVE RESEARCH IN CRITICAL CARE
UNIVERSITY OF MICHIGAN

INTRODUCTION

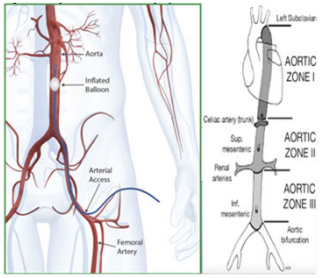
Non-Compressible Torso Hemorrhage (NCTH)

- More than 90% of military casualties and 40% of civilian trauma deaths occur due to hemorrhage
- Torso and deep pelvic hemorrhages pose an intractable challenge in the pre-hospital and Prolonged Field Care (PFC) setting where 9 out of 10 deaths occur

CURRENT STRATEGIES AND CHALLENGES

Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA)

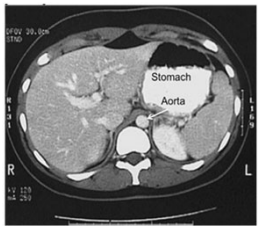
- Approved effective tool for the treatment of NCTH
- Difficult to place in hostile environments
- Zones of placement
  - Zone I: Origin at left subclavian artery to the celiac artery
  - Zone II: Origin at the celiac artery to the renal arteries
  - Zone III: Below the lowest renal artery
- No known field reports of Zone I & II placement for occlusion to intra-abdominal bleeding

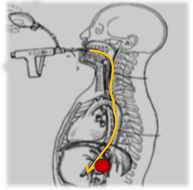


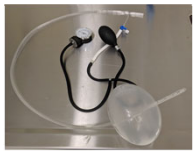
Gastroesophageal Resuscitative Occlusion of the Aorta

Gastroesophageal Occlusion of the Aorta (GROA)

- The close anatomical relationship of the aorta to the stomach suggests that the aorta may be partially or fully occluded from pressure applied from the posterior wall of the stomach and the anterior surface of the thoracic vertebrae.







GROA Device: 4 components

1. **Balloon**
   - Provides structure and force to occlude aorta
2. **Gastroesophageal tube**
   - Allows the device to be easily inserted into the stomach via the esophagus (similar to Salem Sump)
3. **Air pump**
   - Allows for controlled balloon inflation/deflation for partial or full aortic occlusion
4. **Anchoring system: External tourniquet**
   - Provides counter force to prevent deflection and dislodging of tube during pressure application

SPECIFIC AIMS

Aim 1: Design prototype GROA device that can be placed via esophagus into the stomach to produce complete occlusion of the aorta at or above the celiac artery.
Aim 2: Test and compare GROA prototypes to REBOA for staunching severe noncompressible abdominal hemorrhage in large swine animal model of traumatic shock
Aim 3: Demonstrate tandem use of GROA followed by REBOA as an example of pDCR and PFC in a swine model.

METHODS

- Swan-Ganz Catheter: External Jugular Vein
- Right Common Carotid Catheter
- Femoral Artery Catheter (2X)
- Femoral Vein Catheter
- Central Line Infusion
- Hepatic Artery Flow Probe

Instrumentation

Baseline

Device placement & Baseline measurements
- Blood Pressures
- CBC
- Chemistry
- Coagulation

Controlled Arterial Hemorrhage

- 35-40% of total blood volume over 30 minutes
- Class IV Shock

Randomization of Treatment

- GROA
- REBOA
- No Occlusion (Control)

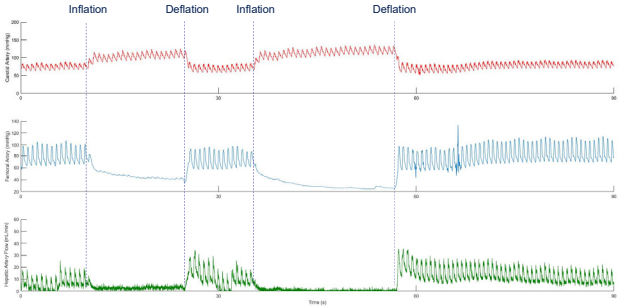
Whole blood and Fluid Resuscitation

- Whole blood autologous transfusion (2 units)
- Ringer's Lactate Solution

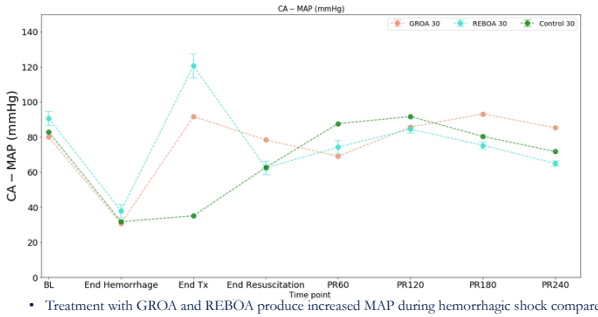
Post Resuscitation Treatment & Monitoring

- Maintain mean arterial pressure ≥ 60 mmHg
- Norepinephrine infusion (4mg/500mL) 5% dextrose in NaCl 0.9%

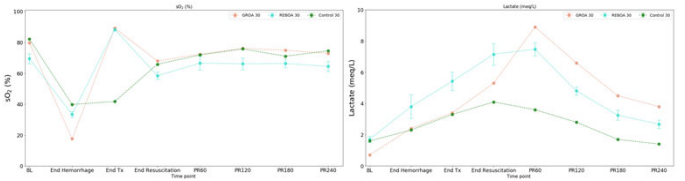
RESULTS



- Carotid pressure increase and loss of femoral pulsatility during GROA indicates full aortic occlusion
- Cessation of hepatic artery flow (0 mL/min) during inflation indicates high zone II aortic occlusion
- Mean pressures and flow return upon GROA device deflation



- Treatment with GROA and REBOA produce increased MAP during hemorrhagic shock compared to control



- Treatment with GROA and REBOA improves SvO_2 during shock. Lactate levels are initially increased in GROA and REBOA groups, however lactate clearance occurs in all groups during post resuscitation period.

CONCLUSION

Preliminary results suggest that GROA improves hemodynamics and oxygenation in swine with class IV hemorrhagic shock similar to the effects and physiological tolerances of REBOA. This study is ongoing to further develop and determine the effects of the device. GROA may serve as a minimally invasive and field deployable countermeasure for staunching NCTH during PFC or pDCR scenarios, or act as a bridge to the use of more advanced techniques such as REBOA or definitive surgical hemostasis.

ACKNOWLEDGEMENTS

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IACUC Protocol: PRO00007709 ACURO Protocol: DM160299

MILITARY HEALTH SYSTEM RESEARCH SYMPOSIUM

August 2019

Award for Excellence

Poster Competition

Honorable Mention