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PRINCIPAL INVESTIGATOR: Kevin R. Ward, MD

CONTRACTING ORGANIZATION: University of Michigan

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14. ABSTRACT

Natural Orifice Transluminal Endoscopic Surgery (NOTES) is an evolving surgical innovation, which allows for intra-cavitary surgeries to be performed with an endoscope passed through a natural orifice (mouth anus, vagina, urethra). It is the purpose of this proposal to leverage the concept of NOTES to develop a method of temporary aortic occlusion using an orally placed gastroesophageal device. This gastroesophageal resuscitative occlusion of the aorta (GROA) will be developed as a field bridge to more invasive and definitive means of control of non-compressible torso hemorrhage (NCTH) such as resuscitative endovascular balloon occlusion of the aorta (REBOA), angiography, and surgery.

Hypothesis: The anatomical relationship between the esophagus and stomach to the descending thoracic and abdominal aorta will allow complete mechanical occlusion of the aorta through the stomach that can prolong short-term survival of severe NCTH.

Specific Aims/Objectives:

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

2) Test and compare GROA prototypes to REBOA for staunching severe NCTH in a large swine animal model of traumatic shock.

3) Demonstrate tandem use of GROA followed by REBOA as an example of point-of-care in field prolonged field care (PFC) and prolonged damage control resuscitation (pDCR) in a swine model of severe NCTH.

Experimental Approach: An iterative design and testing approach will be taken to develop a product, which leverages the anatomical relationship of the esophagus and stomach to the descending thoracic and abdominal aorta. A combination of thoracic and abdominal 3-D reconstructed computed tomography scans across a wide variety of patient types of body habitus (including warfighter phenotypes) will be used to inform the design characteristics of GROA, based on our previous approach using *morphomics* to map the 3-D vascular anatomy of over 2000 individuals in developing new REBOA systems. In-silico model and simulator testing will be used to understand actual tissue qualities and constraints on design characteristics and tolerances for device components including the development of balloons. A reliance on 3-D printing to produce prototypes will ensure rapid iterative development-refinement of GROA.

Preclinical testing using swine will also be used to test the effectiveness of the various GROA iterations to occlude the aorta in proximal Zone II at or above the celiac artery. Physiologic tolerance studies will be performed to understand potential complications and limitations compared to REBOA on hemorrhaged swine. GROA will also be compared to REBOA in a model of NCTH. Finally, tandem use of GROA to REBOA will be studied in experiments to simulate a potential PFC and pDCR situation. The latter will provide proof of feasibility of initial rapid stabilization using GROA followed by transition to the implementation of REBOA.

15. SUBJECT TERMS

Occlusion of the Aorta, Balloon, Stomach, Non-compressible hemorrhage, Resuscitation

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

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

3. ACCOMPLISHMENTS:

3.1. What were the major goals of the project?

3.1.1. 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.

3.1.2. 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.

3.1.3. 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.

This table is adapted from the approved statement of work

Major Tasks – Subtasks - Milestones	Timeline	Progress
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.	Months	
Subtask 1: Local/Institutional IRB approval	0	Completed
Subtask 2: USAMRMC: ACURO Approval	2-3	Completed
Subtask 3: Obtain equipment, hire and train study personnel	2	Completed

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.	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.	4-16	Completed
Milestone Targeted: Local IACUC/Approval	1	Completed
Milestone Targeted: ACURO Approval	2-3	Completed
Milestone Targeted: 2-3 GROA prototypes made	6-12	Completed
Milestone Targeted: Physiologic tolerance studies of GROA in comparison to REBOA completed	16	Completed
Milestone Targeted: One or more peer reviewed publications	12	Tiba MH, McCracken BM, Colmenero CI, et al. Gastroesophageal resuscitative occlusion of the aorta: Physiologic tolerance in a swine model of hemorrhagic shock. <i>J Trauma Acute Care Surg.</i> 2020;89(6):1114-1123. doi:10.1097/TA.0000000000002867
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	12-24	Completed
Subtask 2: Testing of GROA prototypes in swine model of lethal abdominal hemorrhage comparing performance with REBOA and control.	16-24	Completed
Milestone Targeted: Complete comparison studies of GROA and REBOA in swine with severe noncompressible hemorrhagic shock.	24	Completed
Milestone Targeted: One or more peer reviewed publications/year	24	McCracken BM, Tiba MH, Colmenero Mahmood CI, et al. Gastroesophageal resuscitative occlusion of the aorta prolongs survival in a lethal liver laceration model. <i>J Trauma Acute Care Surg.</i> 2022;92(5):880-889. doi:10.1097/TA.0000000000003444
Milestone Targeted: Use preliminary data to attract industry partner and/or begin considering small business spin off for technology transition plan	16-36	Active.
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	24-36	Completed
Subtask 2: Testing of tandem use of GROA to REBOA compared to control. 16-20 animals will be used, 8-10 animals per group	24-36	Completed
Milestone Targeted: Successful demonstration of GROA to REBOA transition.	36	Completed
Milestone Targeted: Creation of final 1-2 human GROA prototypes suitable for consideration for human testing in follow-on studies.	36	Active.
Milestone Targeted: One or more peer reviewed publications/year	36	Tiba MH, McCracken BM, Greer NL, et al. Tandem use of Gastroesophageal Resuscitative Occlusion of the Aorta followed by REBOA in a Lethal Liver Laceration Model. <i>J Trauma Acute Care Surg</i>. Accepted, awaiting publication. McCracken BM, Ward KR, Tiba MH. A review of two emerging technologies designed for pre-hospital treatment of non-compressible abdominal hemorrhage. <i>THOR supplement in Transfusion</i>. 2022. Status: Accepted, awaiting publication.
Milestone Targeted: Use refined data to continue to engage industry partner and/or launch small business spin off for technology transition plan	24-36	Active.

3.2. What was accomplished under these goals?

3.2.1 Morphomics Analyses:

In order to optimize the balloon design to also work in humans, the science of morphomics was utilized. The figures below (fig 1) indicate 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

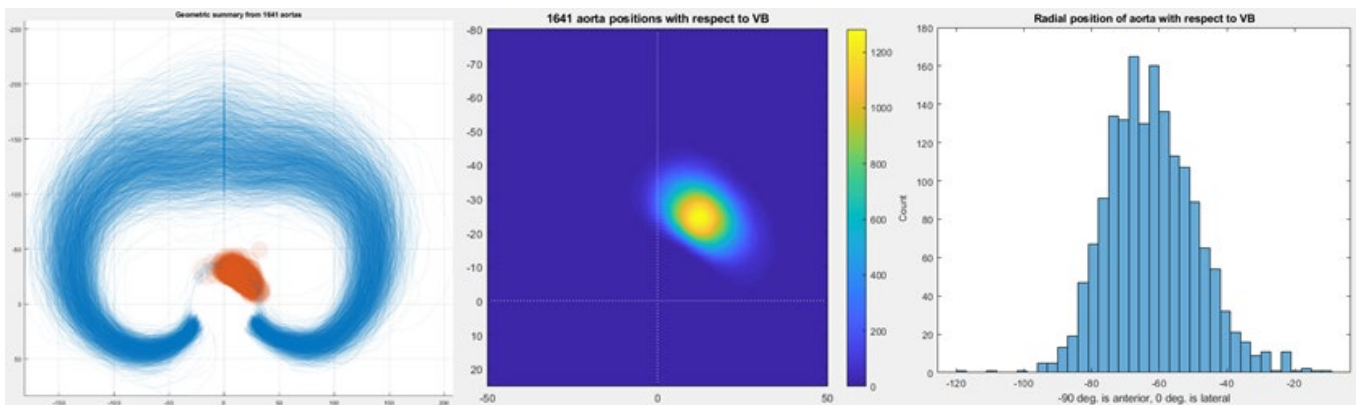


Fig 1. Left: The blue lines represent the outer border of the abdominal cavities. To better visualize the aortas the vertebral bodies have been removed from the image but their position can be easily inferred. The middle and right panels show the Radial relationship to center of vertebral body.

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. The gastroesophageal balloon catheter was designed based on these initial results.

3.2.2 Device Design: Significant Results:

Balloon and catheter design and optimization: We have tested numerous balloon prototypes to find the optimal balance between vessel occlusion, ease of insertion, and strength and durability. We have also explored several different balloon geometries to better focus pressure on the aorta, making occlusion easier. Materials for the catheter and balloon, catheter tip geometry, balloon geometry, ventilation ports, inflation ports, gastric evacuation ports are a few design features that we explored to optimize the catheter's function. Early iterations of the balloons and catheters are presented in figure 2. Following initial material and design concepts, specifications were delivered to medical device manufacturer Interpex medical. The initial engineering design is presented in figure 3. After manufacture, new device passed benchtop evaluation, we then

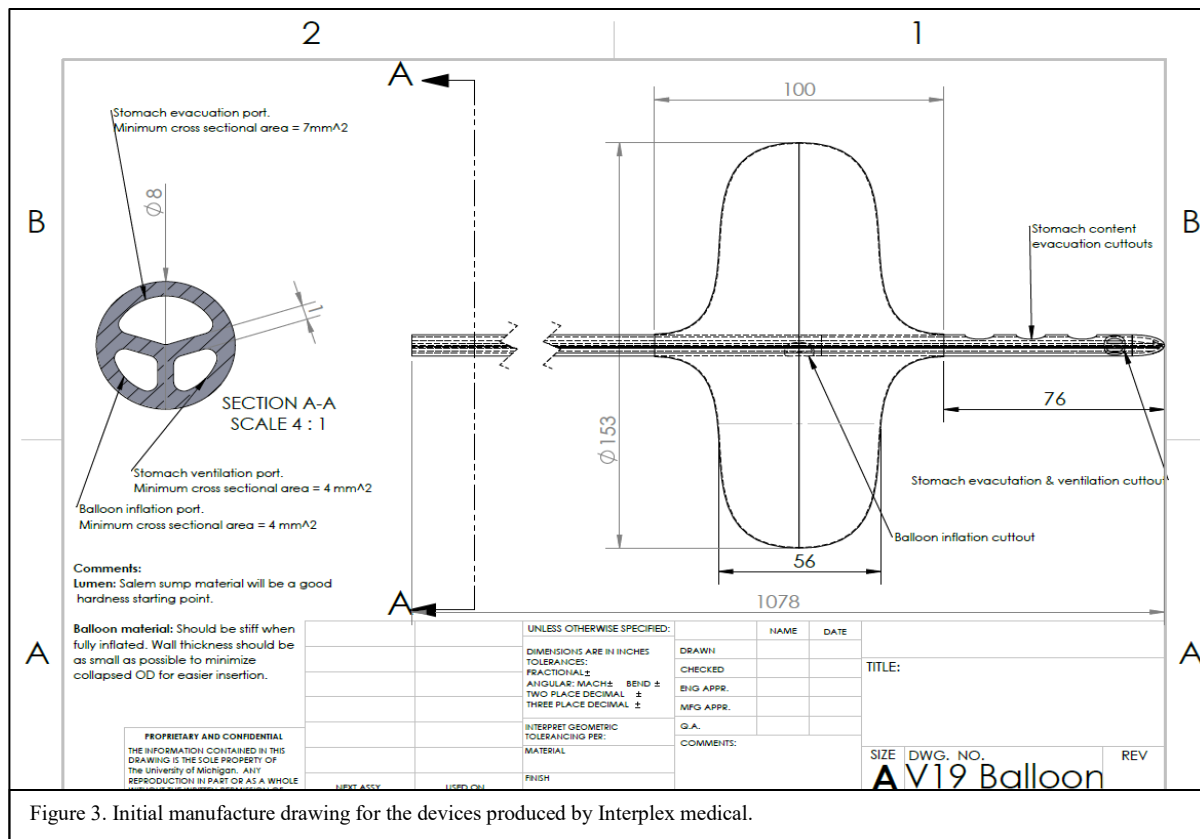


Figure 3. Initial manufacture drawing for the devices produced by Interpex medical.

moved to live animal testing 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. No degradation of the device was observed during in-vivo experiments adding confidence for the correct combination of geometrical design and material properties. This manufactured design was used for all physiological tolerance testing related to specific Aim 1.

While the GROA device was able to create the aortic occlusion, we continued to iterate the device design focusing on mitigating any stomach damage caused by the catheter tip during delivery. Inspired by a telescope configuration, we developed the current and final balloon catheter design allowing the combination use with existing stomach tube designs. The existing stomach tubes, specifically Salem Sump, have demonstrated to enable an easy and safe balloon delivery process. Manufacturing schematics are presented in figure 4. The device design was updated using the Salem Sump tube as a telescoping tip. This allows for the distal-most portion of the catheter, which previously extended beyond the balloon, to be retracted so that only the balloon portion of the catheter is in contact with the gastric mucosa only during deployment. The final manufactured devices used for our studies are pictured in figure 5. The device is orogastrically inserted with the sump tube fully extended through the catheter to access the stomach and provide gastric ventilation. Once placed, the balloon can be inflated to initiate aortic occlusion. Once occlusion is achieved, the telescoping sump tip can be removed to reduce device surface contact with the stomach tissue, which subsequently decreased the mucosal injury during application in our animal studies. This device design was utilized for all animal studies related to specific Aims 2 & 3.

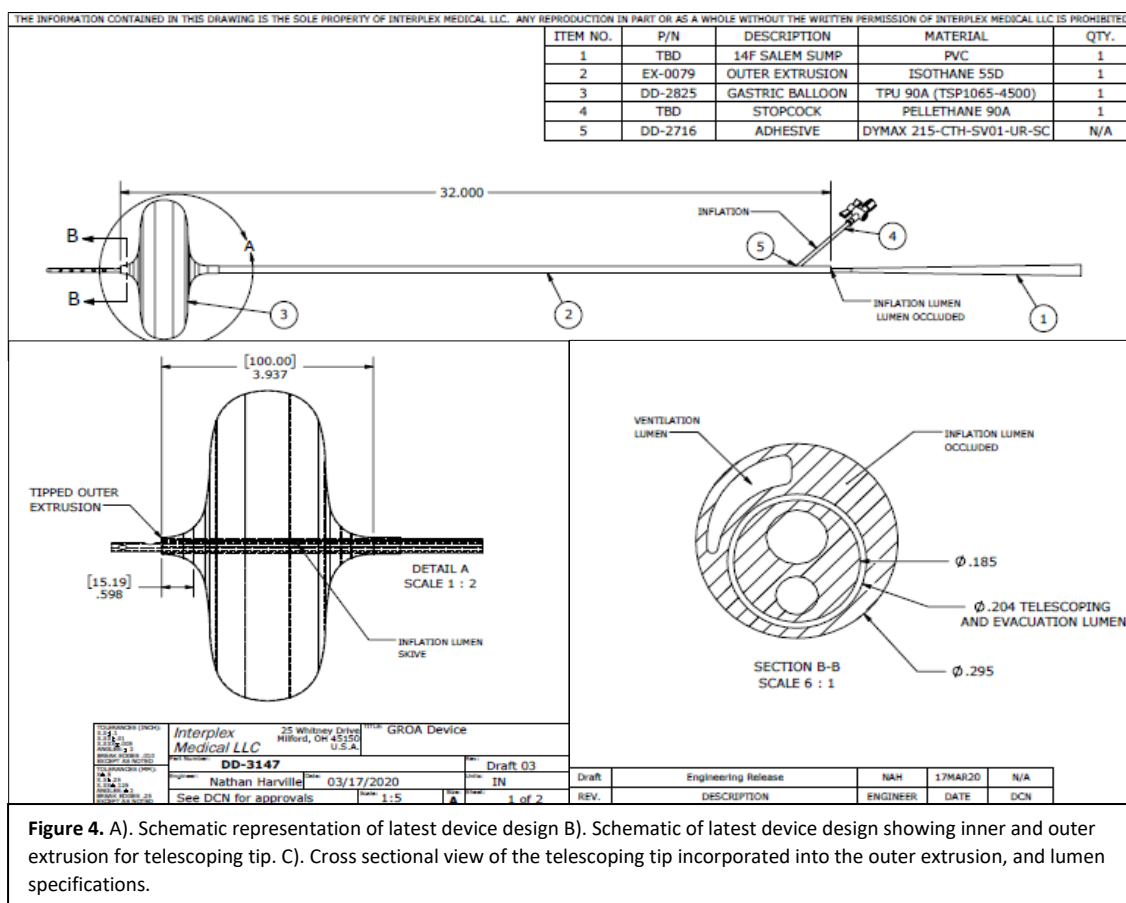




Figure 5. Latest iteration manufactured GROA catheter device with telescoping tip. The device is deflated with the tip fully extended for application (left). Once placed, the device is inflated with the tip in place (center), and once inflated the tip can be telescoped out of the stomach (right).

External pressure assembly design and optimization: In early tests, we noted the need for external pressure to prevent anterior balloon deflection and then specially designed a system to provide the external pressure. The earliest iteration of the assembly is presented in figure 6. The external compression system consists of a back plate and an abdominal plate. When activated, this system prevents lateral and



Figure 6. Initial prototype external compression system with sliding backplate, abdominal plate, and tourniquet style adjustment for compression depth.

anterior deflection of the balloon, keeping the balloon over the aorta. The back plate serves as an anchor for the abdominal plate, which is secured in place by nylon straps. The system can be adjusted to apply controlled posterior-directed pressure. The system is constructed to prevent the application of circumferential pressure around the abdomen as would occur with the use of products such as the abdominal aortic junctional tourniquet. While this initial 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. The newer system consists of a storage box which is deployable into a rigid back plate. Furthermore, the quick-connect snap features, using the buckles and straps, were added as a fixation method to easily connect the abdominal plate to the back

3.2.3 Animal Studies:

Animals use Data:

- Species: Sus Scrofa Domestica
- Total animal number used: 104
- USDA pain category for all animals used: D

3.2.3.1 Major Task 1: Swine testing of initial GROA prototypes on ability to occlude aorta followed by testing of physiologic tolerance of GROA compared to REBOA and control

Significant Results:

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

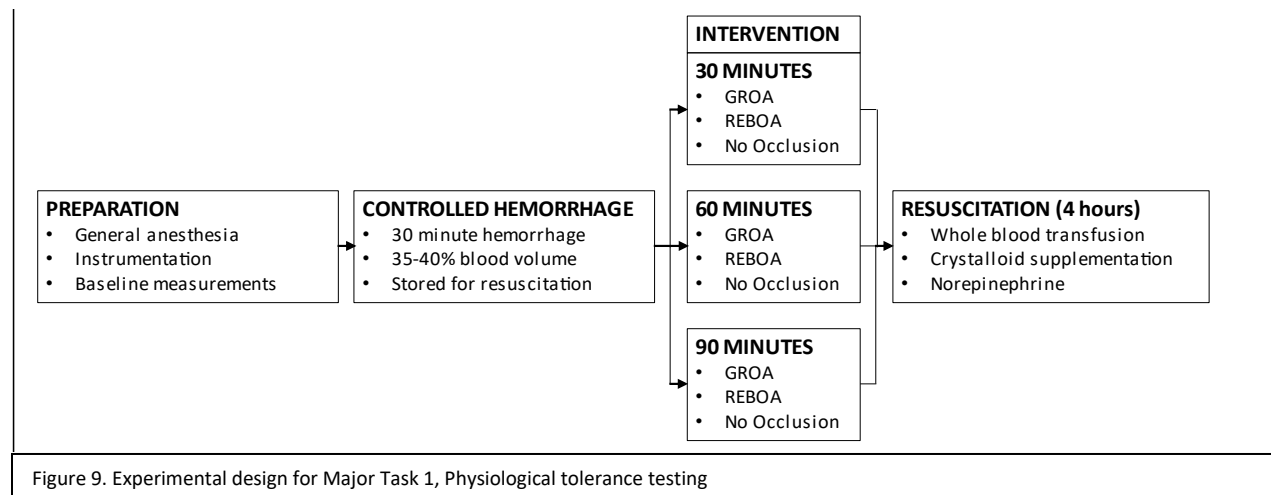


Figure 9. Experimental design for Major Task 1, Physiologic tolerance testing

Methods: Forty-eight animals were used in this study. One animal was excluded because of early death during hemorrhage after removal of 20% of blood volume.

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 below. All animals included in the study survived the duration of their intervention periods.

	30-min Intervention			60-min Intervention			90-min Intervention		
	Control	GROA	REBOA	Control	GROA	REBOA	Control	GROA	REBOA
n	6	5	5	5	5	5	5	6	5
Weight, kg	53 (1.7)	54 (1.1)	49 (5.8)	51 (2.9)	53 (3.6)	53 (2.3)	52 (3.9)	56 (5.9)	49 (4.8)
Hemorrhage volume, %	35 (2.0)	34 (3.0)	35 (1.0)	35 (2.0)	35 (3.0)	35 (3.0)	39 (4.7)	35 (1.4)	40 (7.1)
MAP, mm Hg	80 (7.5)	84 (7.6)	88 (8.1)	97 (9.4)	81 (10.4)	86 (10.5)	82 (15.4)	81 (16.1)	85 (12.5)
Heart rate, bpm	85 (9.2)	84 (11.6)	92 (0.7)	103 (28.7)	85 (2.3)	77 (4.4)	102 (28.1)	90 (9.7)	82 (4.7)
Temperature, °C	36.9 (0.71)	37.2 (0.47)	37.2 (0.44)	37.0 (0.61)	37.7 (0.79)	37.3 (0.43)	36.8 (0.69)	37.5 (0.42)*	36.5 (0.37)
Lactate, mEq/L	1.3 (0.31)	1.3 (0.57)	1.4 (0.64)	1.8 (0.80)	1.4 (0.67)	2.7 (1.46)	2.5 (1.19)	1.8 (0.75)	1.6 (0.52)
S _{mv} O ₂ , %	70.6 (7.39)	69.1 (7.10)	69.6 (5.56)	69.4 (8.07)	71.0 (5.71)	70.7 (5.77)	75.9 (6.78)	68.9 (7.44)	71.9 (4.59)
PetCO ₂ , mm Hg	38.0 (2.22)	38.0 (2.87)	37.8 (1.72)	41.5 (5.15)	38.9 (2.04)	39.8 (2.67)	40.6 (4.64)	39.4 (1.99)	36.6 (3.67)

Data are presented as averages (SD). Statistical significance was set at $\alpha < 0.05$.

*Denotes statistically significant difference between GROA and REBOA.

bpm, Beats per minute; S_{mv}O₂, mixed venous oxygen saturation (%); PetCO₂, end-tidal CO₂ (mm Hg).

The GROA device was found to be effective at achieving and maintaining high zone II aortic occlusion for a period of up to 90 minutes. In a previous unpublished pilot study (n=4) the zone of aortic occlusion was verified by the cessation of flow in the common hepatic artery indicating that GROA occlusion

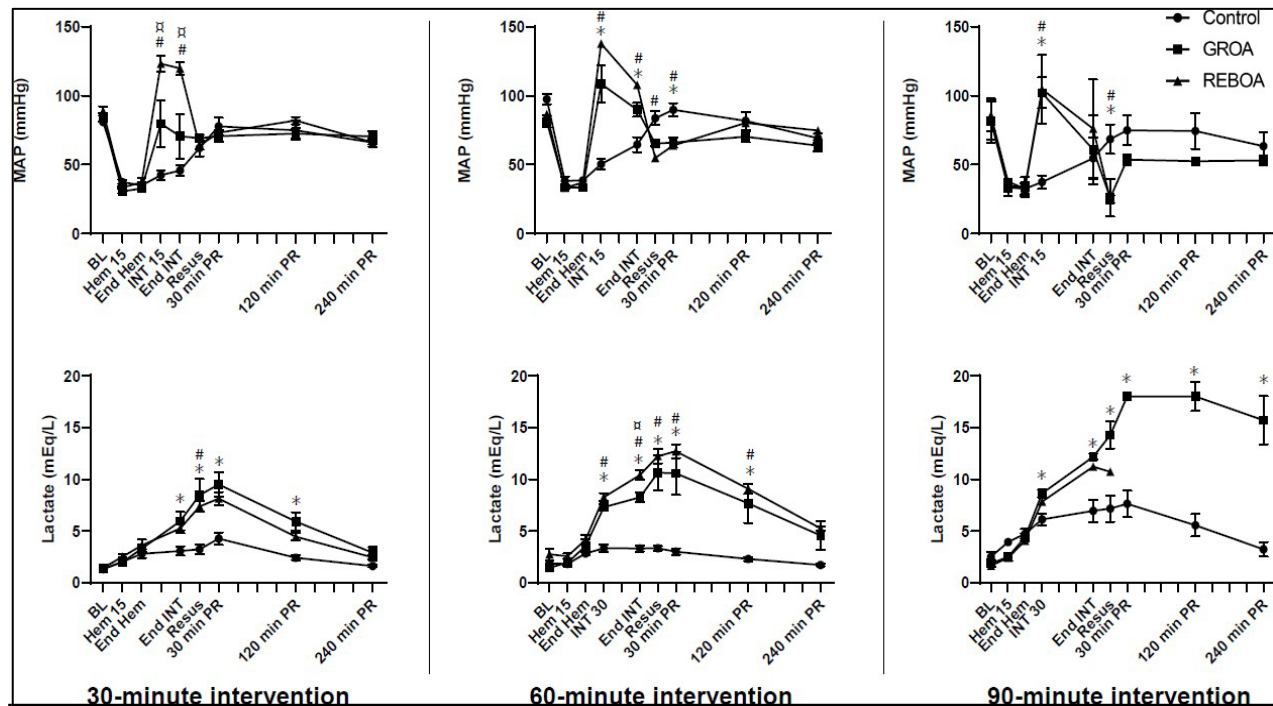


Figure 10: Average and standard error of mean arterial pressure (MAP) of the carotid artery and arterial lactate concentration for 30, 60, and 90-minute interventions. * Denotes statistically significant difference from GROA and control, # Denotes statistically significant difference from REBOA and control, ↑ Denotes statistically significant difference from GROA and REBOA

occurs either directly over or superior to the celiac trunk. The survival rate between REBOA and GROA for all intervention durations was similar except no REBOA animals survived resuscitation after 90

minutes of complete aortic occlusion. With only two animals surviving the 4-hours resuscitation period after 90 minutes of GROA, our study suggest that 90 minutes of complete aortic occlusion is possible but not well tolerated. The overall survival rate between REBOA and GROA intervention in the 30 and 60 minute occlusion groups suggest that the overall tolerance of the GROA device may be equal to the already well characterized physiological tolerance of REBOA for those occlusion times.

Mean Arterial Pressure (MAP) and lactate data for all groups are presented in figure 10. The hemodynamic effects of GROA appear to be similar to those produced by REBOA. Overall increased MAP and SvO₂ suggest increased central redistribution of blood flow and potentially increased perfusion of brain and heart consistent with previous REBOA studies. Lactate was also increased in all GROA groups during occlusion and peaked following reperfusion, however these observations are again similar to REBOA and consistent with previous studies. Lactate burden created by both methods of aortic occlusion were able to be alleviated in the 30- and 60-minute intervention groups by adequate resuscitation. As expected, lactate levels were highest in the 90-minute occlusion GROA group during the reperfusion period but could not be compared to 90-minute REBOA animals since no animals in this

		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 ⁹ /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 ₂ O)	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; PaO₂, 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.

group survived resuscitation. Survival data, resuscitation requirements, airway pressure and organ function metrics are reported in table 2. Increased airway pressure was noted and to be a result of the

GROA balloon contacting the diaphragm during ventilation, however the pressure remains below the 40 cmH₂O threshold associated with increased risk of injury and blood gas analysis verified no change in PaO₂, or PaO₂/FiO₂ during the intervention and recovery period indicating adequate ventilation. Furthermore, neither CVP or PAP were significantly different between the groups indicating that if compression of the inferior vena cava by GROA occurs, decreases on cardiac preload from IVC impingement versus reductions in venous return from aortic occlusion did not affect outcomes. In this study, the GROA device caused mild to moderate gastric mucosal injury which we believe is mainly due to contact pressure injury from balloon, although the REBOA animals demonstrated (lesser) mucosal injury likely from ischemia-reperfusion injury. However, the full extent of this injury will require longer survival studies to allow mucosal ischemia injuries to mature for complete quantification.

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

3.2.3.2 Major Task 2: Testing of GROA prototypes in swine model of lethal abdominal hemorrhage comparing performance with REBOA and control.

Significant Results:

In this study we aimed to determine if the GROA device is capable of stopping lethal abdominal hemorrhage and subsequently improve survival. We hypothesized that the GROA device would stop hemorrhage and increase survival in a lethal model of liver laceration, similar to REBOA, when compared to noninterventional controls. We also assessed the device's effect on physiologic, coagulation, and inflammatory responses, comparing its performance to REBOA and controls.

Methods: Twenty-four animals were used in this study. Animals were randomly assigned to one of three interventions: control (no intervention) n=8, GROA n=8, or REBOA n=8. We chose to limit occlusion of the aorta to 60-minutes since our previous work demonstrated that the overall physiologic tolerance of animals undergoing REBOA and GROA was limited at occlusion times greater than 60 minutes. Experimental design for major task 2 is presented in figure 11.

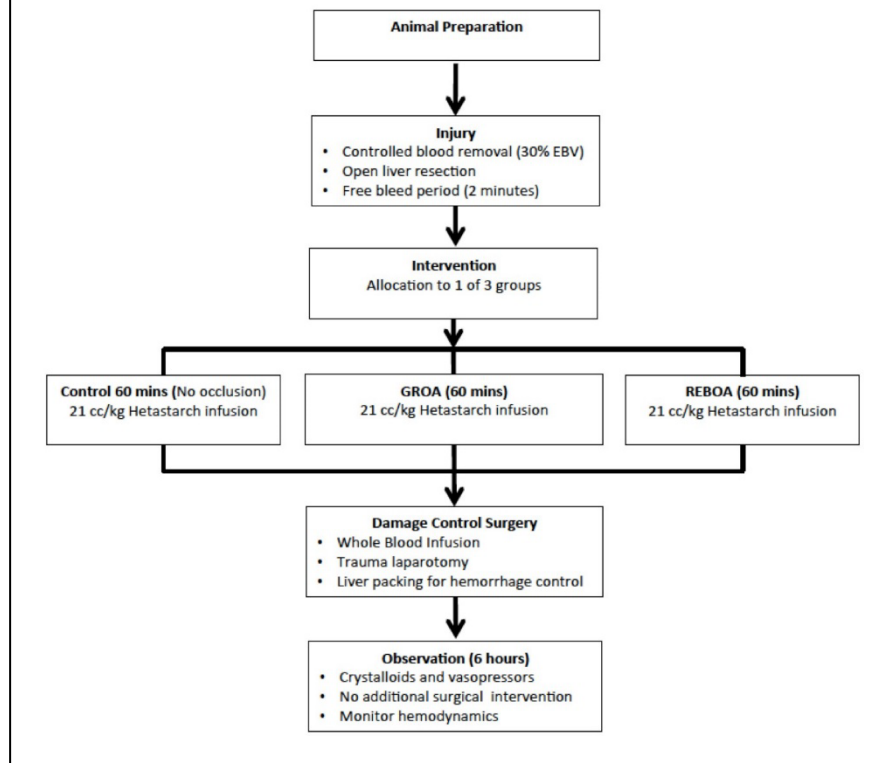
Instrumentation. The right carotid artery was cannulated for measurements of mean arterial pressure (MAP) and collection of blood samples. The left external jugular was cannulated for delivery of resuscitation. The right external jugular was cannulated with a pulmonary artery thermodilution catheter. 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). A midline laparotomy incision was created, extending approximately 10 cm caudally from the xyphoid process, to access the liver for the laceration injury. The liver was marked along a planned transection plane 2 cm to the left of Cantile's line in order to provide a full thickness laceration of the left medial lobe which spans approximately 80% of the cranial-caudal plane. At the conclusion of instrumentation baseline physiologic measurements and laboratory samples were obtained.

Hemorrhage and injury. A controlled arterial hemorrhage was performed removing approximately 30% total blood volume over 20 minutes. Two units of shed blood were collected in citrate phosphate dextrose bags and saved for resuscitation. Two minutes after completion of the controlled hemorrhage, a full thickness (in depth) liver laceration was created using a scalpel. Free-bleeding from the liver was allowed to continue for two minutes before a 60-minute intervention period was initiated.

Intervention and Resuscitation.

Intervention was implemented either by deployment of GROA, REBOA, or control (no intervention). Aortic occlusion was maintained for 60 minutes. At the end of intervention, the GROA and REBOA balloons were slowly deflated, restoring blood flow over a period of approximately seven minutes. Concurrently, resuscitation was initiated using the autologous shed blood and supplemental Ringer's lactate. At the same time the abdomen was opened and the liver was packed for hemostasis (damage control surgery). Supportive care in the form of additional crystalloid and vasopressors (norepinephrine, if needed) were provided while the animals were monitored for an additional 4 hours. Post-mortem tissue samples from the stomachs and aortas were collected for histopathological analysis by a blinded expert veterinarian pathologist.

Figure 11: Experiment 2: Design Comparing GROA to REBOA in NCTH.



Significant Findings & Results: The injury model was found to be rapidly lethal with 7/8 control animals meeting endpoints following liver laceration; median survival time in the control group was 10.5 minutes (12 minutes) after liver injury. The animal which survived post-injury also survived the duration of the post-resuscitation monitoring period. A Kaplan-Meier plot of survival probabilities is presented in figure 12. All animals receiving aortic occlusion using GROA (8/8) or REBOA (8/8) survived the duration of the intervention period (60-minutes) with median survival times of 86 minutes (232 minutes) and 79 minutes (199 minutes) post-resuscitation, respectively. For overall survival from the onset of injury until the end of the 4-hours monitoring period, GROA and REBOA animals experienced a significant improvement in survival compared to controls ($p < 0.01$) with no differences between the occlusion groups. Three animals survived the 4-hours monitoring period in the GROA group compared to two in the REBOA group, with no significant differences in survival time between these two groups.

The hemodynamic effects of GROA and REBOA observed in this study were again similar to previous reports and presented in figure 13. MAP values were increased following aortic occlusion and were maintained throughout the duration of the intervention period with no significant

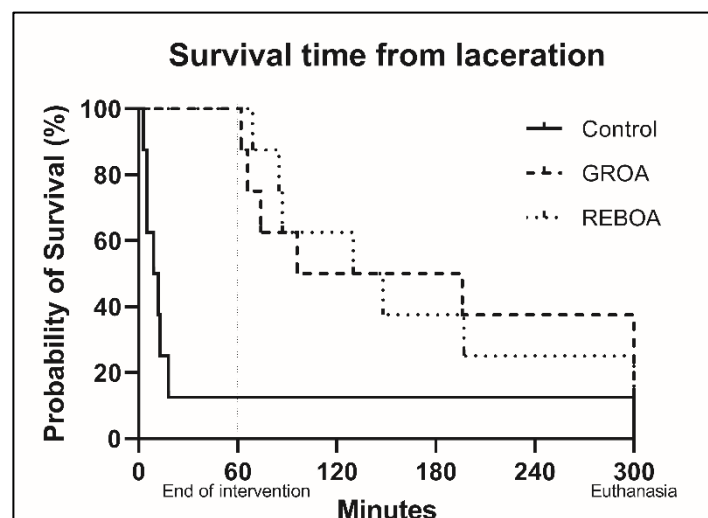
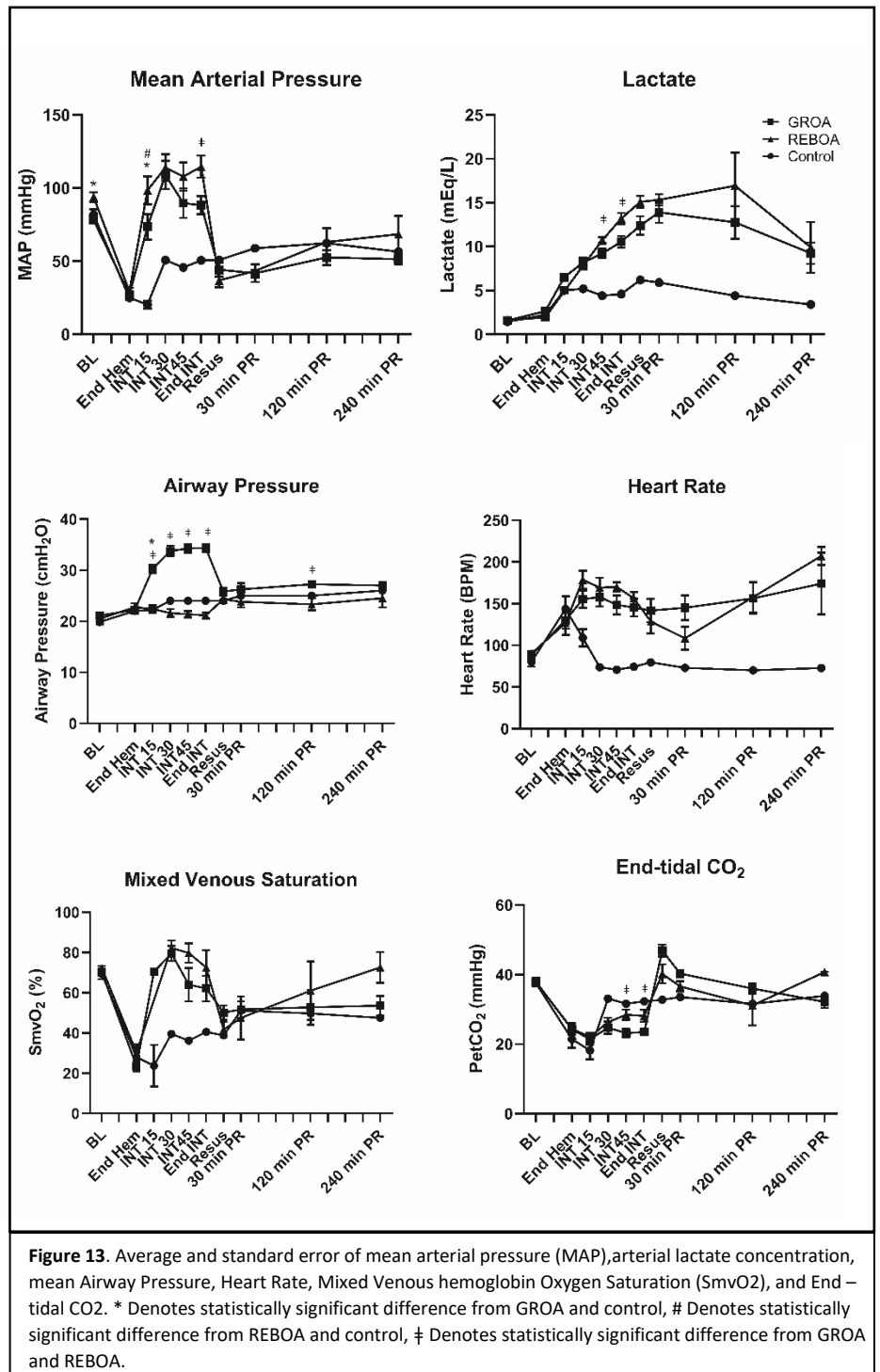


Figure 12. Kaplan-Meier Survival curve showing the estimated probability of survival (y-axis) in minutes (x-axis) following liver laceration injury.

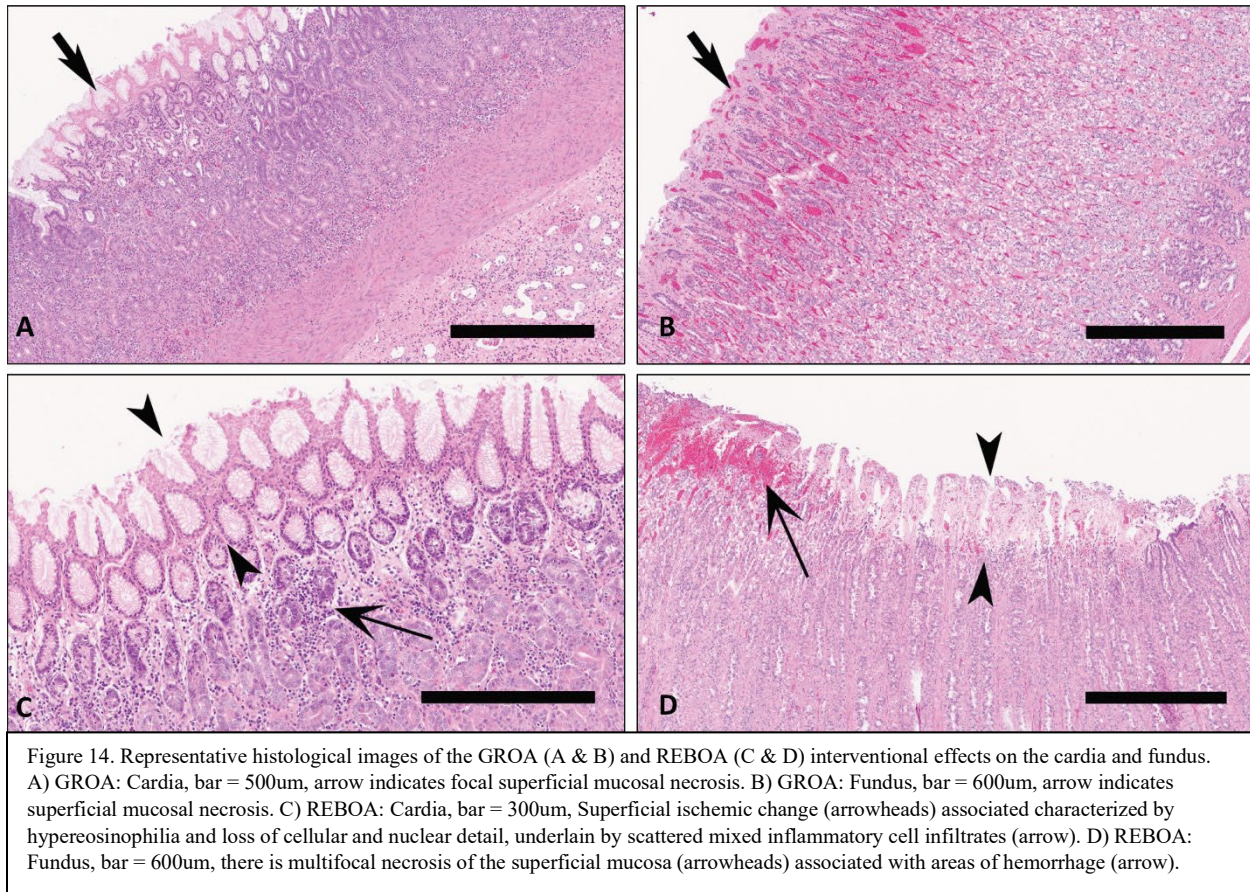
differences between REBOA and GROA for the majority of intervention. MAP was maintained in the surviving animals with no differences between groups. Additional metrics associated with shock including heart rate, mixed venous blood oxygen saturation (SmvO_2), and end-tidal CO_2 are also presented in figure 13. GROA resulted in an increased airway pressure compared to REBOA, with an average value of 33.2 cmH_2O (3.03 cmH_2O) vs 21.6 cmH_2O (1.97 cmH_2O) throughout intervention, ($p < 0.0001$) but returned to baseline after deactivation of the GROA device. No significant differences were noted in arterial blood gas (PaO_2 and PaCO_2) between REBOA and GROA groups during the 60-minute intervention period suggesting no significant effect of GROA on pulmonary gas exchange.

Cytokine and TEG measurements were not different between the aortic occlusion groups in this study. Although a longitudinal inflammatory response was noted in some cytokines, they appear to be independent of the method of aortic occlusion, and therefore more likely related to the occlusion itself and not device specific. Similarly, there was no evidence of clinically significant coagulopathy noted in either intervention group and the ability to generate clots with adequate strength without lysis was consistent across all animals despite the interventions or resuscitation.

Histological analyses of stomach tissue for animals undergoing occlusion using GROA demonstrated changes consistent with mild ischemia likely produced by the pressure that the balloon creates when the abdominal plate is tightened. However, similar changes were noted in REBOA animals pointing towards general ischemia from the aortic occlusion as the potential



cause. The final extent of these changes cannot be known until longer survival studies are performed. Representative histological images are provided in figure 14.



Overall, Initiation of either technology resulted in rapid and improved carotid arterial pressure and increased SmvO₂, suggestive of redistributed blood flow and improvement of brain and cardiac perfusion and improved tissue oxygenation, despite hypovolemia. Further, the application of either REBOA or GROA interventions quickly stopped the lethal hemorrhage which allowed the observed hemodynamic benefits to be maintained for the duration of the 60-minute intervention period without further deterioration. This evidence further suggests the physiological tolerance and response to the device is similar to the well characterized physiologic tolerance of REBOA. Histological analyses of stomach tissue for animals undergoing occlusion using GROA demonstrated changes consistent with mild ischemia likely produced by the pressure that the balloon creates when the abdominal plate is tightened. However, similar changes were noted in REBOA animals pointing towards general ischemia from the aortic occlusion as the potential cause. The final extent of these changes cannot be known until longer survival studies are performed.

Conclusion: This study demonstrated that both GROA and REBOA were highly effective at temporarily stanching NCTH of the abdomen and prolonging survival. The survival benefit combined with the simple application technique of GROA warrants additional studies as a means to improve survival from NCTH of the abdomen.

3.2.3.3 Major Task 3: Testing of tandem use of GROA to REBOA compared to control.

Significant Results:

In this study, we aimed to 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 of severe non-compressible abdominal hemorrhage due to liver laceration. Here we piloted the feasibility of tandem application of GROA followed by REBOA. We hypothesized that the tandem application of REBOA following an initial aortic occlusion with GROA is possible, while demonstrating a survival benefit associated with both technologies, compared to controls. We envision GROA could serve as a field bridge to REBOA allowing aortic occlusion for earlier hemorrhage control.

Methods: Nineteen Yorkshire mix swine (14 males; 5 females) with an average (standard deviation) weight of 52.2 kg (3.5kg) were used and all animals were included in the study. Nine animals (5 males; 4 females) were used in the intervention group and the rest were used as controls. Experimental design is presented in figure 15. **Instrumentation, Hemorrhage and Injury, and Resuscitation** in this study were identical to the methods described previously in Major Task 2. Data for eight of these control animals were published previously (see major task 2, above) and used in this study as historical controls. Given the models lethality, we chose for ethical and humane purposes to utilize the previous experimental set of animals as controls to compare survival between untreated and treated subjects. Sample size, using survival as the primary outcome, was determined based on results from previous studies.

Intervention. The device was placed during the 2 minutes of free bleeding from the liver. The abdominal plate was then tightened followed by GROA balloon inflation to 60-80 mmHg (equating to ~1200 cm³ balloon volume) and aortic occlusion was achieved and confirmed based on loss of femoral artery pulse pressure. Aortic occlusion was maintained with the GROA balloon for 30 minutes. At the 30-minute time mark, without deflation and deactivation of the GROA device, the REBOA catheter was inserted through the previously placed femoral artery introducer to the premeasured distance necessary for highest possible zone II subdiaphragmatic occlusion and inflated with 5-7 mL of saline. Following REBOA inflation, the GROA system was deactivated and removed for the remaining 30-minutes of intervention. Ten minutes prior to the end of the intervention period, intravenous Ringer's lactate solution was administered to increase intravascular volume and prevent hemodynamic collapse during device deactivation.

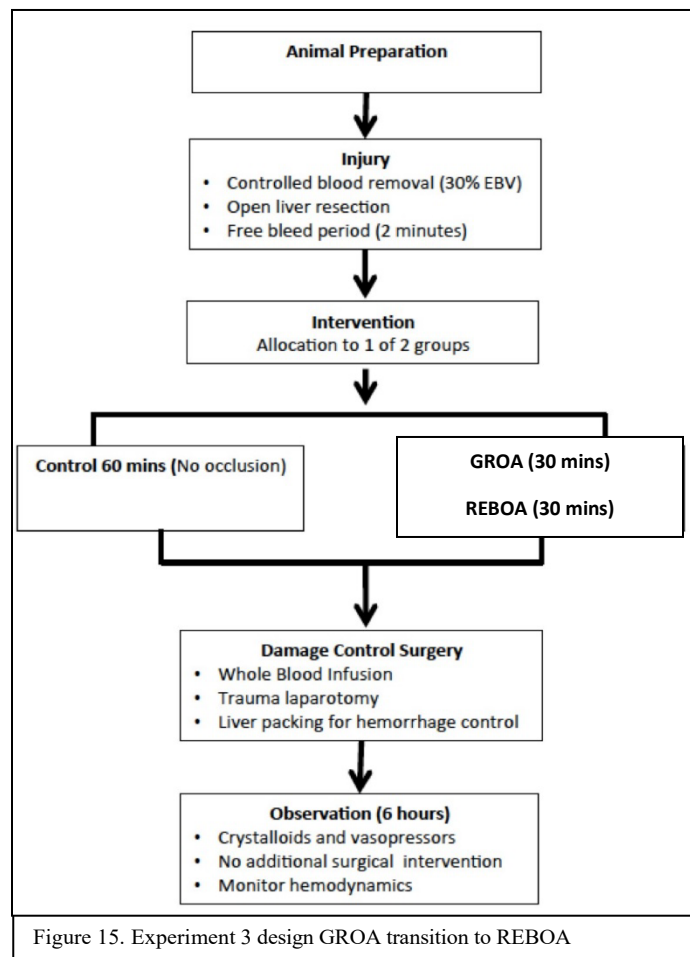
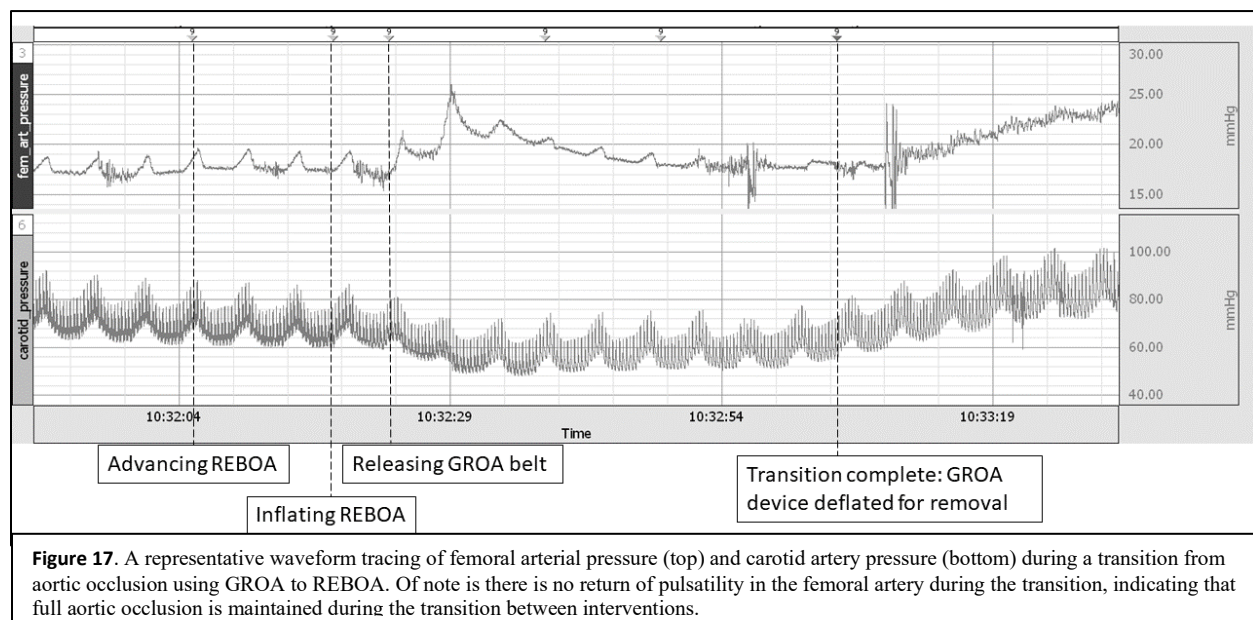
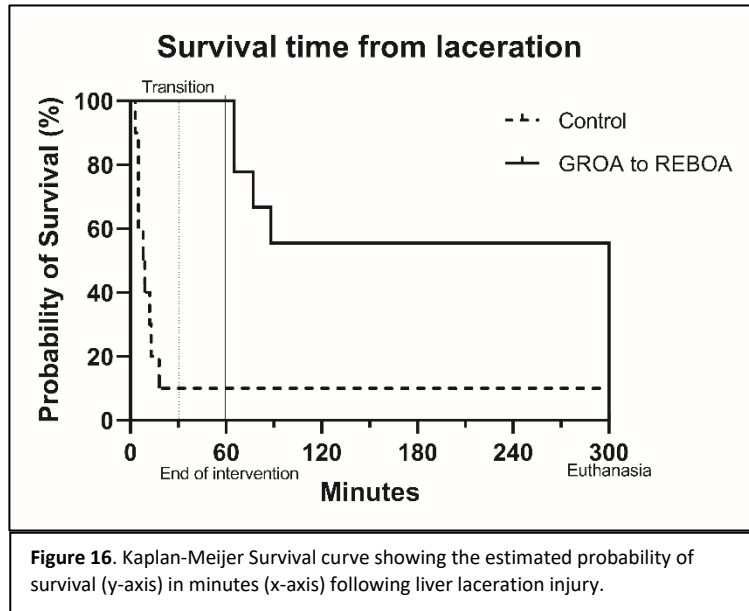


Figure 15. Experiment 3 design GROA transition to REBOA

Significant Findings & Results: All animals receiving the intervention survived the 60-minute intervention period including GROA with transition to REBOA while nine out of ten control animals died during the same period. There was a statistically significant survival benefit due to intervention compared to controls; $p=0.0007$. A Kaplan-Meier plot of survival probabilities is presented in figure 16. Transition from GROA to REBOA was successful in all animals without the loss of aortic occlusion during the transition. A representative animal's femoral and carotid pressure waveforms, during the transition, are presented in figure 17. The average time for the transition from the insertion of REBOA to the full deactivation of the GROA device was 63.2 seconds (18.8 seconds), with a minimum transition time of 30 seconds, and a maximum transition time of 90 seconds. There was no evidence of renewed bleeding signaled by hemodynamic response in any animal after transitioning between interventions. There were no changes in femoral artery pressure from the end of GROA application, 19.1 mmHg (4.05 mmHg) to the initiation of REBOA application, 18.9 mmHg (3.92 mmHg).



MAP, SmvO₂, and PetCO₂ are presented in figure 18. MAP significantly increased following GROA application in the intervention group and remained above a clinically relevant threshold of 65 mmHg for the duration of intervention, regardless of the timepoint or method of aortic occlusion. SmvO₂ also increased during the intervention period, and then returned to baseline levels by the end of the intervention period. Airway pressure increased in all animals following the application of GROA from 23.6 cmH₂O (2.1 cmH₂O) at the end of hemorrhage to 32 cmH₂O (3.5 cmH₂O). Airway pressure significantly decreased following the transition to REBOA, returning to a near baseline value.

Variable	End of GROA	15 minutes of REBOA	Percent Change	p-value
MAP (mmHg)	71 (16)	82.5 (21)	16.3%	0.4372
PAP (mmHg)	22 (3.5)	24 (5.2)	8.5%	0.3892
CVP (mmHg)	9.2 (3.5)	6.7 (1.4)	-27.2%	0.2471
HR (BPM)	155 (55)	157 (34)	1%	0.9960
CO (L/min)	1.5 (0.4)	1.8 (0.6)	18.8%	0.1325
PetCO ₂ (mmHg)	18. (3.4)	25 (7.0)	37%	0.0183*
Airway Pressure (cmH ₂ O)	32 (3.5)	24 (2.0)	-24.8%	0.0001*
PaO ₂ (mmHg)	182 (9.6)	188 (25.0)	3%	0.3971
SmvO ₂ (%)	59.1 (16.4)	65.1 (21.2)	10.1%	0.2586
VO ₂ (mL/kg/min)	4.7 (2.8)	4.11 (1.5)	-12.8%	0.6454

Table 3. Data are presented as averages (SD). Statistical significance was set at $\alpha=0.05$. * Denotes statistically significant difference.

Hemodynamics, metrics of shock and oxygenation remained stable or improved further between the end of GROA and the beginning of REBOA with additional data presented in table 3.

Upon histological examination of post mortem stomach tissue, there was some evidence of mild diffuse inflammatory infiltrates consistent with mild ischemic injury with across all areas of the stomach sampled including the cardia, fundus, and pylorus. However, these findings across all animals were either absent or deemed minimal indicating that the tandem use of GROA to REBOA for aortic occlusion for a intervention time of 60-minutes is well tolerated and does not appear to cause any acute catastrophic gastroesophageal injury. These findings were consistent with our previous studies (Major Tasks 1 & 2) which also demonstrated similar changes when REBOA was used as the sole method of occlusion.

The overall results of this study demonstrate the potential feasibility of utilizing GROA followed by a more controlled transition to REBOA. REBOA was successfully deployed while the GROA device was still activated. In all but one case, the REBOA was advanced past the GROA balloon without releasing any of the external pressure. In one case, the REBOA could not be advanced past the GROA balloon and in this case the REBOA was inflated with ~1-2 mL normal saline, and the GROA external pressure assembly was loosened just enough to allow the balloon to be advanced superior to the GROA balloon and be properly positioned before further inflation. Hemodynamic monitoring did not indicate any additional significant hemorrhage during REBOA transition.

Conclusion: Control of NCTH using endovascular technologies such as REBOA may present logistical challenges in point of injury implementation. The use of less invasive methods and technologies such as the GROA device may present an opportunity for more rapid control of NCTH. The subsequent transition

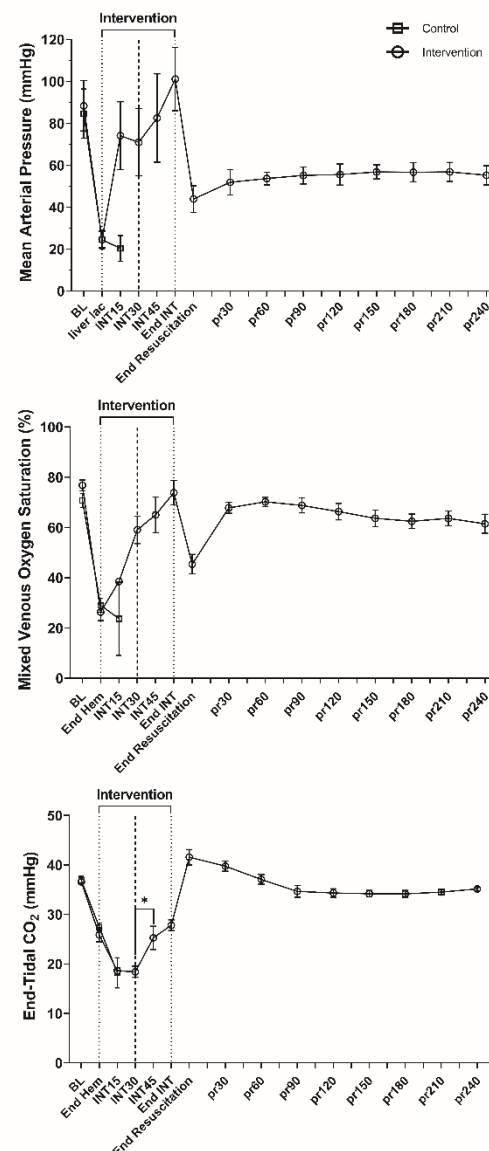


Figure 18. Average and standard error of mean arterial pressure (MAP) of the carotid artery (Top), Mixed Venous Oxygen Saturation (Middle) and End-Tidal CO₂ (Bottom). The area between the dashed lines represents the intervention period. The dotted line represents the time of transition from REBOA to GROA. * Denotes statistically significant differences following transition between GROA and REBOA.

to REBOA may be feasible as casualties move through higher echelons of care toward definitive surgical hemostasis. Additional research and development may be warranted.

Initial Cadaver Testing at Ft. Bragg:

On September 28th, 2021, at the invitation of US Army MEDCOM and the Joint Special Operation Medical Training Center at Ft. Bragg, we visited to explore the potential to examine the use of GROA in a unique perfused cadaver model. Perfused cadaver models are now being used at increasing rates to train combat casualty care providers in advance procedures. Cadavers are perfused using a bypass type circuit. Unfortunately, sudden logistical challenges related to COVID prevented the perfusion team from implementing the model. We were however, given the opportunity to insert the GROA device and identify challenges which may be present in utilizing such a model. Insertion of GROA was successful in one cadaver but not in another. This was due to the stiffness inherent in the cadaver. We are using this information to develop strategies which would allow easier placement in this setting.

We are now in discussion with the team at Ft. Bragg to arrange additional testing in the future. We are also planning to reach out to the SAFEGUARD Medical (<https://safeguardmedical.com/trubodies/>) to better understand the model and to engage them in a potential collaboration for follow-on funding. We believe the model has the potential to be a critical next step in transitioning the GROA technology from preclinical to clinical development and testing.

3.3 What opportunities for training and professional development has the project provided?

An opportunity was provided for several undergraduate students through the University of Michigan Undergraduate Research Opportunity Program (UROP) to observe the device, its development, and participate in preclinical testing and data collection. The students are not supported financially by this award.

3.4 How were the results disseminated to communities of interest?

Several peer reviewed publications have resulted from the data collected by this award. See section 6 below for detailed list.

Several conference abstracts were submitted and accepted for presentation. See section 6 below for detailed list.

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

All activities on all major tasks of this award have been completed. However, we plan to continue development of the device and technique through other future funding opportunities. We have currently submitted a preproposal to the *FY22 JOINT WARFIGHTER MEDICAL RESEARCH PROGRAM* for follow-up funding. The purpose of the application is to logically build on the results of this project. In this application we propose to collaborate with combat surgical experts and colleagues at Madigan Medical Center to conduct additional GROA testing and design optimization required for near-term translation as detailed below and a copy is provided in the appendix.

a. Test GROA and compare to REBOA in a large animal (swine) longer term (72 hour) survival model of lethal hemorrhage to define pathologic and histopathologic complications of aortic occlusion. This is an important next step because prior testing only occurred over periods of 30 to 90 minutes with a four-

hour recovery period, which did not allow us to examine for potential complications as needed for translation.

- b. Test GROA in comparison to REBOA for the ability to occlude the aorta in a perfused human cadaver model of hemorrhage. This will be an important next step to ensure that GROA can routinely and effectively occlude the aorta in humans.
- c. Obtain combat casualty care provider feedback on the use and design of the GROA system to optimize design and utility allowing its future use in combat settings.
- d. Lock in design and components of the GROA system to support the regulatory process for future phase I clinical safety testing.

The proposed Project Period of Performance is from March 1, 2023 - April 30, 2026, with a proposed budget of \$4,050,000. This proposal is currently under review.

In addition, we will continue to further de-risk and optimize the GROA system for FDA evaluation, preparing it for a future phase I clinical safety trial and commercialization.

4. IMPACT:

The overall impact of this project was development and testing of a prototype device for use in the primary disciplines of Emergency and Trauma care capable of rapidly controlling noncompressible torso hemorrhage (NCTH) of the abdomen and pelvis in the setting of potentially lethal trauma. The technology, for the first time, provides hope that control of NCTH could be accomplished at or near the point of injury. The technology is designed to be used by health care providers with skill levels below that of a surgeon or emergency physician.

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

The short-term impact of this work was the successful development of prototypes capable of providing comparable Zone II aortic occlusive performance, physiologic tolerance, and survival in a large animal (swine) model of lethal abdominal hemorrhage. Early device iterations indicated the need for external pressure to be applied in order to prevent deflection of the balloon away from the aorta. The results lead to the development of the external compression system as an adjunct to the GROA catheter 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. This was followed by successful demonstration of 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 human morphomimetics and the iterative designs and manufacturing process will immediately inform future manufacturing, safety, and regulatory requirements. In addition, knowledge gained from the preclinical studies have greatly assisted in understanding the physiologic and anatomical tolerances of the device. All information created by this project will assist in moving the device 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 has created a robust and easy to use device which has been shown in preclinical models to be capable of staunching uncontrolled intrabdominal and/or pelvic bleeding and prolong survival. Further the device has been shown to be complimentary to and compatible with REBOA as more advanced care becomes available. 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.

4.2 What was the impact on other disciplines?

While there was not direct impact of this project on other disciplines during the project period, we expect the product produced and studied in this proposal to potentially impact the disciplines of Vascular Surgery (temporary control of bleeding from ruptured abdominal aortic aneurysm) and Obstetrics (control of massive post-partum hemorrhage). These are examples of non-traumatic noncompressible torso hemorrhage which may benefit from the innovation developed in this proposal.

4.3 What was the impact on technology transfer?

The project resulted in the submission of the patents below which, along with the project results, form the basis for future development, testing, and commercialization of the technology. The technology is envisioned to be a device approved by the FDA for use by civilian and military health care providers for the temporary control of catastrophic noncompressible torso hemorrhage.

During the project period, a start-up company was formed out of the University of Michigan. The new start up is Veteran owned and operated. The company is: Precision Trauma LLC <https://www.ptrauma.com>. Precision Trauma has optioned the technology developed in this proposal and is expected the exercise this option to take a full license.

The technology developed in this proposal is envisioned to eventually improve the skills and abilities of medical first responders and emergency/trauma providers to save lives through the control of catastrophic noncompressible torso hemorrhage. Lives eventually saved by the use of this technology should reduce the economic toll taken by the loss of live from noncompressible torso hemorrhage.

4.4 What was the impact on society beyond science and technology?

The technology developed in this proposal is envisioned to eventually improve the skills and abilities of medical first responders and emergency/trauma providers to save lives through the control of catastrophic noncompressible torso hemorrhage. Lives eventually saved by the use of this technology should reduce the economic toll taken by the loss of live from noncompressible torso hemorrhage.

5 CHANGES/PROBLEMS:

5.1 Changes in approach and reasons for change *Nothing to report*

5.2 Actual or anticipated problems or delays and actions or plans to resolve them

Manufacturing Delay:

Waiting on the device design iterations and manufacturing of GROA prototypes caused a brief delay in animal tolerance testing as outlined in Major Task 1 in early 2019, and subsequently slowed the initiation of studies outlined in Major task 2. This temporary delay was necessary in order to obtain adequate prototypes which allowed for the best use of animals and other resources, and to obtain meaningful study results. Delivery of manufactured prototypes and then an acceleration of animal experiments resolved the delay.

COVID-19 Delay:

On March 18th, 2020, the COVID-19 pandemic resulted in a temporary ramp-down of all non-critical University functions, which included any research which not directly related to COVID-19. Several employees were placed on temporary voluntary furlough effective May 30, 2020 (Colmenero, Greer) to conserve grant funds. As of June 4, 2020, some limited research activities resumed under restrictions including social distancing and PPE use in laboratory spaces. As of June 26, 2020, our laboratory obtained clearance to resume work in full. As of June 29, 2020, animal ordering and housing of swine was allowed. As of July 20, 2020, density requirements were increased which allowed for continuation of animal work and both furloughed staff members were activated to resume work. The State of Michigan and the University of Michigan mandated ramp-downs resulted in unforeseen and uncontrollable circumstances that resulted in a prolonged lag for total data collection for this project. We filed and were granted a no-cost extension to this project to mitigate the delay in testing caused by the COVID-19 pandemic. With the extension, all work was completed as expected.

5.3 Changes that had a significant impact on expenditures *Nothing to report*

5.4 Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents *Nothing to report*

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

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

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

6 PRODUCTS:

6.1 Publications, conference papers, and presentations

Report only the major publication(s) resulting from the work under this award.

Journal publications.

Tiba MH, McCracken BM, Colmenero CI, et al. Gastroesophageal resuscitative occlusion of the aorta: Physiologic tolerance in a swine model of hemorrhagic shock. *J Trauma Acute Care Surg.* 2020;89(6):1114-1123. doi:10.1097/TA.0000000000002867, Status: Published, acknowledgement of federal support: Yes

McCracken BM, Tiba MH, Colmenero Mahmood CI, et al. Gastroesophageal resuscitative occlusion of the aorta prolongs survival in a lethal liver laceration model. *J Trauma Acute Care Surg.* 2022;92(5):880-889. doi:10.1097/TA.0000000000003444, Status: Published, acknowledgement of federal support: Yes

McCracken BM, Ward KR, Tiba MH. A review of two emerging technologies designed for pre-hospital treatment of non-compressible abdominal hemorrhage. *THOR supplement in Transfusion.* 2022. Status: Accepted, awaiting publication, acknowledgement of federal support: Yes

Tiba MH, McCracken BM, Greer NL, et al. Tandem use of Gastroesophageal Resuscitative Occlusion of the Aorta followed by REBOA in a Lethal Liver Laceration Model. *J Trauma Acute Care Surg.* 2022; Status: Accepted, awaiting publication, acknowledgement of federal support: Yes

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

Other publications, conference papers, and presentations.

Danielle Leander, Brendan McCracken, Jeffery Plott, Carmen Colmenero, Anne Marie Weitzel, Brandon Cummings, Albert Shih, Stewart Wang, Jonathan Eliason, Hakam Tiba, Kevin Ward, MD. Gastroesophageal Resuscitative Occlusion of the Aorta (GROA). Poster presentation. Barsan annual research Forum, April 2019, University of Michigan, Ann Arbor MI.

Brendan McCracken, Mohamad Hakam Tiba, MD, Jeffrey Plott, Carmen Colmenero, Danielle Leander, Anne Marie Weitzel, Brandon Cummings, Albert Shih, Stewart Wang, Jonathan Eliason, Kevin Ward. Gastroesophageal Resuscitative Occlusion of the Aorta (GROA). Poster presentation. 2019 Military Health System Research Symposium (MHSRS), Kissimmee, Florida, 2019. Awarded as *Honorable Mention*.

Brendan M. McCracken, Mohamad Hakam Tiba, Carmen I. Colmenero, Jeffery S. Plott, Danielle C. Leander, Nicholas L. Greer, Stewart Wang, Albert Shih, Jonathan Eliason, and Kevin R. Ward. Physiologic Tolerance of Gastroesophageal Resuscitative Occlusion of the Aorta (GROA) in a Swine Model of Hemorrhagic Shock. Accepted for poster presentation. 2020 Military Health System Research Symposium (MHSRS). The conference was cancelled due to the COVID-19 pandemic. *This work resulted in a manuscript.

Brendan M. McCracken, Mohamad Hakam Tiba, Carmen I. Colmenero, Jeffery S. Plott, Danielle C. Leander, Nicholas L. Greer, Stewart Wang, Albert Shih, Jonathan Eliason, and Kevin R. Ward. Gastroesophageal Occlusion of the Aorta (GROA) is effective at stanching hemorrhage and prolonging survival in a swine model of lethal non-compressible abdominal hemorrhage. Accepted for oral presentation. 2021 Military Health System Research Symposium (MHSRS). The conference was cancelled due to the COVID-19 pandemic. *This work resulted in a manuscript.

Brendan M. McCracken, Mohamad Hakam Tiba, Nicholas L. Greer, Traci A. Cramer, Carmen I. Colmenero, Ketut B. Priambada Putra, Albert J. Shih, Kevin R. Ward. Gastroesophageal Resuscitative Occlusion of the Aorta (GROA): Tandem use with REBOA for treatment of lethal abdominal hemorrhage. Accepted for oral presentation. 2021 Military Health System Research Symposium (MHSRS). *This work resulted in a manuscript.

6.2 Website(s) or other Internet site(s)

<https://weil institute.med.umich.edu/>
<https://weil institute.med.umich.edu/product-portfolio/gastroesophageal-resuscitative-occlusion-of-the-aorta>
<https://www.ptrauma.com/>

6.3 Technologies or techniques *Nothing to Report*

6.4 Inventions, patent applications, and/or licenses

6.4.1 Patent application PCT/US2020/046796 “*Gastroesophageal aortic occlusion device and method*” was filed August 18, 2020. US Utility # 17/632,114; Europe *pending*; Japan 2022-509737 *pending*. International publication date: February 25, 2021. The full patent is included in the appendices.

6.4.2 Patent application PCT/US2020/067247 “Anti-hemorrhage device with rigid back plate” was filed December 29, 2020. US Utility # 17/136,573. International publication date: July 22, 2021. The full patent is included in the appendices.

Other Products

As indicated above, a new startup was formed to move the technology forward towards commercialization. The company is Precision Trauma LLC (<https://www.ptrauma.com/>).

7 PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

7.1 What individuals have worked on the project?

<i>Name:</i>	<i>Kevin Ralph Ward</i>
<i>Project Role:</i>	<i>PI</i>
<i>Researcher Identifier: (e.g. ORCID ID)</i>	
<i>Total person months worked</i>	8
<i>Contribution to Project:</i>	<i>Project oversight. Oversight of all data collection and analysis</i>

<i>Name:</i>	<i>Albert J. Shih</i>
<i>Project Role:</i>	<i>Co-I</i>
<i>Researcher Identifier: (e.g. ORCID ID)</i>	
<i>Total person months worked</i>	4
<i>Contribution to Project:</i>	<i>Design of GROA device, data collection and analysis</i>

<i>Name:</i>	<i>Jonathan L. Eliason</i>
<i>Project Role:</i>	<i>Co-I</i>
<i>Researcher Identifier: (e.g. ORCID ID)</i>	
<i>Total person months worked</i>	4
<i>Contribution to Project:</i>	<i>Surgical consultation for animal REBOA and GROA animal experiments.</i>

<i>Name:</i>	<i>Stewart C. Wang</i>
<i>Project Role:</i>	<i>Co-I</i>
<i>Researcher Identifier: (e.g. ORCID ID)</i>	
<i>Total person months worked</i>	3
<i>Contribution to Project:</i>	<i>Oversight of Morphomics analysis for GROA development</i>

<i>Name:</i>	<i>Mohamad Hakam Tiba</i>
<i>Project Role:</i>	<i>Co-I</i>
<i>Researcher Identifier: (e.g. ORCID ID)</i>	
<i>Total person months worked</i>	10
<i>Contribution to Project:</i>	<i>Oversight of animal laboratory, project management, data collection and analysis</i>

<i>Name:</i>	Denise M. Wieck
<i>Project Role:</i>	<i>Secretarial/Administrative</i>
<i>Researcher Identifier: (e.g. ORCID ID)</i>	
<i>Total person months worked</i>	7
<i>Contribution to Project:</i>	<i>Project administrative duties</i>

<i>Name:</i>	Brendan M. McCracken
<i>Project Role:</i>	<i>Research Staff, Laboratory Assistant Director</i>
<i>Researcher Identifier: (e.g. ORCID ID)</i>	
<i>Total person months worked</i>	12
<i>Contribution to Project:</i>	<i>Animal laboratory oversight, project management, data collection, data analysis</i>

<i>Name:</i>	Carmen I. Colmenero Mahmood
<i>Project Role:</i>	<i>Research staff, Laboratory Technician</i>
<i>Researcher Identifier: (e.g. ORCID ID)</i>	
<i>Total person months worked</i>	18
<i>Contribution to Project:</i>	<i>Animal lab duties, data collection</i>

<i>Name:</i>	Chandler Rygalski
<i>Project Role:</i>	<i>Research staff, Laboratory Technician</i>
<i>Researcher Identifier: (e.g. ORCID ID)</i>	
<i>Total person months worked</i>	4
<i>Contribution to Project:</i>	<i>Animal lab duties, data collection</i>

<i>Name:</i>	Danielle C. Leander
<i>Project Role:</i>	<i>Research staff, Laboratory Technician</i>
<i>Researcher Identifier: (e.g. ORCID ID)</i>	
<i>Total person months worked</i>	17
<i>Contribution to Project:</i>	<i>Animal lab duties, data collection</i>

<i>Name:</i>	Nicholas L. Greer
<i>Project Role:</i>	<i>Research Staff, Laboratory Technician</i>
<i>Researcher Identifier: (e.g. ORCID ID)</i>	
<i>Total person months worked</i>	14
<i>Contribution to Project:</i>	<i>Animal lab duties, data collection</i>

<i>Name:</i>	Traci Cramer
<i>Project Role:</i>	<i>Research Staff, Laboratory Technician</i>
<i>Researcher Identifier: (e.g. ORCID ID)</i>	
<i>Total person months worked</i>	1
<i>Contribution to Project:</i>	<i>Animal lab duties, data collection</i>

<i>Name:</i>	Anne Marie Wietzel
<i>Project Role:</i>	<i>Research Staff, Laboratory Technician</i>
<i>Researcher Identifier: (e.g. ORCID ID)</i>	
<i>Total person months worked</i>	<i>1</i>
<i>Contribution to Project:</i>	<i>Animal lab duties, data collection</i>

<i>Name:</i>	Jeffrey S. Plott
<i>Project Role:</i>	<i>Device Design Engineer</i>
<i>Researcher Identifier: (e.g. ORCID ID)</i>	
<i>Total person months worked</i>	<i>16</i>
<i>Contribution to Project:</i>	<i>Device design: Technical design and Fabrication</i>

<i>Name:</i>	Miguel Funes Lora
<i>Project Role:</i>	<i>Device Design Engineer</i>
<i>Researcher Identifier: (e.g. ORCID ID)</i>	
<i>Total person months worked</i>	<i>16</i>
<i>Contribution to Project:</i>	<i>Device design: Technical design and Fabrication</i>

<i>Name:</i>	Dian Rui-Li
<i>Project Role:</i>	<i>Device Design Engineer</i>
<i>Researcher Identifier: (e.g. ORCID ID)</i>	
<i>Total person months worked</i>	<i>1</i>
<i>Contribution to Project:</i>	<i>Device design: Technical design and Fabrication</i>

<i>Name:</i>	Lei Chen
<i>Project Role:</i>	<i>Device Design Engineer</i>
<i>Researcher Identifier: (e.g. ORCID ID)</i>	
<i>Total person months worked</i>	<i>3</i>
<i>Contribution to Project:</i>	<i>Device design: Technical design and Fabrication</i>

<i>Name:</i>	Zhaokun Brandon Zhang
<i>Project Role:</i>	<i>Device Design Engineer</i>
<i>Researcher Identifier: (e.g. ORCID ID)</i>	
<i>Total person months worked</i>	<i>1</i>
<i>Contribution to Project:</i>	<i>Device design: Technical design and Fabrication</i>

<i>Name:</i>	Ketut Bagus Priambada Putra
<i>Project Role:</i>	<i>Device Design Engineer</i>
<i>Researcher Identifier: (e.g. ORCID ID)</i>	
<i>Total person months worked</i>	<i>14</i>
<i>Contribution to Project:</i>	<i>Device design: Technical design and Fabrication</i>

<i>Name:</i>	Brian Ross
<i>Project Role:</i>	<i>Morphomics analysis</i>

<i>Researcher Identifier: (e.g. ORCID ID)</i>	
<i>Total person months worked</i>	12
<i>Contribution to Project:</i>	<i>Collection, vetting and analysis of morphomic data.</i>

<i>Name:</i>	Edward Brown
<i>Project Role:</i>	<i>Morphomics analysis</i>
<i>Researcher Identifier: (e.g. ORCID ID)</i>	
<i>Total person months worked</i>	4
<i>Contribution to Project:</i>	<i>Collection, vetting and analysis of morphomic data.</i>

<i>Name:</i>	Sven Holcombe
<i>Project Role:</i>	<i>Morphomics analysis</i>
<i>Researcher Identifier: (e.g. ORCID ID)</i>	
<i>Total person months worked</i>	3
<i>Contribution to Project:</i>	<i>Collection, vetting and analysis of morphomic data.</i>

<i>Name:</i>	Daniel Taylor
<i>Project Role:</i>	<i>Data Engineer</i>
<i>Researcher Identifier: (e.g. ORCID ID)</i>	
<i>Total person months worked</i>	6
<i>Contribution to Project:</i>	<i>Data Signal processing, data storage and analysis</i>

<i>Name:</i>	Brandon C. Cummings
<i>Project Role:</i>	<i>Research staff, Data engineer</i>
<i>Researcher Identifier: (e.g. ORCID ID)</i>	
<i>Total person months worked</i>	6
<i>Contribution to Project:</i>	<i>Data collection, signal processing and data analysis</i>

<i>Name:</i>	Jonathan Motyka
<i>Project Role:</i>	<i>Data Engineer</i>
<i>Researcher Identifier: (e.g. ORCID ID)</i>	
<i>Total person months worked</i>	3
<i>Contribution to Project:</i>	<i>Data Signal processing, data storage and analysis</i>

<i>Name:</i>	Mark Salamango
<i>Project Role:</i>	<i>Data Engineer</i>
<i>Researcher Identifier: (e.g. ORCID ID)</i>	
<i>Total person months worked</i>	1
<i>Contribution to Project:</i>	<i>Data Signal processing, data storage and analysis</i>

7.1 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*

7.2 What other organizations were involved as partners? *Nothing to report.*

8 SPECIAL REPORTING REQUIREMENTS

8.1 QUAD CHARTS: *Uploaded separately from this report*

- 9 **APPENDICES:** *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc. Reminder: Pages shall be consecutively numbered throughout the report. **DO NOT RENUMBER PAGES IN THE APPENDICES.***

9.1 Journal publications.

Tiba MH, McCracken BM, Colmenero CI, et al. Gastroesophageal resuscitative occlusion of the aorta: Physiologic tolerance in a swine model of hemorrhagic shock. *J Trauma Acute Care Surg.* 2020;89(6):1114-1123. doi:10.1097/TA.0000000000002867, Status: Published, acknowledgement of federal support: Yes **page 29**

McCracken BM, Tiba MH, Colmenero Mahmood CI, et al. Gastroesophageal resuscitative occlusion of the aorta prolongs survival in a lethal liver laceration model. *J Trauma Acute Care Surg.* 2022;92(5):880-889. doi:10.1097/TA.0000000000003444, Status: Published, acknowledgement of federal support: Yes **page 39**

Visual Abstract: Gastroesophageal resuscitative occlusion of the aorta prolongs survival in a lethal liver laceration model. **page 49**

McCracken BM, Ward KR, Tiba MH. A review of two emerging technologies designed for pre-hospital treatment of non-compressible abdominal hemorrhage. *THOR supplement in Transfusion.* 2022. Status: Accepted, awaiting publication, acknowledgement of federal support: Yes **page 50**

Tiba MH, McCracken BM, Greer NL, et al. Tandem use of Gastroesophageal Resuscitative Occlusion of the Aorta followed by REBOA in a Lethal Liver Laceration Model. *J Trauma Acute Care Surg.* 2022; Status: Accepted, awaiting publication, acknowledgement of federal support: Yes **page 76**

Visual Abstract: Tandem use of Gastroesophageal Resuscitative Occlusion of the Aorta followed by REBOA in a Lethal Liver Laceration Model. **page 106**

9.2 Abstracts, conference papers, and presentations.

Abstract and Poster: Danielle Leander, Brendan McCracken, Jeffery Plott, Carmen Colmenero, Anne Marie Weitzel, Brandon Cummings, Albert Shih, Stewart Wang, Jonathan Eliason, Hakam Tiba, Kevin Ward, MD. Gastroesophageal Resuscitative Occlusion of the Aorta (GROA). Poster presentation. Barsan annual research Forum, April 2019, University of Michigan, Ann Arbor MI. **page 107**

MHSRS-19-01529 Abstract and Poster: Brendan McCracken, Mohamad Hakam Tiba, MD, Jeffery Plott, Carmen Colmenero, Danielle Leander, Anne Marie Weitzel, Brandon Cummings, Albert Shih, Stewart Wang, Jonathan Eliason, Kevin Ward. Gastroesophageal Resuscitative Occlusion of the Aorta (GROA). Poster presentation. 2019 Military Health System Research Symposium (MHSRS), Kissimmee, Florida, 2019. Awarded for excellence as *Honorable Mention*. **Page 109**

MHSRS-20-01454 Abstract: Brendan M. McCracken, Mohamad Hakam Tiba, Carmen I. Colmenero, Jeffery S. Plott, Danielle C. Leander, Nicholas L. Greer, Stewart Wang, Albert Shih, Jonathan Eliason, and Kevin R. Ward. Physiologic Tolerance of Gastroesophageal Resuscitative Occlusion of the Aorta (GROA) in a Swine Model of Hemorrhagic Shock. Accepted for poster presentation. 2020 Military Health System Research Symposium (MHSRS). The conference was cancelled due to the COVID-19 pandemic. *This work resulted in a manuscript. **Page 112**

MHSRS-21-04075 Abstract: Brendan M. McCracken, Mohamad Hakam Tiba, Carmen I. Colmenero, Jeffery S. Plott, Danielle C. Leander, Nicholas L. Greer, Stewart Wang, Albert Shih, Jonathan Eliason, and Kevin R. Ward. Gastroesophageal Occlusion of the Aorta (GROA) is effective at stanching hemorrhage and prolonging survival in a swine model of lethal non-compressible abdominal hemorrhage. Accepted for oral presentation. 2021 Military Health System Research Symposium (MHSRS). The conference was cancelled due to the COVID-19 pandemic. *This work resulted in a manuscript. **Page 114**

MHSRS-22-05913 Abstract: Brendan M. McCracken, Mohamad Hakam Tiba, Nicholas L. Greer, Traci A. Cramer, Carmen I. Colmenero, Ketut B. Priambada Putra, Albert J. Shih, Kevin R. Ward. Gastroesophageal Resuscitative Occlusion of the Aorta (GROA): Tandem use with REBOA for treatment of lethal abdominal hemorrhage. Accepted for oral presentation. 2021 Military Health System Research Symposium (MHSRS). *This work resulted in a manuscript. **Page 115**

9.3 Patents

Patent application PCT/US2020/046796 “*Gastroesophageal aortic occlusion device and method*” US Utility 17/632,114; Europe *pending*; Japan 2022-509737 *pending*. International publication date: February 25, 2021. **Page 117**

Patent application PCT/US2020/067247 “*Anti-hemorrhage device with rigid back plate*” US Utility # 17/136,573. International publication date: July 22, 2021. **Page 143**

9.4 Submitted Preproposal: FY22 JOINT WARFIGHTER MEDICAL RESEARCH PROGRAM Page 164

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

Mohamad H. Tiba, MD, MS, Brendan M. McCracken, BS, Carmen I. Colmenero, BS, Jeffery S. Plott, PhD, Danielle C. Leander, BS, Nicholas L. Greer, BS, Stewart C. Wang, MD, Albert J. Shih, PhD, Jonathan L. Eliason, MD, and Kevin R. Ward, MD, Ann Arbor, Michigan

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

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

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

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

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

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

exists.⁹ These dire outcomes for patients with NCTH highlight the urgent need to further explore options for rapid control of hemorrhage in prehospital and field care environments.

Aortic occlusion is an effective temporary countermeasure against NCTH⁸; however, many implementation barriers exist for its timely application. Beyond thoracotomy with aortic cross-clamping, resuscitative endovascular balloon occlusion of the aorta (REBOA) is the only currently available method for such occlusion.¹⁰ Since its emergence, the implementation of REBOA is gaining popularity^{11–15}; however, its deployment to field or point of injury care may be logistically problematic. Current standards require REBOA to be implemented by or in conjunction with acute care surgeons,¹⁶ and vascular access can be time-consuming and requires surgical or ultrasound guided placement. In far-forward treatment scenarios, surgical capabilities may be limited, and portable imaging equipment may not be available. These challenges continue to be a barrier to the use of aortic occlusion for NCTH in austere environments (including civilian prehospital use), necessitating the exploration of alternatives.

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

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From the Department of Emergency Medicine (M.H.T., B.M.M., C.I.C., D.C.L., N.L.G., K.R.W.), Michigan Center for Integrative Research in Critical Care (M.H.T., B.M.M., C.I.C., J.S.P., D.C.L., N.L.G., S.C.W., A.J.S., J.L.E., K.R.W.), Biomedical Engineering (J.S.P., A.J.S., K.R.W.), Mechanical Engineering (J.S.P., A.J.S.), and Department of Surgery (J.S.P., S.C.W., J.L.E.), University of Michigan, Ann Arbor, Michigan.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.jtrauma.com).

Address for reprints: Kevin R. Ward, MD, Department of Emergency Medicine, University of Michigan, 2800 N Plymouth Rd, North Campus Research Complex, Bldg 26-323N, Ann Arbor, MI 48109; email: keward@umich.edu.

DOI: 10.1097/TA.0000000000002867

a zone II aortic occlusion¹⁷ (celiac trunk to the most caudal renal artery).

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

MATERIALS AND METHODS

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

Device Description

The GROA device (Fig. 1) consists of four components: a gastroesophageal tube, a balloon, an air pump/pressure gauge assembly, and an external compression system. The gastroesophageal tube includes three lumens for suction and evacuation of gastric contents, air vent to avoid vacuum/pneumatic tension in the stomach, and balloon inflation and deflation. The balloon inflates to an ellipsoid shape with a diameter of approximately 17 cm reaching a total volume of approximately 1,600 cm³ when fully inflated, which is less than an adult stomach volume capacity of 2,000 cm³ to 4,000 cm³, providing the structure necessary to occlude the aorta when downward external pressure is applied to the epigastric area. The dimensions

of the balloon and tube were based on morphomic analysis of human adult abdominal and chest CT scans in a manner similar to that used to develop recent REBOA technology.¹⁹ The air pump/pressure gauge assembly allows for controlled balloon inflation/deflation and visual feedback on the pressure of the balloon. The external compression system consists of a back plate and an abdominal plate. When activated, this system prevents lateral and anterior deflection of the balloon, keeping the balloon over the aorta. The back plate serves as an anchor for the abdominal plate, which is secured in place by nylon straps. The system can be adjusted to apply controlled posterior-directed pressure. The system is constructed to prevent the application of circumferential pressure around the abdomen as would occur with the use of products such as the abdominal aortic junctional tourniquet.

Preparation

Male Yorkshire-mix swine were fasted overnight with ad libitum access to water. Anesthesia was induced with a combination of tiletamine/zolazepam (4–6 mg/kg) and xylazine (2 mg/kg) followed by 1% to 2% isoflurane delivered in 30% to 40% O₂ for the duration of the experiment. Animals were intubated using a 7.5-mm endotracheal tube and ventilated with a tidal volume of 7 to 8 mL/kg. Respiratory rate was adjusted to achieve an end-tidal CO₂ (PetCO₂) between 35 mm Hg and 45 mm Hg. Temperature was maintained between 37.0°C and 39.0°C during instrumentation using a temperature blanket (Blanketrol; Sub-Zero Medical, Cincinnati, OH). Electrocardiogram was monitored using a standard three-lead configuration (SurgiVet Advisor; Smiths Medical, Dublin, OH).

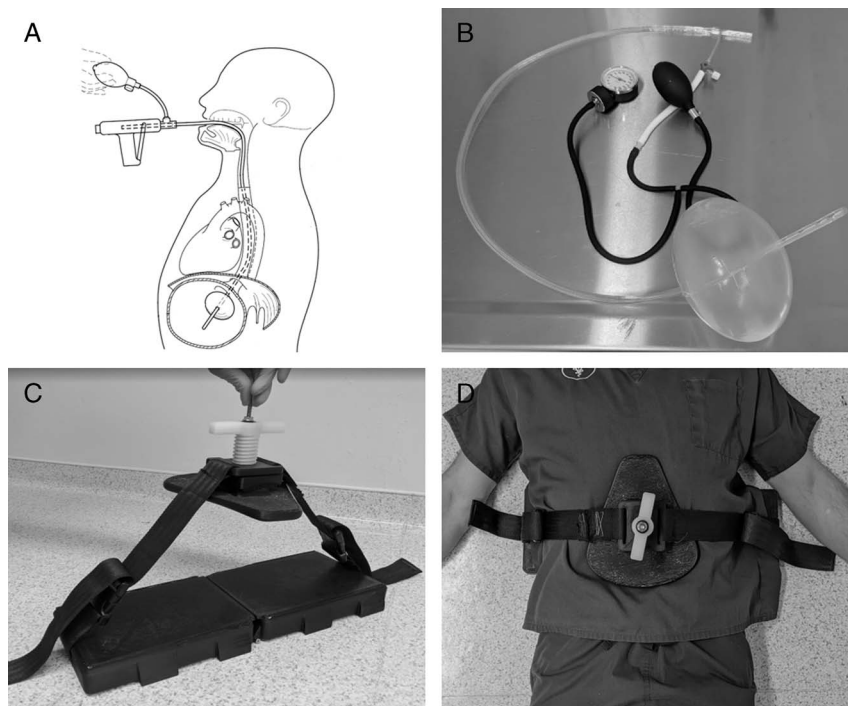


Figure 1. (A) Schematic view of GROA device inserted into stomach through the esophagus and inflated. (B) The GROA prototype device composed of a gastroesophageal tube, a balloon (inflated), and an air pump/pressure gauge assembly. (C) External compression system including back plate, abdominal plate,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

Instrumentation

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

Study Design

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

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

Immediately following hemorrhage, interventions were deployed. In the control groups, there was no intervention, and animals were observed for the duration of the assigned intervention period (30–90 minutes). In the REBOA groups, the balloon was inflated using 5 to 7 mL of saline. In the GROA groups, the balloon was inflated with air to a pressure of 60 to 80 mm Hg (approximate volume of 1600 cm³). Controlled external pressure was applied using the abdominal plate assembly until aortic occlusion was achieved. Occlusion in GROA and REBOA groups was verified by loss of femoral artery waveform. Example occlusion data are shown in Figure 4. After aortic occlusion, animals were monitored for the duration of their intervention periods.

Resuscitation

Resuscitation was initiated following the intervention phase similar to that described by Markov et al.²⁰ Resuscitation included shed blood transfusion (900 mL), followed by intravenous lactated Ringer's solution infusion. Intravenous calcium chloride (100 mg/mL Ca²⁺) was administered to maintain Ca²⁺ levels 1.0 mmol/L to 1.3 mmol/L. In the control groups, whole blood resuscitation was initiated at the end of the intervention period. In the aortic occlusion groups, whole blood administration started 10-minutes before the end of the intervention period to raise MAP and mitigate acute hemodynamic decompensation

associated with reperfusion injury. At the end of intervention for the aortic occlusion groups, devices were slowly released over an average period of 7 minutes to 10 minutes. Blood pressure was titrated to a target MAP of >60 mm Hg using intravenous lactated Ringer's supplemented by administration of norepinephrine (4 mg) in 5% dextrose in NaCl 0.9% (500 mL), titrated to effect. Postresuscitation monitoring and data collection continued for 4 hours while blood samples were collected at designated points. All animals were euthanized with potassium chloride under isoflurane at the completion of the monitoring period.

Data Collection

Measurements of MAP, femoral arterial pressure, CVP, PAP, peak airway pressure, heart rate, temperature, mixed venous oxygen saturation (SvO₂), PetCO₂, and ECG were recorded continuously (MP160; Biopac Systems Inc., Goleta, CA). Arterial and mixed venous blood gases were analyzed every 30 minutes (ABL800flex; Radiometer America Inc., Brea, CA). Complete blood count (Vetscan HM5; Abaxis, Inc., Union City, CA) and thromboelastography (TEG 5000; Haemonetics Corp., Braintree, MA) samples were obtained at the end of hemorrhage period, end of intervention, end of resuscitation, and every 2 hours thereafter. Comprehensive diagnostic chemistry profiles (VetScan; Abaxis Inc., Union City, CA) were sampled at baseline and end of experiment for all groups. Following euthanasia, stomach and aortic samples were harvested for histological analysis by a blinded veterinary pathologist.

Statistical Analysis

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

RESULTS

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

Survival

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

Mean Arterial Pressure

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

TABLE 1. Baseline Hemodynamic Characteristics and Hemorrhage Volume by Group

	30-min Intervention			60-min Intervention			90-min Intervention		
	Control	GROA	REBOA	Control	GROA	REBOA	Control	GROA	REBOA
n	6	5	5	5	5	5	5	6	5
Weight, kg	53 (1.7)	54 (1.1)	49 (5.8)	51 (2.9)	53 (3.6)	53 (2.3)	52 (3.9)	56 (5.9)	49 (4.8)
Hemorrhage volume, %	35 (2.0)	34 (3.0)	35 (1.0)	35 (2.0)	35 (3.0)	35 (3.0)	39 (4.7)	35 (1.4)	40 (7.1)
MAP, mm Hg	80 (7.5)	84 (7.6)	88 (8.1)	97 (9.4)	81 (10.4)	86 (10.5)	82 (15.4)	81 (16.1)	85 (12.5)
Heart rate, bpm	85 (9.2)	84 (11.6)	92 (0.7)	103 (28.7)	85 (2.3)	77 (4.4)	102 (28.1)	90 (9.7)	82 (4.7)
Temperature, °C	36.9 (0.71)	37.2 (0.47)	37.2 (0.44)	37.0 (0.61)	37.7 (0.79)	37.3 (0.43)	36.8 (0.69)	37.5 (0.42)*	36.5 (0.37)
Lactate, mEq/L	1.3 (0.31)	1.3 (0.57)	1.4 (0.64)	1.8 (0.80)	1.4 (0.67)	2.7 (1.46)	2.5 (1.19)	1.8 (0.75)	1.6 (0.52)
SmvO ₂ , %	70.6 (7.39)	69.1 (7.10)	69.6 (5.56)	69.4 (8.07)	71.0 (5.71)	70.7 (5.77)	75.9 (6.78)	68.9 (7.44)	71.9 (4.59)
PetCO ₂ , mm Hg	38.0 (2.22)	38.0 (2.87)	37.8 (1.72)	41.5 (5.15)	38.9 (2.04)	39.8 (2.67)	40.6 (4.64)	39.4 (1.99)	36.6 (8.67)

Data are presented as averages (SD). Statistical significance was set at $\alpha < 0.05$.

*Denotes statistically significant difference between GROA and REBOA.

bpm, Beats per minute; SmvO₂, mixed venous oxygen saturation (%); PetCO₂, end-tidal CO₂ (mm Hg).

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

Lactate

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

Mixed Venous Oxygen Saturation

SvO₂ is presented in Figure 3. SvO₂ increased following occlusion in both GROA and REBOA groups relative to controls at 30 minutes, to levels of 60.6% (22.90%) and 81.5% (15.31%), versus 42.4% (15.45%), respectively ($p < 0.05$). SvO₂ in the GROA group was significantly lower than in the REBOA group

($p = 0.0078$) at the same period. At 60 minutes of occlusion, SvO₂ in the GROA and control groups was similar: 50.6% (15.88%) versus 50.6% (16.68%), respectively, while REBOA remained significantly increased: 71.0% (21.27%) ($p < 0.05$). No significant differences between GROA, REBOA, or control groups were observed at 90 minutes of intervention. SvO₂ returned and was maintained near baseline levels following resuscitation in all groups except the 90-minute REBOA group in which no animals survived.

End Tidal CO₂

PetCO₂ decreased in both GROA and REBOA groups relative to controls following at 30 minutes of occlusion to levels of 25.1 (6.88) mm Hg and 30.3 (4.59) mm Hg, versus 37.2 (4.41) mm Hg, respectively ($p < 0.05$). PetCO₂ in the GROA groups was significantly lower than the REBOA groups ($p = 0.028$) at the same period. This decrease maintained significance for the duration of the intervention periods and then returned to near baseline levels following device deactivation and resuscitation in the 30-minute and 60-minute intervention groups. PetCO₂ remained depressed in the two surviving GROA 90-minute animals 31.7 (1.68) mm Hg ($p = 0.0233$) (Fig. 3). Similarly, mean PaCO₂ was decreased in the intervention groups relative to controls; however, PaCO₂ in GROA and REBOA groups were not different during intervention (Table 2).

Resuscitation Requirements

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

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

	30-min Intervention			60-min Intervention			90-min Intervention		
	Control	GROA	REBOA	Control	GROA	REBOA	Control	GROA	REBOA
Survival Ratio	3:6	4:5	5:5	5:5	5:5	4:5	5:5	2:6	0:5
Resuscitation									
Crystalloids: LR mL/kg/h	6.1 (1.97)	5.5 (1.14)	3.9 (2.53)	4.5 (2.57)	7.4 (6.62)	5.8 (3.08)	7.2 (7.83)	23.4 (3.84)*	—
Norepinephrine mcg/kg/h	0.01 (0.036)	0.39 (0.587)	0.04 (—)	—	2.57 (3.40)	0.85 (1.054)	0.01 (0.017)	6.53 (9.829)*	—
Metrics									
pH									
Baseline	7.42 (0.023)	7.40 (0.019)	7.49 (0.084)	7.38 (0.038)	7.39 (0.036)	7.38 (0.069)	7.45 (0.056)	7.39 (0.051)	7.46 (0.023)
End int	7.42 (0.058)	7.40 (0.070)	7.41 (0.046)	7.35 (0.025)	7.33 (0.075)	7.3 (0.044)	7.38 (0.027)	7.32 (0.080)	7.37 (0.076)
End exp	7.44 (0.046)	7.41 (0.015)	7.44 (0.033)	7.41 (0.022)	7.37 (0.028)	7.37 (0.059)	7.45 (0.013)	7.20 (0.119)*	—
Hb, g/dL									
Baseline	9.3 (1.39)	9.2 (1.57)	10.0 (0.76)	9.7 (1.37)	9.3 (0.29)	9.4 (1.77)	11.0 (0.72)	9.3 (0.66)	10.4 (0.40)
End int	9.1 (1.21)	9.2 (1.80)	10.5 (0.56)	9.6 (1.51)	9.6 (1.15)	9.7 (1.71)	10.8 (1.47)	8.9 (0.86)	10.4 (1.10)
End exp	9.3 (2.11)	9.1 (1.99)	10.2 (1.61)	9.7 (1.71)	10.3 (1.35)	10.9 (2.11)	10.4 (1.16)	10.3 (1.70)	—
PLT, 10 ⁹ /L									
Baseline	252 (138.6)	320 (76.7)	231 (108.0)	312 (114.3)	297 (92.7)	245 (104.7)	272 (78.6)	340 (72.0)	282 (67.3)
End int	354 (86.6)	300 (56.6)	283 (73.2)	297 (116.8)	260 (96.6)	220 (86.2)	287 (16.1)	318 (57.0)	217 (80.4)
End exp	266 (67.1)	310 (74.6)	236 (79.5)	242 (101.0)	232 (106.5)	182 (79.6)	243 (66.3)	174 (127.9)*	—
K ⁺ , mmol/L									
Baseline	3.8 (0.17)	3.7 (0.23)	3.5 (0.20)	3.5 (0.21)	3.7 (0.27)	3.6 (0.12)	3.6 (0.22)	3.8 (0.53)	3.6 (0.27)
End int	4.5 (0.4)	4.8 (0.62)	4.2 (0.38)	3.9 (0.56)	4.5 (0.54)	4.4 (0.42)	4.3 (0.43)	4.0 (0.47)	4.3 (0.36)
End exp	4.2 (0.15)	4.5 (0.45)	4.4 (0.27)	4.4 (0.15)	5.3 (0.93)	4.9 (0.66)	4.9 (0.57)	6.5 (2.12)	—
Ca ⁺⁺ , mmol/L									
Baseline	1.25 (0.077)	1.29 (0.076)	1.17 (0.082)	1.21 (0.069)	1.31 (0.052)	1.22 (0.047)	1.26 (0.068)	1.28 (0.072)	1.31 (0.088)
End int	1.22 (0.080)	1.25 (0.065)	1.19 (0.078)	1.21 (0.071)	1.20 (0.091)	1.18 (0.043)	1.21 (0.085)	1.22 (0.063)	1.21 (0.136)
End exp	1.33 (0.078)	1.26 (0.079)	1.14 (0.115)	1.18 (0.046)	1.27 (0.073)*†	1.13 (0.051)	1.23 (0.135)	1.17 (0.007)	—
PaO ₂ /FiO ₂									
Baseline	463 (55.1)	477 (10.3)	497 (36.7)	412 (133.8)	383 (114.3)	458 (41.2)	443 (57.3)	422 (97.7)	473 (61.9)
End int	452 (23.7)	454 (173.8)	538 (44.8)	411 (56.3)	456 (63.4)	546 (31.3)**†	444 (39.0)	382 (145.1)	518 (109.5)
End exp	439 (31.3)	372 (104.4)	434 (37.5)	408 (57.8)	400 (84.4)	447 (100.5)	383 (23.2)	336 (152.6)	—
PaCO ₂ , mm Hg									
Baseline	38 (1.5)	40 (2.1)	37 (1.3)	41 (4.5)	40 (4.1)	41 (4.3)	41 (4.1)	37 (5.7)	40 (3.4)
End int	34 (5.1)	26 (4.4)*	31 (3.3)	43 (2.7)	30 (9.5)*	30 (1.4)**	39 (5.8)	20 (2.7)*	27 (3.7)**
End exp	39 (2.0)	37 (10.0)	39 (1.5)	41 (3.4)	40 (2.6)	40 (1.6)	42 (1.7)	32 (17.3)	—
PaO ₂ , mm Hg									
Baseline	151 (14.8)	163 (16.5)	152 (9.8)	141 (44.3)	139 (44.6)	167 (33.5)	144 (26.8)	140 (41.0)	156 (28.1)
End int	146 (28.3)	150 (51.3)	161 (11.1)	149 (15.6)	172 (16.6)	196 (42.0)	139 (14.4)	138 (49.0)	175 (37.2)
End exp	131 (17.9)	142 (12.2)	130 (17.9)	147 (16.0)	152 (36.7)	159 (14.0)	120 (9.7)	152 (73.5)	—
AP, cmH ₂ O									
Baseline	20 (0.8)	22 (2.8)	21 (1.4)	22 (3.1)	24 (2.1)	21 (3.0)	22 (4.4)	23 (1.6)	20 (1.5)
End int	20 (0.9)	30 (4.6)*†	21 (1.2)	23 (2.1)	30 (2.9)*†	21 (1.9)	22 (3.6)	31 (2.5)*†	23 (1.8)
End exp	20 (0.9)	21 (2.3)	20 (1.0)	23 (1.2)	25 (3.2)	22 (2.1)	21 (3.8)	26 (1.4)	—
BUN, mg/dL									
Baseline	5 (1.2)	6 (0.8)	5 (1.5)	5 (1.4)	8 (2.0)	6 (1.3)	6 (1.5)	5 (1.0)	6 (1.8)
End exp	10 (1.1)	9 (1.0)	9 (1.1)	9 (1.8)	11 (1.5)	10 (1.7)	11 (2.7)	8 (1.4)	—
CRE, mg/dL									
Baseline	1.3 (0.17)	1.2 (0.081)	1.3 (0.22)	1.2 (0.10)	1.4 (0.18)	1.3 (0.19)	1.4 (0.24)	1.1 (0.08)	1.1 (0.31)
End exp	1.5 (0.05)	1.5 (0.23)	1.6 (0.08)	1.5 (0.27)	2.3 (0.47)*	2.3 (0.38)**	1.7 (0.37)	2.3 (0.14)	—

Continued next page

TABLE 2. (Continued)

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

Data are presented as averages (SD). One-way ANOVA using Tukey's correction for multiple comparisons was used for intergroup analysis. Statistical significance was set at $\alpha < 0.05$.

*Denotes statistically significant difference between GROA and control.

**Denotes statistically significant difference between REBOA and control.

†Denotes statistically significant difference between GROA and REBOA.

ANOVA, analysis of variance; Hb, hemoglobin; PLT, platelets; K⁺, potassium; Ca⁺⁺, calcium; PaO₂, partial pressure of arterial oxygen; FiO₂, fraction of inspired oxygen; PaCO₂, partial pressure of carbon dioxide; AP, arterial pressure; BUN, blood urea nitrogen; CRE, creatinine; ALT, alanine aminotransferase; TBIL, total bilirubin; End int, end of intervention period; End exp, end of experiment; LR, lactated ringer's.

Organ Function

Parameters for renal and hepatic function are presented in Table 2. Chemistry profiles indicated a statistically significant increase in creatinine levels in the GROA and REBOA relative to controls after 60 minutes of occlusion reaching levels of 2.3 (0.47), 2.3 (0.38), and 1.5 (0.27) mg/dL, respectively. A similar

increase in the GROA 90-minute group, 2.3 (0.14) mg/dL, was observed but did not achieve statistical significance. Thromboelastography analysis revealed no clinically relevant changes in reaction time (*R*), clot formation kinetics (*K* and α), measures of clot firmness (maximum amplitude [MA] or time to MA), or lysis (LY30), suggesting no evidence of coagulopathy between groups.

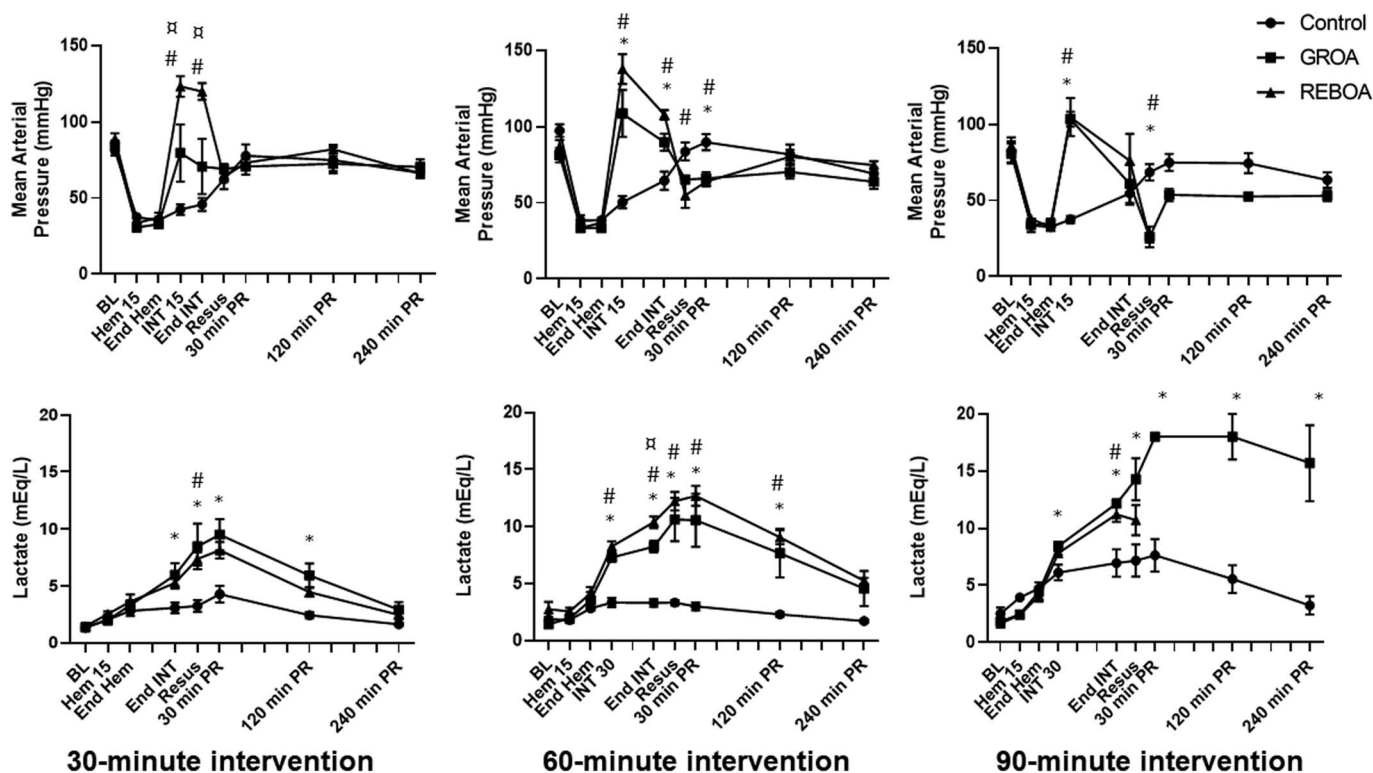


Figure 2. Average and standard error of MAP of the carotid artery and arterial lactate concentration for 30-minute, 60-minute, and 90-minute interventions. *Denotes statistically significant difference from GROA and control. #Denotes statistically significant difference from REBOA and control. □Denotes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

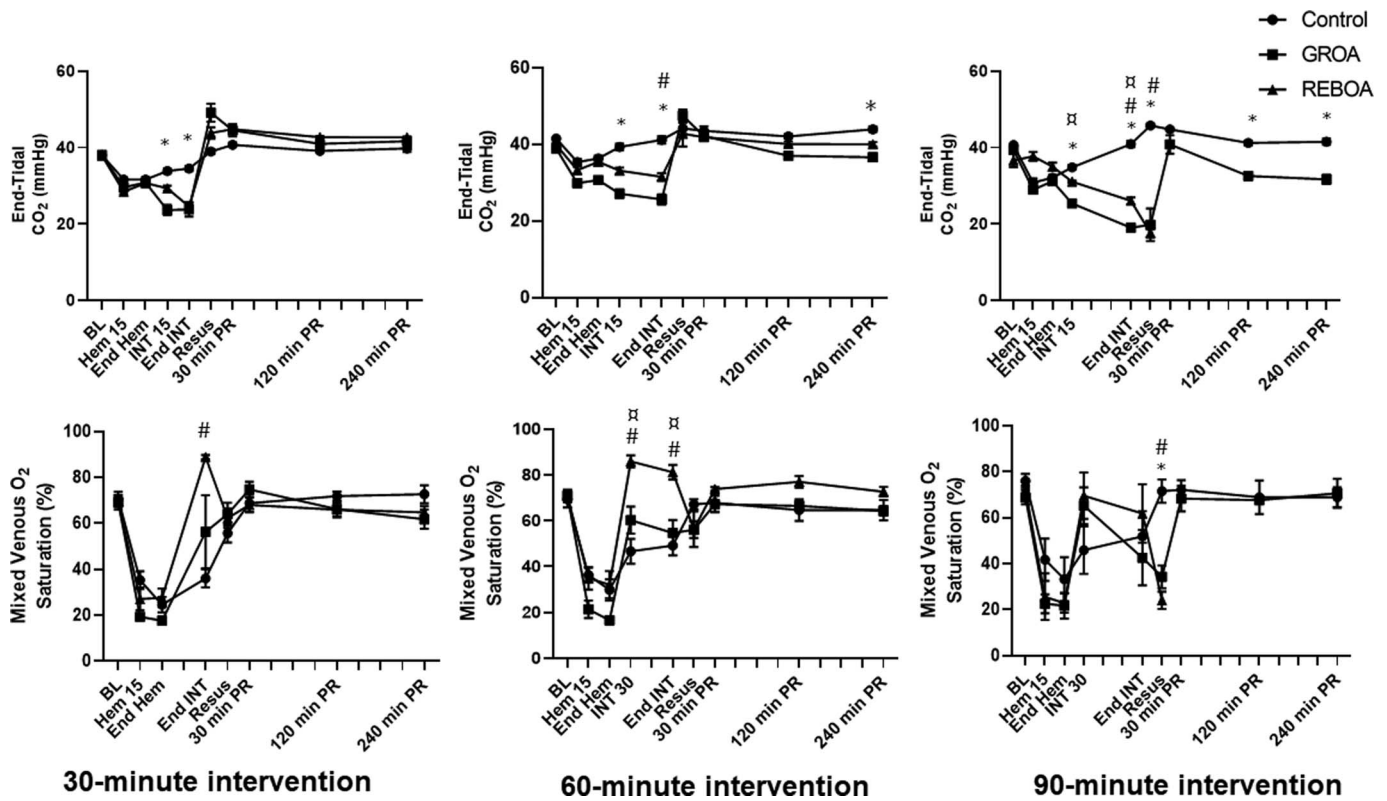


Figure 3. Average and standard error of end-tidal CO₂ (PetCO₂) and mixed venous oxygen saturation (SmvO₂), for 30-minute, 60-minute, and 90-minute interventions. *Denotes statistically significant difference from GROA and control. #Denotes statistically significant difference from REBOA and control. □Denotes statistically significant difference from GROA and REBOA. BL, baseline; Hem 15, 15 minutes into hemorrhage; End Hem, end of hemorrhage; INT 15, 15 minutes into intervention; INT 30, 30 minutes into intervention; End INT, end of intervention; Resus, resuscitation; PR, postresuscitation.

Airway, Central Venous, and PAPs

Animals receiving GROA intervention showed a significant increase in peak airway pressures relative to REBOA and control groups (31 [3.1] cmH₂O, 22.7 [2.7] cmH₂O, and 22.4

[2.9] cmH₂O, respectively) during intervention ($p < 0.0001$). Intergroup airway pressure data are presented in Table 2. The airway pressure was elevated immediately following the GROA device application period and was maintained until device

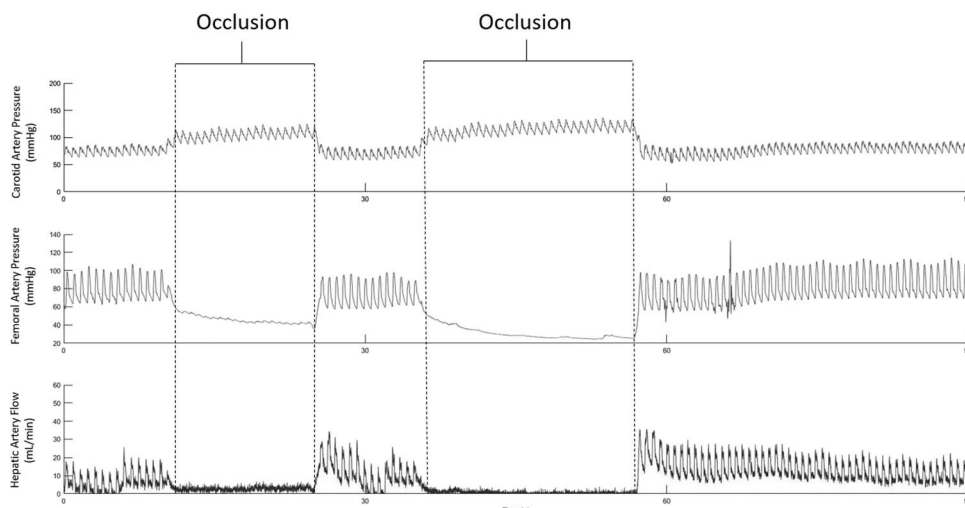


Figure 4. The GROA device's effect on carotid artery pressure (mm Hg), femoral artery pressure (mm Hg), and hepatic artery flow (mL/min). Noted are the increases in carotid pressure and the cessation of pulsatile flow in both the femoral artery and hepatic artery during device inflation, verifying zone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

deactivation with a range of 25 to 39 cmH₂O across all animals. Airway pressures returned to baseline following device deactivation and maintained throughout the postresuscitation monitoring period. Airway pressure data are available in Supplemental Digital Content 2 (Supplementary Fig. 2, <http://links.lww.com/TA/B732>). Central venous and PAPs changes during hemorrhage, intervention period, and resuscitation showed no differences between the three groups at any of the intervention periods (30 minutes, 60 minutes, and 90 minutes) (Supplemental Digital Content 3, Supplementary Fig. 3, <http://links.lww.com/TA/B733>).

Histology

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

DISCUSSION

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

The survival rate between REBOA and GROA for all intervention durations was similar except that no REBOA animals survived resuscitation after 90 minutes of complete aortic occlusion. With only two animals surviving the 4-hour resuscitation period after 90 minutes of GROA, our study suggest that 90 minutes of complete aortic occlusion is possible but not well

tolerated. We were thus not able to duplicate the level of REBOA tolerance reported by Markov et al.²⁰ The overall survival rate between REBOA and GROA intervention in the 30-minute and 60-minute occlusion groups suggest that the overall tolerance of the GROA device may be equal to the already well-characterized physiological tolerance of REBOA for those occlusion times.^{20–23}

The hemodynamic effects of GROA appear to be similar to those produced by REBOA. Overall, increased MAP and SvO₂ suggest increased central redistribution of blood flow and potentially increased perfusion of brain and heart consistent with previous REBOA studies.^{24,25} Lactate was also increased in all GROA groups during occlusion and peaked following reperfusion; however, these observations are again similar to REBOA and consistent with previous studies. Lactate burden created by both methods of aortic occlusion were able to be alleviated in the 30-minute and 60-minute intervention groups by adequate resuscitation. As expected, lactate levels were highest in the 90-minute occlusion GROA group during the reperfusion period but could not be compared with 90-minute REBOA animals since no animals in this group survived resuscitation.

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

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

40 cmH₂O threshold associated with increased risk of injury,²⁹ and blood gas analysis verified no change in PaO₂ or PaO₂/FiO₂ during the intervention and recovery period, indicating adequate ventilation. Furthermore, neither CVP or PAP was significantly different between the groups, indicating that, if compression of the inferior vena cava (IVC) by GROA occurs, decreases on cardiac preload from inferior vena cava impingement versus reductions in venous return from aortic occlusion did not affect outcomes.

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

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

CONCLUSIONS

In this study, GROA was effective in creating zone II aortic occlusion and may therefore be capable of temporarily staunching severe NCTH and improving survival. Based on hemodynamics, survival rate, and acute phase organ response data, the physiological tolerance of GROA appears similar to REBOA. This

study warrants ongoing evaluation of the efficacy of GROA to staunch uncontrolled hemorrhage. Gastroesophageal resuscitative occlusion of the aorta may serve as a fast, effective, and short-term method of achieving hemostasis until definitive surgical interventions may be performed.

AUTHORSHIP

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

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DISCLOSURE

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

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Gastroesophageal resuscitative occlusion of the aorta prolongs survival in a lethal liver laceration model

Brendan M. McCracken, MS, Mohamad Hakam Tiba, MD, MS, Carmen I. Colmenero Mahmood, BS, Danielle C. Leander, BS, Nicholas L. Greer, BS, Jeffery S. Plott, PhD, Albert J. Shih, PhD, Stewart C. Wang, MD, Jonathan L. Eliason, MD, and Kevin R. Ward, MD, Ann Arbor, Michigan

BACKGROUND: Noncompressible torso hemorrhage management remains a challenge especially in the prehospital setting. We evaluated a device designed to occlude the aorta from the stomach (gastroesophageal resuscitative occlusion of the aorta [GROA]) for its ability to stop hemorrhage and improve survival in a swine model of lethal liver laceration and compared its performance to resuscitative endovascular balloon occlusion of the aorta (REBOA) and controls.

METHODS: Swine ($n = 24$) were surgically instrumented and a 30% controlled arterial hemorrhage over 20 minutes was followed by liver laceration. Animals received either GROA, REBOA, or control (no treatment) for 60 minutes. Following intervention, devices were deactivated, and animals received whole blood and crystalloid resuscitation. Animals were monitored for an additional 4 hours.

RESULTS: The liver laceration resulted in the onset of class IV shock. Mean arterial blood pressure (MAP) (standard deviation) decreased from 84.5 mm Hg (11.69 mm Hg) to 27.1 mm Hg (5.65 mm Hg) at the start of the intervention. Seven of eight control animals died from injury prior to the end of the intervention period with a median survival (interquartile) time of 10.5 minutes (12 minutes). All GROA and REBOA animals survived the duration of the intervention period (60 minutes) with median survival times of 86 minutes (232 minutes) and 79 minutes (199 minutes) after resuscitation, respectively. The GROA and REBOA animals experienced a significant improvement in survival compared with controls ($p = 0.01$). Resuscitative endovascular balloon occlusion of the aorta resulted in higher MAP at the end of intervention 114.6 mm Hg (22.9 mm Hg) compared with GROA 88.2 mm Hg (18.72 mm Hg) ($p = 0.024$), as well as increased lactate compared with GROA $13.2 \text{ meq}\cdot\text{L}^{-1}$ ($1.56 \text{ meq}\cdot\text{L}^{-1}$) versus $10.5 \text{ meq}\cdot\text{L}^{-1}$ ($1.89 \text{ meq}\cdot\text{L}^{-1}$) ($p = 0.028$). Histological examination of the gastric mucosa in surviving animals revealed mild ischemic injury from both GROA and REBOA.

CONCLUSION: The GROA and REBOA devices were both effective at temporarily stanching lethal noncompressible torso hemorrhage of the abdomen and prolonging survival. (*J Trauma Acute Care Surg.* 2022;92: 880–889. Copyright © 2021 Wolters Kluwer Health, Inc. All rights reserved.)

KEY WORDS: Shock; noncompressible torso hemorrhage; aorta; resuscitation; REBOA.

Despite recent advances in acute trauma care and resuscitation, hemorrhage remains the leading cause of preventable death after trauma, where death often occurs before a medical treatment facility is reached.¹ Hemorrhage from potentially survivable injuries is responsible for more than 40% of civilian trauma deaths and 90% of military combat casualties.^{2–4} Despite recent advancements in trauma and hemorrhage management, treatment of noncompressible torso hemorrhage (NCTH) continues to pose almost intractable challenges, especially in the

prehospital setting where almost 9 of 10 deaths occur.^{3,5} Noncompressible torso hemorrhage is a high-grade injury present in one or more of the following anatomic domains: thoracic cavity (including pulmonary parenchymal injuries), solid abdominal organ, major vascular, or pelvic trauma; plus, hemodynamic instability or the need for immediate hemorrhage control.^{5,6}

The National Trauma Data Bank estimates that more than 20,000 US civilians suffered from NCTH injury between 2007 and 2009, of which 45% were fatal⁷; the same can be said for military personnel. Holcomb et al.⁸ reported that among deaths of Special Operations Forces personnel between 2001 and 2004, 15% were considered survivable, and of those 50% were caused by truncal hemorrhage. Rapid surgical management is the current mainstay treatment of NCTH.⁵ However, early presurgical management of NCTH poses a significant challenge. Even if a victim of NCTH manages to reach the first echelon of care, they often arrive with limited physiologic reserve, resulting in poor outcomes.⁹

Recent efforts to save victims of severe NCTH have resulted in the resurrection of balloon occlusion of the aorta as a potential to extend the window of opportunity to definitive surgical care. The technique and technology currently termed resuscitative endovascular balloon occlusion of the aorta (REBOA) has demonstrated promise in this regard.^{10–13} While field use

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From the Department of Emergency Medicine (B.M.M., M.H.T., C.I.C., D.C.L., N.L.G., K.R.W.), Michigan Center for Integrative Research in Critical Care (MCIRCC) (B.M.M., M.H.T., C.I.C., D.C.L., N.L.G., J.S.P., A.J.S., S.C.W., J.L.E., K.R.W.), Department of Biomedical Engineering (J.S.P., A.J.S., K.R.W.), Department of Mechanical Engineering (J.S.P., A.J.S.), and Department of Surgery (S.C.W., J.L.E.), University of Michigan, Ann Arbor, Michigan.

B.M.M. and M.H.T. made equal contributions to this study.

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Address for reprints: Kevin R. Ward, MD, 2800 N. Plymouth Rd, North Campus Research Complex, Ann Arbor, MI 48109; email: keward@med.umich.edu.

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of REBOA has recently been reported, its widespread application in austere field environments may be difficult to scale given the significant training required for use and logistical challenges of rapid femoral artery cannulation for use.¹³

Recognizing these challenges, we have developed an investigational adjunct device and approach termed “gastroesophageal resuscitative occlusion of the aorta” (GROA). Gastroesophageal resuscitative occlusion of the aorta consists of a gastroesophageal balloon catheter that is orogastrically inserted into the stomach via the esophagus. We have shown in a previous investigation that when inflated and when external abdominal pressure is applied, it is capable of occluding the descending aorta between the posterior stomach and anterior thoracic vertebrae, therefore stopping blood flow distal of the occlusion.¹⁴ Here, we aimed to determine if the GROA device is capable of stopping lethal abdominal hemorrhage and subsequently improve survival. We hypothesized that the GROA device would stop hemorrhage and increase survival in a lethal model of liver laceration, similar to REBOA, when compared with noninterventional controls. We also assessed the device's effect on physiologic, coagulation, and inflammatory responses, comparing its performance with REBOA and controls.

MATERIALS AND METHODS

This study was approved by the University of Michigan Institutional Animal Care and Use Committee and the United States Army Animal Care and Use Research Office following the principles in the *Guide for the Care and Use of Laboratory Animals*.¹⁵

Preparation and Anesthesia

Twenty-four male swine (Yorkshire mix) with an average weight of 51.6 kg (4.67 kg) were acclimated for at least 5 days before use. The day before the experiment, the animals were fasted for 12 hours with free access to water. All animals were sedated with an intramuscular injection of tiletamine/zolazepam (4–6 mg·kg⁻¹) and xylazine (2 mg·kg⁻¹). General anesthesia was maintained for the duration of the experiment with inhalant isoflurane (1–3%) in 30% to 35% inspired oxygen (FiO₂). Animals were intubated and mechanically ventilated with a tidal volume of 7 mL·kg⁻¹ to 8 mL·kg⁻¹, positive end-expiratory pressure of 5 cmH₂O, and a respiratory rate titrated to maintain end-tidal CO₂ between 35 mm Hg and 45 mm Hg. ECG and pulse oximetry (SpO₂) monitoring was performed (SurgiVet Advisor; Smiths Medical, Dublin, OH). Body temperature was maintained at 36°C to 38°C during surgery and the resuscitation phase of the experiment using a feedback-controlled temperature management system (Blanketrol; Sub-Zero Medical, Cincinnati, OH).

Instrumentation

All animals underwent surgical isolation and cannulation of the right carotid artery for measurements of mean arterial pressure (MAP) and collection of blood samples. Both femoral arteries were isolated; the right artery was cannulated with a 9F introducer (Arrow; Teleflex, Morrisville, NC) for implementation of controlled hemorrhage and placement of ER-REBOA catheters (Prytime Medical, Boerne, TX), and the left was cannulated for femoral arterial pressure measurements. Both external

jugular veins were cannulated for the subsequent resuscitation, and the placement of a pulmonary artery catheter (CCOmbo V; Edwards Lifesciences, Irvine, CA) for monitoring central venous pressure and pulmonary artery pressure. Ringer's lactate solution was administered intravenously at a rate of approximately 3 mL·kg⁻¹·h⁻¹ to 4 mL·kg⁻¹·h⁻¹ during surgical procedures. A midline laparotomy incision was created, extending approximately 10 cm caudally from the xyphoid process, to access the liver for the laceration injury. Upon completion of instrumentation procedures, baseline blood samples were collected for arterial and venous blood gas analysis (ABL800flex; Radiometer America Inc, Brea, CA), complete blood count (Vetscan HM5; Abaxis, Inc., Union City, CA), and comprehensive serum chemistry profile (VetScan; Abaxis Inc.). Porcine cytokine/chemokine (MILLIPLEX MAP magnetic bead panel kit; Millipore Corp, Billerica, MA) and thromboelastography (TEG) using citrated native blood samples (TEG 5000; Haemonetics Corp. Braintree, MA) were also performed according to the manufacturer's standard.

Hemorrhage and Injury

Animals were randomly assigned to one of three interventions: control (no intervention; n = 8), GROA (n = 8), or REBOA (n = 8). For animals undergoing REBOA or GROA interventions, these devices were placed prior to hemorrhage. The REBOA catheter (ER-REBOA; Prytime Medical) was placed according to estimated external measurements to provide zone II occlusion with the balloon just inferior to the diaphragm as described previously.¹⁴ The GROA device has been previously described¹⁴ and is presented in Figure 1. It consists of a triple lumen gastroesophageal tube with an inflatable ellipsoid-shaped balloon at its tip. The balloon may be inflated (ex vivo) to a maximum volume of approximately 1,600 cm³. A 14F gastric tube is placed through a lumen in the GROA device and used to guide the balloon by orogastric route into the stomach. The gastric tube can be retracted after balloon inflation (Fig. 1B). The GROA device also includes an adjustable external pressure system consisting of a back and abdominal plate, which provides the posterior-directed pressure necessary to occlude the aorta (Figs. 1C–D). The GROA balloon catheter was placed into the stomach through the esophagus as previously described.¹⁴ For all groups, a controlled hemorrhage was performed removing approximately 30% total blood volume over 20 minutes. Hemorrhage was paused, if necessary, to maintain MAP near 30 mm Hg. Two 450-mL units of shed blood were collected into citrate phosphate dextrose bags (Fenwal Inc, Lake Zurich, IL) and saved for the subsequent autologous transfusion during resuscitation. Two minutes after completion of the controlled hemorrhage, a full thickness (in depth) liver laceration was created using a scalpel. The laceration was created approximately 2 cm to the left of Cantlie's line¹⁶ and spanned approximately 80% of the cranial-caudal surface of the left medial lobe to the caudal tip of the lobe creating a grade-V liver injury¹⁷ similar in severity to previous reports.^{18,19} Representative images of the laceration are available in Supplemental Figure 1, <http://links.lww.com/TA/C175>. The liver lobes were left separated after laceration and the abdomen was quickly closed using towel clamps. Free-bleeding from the liver was allowed to continue for 2 minutes before a 60-minute intervention period was initiated.

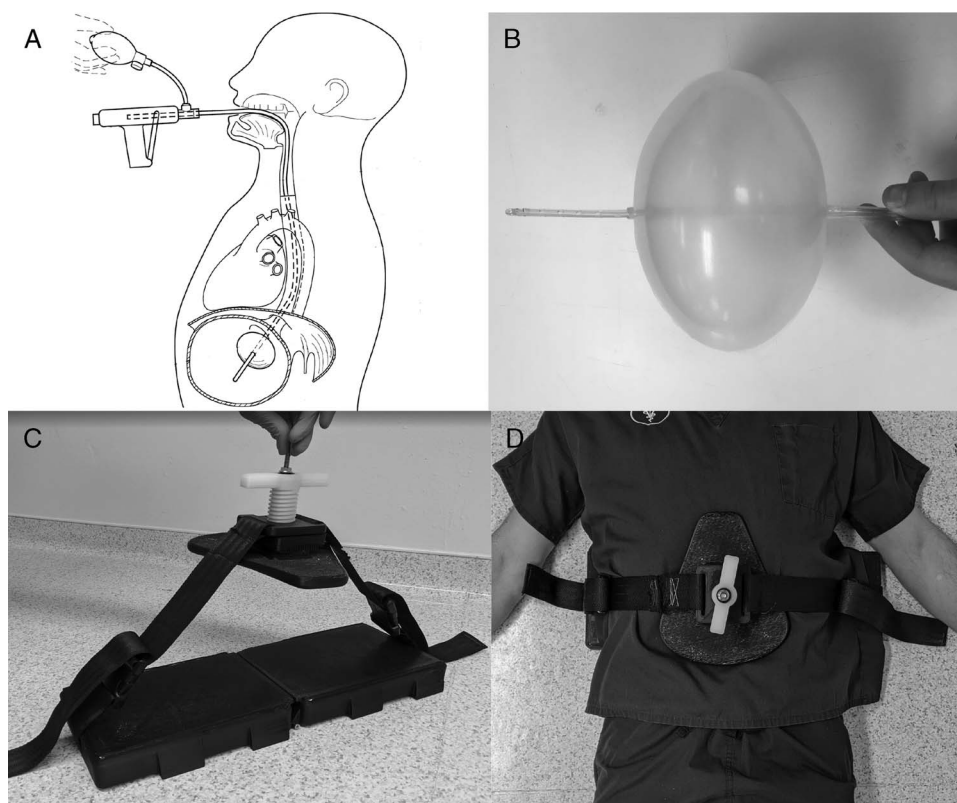


Figure 1. (A) Schematic view of GROA device inserted into stomach through the esophagus and inflated. (B) GROA prototype device composed of a triple lumen gastroesophageal tube with retractable 14F orogastric tube placed through a central lumen in the tube, and ellipsoid balloon (inflated). (C) External compression system including back plate, abdominal plate, and tourniquet. (D) Anterior view of external compression system applied to a person.

Intervention and Resuscitation

In the GROA group, the abdominal plate assembly was placed and positioned during the 2-minute period of free hemorrhage after closure of the abdomen. Two minutes after laceration, the REBOA and GROA balloons were inflated, and aortic occlusion was verified by loss of femoral artery pulse wave; the REBOA balloon was inflated with 5 to 7 mL of saline. For the GROA intervention, the abdominal plate was secured against the anterior surface of the abdomen by tightening the lateral straps, followed by inflation of the GROA balloon to an internal pressure of 60 mm Hg to 80 mm Hg (resulting in 1,200 cm³ balloon volume). The abdominal plate was further tightened if necessary to produce aortic occlusion. Aortic occlusion was maintained for 60 minutes for both REBOA and GROA. Fifteen minutes following the initiation of intervention, animals continuing to survive received intravenous (IV) Ringer's lactate (1,000 mL) to support blood pressure and to promote hemorrhage as an additional challenge. At the end of intervention, the GROA and REBOA balloons were slowly deflated, restoring blood flow over a period of approximately 7 minutes. Concurrently, resuscitation was initiated using the autologous shed blood and supplemental Ringer's lactate. The abdomen was quickly opened, and a Pringle maneuver was performed with a mean (SD) application time of 13.85 minutes (5.32 minutes) to slow hepatic hemorrhage while gauze pads, laparotomy sponges and hemostatic dressings (Quikclot control +[Teleflex] and Celox EMS [Medtrade Products, Electra House,

Crewe Business Park, Crewe, UK]) were applied to the hemorrhaging surfaces of the liver. When hemostasis was achieved (visually), the clamp was removed from the hepatic vascular bundle and the remainder of the shed blood was infused. After completion of resuscitation with autologous blood, MAP was maintained between 40 mm Hg and 60 mm Hg using IV fluids and/or norepinephrine (4 mg) diluted to 8 µg⁻¹mL⁻¹ in 5% dextrose and 0.9% NaCl, similar to previous studies.^{14,20} This pressure was chosen as permissive hypotension to slow residual hemorrhage after device removal.

Data Collection

Monitoring was continued for up to 4 hours following resuscitation, or until animals met predetermined euthanasia endpoints of MAP less than 20 mm Hg combined with an end-tidal CO₂ < 15 mm Hg. Animals were euthanized at the conclusion of the study using an IV injection of potassium chloride (1–2 mEq·kg⁻¹) while under general anesthesia. Following euthanasia, the esophagus, stomach, and aortas were harvested for histological analysis by a veterinary pathologist blinded to the intervention.

Statistical Analysis

To achieve a power greater than 0.90, eight animals per group were needed, assuming 90% survival in the treatment groups and 10% survival in the control group. Type 1 error was

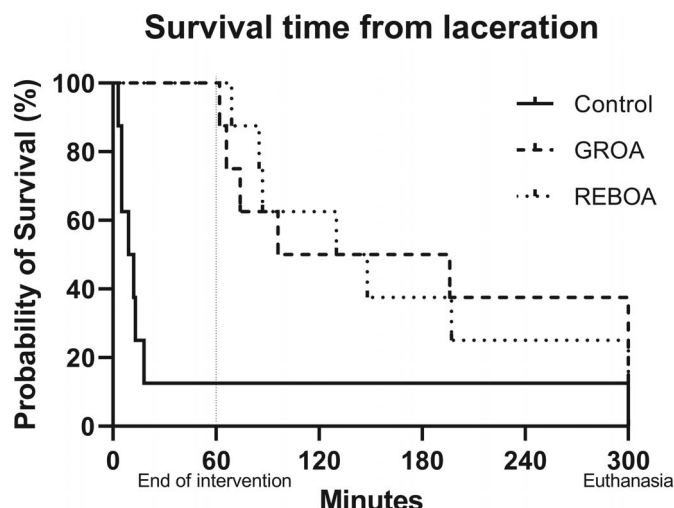


Figure 2. Kaplan-Meier probability of survival between GROA (dashed line) and REBOA (dotted line) treated intervention groups and control group (solid line). Analysis demonstrates significant survival differences between control animals and those undergoing REBOA and GROA interventions ($p < 0.01$).

determined at $\alpha = 0.05$. All descriptive data are presented as mean (standard deviation [SD]) or median (interquartile). A Wilcoxon test using Tukey's correction for multiple comparisons was used for survival analysis. Continuous outcomes were assessed using repeated-measures mixed-model regression, one-way analysis of variance with Tukey's correction for multiple comparisons and paired and unpaired t tests as applicable. Statistical significance was considered as $\alpha = 0.05$. All data were analyzed using SAS 9.4 (SAS corporation, Cary, NC) and PRISM 9 (GraphPad Software, San Diego, CA).

RESULTS

The controlled hemorrhage combined with liver laceration resulted in the rapid onset of class IV shock across all animals. A significant reduction in average MAP from 84.5 mm Hg

(11.69 mm Hg) at baseline to 27.1 mm Hg (5.65 mm Hg) occurred before the start of intervention ($p < 0.0001$).

Survival

The injury model was found to be rapidly lethal with seven of eight control animals meeting endpoints following liver laceration; median survival time in the control group was 10.5 minutes (12 minutes) after liver injury. The animal which survived postinjury also survived the duration of the postresuscitation monitoring period. A Kaplan-Meier plot of survival probabilities is presented in Figure 2. All animals receiving aortic occlusion using GROA (8/8) or REBOA (8/8) survived the duration of the intervention period (60 minutes) with median survival times of 86 minutes (232 minutes) and 79 minutes (199 minutes) postresuscitation, respectively. For overall survival from the onset of injury until the end of the 4-hour monitoring period, GROA and REBOA animals experienced a significant improvement in survival compared with controls ($p < 0.01$) with no differences between the occlusion groups. Three animals survived the 4-hour monitoring period in the GROA group compared with two in the REBOA group, with no significant differences in survival time between these two groups (Fig. 2).

Hemodynamics

The MAP data are presented in Figure 3. The GROA and REBOA animals experienced a similar and significant increase in average MAP following device deployment, gaining statistical significance from control by 15 minutes into the intervention ($p < 0.01$). The aorta was effectively impinged by both REBOA and GROA device activation as was evident by the loss of the pulsatile signal in the femoral artery. The MAP values were increased following aortic occlusion and were maintained throughout the duration of the intervention period with no significant differences between REBOA and GROA for the majority of intervention. At the end of intervention, REBOA resulted in a higher MAP 114.6 mm Hg (22.9 mm Hg) compared with GROA 88.2 mm Hg (18.72 mm Hg) ($p = 0.024$). Following resuscitation, MAP was maintained in the surviving animals with average values ranging from 41.7 mm Hg to 54.9 mm Hg in the GROA group and 43.3 mm Hg to 78.2 mm Hg

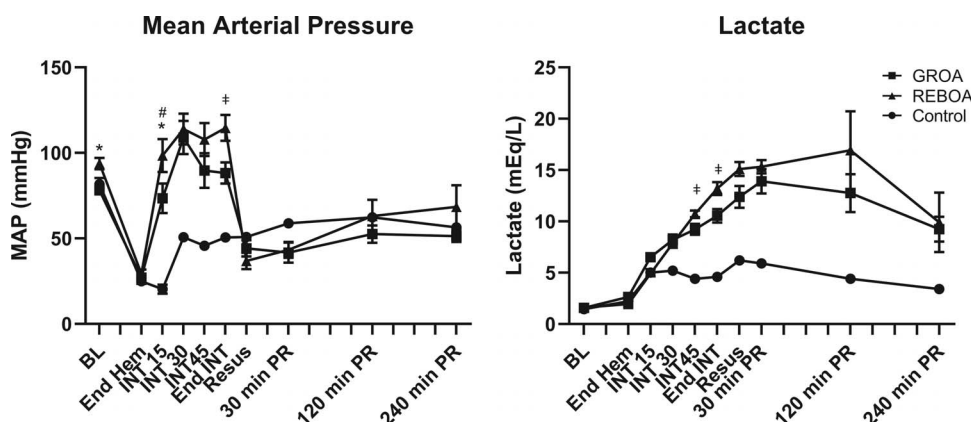


Figure 3. Average and standard error of MAP of the carotid artery and arterial lactate concentration during intervention (left) and for the duration of resuscitation (right). BL, baseline; end hem, end of hemorrhage; INT 15, 15 minutes into intervention; INT 30, 30 minutes into intervention; INT 45, 45 minutes into intervention; PR, postresuscitation. *Statistically significant difference from GROA and control, #Statistically significant difference from REBOA and control, *Statistically significant difference from GROA and REBOA.

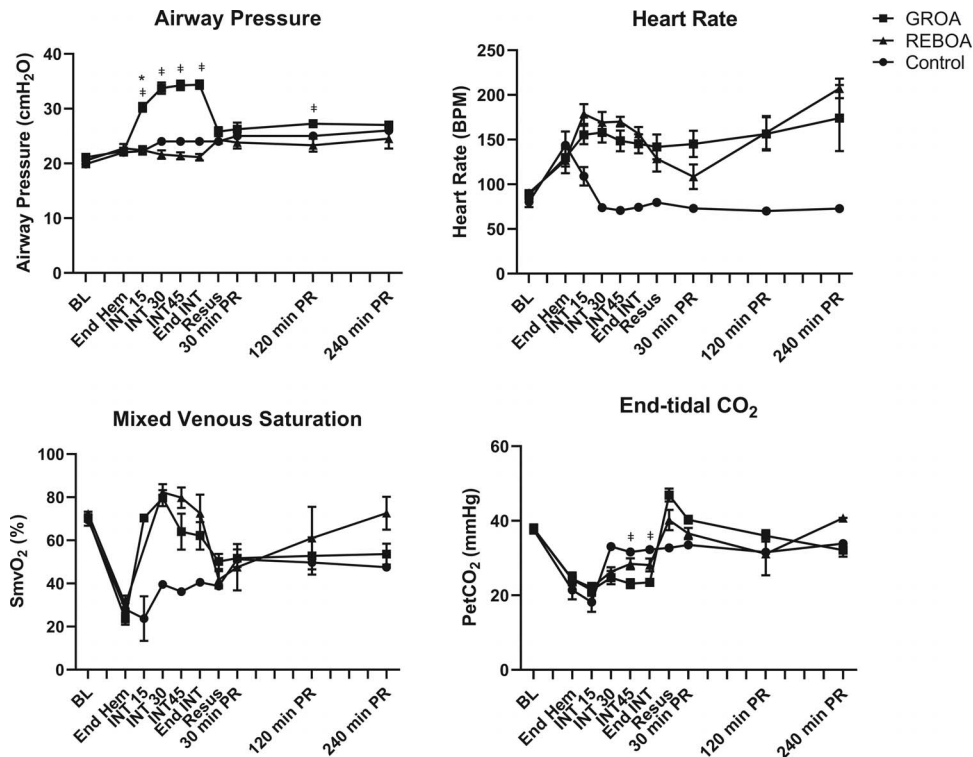


Figure 4. Average and standard error of mean airway pressure, heart rate, mixed venous hemoglobin oxygen saturation (SmvO_2), and end-tidal CO_2 . *Statistically significant difference from GROA and control, #Statistically significant difference from REBOA and control, ‡Denotes statistically significant difference from GROA and REBOA.

in the REBOA group, with no differences between groups, including the one surviving control animal. Additional metrics associated with shock including heart rate, mixed venous blood oxygen saturation (SmvO_2), and end-tidal CO_2 are presented in Figure 4. Heart rate increased across all animals from 86 bpm (15.7 bpm) at baseline to 130 bpm (39.8 bpm) at the start of intervention. Heart rate remained elevated throughout the intervention period in the GROA and REBOA groups with no significant difference between groups. SmvO_2 decreased in all animals from a baseline level of 70.7% (5.64%) to 27.3% (9.74%) at the onset of intervention, however, returned to and maintained baseline levels during GROA and REBOA interventions with no difference between occlusion groups. Similarly, PetCO_2 also decreased across all animals due to injury and hemorrhage from 37.8 mm Hg (2.68 mm Hg) at baseline to 23.4 mm Hg (5.79 mm Hg) at the start of intervention. PetCO_2 remained decreased in both aortic occlusion groups for the duration of intervention; however, REBOA resulted in a slightly higher PetCO_2 by the end of intervention compared with GROA, 28.2 mm Hg (5.23 mm Hg) versus 23.5 mm Hg (2.85 mm Hg), respectively ($p = 0.04$). Lactate increased in all groups from the onset of injury throughout the intervention period. At the end of intervention GROA resulted in a lower lactate accumulation of 10.5 $\text{mEq}\cdot\text{L}^{-1}$ (1.89 $\text{mEq}\cdot\text{L}^{-1}$) compared with REBOA, 13.2 $\text{mEq}\cdot\text{L}^{-1}$ (1.56 $\text{mEq}\cdot\text{L}^{-1}$) ($p = 0.028$). Lactate levels peaked following resuscitation in both occlusion groups reaching levels of 16.9 $\text{mEq}\cdot\text{L}^{-1}$ (3.78 $\text{mEq}\cdot\text{L}^{-1}$) in the REBOA group and 13.9 $\text{mEq}\cdot\text{L}^{-1}$ (1.19 $\text{mEq}\cdot\text{L}^{-1}$) in the GROA group. In surviving animals, at 4 hours, lactate, on

average, cleared to similar values of 9.2 $\text{mEq}\cdot\text{L}^{-1}$ (1.21 $\text{mEq}\cdot\text{L}^{-1}$) in the GROA group and 9.9 $\text{mEq}\cdot\text{L}^{-1}$ (2.89 $\text{mEq}\cdot\text{L}^{-1}$) in the REBOA group with no statistical differences. Gastroesophageal resuscitative occlusion of the aorta resulted in an increased airway pressure compared with REBOA, with an average value of 33.2 cmH_2O (3.03 cmH_2O) versus 21.6 cmH_2O (1.97 cmH_2O) throughout intervention ($p < 0.0001$) but returned to baseline after deactivation of the GROA device. No significant differences were noted in arterial blood gas (PaO_2 and PaCO_2) between REBOA and GROA groups during the 60-minute intervention period, suggesting no significant effect of GROA on pulmonary gas exchange.

Chemistry/Hematology

Serum chemistry and hematology results are contained in Table 1. Hemoglobin was higher in the GROA group at the end of resuscitation compared with REBOA, 9.56 $\text{g}\cdot\text{dL}^{-1}$ (1.157 $\text{g}\cdot\text{dL}^{-1}$) and 7.42 $\text{g}\cdot\text{dL}^{-1}$ (1.415 $\text{g}\cdot\text{dL}^{-1}$), respectively ($p = 0.0364$). No additional intergroup differences were noted in serum chemistry or complete blood count assays.

Coagulation

The TEG analysis demonstrated no intergroup differences for R (clotting reaction time), K (the difference between clotting time r and significant firmness of the clot, maximum amplitude (MA) or maximum clot strength, time to MA, or clotting index. Detailed data are shown in Table 1.

TABLE 1. Cytokines, Hematology, TEG, and Chemistry Metrics Reported by Group and Experimental Timepoint

		Control	GROA	REBOA	
		(n = 8)	(n = 8)	(n = 8)	<i>p</i>
Cytokines					
TNFα (ng·mL ⁻¹)	Baseline	0.14 (0.305)	0.13 (0.165)	0.20 (0.015)	0.4784
	Int 45	—	0.08 (0.096)	0.09 (0.168)	0.9943
	End Res	—	0.03 (0.025)	0.03 (0.047)	0.9804
	End Exp	—	0.08 (0.012)	0.05 (0.021)	0.3892
IL-1α (ng·mL ⁻¹)	Baseline	0.005 (0.005)	0.01 (0.010)	0.02 (0.017)	0.1649
	Int 45	—	0.01 (0.005)	0.01 (0.016)	0.6273
	End Res	—	0.01 (0.004)	0.01 (0.015)	0.7807
	End Exp	—	0.02 (0.011)	0.01 (0.005)	0.6838
IL-6 (ng·mL ⁻¹)	Baseline	0.03 (0.033)	0.01 (0.007)	0.03 (0.027)	0.5663
	Int 45	—	0.22 (0.149)	0.20 (0.054)	0.9382
	End Res	—	0.29 (0.215)	0.23 (0.057)	0.8019
	End Exp	—	2.08 (0.570)	1.70 (1.392)	0.8974
IL-10 (ng·mL ⁻¹)	Baseline	0.05 (0.046)	0.09 (0.073)	0.09 (0.074)	0.4896
	Int 45	—	0.11 (0.063)	0.12 (0.065)	0.9919
	End Res	—	0.08 (0.043)	0.07 (0.030)	0.9638
	End Exp	—	0.21 (0.143)	0.164 (0.060)	0.8971
IL-18 (ng·mL ⁻¹)	Baseline	0.37 (0.160)	0.43 (0.174)	0.58 (0.613)	0.5372
	Int 45	—	1.00 (0.634)	1.18 (0.534)	0.8290
	End Res	—	2.49 (1.953)	2.79 (1.764)	0.9532
	End Exp	—	3.24 (1.930)	3.82 (1.695)	0.9402
TEG					
R (min)	Baseline	10.49 (3.936)	7.08 (2.254)	10.36 (4.402)	0.1646
	Int 45	—	6.90 (3.184)	6.25 (2.250)	0.9603
	End Res	—	8.15 (1.791)	9.22 (3.203)	0.6026
	End Exp	—	8.47 (0.865)	9.65 (2.250)	0.5686
K (min)	Baseline	2.89 (1.238)	1.75 (0.505)	2.84 (1.348)	0.1146
	Int 45	—	1.89 (0.481)	2.14 (1.601)	0.6983
	End Res	—	1.93 (0.864)	2.78 (1.032)	0.2542
	End Exp	—	2.27 (0.403)	3.20 (1.200)	0.4057
MA (mm)	Baseline	70.80 (3.064)	73.25 (3.046)	71.1 (7.228)	0.5950
	Int 45	—	66.85 (3.996)	67.16 (9.734)	0.9385
	End Res	—	68.20 (6.489)	59.05 (6.319)	0.0824
	End Exp	—	68.17 (0.573)	69.95 (5.350)	0.6875
TMA (min)	Baseline	31.45 (10.018)	23.41 (4.181)	28.73 (5.983)	0.1266
	Int 45	—	24.23 (4.031)	24.01 (6.425)	0.9420
	End Res	—	25.35 (5.403)	30.08 (6.858)	0.3294
	End Exp	—	28.73 (2.010)	30.65 (6.450)	0.7357
CI	Baseline	2.94 (0.927)	3.73 (0.911)	2.90 (1.997)	0.4615
	Int 45	—	2.75 (1.03)	3.05 (1.700)	0.6959
	End Res	—	2.75 (1.110)	1.25 (1.355)	0.1384
	End Exp	—	2.77 (0.368)	2.95 (1.150)	0.8549
CBC					
WBC (10 ⁹ /L)	Baseline	13.81 (3.875)	17.41 (3.269)	14.49 (4.644)	0.2201
	Int 45	—	15.17 (2.404)	12.46 (3.365)	0.1040
	End Res	—	13.70 (2.827)	9.57 (3.237)	0.0747
	End Exp	—	24.46 (2.190)	34.15 (10.945)	0.3324
Neu (10 ⁹ /L)	Baseline	3.96 (2.009)	5.24 (1.393)	5.08 (2.138)	0.3966
	Int 45	—	4.16 (1.799)	3.97 (1.687)	0.8466
	End Res	—	3.38 (1.649)	2.91 (0.777)	0.5867
	End Exp	—	17.38 (2.630)	28.60 (11.815)	0.3068

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TABLE 1. (Continued)

		Control	GROA	REBOA	<i>p</i>
		(n = 8)	(n = 8)	(n = 8)	
RBC (10 ¹² /L)	Baseline	6.39 (0.632)	6.18 (0.951)	6.44 (0.423)	0.7560
	Int 45	—	5.39 (1.099)	5.03 (0.457)	0.4386
	End Res	—	5.72 (0.957)	4.96 (0.819)	0.2319
	End Exp	—	5.71 (1.389)	7.44 (0.480)	0.2812
Hgb (g·dL ⁻¹)	Baseline	9.43 (0.931)	10.26 (1.384)	9.85 (0.483)	0.3148
	Int 45	—	8.10 (1.711)	7.80 (0.870)	0.6855
	End Res	—	9.56 (1.157)**	7.42 (1.415)**	0.0364
	End Exp	—	10.77 (1.195)	12.35 (1.050)	0.3234
PLT (10 ⁹ /L)	Baseline	307.38 (62.825)	313.13 (85.002)	333.50 (35.812)	0.7312
	Int 45	—	238.75 (45.002)	236.88 (27.011)	0.9260
	End Res	—	215.20 (34.982)	233.00 (10.616)	0.3125
	End Exp	—	213.00 (70.143)	280.00 (11.310)	0.3733
Chemistry					
ALP (μ·L ⁻¹)	Baseline	124.88 (25.473)	121.38 (29.559)	126.88 (50.601)	0.9610
	Int 45	—	—	—	—
	End Res	—	—	—	—
	End Exp	—	139.67 (51.874)	135.50 (35.500)	0.9436
ALT (μ·L ⁻¹)	Baseline	48.75 (10.767)	44.13 (8.462)	42.125 (5.418)	0.3457
	Int 45	—	—	—	—
	End Res	—	—	—	—
	End Exp	—	79.00 (30.627)	61.00 (2.828)	0.566
TBIL (mg·dL ⁻¹)	Baseline	0.26 (0.484) *	0.20 (0.050) *	0.21 (0.033)	0.0371
	Int 45	—	—	—	—
	End Res	—	—	—	—
	End Exp	—	0.30 (0.173)	0.30 (0.000)	0.999
CRE (mg·dL ⁻¹)	Baseline	1.23 (0.130)	1.23 (0.238)	1.23 (0.120)	0.3847
	Int 45	—	—	—	—
	End Res	—	—	—	—
	End Exp	—	2.10 (0.163)	2.65 (0.150)	0.0599
GLU (mg·dL ⁻¹)	Baseline	99.00 (17.263)	101.50 (22.260)	85.63 (17.492)	0.2707
	Int 45	—	—	—	—
	End Res	—	—	—	—
	End Exp	—	82.67 (24.226)	76.50 (13.500)	0.816

Data are presented as averages (SD). Statistical significance was set at $\alpha = 0.05$.

*Statistically significant difference between GROA and control.

**Statistically significant difference between GROA and REBOA.

TNF α , tumor necrosis factor alpha; IL, interleukin; WBC, white blood cell; Neu, neutrophil; RBC, red blood cell; Hgb, hemoglobin; PLT, platelet; ALP, alkaline phosphatase; ALT, alanine aminotransferase; TBIL, total bilirubin; CRE, creatinine; GLU, glucose; Int 45, 45 minutes of intervention; End Res, end of resuscitation; End Exp, end of experiment; R, clotting reaction time; K, the difference between clotting time r and significant firmness of the clot; TMA, time to MA; CI, clotting index.

Cytokines

The following cytokines (IL-1 α , IL-6, IL-10, IL-18, and TNF α) were measured at baseline, end of intervention, end of resuscitation, and 240-minute postresuscitation (Table 1). There was statistically significant difference in IL-6 between 240 minutes postresuscitation and all other time points in both GROA and REBOA groups ($p < 0.0001$). Also, IL-18 showed a significant difference in the GROA group between baseline and end of resuscitation and well as baseline and 240 minutes postresuscitation ($p = 0.0182$ and $p = 0.0134$) respectively. In the REBOA group, IL-18 showed a significant difference between baseline and end of resuscitation, baseline and 240 minutes postresuscitation, as well as end of intervention and 240 minutes postresuscitation ($p = 0.0101$, $p = 0.0121$, and $p = 0.0470$, respectively). The

remaining cytokines did not show any difference between the time points for any group. Intergroup analysis showed no significant difference between GROA and REBOA at any time points.

Histology

Representative samples from the longest surviving animals in each group (three—GROA, three—REBOA, and two—controls) were selected for histological examination (Fig. 5, Supplemental Figure 2, <http://links.lww.com/TA/C176>, and Supplemental Figure 3, <http://links.lww.com/TA/C177>). The stomach tissue from both GROA and REBOA interventions showed changes which ranged from no findings (one of three animals in both groups) to mild ischemic superficial necrosis (one of three animals in both groups) and mixed inflammatory infiltrates within mucosa and

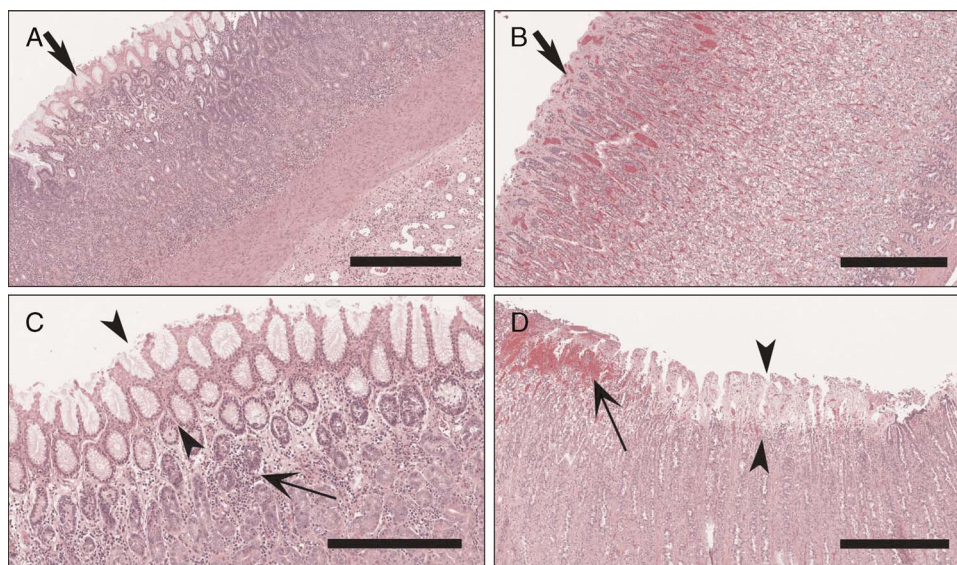


Figure 5. Representative histological images of the GROA (A, B) and REBOA (C, D) interventional effects on the cardia and fundus. (A) GROA: cardia, bar = 500 μ m, arrow indicates focal superficial mucosal necrosis. (B) GROA: fundus, bar = 600 μ m, arrow indicates superficial mucosal necrosis. (C) REBOA: cardia, bar = 300 μ m, Superficial ischemic change (arrowheads) associated characterized by hypereosinophilia and loss of cellular and nuclear detail, underlain by scattered mixed inflammatory cell infiltrates (arrow). (D) REBOA: fundus, bar = 600 μ m, there is multifocal necrosis of the superficial mucosa (arrowheads) associated with areas of hemorrhage (arrow).

submucosa, with scattered apoptotic debris in the deep mucosa associated with mild edema (one of three animals in both groups). In one GROA animal, additional inflammatory infiltrates were noted along the serosal surface. Focal necrosis with underlying disrupted mucosa and submucosal edema was observed in both aortic occlusion groups, however, it was deemed to be mild. There were no significant changes in sections of the esophagus or aorta in any group. Stomach samples from control animals did not show significant evidence of injury.

DISCUSSION

The high rate of death for both civilians and military personnel from NCTH^{3,5} suggests the need for new technologies that are capable of temporarily controlling severe NCTH, especially at the point of injury until a higher level of care is reached. The GROA device is envisioned to be deployed in cases of NCTH as a bridge to definitive surgical hemostasis similar to REBOA or until REBOA can be placed. However, the main advantage of GROA over REBOA is its potential capability to establish more rapid aortic occlusion in austere conditions, such as point or near point of injury, as well as higher echelons of care in both military and nonmilitary settings. This would include nontrauma civilian medical centers where access to surgical resources might be limited. In this study, we tested GROA's ability to prolong survival in a lethal model of NCTH.

We chose to limit occlusion of the aorta to 60 minutes since our previous work demonstrated that the overall physiologic tolerance of animals undergoing REBOA and GROA was limited at occlusion times greater than 60 minutes.¹⁴ The lethality of the hemorrhage model used in this study was previously described by Russo et al.²¹ and further demonstrated in this study as indicated by the control group's near immediate exsanguination

postinjury and the subsequent hemorrhage and death after device deactivation in some of the animals in the REBOA and GROA groups, even after surgical hemostasis was attempted. However, this extreme example of lethality emphasizes GROA's effectiveness at stopping hemorrhage suggesting high potential as a bridge to definitive therapeutics. Like REBOA, GROA prolonged survival over 60 minutes of intervention in all animals, and with the limited additional liver injury repair, 5 of 16 combined animals (31%) survived to 4 hours postdeactivation (three of eight in GROA and two of eight in REBOA). Most of the deaths that occurred after device deflation in both REBOA and GROA (three of eight in GROA and six of eight in REBOA) resulted from the renewed hemorrhage from the liver injury because of the limitation of being able to provide additional blood products and definitive repair of the liver injury. The remaining animals which experienced postdeactivation death (2 of 8 in the GROA group) are attributed to reperfusion injury following device deflation.

The hemodynamic effects of GROA and REBOA observed in this study were again similar to previous reports.^{14,22,23} Initiation of either technology resulted in rapid and improved carotid arterial pressure and increased SmvO_2 , suggestive of redistributed blood flow and improvement of brain and cardiac perfusion and improved tissue oxygenation, despite hypovolemia. Further, the application of either REBOA or GROA interventions quickly stopped the lethal hemorrhage, which allowed the observed hemodynamic benefits to be maintained for the duration of the 60-minute intervention period without further deterioration.

Cytokine and TEG measurements were not different between the aortic occlusion groups in this study. The longitudinal inflammatory responses noted in some cytokines appear to be independent of the method of aortic occlusion, and therefore more likely related to the occlusion itself and not device specific. Similarly, there was no evidence of clinically significant coagulopathy

noted in either intervention group and the ability to generate clots with adequate strength without lysis was consistent across all animals despite the interventions or resuscitation. Overall, this evidence further suggests the physiological tolerance and response to the device is similar to the well characterized physiologic tolerance of REBOA.

Both aortic occlusion techniques in this study were effective at stopping hemorrhage, prolonging survival, and allowing for resuscitation. In our previous study on physiologic tolerance, we demonstrated that GROA can produce a high zone 2 occlusion as evidenced by loss of hepatic artery blood flow.¹⁴ The current study underscores this in GROA's ability to do this by stanching lethal liver hemorrhage in this model. This is an advantage over other point-of-injury devices, such as abdominal aortic junctional tourniquet, which is designed to create a zone 3 occlusion and has only been compared with REBOA for such.^{24–26} While there were no significant differences in survival between the REBOA and GROA groups, it is important to note that both devices were preplaced prior to hemorrhage. The GROA device is envisioned to be placed similar to an orogastric tube. In our experience (unpublished), we are routinely able to place the GROA balloon catheter with the accompanying abdominal plate and activate the device achieving aortic occlusion in under 120 seconds. Had we performed a study in which both GROA and REBOA devices were actively placed after the start of hemorrhage, differences in survival between groups may have been detected. The time to application of REBOA (from injury onset) remains the largest limitation to its use as an effective prehospital intervention. With an application time ranging from 34 minutes to 57 minutes reported in a clinical feasibility study for treatment of cardiac arrest,²⁷ the time to REBOA application exceeds the 30-minute period in which as many as 45% of deaths due to severe hemorrhage in the field occur.^{28,29} This application time is likely largely due to difficulties in cannulating the femoral artery.^{30–32} We envision military medics and civilian first responders to be able to effectively apply the GROA device; however, future feasibility studies will need to be performed. Unlike REBOA, in a real-time clinical use scenario, the GROA device will require deflation during surgery limiting its use during surgery and ongoing hemorrhage. However, we envision that it will be feasible to transition from GROA to REBOA in a more controlled setting prior to surgery, or other hemostatic strategies such as interventional radiology.

Histological analyses of stomach tissue for animals undergoing occlusion using GROA demonstrated changes consistent with mild ischemia likely produced by the pressure that the balloon creates when the abdominal plate is tightened. However, similar changes were noted in REBOA animals pointing toward general ischemia from the aortic occlusion as the potential cause. The final extent of these changes cannot be known until longer survival studies are performed.

LIMITATIONS

The major limitation to this study was the renewal of severe hemorrhage after the aortic occlusion devices were deflated. The renewed hemorrhage combined with the limited blood products for resuscitation, and limited surgical repair of the liver injury, resulted in death in most animals over varying times in the

postresuscitation monitoring period, which is problematic for the interpretation of intergroup comparisons of hemodynamics or other physiologic metrics. Similarly, the study was only powered to detect survival difference from controls rather than discrete differences in hemodynamics or other metrics, or equivalences between interventions. These differences (or lack thereof) should be interpreted (not inferred) with caution, although the data is highly consistent with previous studies of both GROA and REBOA, which gives confidence to the adequacy of the study size. Although our study does not show respiratory compromise caused by GROA, airway management was provided using mechanical ventilation. More studies are needed to elucidate the effects on concurrent lung injury, and any use contemplated in patients without airway control. We would envision the use of GROA mainly in patients experiencing severe shock due to NCTH in which airway control is likely to be needed, similar to that of REBOA. Also like REBOA, subsequent ischemia caused by GROA is also likely to require analgesia, sedation, and subsequent airway control. We did not measure intracranial pressure so cannot comment on the effects of GROA activation (and its potential to increase intra-abdominal pressure) would have on this important variable. However, it is likely that the resulting increase in MAP would overall increase net cerebral perfusion pressure in the setting of severe hemorrhagic shock and traumatic brain injury.

Only male animals were used for this study. Future studies will need to include female subjects. Lastly, long-term outcomes were not evaluated. Further studies are needed to evaluate the long-term effects of GROA use, as well as test the devices capabilities over a wide range of clinically relevant injuries, and eventually, the feasibility of human application in the prehospital environment, including need for airway management, means to ensure complete aortic occlusion, and other important issues to maximize efficacy while minimizing complications. However, it was first important to demonstrate the performance of GROA to control life-threatening NCTH and to compare it to REBOA.

CONCLUSION

This study demonstrates that both GROA and REBOA were highly effective at temporarily stanching NCTH of the abdomen and prolonging survival. The survival benefit combined with the simple application technique of GROA warrants additional studies as a means to improve survival from NCTH of the abdomen.

AUTHORSHIP

B.M.M., M.H.T., K.R.W.: literature search, study design, device design, data collection, data analysis, data interpretation, writing, critical revision. J.S.P., A.J.S.: study design, device design, data interpretation, writing, critical revision. S.C.W., J.L.E.: study design, data interpretation, writing, critical revision. C.C., D.C.L., N.L.G.: data collection, data analysis, writing, critical revision.

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DISCLOSURE

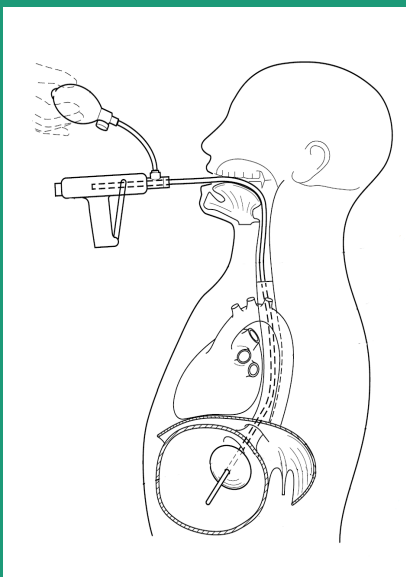
K.R.W. and J.S.P. have intellectual property associated with the device used in this study through the University of Michigan. The technology has been licensed to Precision Trauma LLC. K.R.W. and J.S.P. have equity in the company. The remaining authors declare no conflicts of interest.

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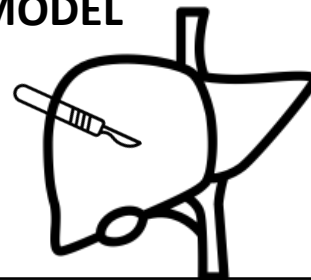
Gastroesophageal Resuscitativ Occlusion of the Aorta (GROA) Prolongs Survival in a Lethal Liver Laceration Model

- **Non-Compressible Hemorrhage** is a leading cause of death from potentially survivable injuries.
- **GROA** allows for **aortic occlusion** and *may prolong survival* from lethal hemorrhage.



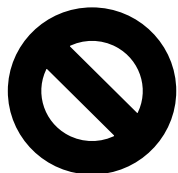
PORCINE INJURY MODEL

30% arterial hemorrhage
Grade-V liver laceration



INTERVENTIONS

Control (n=8)



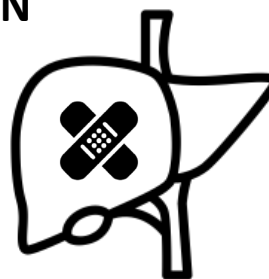
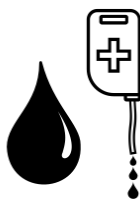
GROA (n=8)



REBOA (n=8)



RESUSCITATION



RESULTS:

Survival through Intervention

	# Survived	% Survival
Control	1/8	12.5%
GROA	8/8	100%
REBOA	8/8	100%

Conclusion: GROA and REBOA were both effective at temporarily stanching lethal abdominal hemorrhage and prolonging survival.

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A Review of Two Emerging Technologies for Pre-Hospital Treatment of non-Compressible Abdominal Hemorrhage

Brendan M. McCracken^{1,2*}, Kevin R. Ward^{1,2,3*}, Mohamad Hakam Tiba^{1,2*}

1. Department of Emergency Medicine, University of Michigan, Ann Arbor, Michigan
2. The Max Harry Weil Institute for Critical Care Research and Innovation, University of Michigan, Ann Arbor, Michigan
3. Department of Biomedical Engineering, University of Michigan, Ann Arbor, Michigan

* Denotes equal contributions to this article.

Authors in order:

Brendan M. McCracken: bmccrac@med.umich.edu

Kevin R. Ward: keward@med.umich.edu

Mohamad Hakam Tiba: tibam@med.umich.edu

Corresponding Author:

Mohamad Hakam Tiba, MD, MS

2800 N. Plymouth Road

North Campus Research Complex

Ann Arbor, MI, 48109

Fax: (734) 763-9389

Phone: (734) 764-6702

E-Mail: tibam@med.umich.edu

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Conflicts of Interest: All Authors have intellectual property associated with the devices discussed in this review through the University of Michigan. These technologies have been licensed to Precision Trauma LLC. Kevin R. Ward has equity in the company.

Keywords: Shock, Non-compressible hemorrhage, Abdominal organ injury, Resuscitation, Aorta, GROA, REBOA Inflatable device

Figures: 4

Tables: 1

References: 34

Short running headline: Emerging abdominal hemostasis devices

Introduction

Management of both battlefield and civilian trauma victims suffering from non-compressible torso hemorrhage (NCTH) remains a significant challenge with exsanguination continuing to be the leading cause of mortality from potentially survivable injuries.¹⁻⁴ Death from hemorrhage may occur rapidly and often before arrival at a medical facility capable of providing definitive surgical hemostasis.^{2,5} Such challenges present a critical need for new technologies in the realm of pre-hospital and even early in-hospital hemostasis. Whether in the austere (battlefield) or the civilian prehospital emergency medical services environment, the ability to treat NCTH is very limited.⁶ Furthermore, logistical challenges such as transportation delays and mass casualty incidents highlight the need for providing temporary hemostasis before the arrival at a high-level care facility. In summary, most patients who succumb to NCTH do so in the pre-hospital or austere environment before surgical care because of limited resources. Even the ability to provide rapid temporary hemostasis in the emergency department or trauma center environment can present significant challenges.

Surgical management remains the pinnacle treatment for NCTH, however for the reasons mentioned above, is not viable as an early intervention near the point of injury. Coupled with the lack of resources for early resuscitation, mechanical hemorrhage control continues to be of interest to employ following the determination of severe hemorrhage in a forward setting⁷. Current approved technologies for mechanical hemostasis include extremity and junctional tourniquets, pelvic binders, and endovascular balloon occlusion of the aorta. Additional investigational techniques such as abdominal insufflation, and intra-abdominal foams are at various stages of development but are not currently cleared for clinical use⁸⁻¹⁰.

Aortic occlusion

Occlusion of the descending aorta will certainly reduce or cease intraabdominal and pelvic hemorrhage. While feasible in the trauma center and operating room, surgical occlusion via thoracotomy and aortic cross clamping is not feasible in the field or routinely feasible in the non-trauma center emergency department setting. Recent efforts to save victims of severe NCTH have resulted in the resurrection of balloon occlusion of the aorta as a potential to extend the window of opportunity for definitive surgical care. The technique and technology currently termed Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) has demonstrated promise in this regard¹¹⁻¹⁴. The REBOA device can be placed allowing for aortic occlusion at various levels (Zones 1,2,3) depending on where the location of NCTH is suspected. REBOA has gained popularity¹¹⁻¹⁵, but is currently limited to trauma centers¹⁶ and while it has been successfully implemented in trauma center and limited combat applications¹⁷, has not yet been fully utilized in prehospital or austere environments for multiple logistic reasons. The largest barrier to implementation may be the time between injury and aortic occlusion, which is driven by the necessity for vascular access requiring highly skilled operators or imaging equipment, or failure to cannulate the femoral artery¹⁸⁻²⁰.

The other approved mechanical method available for aortic occlusion is the Abdominal Aortic Junctional Tourniquet (AAJT). The AAJT has been demonstrated to be capable of occluding the infrarenal aorta and thus may be effective as an aortic zone 3 occlusion device for control of bleeding below that level such as pelvic hemorrhage^{9,21-24}. It achieves this by the mechanical targeting of pressure directly downward towards the abdominal aorta. This is different from the previously used technologies called the military antishock trousers (MAST) or pneumatic antishock garments (PASG) which have been determined to be ineffective for creating abdominal or pelvic tamponade of severe arterial bleeding and are no longer recommended²⁵.

The abdominal/pelvic compartment of the MAST/PASG devices are pneumatically inflated and produce circumferential pressure around the lower torso. There is no discrete directed inward pressure provided to the abdominal or pelvic cavity such as that produced by the AAJT. As such, unless intraabdominal pressure is increased above systolic arterial blood pressure, bleeding will continue and could potentially be worsened. Even with the AAJT, because of infrarenal occlusion (Zone 3), there is the potential of the AAJT to increase hemorrhage if bleeding is occurring from the liver or spleen (Zone 2) due to increased hydrostatic pressures that may be produced proximal to the site of occlusion.

To further address the unmet need for temporary pre-hospital stabilization of the victim of non-compressible abdominal hemorrhage, our team has developed two technologies known as Gastroesophageal Resuscitative Occlusion of the Aorta (GROA)^{26,27}, and the Intra-Peritoneal Hemostasis Device (IPHD)²⁸. The main motivation for the development of these technologies is to allow for the rapid treatment of NCTH in austere combat environments, civilian pre-hospital, and higher echelons of care including emergency department and trauma center settings when surgical expertise and/or resources may be delayed. In this narrative review, we aim to summarize the design and application features of these devices, as well as summarize previous pre-clinical testing related to the treatment of NCTH.

Description of GROA and studies

GROA is an investigational device and approach which utilizes aortic impingement via a gastroesophageal balloon that is orogastrically placed into the stomach. The device and approach leverage the anatomical relationship of the abdominal aorta, stomach, and thoracic vertebral bodies. The design and dimensions (described below) were based on morphomic analysis of human adult abdominal and chest CT scans (FIGURE 1) similar to that used to develop recent

REBOA technology²⁹. In two previous investigations, we have shown that when the device is inserted, an external pressure system is activated, and the balloon inflated, it can provide high zone-2 (celiac or supraceliac) aortic occlusion by compressing the aorta between the posterior wall of the stomach and the anterior thoracic vertebrae. The main components of the system include a gastroesophageal tube with an ellipsoid shaped balloon, an air pump/pressure gauge assembly, and an adjustable external compression system (FIGURE 2). Unlike the Sengstaken-Blakemore tube, the GROA gastric balloon is larger and less compliant in order to produce aortic occlusion over an area where the aorta is expected to lie in relationship with the thoracic vertebra. The gastroesophageal tube includes lumens for suction and evacuation of gastric contents, air vent to avoid vacuum/pneumatic tension in the stomach, and balloon inflation and deflation. A 14F gastric tube is placed through a central lumen in the GROA device and used to guide the balloon by orogastric route into the stomach. The air pump/pressure gauge assembly allows for controlled balloon inflation/deflation and visual feedback on the pressure of the balloon. The external compression system consists of a back plate and an abdominal plate. When activated, this system prevents lateral and anterior deflection of the balloon, keeping the balloon over the aorta. The balloon inflates to an ellipsoid shape that provides the structure necessary to occlude the aorta when external pressure system is applied to the epigastric area.

Our initial GROA study aimed at evaluating the feasibility of achieving aortic occlusion and exploring the physiological tolerance to the device compared to REBOA (ER-REBOA, PRYTIME Medical, Boerne, TX) over application times ranging from 30 to 90 minutes in a swine model of controlled hemorrhagic shock and resuscitation²⁶. In this study, aortic occlusion was achieved in every GROA application and 15 out of 16 animals treated with GROA survived the duration of the device application period. Only two animals in the 90-minute occlusion group

(2 out of 6) were able to be resuscitated to survive after the device was removed suggesting that 90 minutes of aortic occlusion, while possible, is not well tolerated in this model.

Survival rates for animals treated with REBOA using this model were also very similar to GROA across all groups. In the 30 and 60-minute application groups for both GROA and REBOA, 9 out of 10 animals survived post resuscitation period. No animals receiving the 90-minute REBOA intervention survived the post-resuscitation period which further suggests that the poor outcome was related to the aortic occlusion itself and not specific to the device used for occlusion. Overall, this study concluded that up to 60 minutes of aortic occlusion with GROA was both tolerated and feasible, and while the GROA device could create and maintain occlusion and survival for 90-minutes, resuscitation following aortic occlusion for this time was not well tolerated.

In the above study, we attached an ultrasonic flow probe to the hepatic artery. During activation of the GROA device, loss of hepatic artery blood flow was noted during aortic occlusion (FIGURE 2, bottom panel). This indicates that GROA was effective in creating a high zone 2 aortic occlusion at or superior to the hepatic artery, and the survival rate and overall tolerance to the GROA device appears very similar to the already well characterized and FDA cleared REBOA device.

In a follow-up study, GROA's ability to stanch NCTH was evaluated using a highly lethal grade V liver laceration model comparing GROA to REBOA and controls²⁷. Occlusion time in this study was limited to 60-minutes based on the previous tolerance testing²⁶. The model was rapidly lethal for the control group resulting in a median survival time of only 10.5 minutes from the onset of injury. This study reaffirmed the ability to successfully apply GROA and achieve aortic occlusion in all animals. In overall survival, GROA was successful at prolonging

survival compared to controls, with no difference in survival noted between the GROA and REBOA devices. The survival benefit observed in this study strongly suggested that the lethal hemorrhage was quickly stopped by GROA and resulted in rapid improvement of MAP and mixed venous oxygen saturation (SvO₂). Further evidence of hemorrhage control was observed as the physiologic benefits of aortic occlusion of GROA were maintained without significant deterioration for the duration of the intervention period. Inflammatory markers (cytokines IL-6 and IL-8) were elevated in both GROA and REBOA aortic occlusion groups and therefore were attributed to aortic occlusion, rather than the occlusion device itself. While there was no significant difference in survival between the REBOA and GROA groups, both GROA and REBOA were preplaced prior to injury. A description of all models reviewed, including survival data are presented in Table 1.

In our experience (data not published), we are routinely able to place the GROA balloon catheter with the accompanying abdominal plate and activate the device to achieve aortic occlusion in under 120 seconds. Had the GROA and REBOA devices been actively placed after the start of hemorrhage, a difference in survival favoring GROA would have likely been detected. The time to application of REBOA (from injury onset) remains the largest limitation to its use as an effective pre-hospital intervention. With an application time ranging from 34-57 minutes reported in a clinical feasibility study for treatment of cardiac arrest¹⁸, the time to REBOA application exceeds time periods in which as many as 45% of deaths due to severe hemorrhage in the field occur. This application time is likely largely due to difficulties in cannulating the femoral artery²⁷. While we envision military medics and civilian first responders to be able to effectively apply the GROA device, future feasibility studies will need to be performed.

Unlike REBOA, in a real-time clinical use scenario, the GROA device will require deflation during surgery limiting its use during surgery and ongoing hemorrhage. However, we have recently completed a study using the same model of lethal liver hemorrhage to demonstrate the feasibility of transitioning GROA to REBOA without any change in survival. This provides a value proposition for both prehospital and emergency department/trauma center use where GROA could be placed and activated allowing time for near term placement of REBOA for transport, surgery, or other hemostatic strategies such as interventional radiology.

In the combination of studies, the hemodynamic response created by GROA is similar to REBOA. Immediate improvement in mean arterial pressure (MAP) was observed in response to GROA and REBOA and there were no differences between the aortic occlusion methods in MAP, central venous pressure (CVP), pulmonary artery pressure (PAP) and lactate burden. Further, there were no differences in resuscitation requirements or organ function measured by serum chemistry, thromboelastography, inflammatory cytokines (IL-6 and IL-8). Only minor differences in SvO₂, and end-tidal CO₂ during GROA occlusion were noted. An elevation of airway pressure was observed and associated with the GROA intervention in all animals. The increase in airway pressure was, however, mild and transient averaging 31 cm H₂O (ranging from 25-39 cmH₂O) and did not affect ventilation or oxygenation parameters. While intrabdominal pressure is expected to increase, it was not measured during GROA use. This important information should be collected in the future, especially during the reperfusion period to evaluate for evidence of the development of post-surgical abdominal compartment syndrome.

In both studies, histological analyses of stomach tissue for animals undergoing occlusion using GROA demonstrated changes consistent with mild ischemia likely produced by the pressure that the balloon creates when the abdominal plate is tightened. However, similar

changes were noted in REBOA animals pointing towards general ischemia from the aortic occlusion as a potential contributor. The final extent of these changes cannot be known until longer survival studies are performed. No histologic changes were noted in the aorta in either occlusion method.

These studies demonstrated that GROA was consistently effective at creating aortic impingement and thus temporarily capable of stanching lethal hemorrhage and prolonging survival. Considering the survival benefit in combination with a fast and easy application technique, GROA appears to be a promising technique to improve survival from non-compressible abdominal hemorrhage.

Description of IPHD and studies

The IPHD is another investigational device being explored for the treatment of NCTH. Its development and testing were inspired by the proposed mechanisms of action of ResQFoam (Arsenal Medical, Inc, Waltham, MA). Developed with over 30 million dollars in funding by the Department of Defense, it is a self-expanding polyurethane designed to be injected into the abdominal cavity to stanch hemorrhage by covering and compressing bleeding surfaces and has been shown to improve survival in a large animal lethal, closed-cavity, hepatoportal injury model^{30,31} and is currently undergoing clinical trial. Such a strategy may have implementation advantages over REBOA, especially in the field setting. However, there may be potential drawbacks since the expansion of the material cannot be controlled or titrated after injection and has been associated with complications such as bowel injury and possibly abdominal compartment syndrome³². In addition, patients receiving this therapy will require surgery to remove the material even if techniques such as interventional radiology are successful in creating definitive hemostasis.

Since the major proposed mechanisms for the hemostasis produced by ResQFoam is pressure produced by the expanding foam, we hypothesized that insertion of an inflatable balloon into the peritoneal cavity can create direct or indirect pressure on hemorrhaging sites to produce hemostasis but without some of the previously mentioned drawbacks of ResQFoam. The core component of the device is a square, pillow-shaped, and semi-compliant balloon intended for intra-peritoneal placement (FIGURE 3). Prior to use, the balloon is pre-loaded inside a trocar-tipped applicator. Intraperitoneal access is gained through a small abdominal incision. The introducer is placed through the incision and a plunger is used to deploy the balloon into the peritoneal space where it can then be inflated. The balloon is roughly 18 cm x 18cm x 10cm when inflated and attached to an externalized line which allows for inflation/deflation. While we are still exploring the optimal shape of the balloon, the square shape was chosen to maximize the balloon surface contact area with abdominal organs and the anterior abdominal wall (324 cm^2 as opposed to $\sim 254\text{ cm}^2$ for a round shaped balloon). Similar to the GROA device, the inflation/deflation mechanism of the IPHD also utilizes an air pump and pressure gauge assembly.

In a pilot study, the IPHD was evaluated for its ability to temporarily control hemorrhage and subsequently improve survival in a model of rapidly lethal, multi-organ hemorrhage including a grade-V liver laceration (the same method as used in the aforementioned GROA study) combined with a severe spleen and kidney laceration^{27,28}. The group of animals treated with IPHD were compared to controls (no IPHD) for survival, hemodynamics, and other metrics of shock. All control animals (3/3) died within 15-43 minutes from injury while all IPHD-treated animals (5/5) survived the duration of the 60-minute intervention period. Animals treated with IPHD responded to the treatment with overall improvement in MAP, shock index, SvO₂ and

cardiac output during the intervention period; control animals steadily decreased in these parameters until death endpoints were met. To underscore the severity of the created injuries, all animals in the IPHD group died after deflation of the device due to reactivation of hemorrhage.

The study concluded that the IPHD intervention was effective at prolonging survival compared to controls, due to the slowing or stopping of hemorrhage from multiple organ sources supporting the concept that when the IPHD is activated within a closed space (peritoneum), the balloon likely causes direct tamponade when contacting bleeding surfaces and indirect tamponade by displacing nonbleeding tissues that then contact and apply pressure to the hemorrhaging surfaces resulting in hemostasis.

Of particular interest and a potential advantage over both GROA and REBOA is the fact that the IPHD produced hemostasis without the need to occlude the aorta despite the severity of injuries. With application of additional pressure to the external abdomen we were also able to easily occlude the aorta without occluding hepatic artery blood flow as measured by an ultrasonic flow probe (FIGURE 3, bottom). Similar to GROA, the IPHD would need to be deactivated and removed at the time of surgery. However, as pointed out earlier, the transition from the IPHD to REBOA should be feasible allowing for control of NCTH at the time of surgery.

The study is limited as a pilot study and under-powered to detect discrete hemodynamic effects, however the preliminary results generated indicate feasibility of application, a survival benefit, and other favorable physiological effects. Based on these effects, additional research for such a device is warranted for NCTH.

IPHD and GROA summary effect on survival vs. control

Since the models used for the pilot IPHD and GROA survival studies were nearly identical in their lethality, it is feasible to pool control data from both studies and present the survival of GROA and IPHD against all controls. A Kaplan Meier curve showing survival from the onset of injury is presented in FIGURE 4. A log-rank test of the survival curves on the pooled data shows similar and significant survival effect from both GROA and IPHD relative to controls. The GROA median survival was 146 minutes after injury and 90 minutes for the IPHD, while median survival across all controls was only 13 minutes $p=0.0039$. Also of note is that all animals receiving either intervention survived the duration of the intervention period and expired during the resuscitation and post resuscitation phases due to renewed massive hemorrhage following device removal, or from reperfusion injury. These data suggest there is a distinct survival benefit associated with each technology and intervention when compared to controls.

Advantages of GROA and IPHD

With 45% of deaths from severe hemorrhage occurring in the field^{33,34} new technologies to stop or slow hemorrhage in the pre-hospital or austere environment will be required if this statistic is to significantly improve. These pre-clinical studies for both GROA and IPHD suggest that either approach may be effective for mechanical stanching of high zone-2 torso hemorrhage and are potentially feasible for pre-hospital application. GROA and the IPHD both hold application advantages that could considerably reduce the time to mechanical hemorrhage control after injury.

The GROA device is less invasive than other techniques and does not require any surgical intervention or imaging to be placed. With a physiologic tolerance profile similar to REBOA, these characteristics may favor GROA as a first line tool or initial approach for suspected cases of massive hemorrhage that would require aortic occlusion. GROA's use as an

adjunct or bridge to REBOA or surgical intervention would seem to be feasible as indicated earlier. Therefore, it is envisioned that military medics, civilian first-responders (paramedics), and hospital trauma providers would also be able to effectively apply the GROA device.

The IPHD requires a slightly more invasive approach for application as it is deployed percutaneously within the abdomen. Despite this and given the emergence of other intraperitoneal resuscitation techniques such as ResQFoam, we envision the application of this technology to be feasible. Like GROA, the device was rapidly placed and removed without complication in the pilot study.

The IPHD may also offer a more titratable approach for managing hemorrhagic abdominal injuries. The ability to titrate pressure and easily remove the device through the application incision does not commit the patient to subsequent laparotomy if less invasive treatments such as interventional radiology may be sufficient for definitive hemostasis. An additional benefit of the IPHD also includes the potential for selective occlusion of the aorta. While the IPHD has demonstrated the capability of hemorrhage control from lethal hepatoportal injury without requiring occlusion of the aorta, for some injury patterns such as those to lower abdominal arteries (renal or iliac), selective occlusion of the aorta is possible if warranted.

Lastly, a considerable benefit common to both devices is the preservation of physiologic reserve. In all three pre-clinical studies, important hemodynamic parameters rapidly improved after the devices were activated. Reducing hemorrhage while maintaining perfusion to the heart and brain, or at minimum slowing hemodynamic deterioration with a mechanical device as early as possible, may ultimately limit the accumulation of lethal levels of oxygen debt. This effect may be paramount to optimizing resuscitation once more advanced care and definitive hemostasis are available.

A final consideration is that all three of the studies covered in this review are preliminary in nature and focused on feasibility of application, physiologic tolerance, and survival during the intervention, and over a short post resuscitation monitoring period. Beyond that, all the studies remain underpowered to detect discrete differences in other outcomes i.e., hemodynamics between methods. This does not, at this time, allow for the assessment of superiority or non-inferiority relative to any other technologies used for non-compressible hemorrhage, approved or investigational. Despite this, we believe that all three studies have generated powerful preliminary data which gives a certain confidence to the feasibility of application and tolerance to the devices, a clear initial survival benefit from the devices' application, and evidence of improved hemodynamics. Regardless, as the technologies described here move forward, long-term pre-clinical studies and human application feasibility studies are needed, and eventually clinical trials where we may begin to truly understand the extent of the physiologic effects, survival benefits, and adverse consequences of their application. The next phase of development and testing of these devices include design refinement and testing in perfused cadaver models.

Overall conclusion

Two emerging technologies discussed in this review were designed with a common target objective: Early-phase transitory control of non-compressible abdominal hemorrhage which is capable of temporarily prolonging survival during transport or before advanced surgical or resuscitative care is available. Both technologies share the promise of pre-hospital application, can be deployed quickly and consistently, and both have shown to improve hemodynamics, reduce shock, preserve physiologic reserve, and ultimately prolong survival from otherwise rapidly lethal exsanguination.

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Figure Legend

FIGURE 1: Left panel (A); Morphomic analysis of the aorta position 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. Right panel (B); Frequency of the radial position of the aorta in respect to the vertebral body in the same population.

FIGURE 2: Top left panel; an illustrated version of the GROA device applied to a human; (A) air pump/pressure gauge assembly, (B) gastroesophageal tube (C) Ellipsoid shaped gastric balloon, (D) Retractable 14F tip. Top right panel; Adjustable external compression system. Bottom panel; Arterial pressure from the carotid and femoral arteries, and hepatic artery flow during GROA occlusion.

FIGURE 3: Top left panel; Illustration of an automated applicator and intraperitoneal balloon deployment. Top right panel; Illustration of the IPHD balloon inflated after intraperitoneal

deployment and external pressure being applied for selective aortic occlusion. Bottom panel; Arterial pressure from the carotid and femoral arteries, and hepatic artery flow during user selected aortic occlusion.

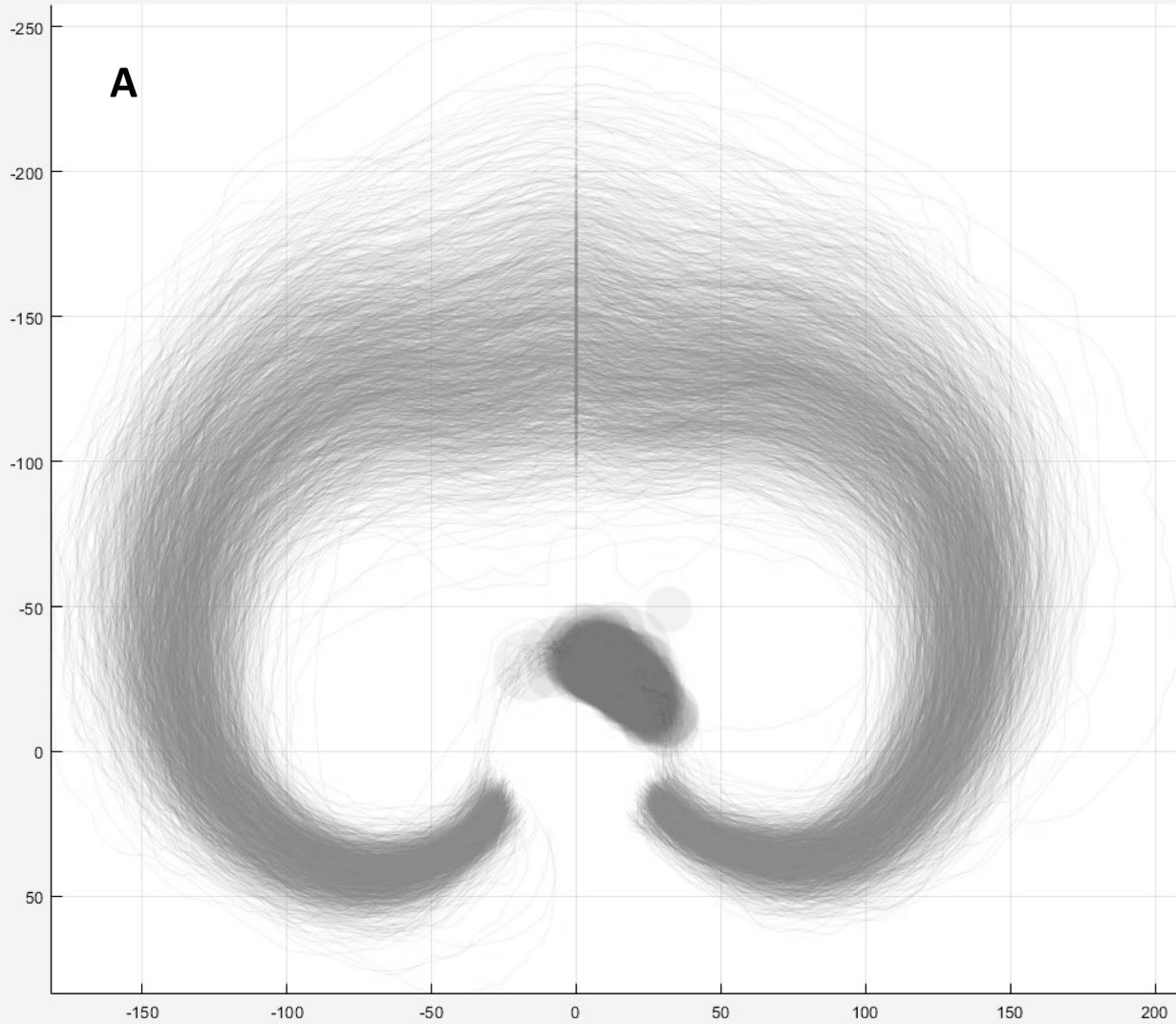
FIGURE 4: Kaplan Meier plot of survival proportions in a preclinical swine model of rapidly lethal abdominal hemorrhage; GROA ($n=8$) and IPHD ($n=5$) treated animals are represented as dashed and dotted dashed lines, respectively, and plotted against controls ($n=11$) (solid line).

Table 1. Description of models used to evaluate GROA and IPHD

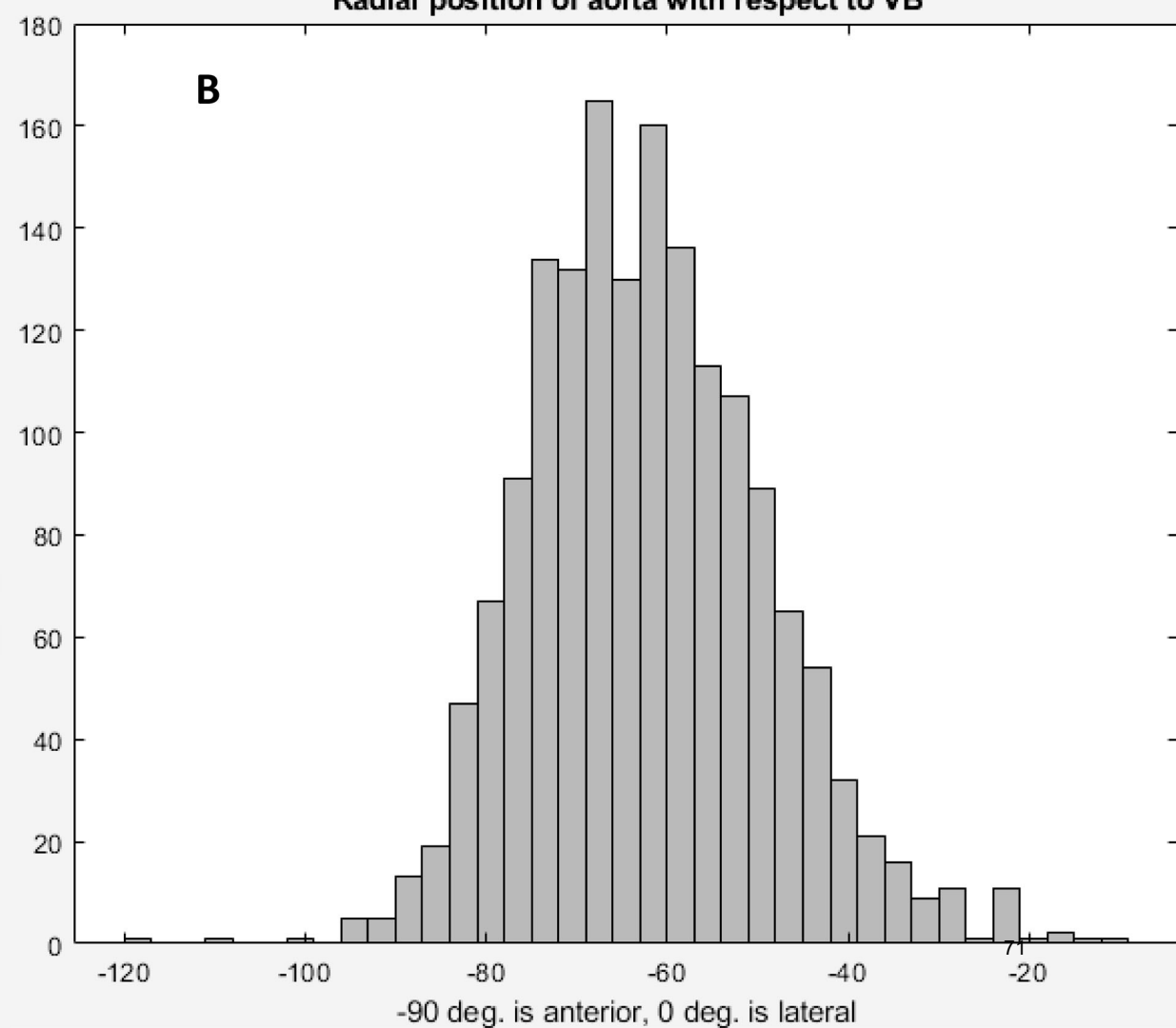
Study	Controlled hemorrhage (%), (min)	Source of uncontrolled hemorrhage	Uncontrolled hemorrhage Time (min)	Shock Classification	MAP at start of intervention (mmHg)	Lactate at start of intervention (mEq/L)	Duration of Intervention (min)	Survival: intervention (%)	Survival: monitoring (%)
GROA - Tolerance	35, 30	N/A	N/A	Class III-IV	33.5 (5.10)	4.03 (1.75)	30, 60, 90	100, 100, 83	80, 100, 33
GROA - Survival	30, 20	Liver Laceration	2	Class IV	27.1 (5.65)	2.64 (0.95)	60	100	37.5
IPHD	30, 20	Liver, Spleen, Kidney	2	Class IV	24.3 (3.73)	2.34 (0.29)	60	100	0

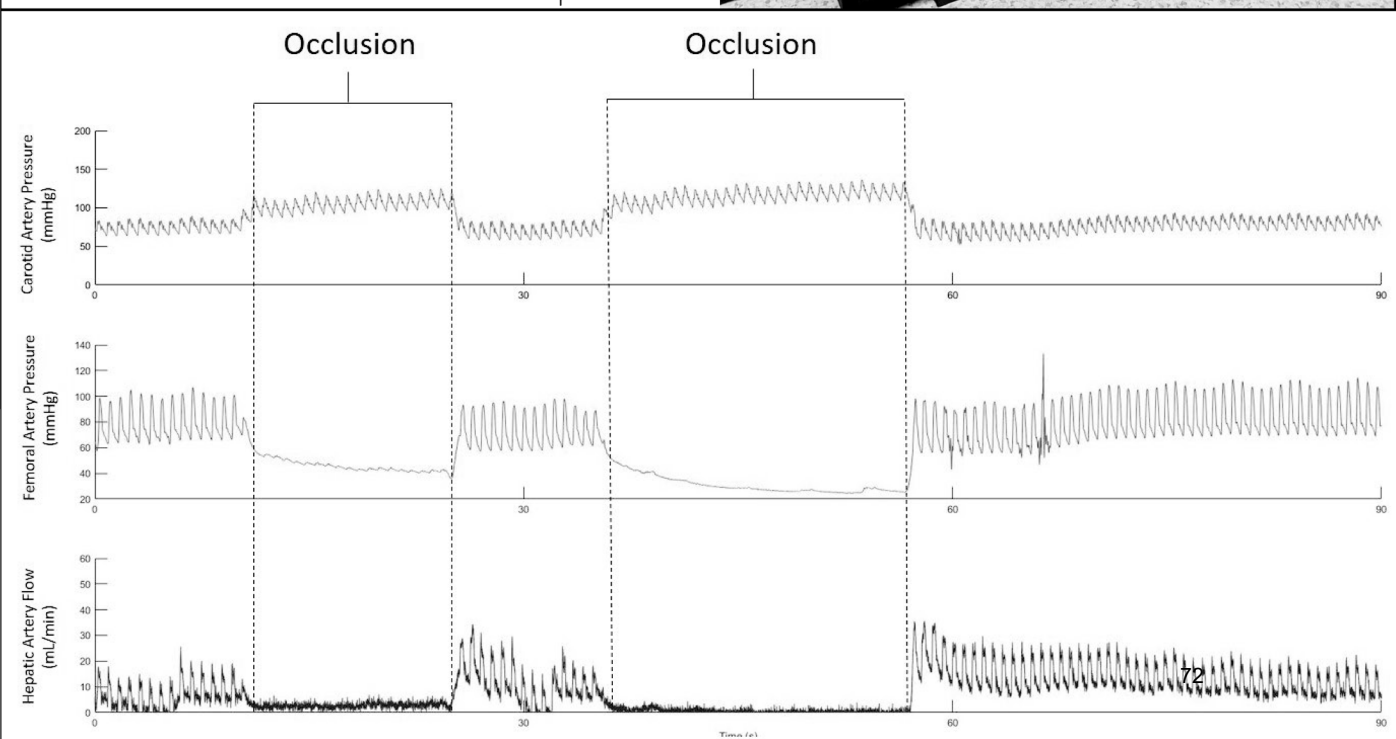
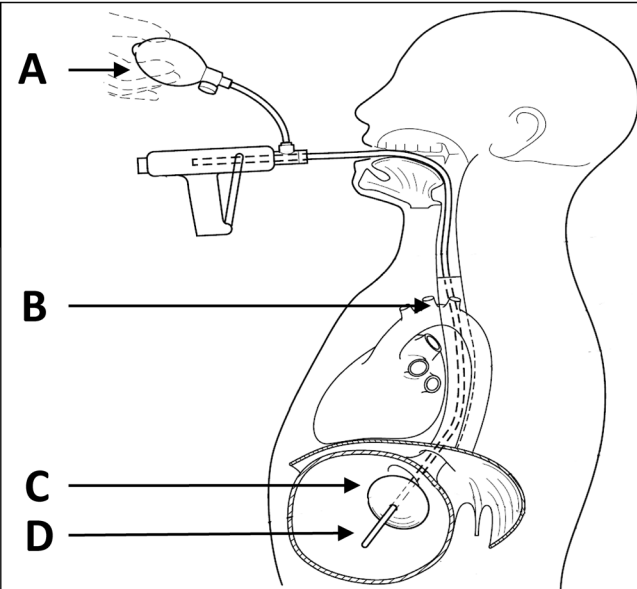
Data are presented as mean (standard deviation) or as percentage.

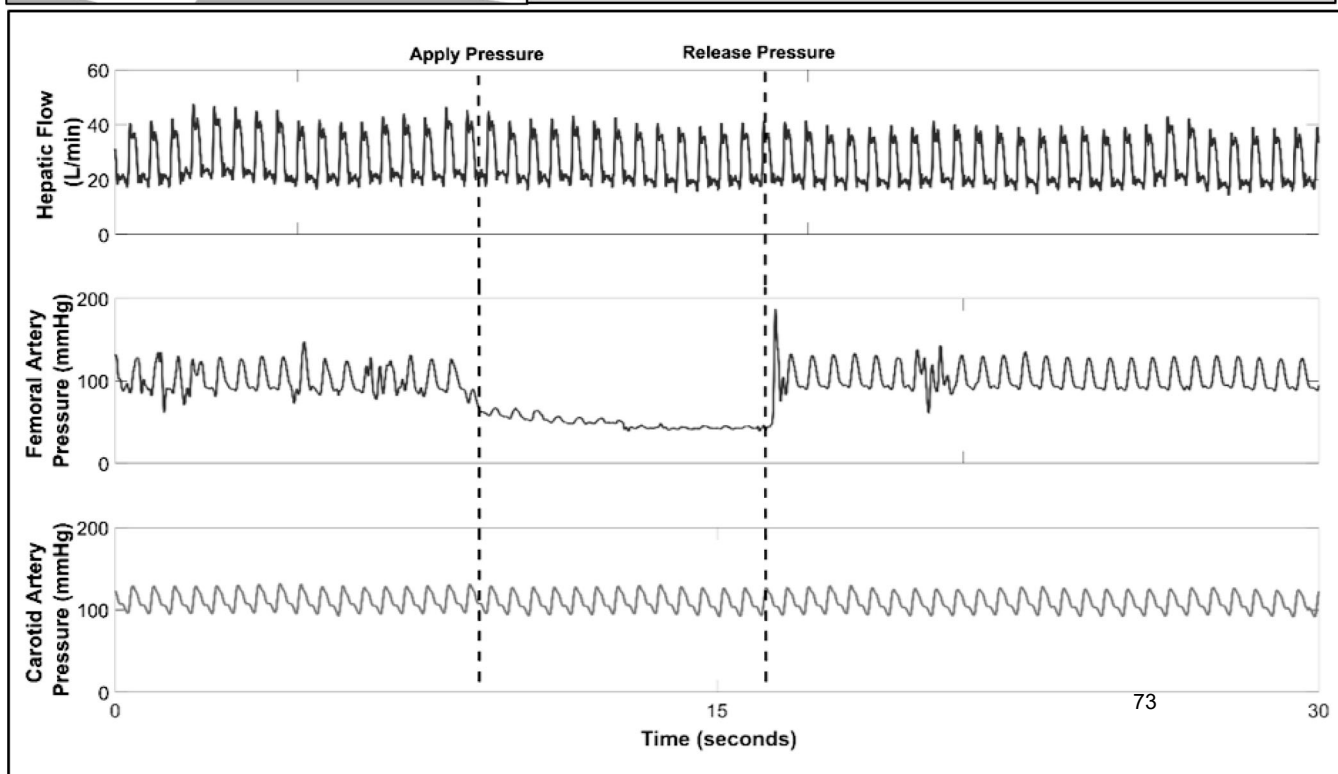
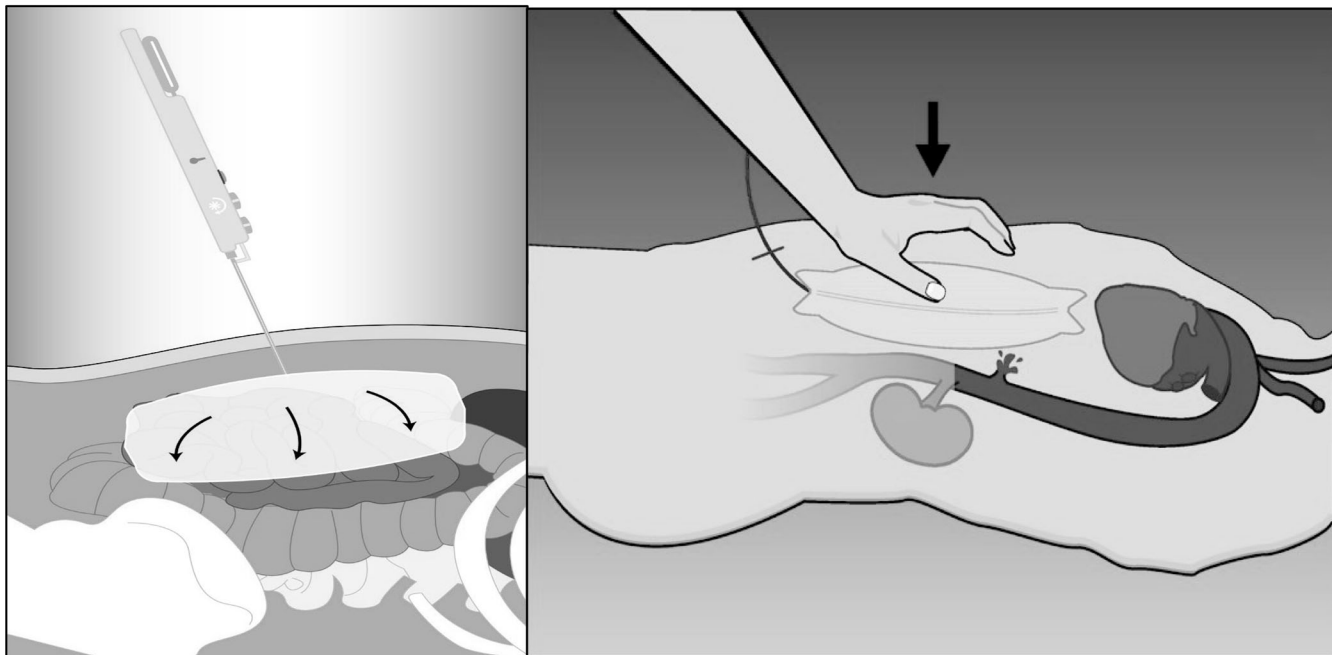
Geometric summary from 1641 aortas



Radial position of aorta with respect to VB







End of Intervention

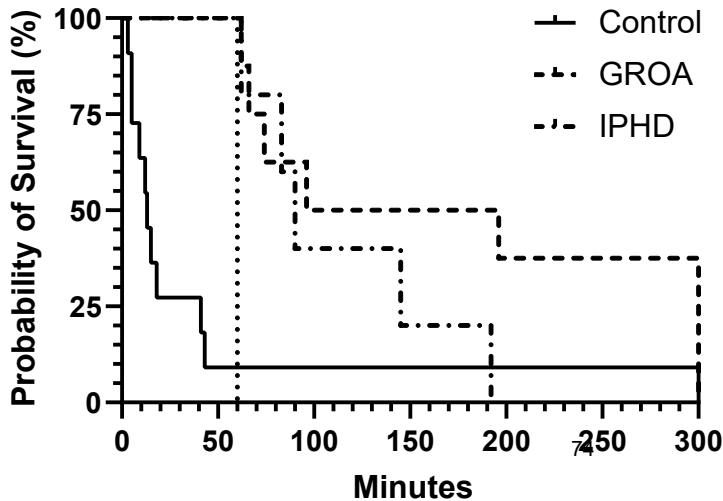


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GROA - Tolerance	35, 30	N/A	N/A	Class III-IV	33.5 (5.10)	4.03 (1.75)	30, 60, 90	100, 100, 83	80, 100, 33
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Data are presented as mean (standard deviation) or as percentage.

Tandem use of Gastroesophageal Resuscitative Occlusion of the Aorta followed by REBOA in a Lethal Liver Laceration Model

Short title: Tandem use of GROA followed by REBOA

Mohamad Hakam Tiba^{1,2, *}, Brendan M. McCracken^{1,2, *}, Nicholas L. Greer^{1,2}, Traci A. Cramer^{1,2}, Carmen I. Colmenero Mahmood^{1,2}, Ketut B. Priambada Putra⁴, Jeffery S. Plott^{2,3,4}, Albert J. Shih^{2,3,4}, Stewart C. Wang^{2,5}, Jonathan L. Eliason^{2,5}, Kevin R. Ward^{1,2,3}

1. Department of Emergency Medicine, University of Michigan, Ann Arbor, Michigan
2. The Max Harry Weil Institute for Critical Care Research and Innovation, University of Michigan, Ann Arbor, Michigan
3. Department of Biomedical Engineering, University of Michigan, Ann Arbor, Michigan
4. Department of Mechanical Engineering, University of Michigan, Ann Arbor, Michigan
5. Department of Surgery, University of Michigan, Ann Arbor, Michigan

* Denotes equal contributions to this study.

Authors in order:

Mohamad Hakam Tiba, MD, MS: tibam@med.umich.edu

Brendan M. McCracken, MS: bmccrac@med.umich.edu

Nicholas L. Greer, BS: nlgreer@med.umich.edu

Traci A. Cramer, MS: crtraci@med.umich.edu

Carmen I. Colmenero Mahmood, BS: cico@med.umich.edu

Ketut B. Priambada Putra, PhD: bagus@umich.edu

Jeffery S. Plott, PhD: plottjs@umich.edu

Albert J. Shih, PhD: shiha@umich.edu

Stewart C. Wang, MD: stewartw@med.umich.edu

Jonathan L. Eliason, MD: jonaelia@med.umich.edu

Kevin R. Ward, MD: keward@med.umich.edu

Corresponding Author:

Kevin R. Ward, MD

2800 N. Plymouth Road

North Campus Research Complex

Ann Arbor, MI, 48109

Fax: (734) 763-9389

Phone: (734) 764-6706

E-Mail: keward@med.umich.edu

Conflicts of Interest and Source of Funding:

Authors KRW, and JSP have intellectual property associated with the device used in this study.

Authors KRW and JSP have equity shares in the company that is licensing the technology.

Author JLE is a medical advisory board member for Prytime Medical Devices Inc. He receives royalty distributions and holds stock options in the company. The remaining authors declared no conflict. This work is supported in full by a grant from the United States Department of Defense, contract number: W81XWH-18-1-0033.

Background: Gastroesophageal Resuscitative Occlusion of the Aorta (GROA) has been shown effective in creating zone II aortic occlusion capable of temporarily improving survival in animal models of lethal non-compressible torso hemorrhage (NCTH). In this study, tandem application of GROA transitioning to resuscitative endovascular balloon occlusion of the aorta (REBOA) is explored to demonstrate feasibility as a potential point-of-injury bridge to more advanced care, using a swine model of lethal abdominal hemorrhage.

Methods: Swine ($n=19$) were anesthetized, instrumented, and subjected to a combination of controlled and uncontrolled hemorrhage from a grade-V liver laceration. Animals were designated as intervention ($n=9$; GROA to REBOA) or control ($n=10$), for 60-minutes. Following intervention, devices were deactivated, and animals received blood and crystalloid resuscitation. Animals were monitored for four hours.

Results: Injury resulted in onset of class IV shock in all animals with a mean arterial blood pressure ((MAP) (standard deviation)) of 24.5 (4.11) mmHg at the start of intervention. Nine of ten controls died during the intervention period with a median (interquartile) survival time of 8.5 minutes (9.25 minutes). All animals receiving the intervention survived both the 60-minute intervention period demonstrating a significant survival improvement ($p=0.0007$). Transition from GROA to REBOA was successful in all animals with a transition time ranging from 30 to 90 seconds. MAP significantly improved in animals receiving GROA to REBOA for the duration of intervention, regardless of the method of aortic occlusion, with a range of 70.9 mmHg (16.04 mmHg) to 101.1 mmHg (15.3 mmHg). Additional Hemodynamics, metrics of shock, and oxygenation remained stable during intervention.

Conclusion: Less invasive technologies such as GROA may present an opportunity to control NCTH more rapidly, with a subsequent transition to more advanced care such as REBOA.

Level of evidence: This basic science paper does not require a level of evidence.

Study type: Therapeutic.

Keywords: Shock; Noncompressible Torso Hemorrhage; Aorta; Resuscitation; REBOA.

Introduction

Hemorrhage from potentially survivable injuries is estimated to be responsible for more than 90% of military combat casualties and 40% of civilian trauma deaths(1-3). In spite of recent advancements in hemorrhage management, such as the treatment of extremity and junctional hemorrhage(4-6), treatment of non-compressible torso hemorrhage (NCTH) continues to pose almost intractable challenges, especially in the prehospital setting where almost nine out of ten deaths occur(1, 7). Casualties with significant hemorrhage from NCTH who manage to reach a higher echelon of care often present in extremis, with no physiologic reserve, where immediate resuscitative thoracotomy and aortic cross-clamping may be employed but for which poor outcomes exists(8).

The recent revolution in endovascular surgery has resulted in the advent of balloon occlusion of the aorta. Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) is an evolving and promising technology. It was developed to provide immediate hemorrhage control and offer a physiologic bridge to definitive surgery or other hemostatic techniques such as interventional radiology(9-12). Significant research has been produced to date to examine the utility of REBOA, its physiologic tolerance and its potential adverse effects, such as the distal ischemia produced by prolonged aortic occlusion(13-16). Current improvements in REBOA design are leading to smaller easier to place catheters and the potential to create partial aortic occlusion. Such improvements will allow for the reduction in the ischemic burden and the resulting reperfusion injury and complications after its deactivation(17-22). Nonetheless, the major challenge in the utilization of REBOA seems to be the time interval and physiologic status of casualties between the time of initial injury and the time of REBOA's implementation. While successful combat and civilian field applications of REBOA have recently been

reported(23), application time ranged from 34-57 minutes(24), making its widespread field application limited by logistical challenges(12).

It has been demonstrated previously that an investigational device and technique called gastroesophageal resuscitative occlusion of the aorta (GROA) is effective in creating zone II aortic occlusion and capable of temporarily staunching severe NCTH and improving survival with physiological tolerances similar to REBOA in a large animal model of lethal abdominal hemorrhage(25, 26). In this study we piloted the feasibility of tandem application of GROA followed by REBOA as an example of in-field point-of-care use in a swine model of lethal liver laceration. We hypothesized that the tandem application of REBOA following an initial aortic occlusion with GROA is possible, while demonstrating a survival benefit associated with both technologies, compared to controls. We envision GROA could serve as a field bridge to REBOA allowing aortic occlusion for earlier hemorrhage control.

Methods:

All procedures were carried out in an AAALAC (American Association for Accreditation of Laboratory Animal Care) accredited institution under approval from the Institutional Animal Care and Use Committee (IACUC) and the United States Army Animal Care and Use Research Office (ACURO), following the *Guide for the Care and Use of Laboratory Animals*(27). The equator network ARRIVE guidelines were used to ensure proper reporting of methods, results, and discussion and are available as supplemental digital content (SDC 1).

Sedation: Nineteen Yorkshire mix swine (14 males; 5 females) with an average (standard deviation) weight of 52.2 kg (3.5kg) were used and all animals were included in the study. Nine animals (5 males; 4 females) were used in the intervention group and the rest were used as controls. Data for eight of these control animals were published previously and used in this paper

as historical controls. Of note is that identical injury methods for all control ($n=10$) and intervention animals ($n=9$) were used in this study. Sample size, using survival as the primary outcome, was determined based on results from previous studies(25, 26).

All animals were acclimated for at least 5 days before use, fasted overnight with full access to water. On the day of the experiment, animals were sedated using a mixture of 4-6 mg/kg tiletamine/zolazepam and 2 mg/kg xylazine. Subsequently, they were intubated and maintained on 1-2% isoflurane in 30-40% oxygen and a balance of nitrogen. Animals were mechanically ventilated with 7-8 mL/kg tidal volume and 5 cmH₂O positive end-expiratory pressure. Respiratory rate was adjusted to maintain end-tidal CO₂ (PetCO₂) between 35-45 mmHg. Electrocardiogram and pulse oximetry (SpO₂) were monitored (SurgiVet Advisor, Smiths Medical, Dublin, OH) and body temperature was maintained between 37 C - 39 C using a temperature blanket (Blanketrol: Sub-Zero Medical, Cincinnati, OH).

Instrumentation: Both left, and right external jugular veins were cannulated for delivery of blood/fluid resuscitation and placement of a pulmonary artery catheter (CCOmbo V, 8 F; Edwards Lifesciences, Irvine, CA) for monitoring central venous pressure (CVP), pulmonary artery pressure (PAP), and cardiac output. The right carotid artery was cannulated to monitor mean arterial pressure (MAP) and for blood sample collection. The right femoral artery was cannulated using a 9F introducer (Arrow, Teleflex, Morrisville, NC) for placement of ER-REBOA catheter (Prytime Medical, Boerne, TX), and the left femoral artery was cannulated for femoral arterial pressure monitoring and as a source of the controlled arterial hemorrhage. The liver was accessed through a mid-line laparotomy which was extended 10 cm caudally from the xyphoid process.

Injury: Controlled hemorrhage was initiated removing 30% of the animals' blood volume over the course of 20 minutes. The controlled hemorrhage was paused if necessary to maintain MAP > 30 mmHg. Shed blood was collected in two 450 mL citrate phosphate dextrose bags (Fenwal Inc, Lake Zurich, IL) and used for the autologous transfusion during resuscitation. Animals were assigned into one of two groups: control (no intervention) ($n=10$; 9 male, 1 female) and 60-minute intervention ($n=9$; 5 males, 4 females). The latter received 30-minutes of GROA followed by 30-minutes of REBOA. It was unfeasible to randomize given the previously performed controls, and operators could not be blinded to the intervention group. Following the controlled hemorrhage, a full thickness Grade V liver laceration was created starting approximately 2 cm left of Cantlie's line(28) and spanning roughly 80% of the cranial-caudal surface of the left medial lobe as described in McCracken *et al.*(26). The lacerated lobes were intentionally separated, and the abdomen quickly closed using towel clamps. The liver was allowed to bleed freely for two minutes before initiating intervention.

Intervention and Resuscitation: The GROA device has been previously described(25, 26). Briefly, it is made of a triple lumen gastroesophageal tube with an inflatable ellipsoid balloon at the end with a max ex-vivo volume of $\sim 1600\text{cm}^3$. A 14F sump tube is placed through the GROA device to help guide the balloon through the esophagus and into the stomach. In addition to the GROA balloon device is an external pressure system consisting of both a back and abdominal plate used to exert pressure on the inflated GROA balloon inside the stomach to occlude the aorta. The device was placed during the 2 minutes of free bleeding from the liver. The abdominal plate was then tightened followed by GROA balloon inflation to 60-80 mmHg (equating to $\sim 1200\text{ cm}^3$ balloon volume) and aortic occlusion was achieved and confirmed based on loss of femoral artery pulse pressure. Aortic occlusion was maintained with the GROA balloon for 30

minutes. At the 30-minute time mark, without deflation and deactivation of the GROA device, the REBOA catheter was inserted through the previously placed femoral artery introducer to the premeasured distance necessary for highest possible zone II subdiaphragmatic occlusion and inflated with 5-7 mL of saline. Following REBOA inflation, the GROA system was deactivated and removed for the remaining 30-minutes of intervention. Ten minutes prior to the end of the intervention period, intravenous Ringer's lactate solution was administered to increase intravascular volume and prevent hemodynamic collapse during device deactivation. At the end of intervention, the abdomen was opened to perform a Pringle maneuver for hemorrhage control while hemostatic dressings (Quikclot control+, Teleflex, Morrisville, NC) and/or Celox EMS (Medtrade products, Electra House, Crewe Business Park, Crewe, UK) were applied to the lacerated liver surfaces. Simultaneously to the Pringle maneuver, the ringer's lactate infusion was discontinued and autologous whole blood transfusion was initiated. The single surviving animal from the control group received the same resuscitation protocol as the animals in the intervention group. The REBOA device was then slowly deflated over an average (standard deviation) period of 4.0 min (1.3 min). Following REBOA deflation, the hepatic clamp was removed, and a target MAP of 40-60 mmHg was maintained using lactated Ringer's to achieve a permissive hypotension strategy to slow residual hemorrhage during the post-resuscitation monitoring period. Monitoring and data collection proceeded for 4 hours after resuscitation, or until animals met predetermined endpoints (MAP < 20 mmHg and PetCO₂ < 15 mmHg).

Data Collection: Carotid artery pressure, femoral artery pressure, CVP, PAP, heart rate, mixed venous saturation (S_{mvO₂}), and electrocardiogram were continuously recorded (MP160; Biopac Systems Inc., Goleta, CA). Arterial and mixed venous blood gases were sampled every 30 minutes (ABL800flex; Radiometer America Inc., Brea, CA).

Thromboelastography (TEG 5000, Haemonetics Corp., Braintree, MA) and complete blood count (Vetscan HM5, Abaxis, Inc., Union City, CA) samples were collected at the end of hemorrhage, end of intervention, end of resuscitation, and every 2 hours thereafter.

Comprehensive diagnostic chemistry profiles (Vetscan; Abaxis Inc., Union City, CA) were collected at baseline and end of experiment. At the conclusion of the monitoring period, or when endpoints were met, animals were euthanized under general anesthesia using 1-2 mEq/kg of intravenous potassium chloride. Sections of the stomach, aorta, and esophagus were obtained for histological analysis by a veterinary pathologist, blinded to the intervention.

Statistical Analysis: All animals in the intervention group ($n=9$) and controls ($n=10$) were used for statistical data analyses. All data are presented as mean (standard deviation) or median (interquartile). A Wilcoxon test was used for survival analysis. Continuous variables were assessed using repeated measures mixed-model regression, one-way analysis of variance with Tukey's correction for multiple comparisons and paired or un-paired t-tests as applicable. Statistical significance was considered at $\alpha=0.05$. All data were analyzed using SAS 9.4 (SAS corporation, Cary, NC) and PRISM 9 (GraphPad Software, San Diego, CA). Potential confounders were not controlled.

Results:

All animals experienced a significant drop in MAP during controlled hemorrhage and subsequent liver laceration resulting in an average decrease of 61.0 mmHg, from 86 mmHg (11.3 mmHg) at baseline, to 24.5 mmHg (4.1 mmHg) at the start of intervention ($p<0.001$). After liver laceration and at the start of intervention, mean (SD) MAP in the intervention group at was 24.5 mmHg (4.0 mmHg) compared to 24.5 mmHg (4.5 mmHg) in the control group, with no differences between groups.

Survival:

Nine out of ten control animals died post liver laceration with a median (interquartile) survival time of 8.5 min (9.25 min). The animal which survived post-injury also survived the duration of the post-resuscitation monitoring period. All animals receiving the intervention survived the 60-minute intervention period including GROA with transition to REBOA. A Wilcoxon test comparing survival curves indicated a statistically significant survival benefit from the intervention compared to controls ($p=0.0007$). Five out of the nine 60-minute intervention animals survived for 4-hours post resuscitation. The other four animals survived 11 min (20 min) following the end of intervention. The animals' deaths were attributed to a combination of renewed hemorrhage and reperfusion injury. A Kaplan-Meier plot of survival probabilities is presented in figure 1.

Hemodynamics:

MAP, SmvO₂, and PetCO₂ are presented in figure 2. MAP significantly increased following GROA application in the intervention group. MAP improved from 24.5 mmHg (4 mmHg) to 70.9 mmHg (16 mmHg) prior to transition to REBOA, ($p<0.001$). On average, MAP remained above a clinically relevant threshold of 65 mmHg for the duration of intervention, regardless of the timepoint or method of aortic occlusion, with a range of from 71 mmHg (16.0 mmHg) to 101 mmHg (15.3 mmHg). SmvO₂ decreased in all animals from a baseline level of 73.6% (8.14%) to 27.8% (9.30%) following hemorrhage ($p<0.001$), however, it increased during the intervention period, and then returned to baseline levels by the end of the intervention period. PetCO₂ decreased from a baseline of 36.7 mmHg (2.05 mmHg) to 26.7 mmHg (3.47 mmHg) following hemorrhage ($p<0.001$), and further decreased following the to the application of GROA. After transition to REBOA, PetCO₂

significantly increased. Values for hemodynamics during the transition from GROA to REBOA are presented in table 1.

Airway pressure and lactate data are presented in figure 3. Airway pressure increased in all animals following the application of GROA from 23.6 cmH₂O (2.1 cmH₂O) at the end of hemorrhage to 32 cmH₂O (3.5 cmH₂O). Airway pressure significantly decreased following the transition to REBOA, returning to a near baseline value. Lactate increased following hemorrhage and injury and continued to increase for the duration of the intervention period. Peak lactate levels of 13.5 mEq/L (3.29 mEq/L) were observed 30 minutes following resuscitation, and subsequent lactate clearance occurred at an average rate of 1.56 mEq/L/hr in the surviving animals thereafter. Average lactate levels of 7.3 mEq/L (1.27 mEq/L) were observed at the end of monitoring period.

Transition from GROA to REBOA was successful in all animals without the loss of aortic occlusion during the transition. A representative animal's femoral and carotid pressure waveforms, during the transition, are presented in figure 4. The average time for the transition from the insertion of REBOA to the full deactivation of the GROA device was 63.2 seconds (18.8 seconds), with a minimum transition time of 30 seconds, and a maximum transition time of 90 seconds. There was no evidence of renewed bleeding signaled by hemodynamic response in any animal after transitioning between interventions. There were no changes in femoral artery pressure from the end of GROA application, 19.1 mmHg (4.05 mmHg) to the initiation of REBOA application, 18.9 mmHg (3.92 mmHg). Hemodynamics, metrics of shock and oxygenation remained stable or improved further between the end of GROA and the beginning of REBOA with additional data presented in table 1.

No significant changes in coagulation as measured by thromboelastography were

noted. Blood serum chemistry indicated mild elevations compared to baseline in alkaline phosphatase, alanine transaminase, and creatinine at the end of the experiment. Similarly, a mild increase in hemoglobin was noted at the end of the experiment. Additional detailed data on these metrics are presented in table 2.

Histopathology:

There were no significant findings in the esophageal mucosa or aorta of any animals examined. In the intervention group, evidence of mucosal inflammation ranged from no findings to minimal. Mild inflammation was noted as an increase in inflammatory cell infiltrates in the lamina propria of most sections of stomach. In sections of cardia, there were increased numbers of mixed inflammatory infiltrates within the mucosa, associated with scattered apoptotic debris in the superficial mucosa. In sections of fundus, there were dense mixed inflammatory infiltrates expanding into the lamina propria, multifocally extending into the submucosal layers, and multifocal foci of minimal superficial mucosal necrosis. In sections of pylorus, there were multifocal foci within the superficial mucosa that were disrupted, with loss of surface mucosa and karyorrhectic cellular debris. To summarize, there was some evidence of mild diffuse inflammatory infiltrates consistent with mild ischemic injury with across all areas of the stomach sampled including the cardia, fundus, and pylorus. However, these findings across all animals was either absent or deemed minimal indicating that the tandem use of GROA to REBOA for aortic occlusion for a intervention time of 60-minutes is well tolerated and does not appear to cause any acute catastrophic gastroesophageal injury. These findings were consistent with our previous studies which also demonstrated similar changes when REBOA was used as the sole method of occlusion(26).

Discussion:

The opportunity to extend the window of treatment from point of injury to definitive surgical hemostasis using new technologies is highly warranted given the high rate of prehospital mortality due to NCTH. While the application of REBOA in an in-hospital setting is clearly feasible and has been demonstrated to be of value, the transition of this technology for routine field use by combat medics or civilian paramedics will likely face logistical challenges. Such challenges include but are not limited to technical skill maintenance, and environmental conditions. These challenges are likely to be compounded as the severity of injury and hemorrhage increase. Even in the emergency department and trauma center, rapid application of REBOA can be challenging due to patient body habitus, operator experience, and other factors. In this study we sought to pilot the feasibility of the tandem use of GROA to REBOA as a potential bridge from a point-of-injury use to emergency department or trauma center implementation of REBOA. We utilized a highly lethal grade V liver laceration model of NCTH which (excluding one survivor) had survival times between 3 and 18 minutes without treatment. Given its lethality, we chose for ethical and humane purposes to utilize a previous experimental set of animals as controls to compare survival between untreated and treated subjects.

The results of this study demonstrate the potential feasibility of utilizing GROA followed by a more controlled transition to REBOA. REBOA was successfully deployed while the GROA device was still activated. In all but one case, the REBOA was advanced past the GROA balloon without releasing any of the external pressure. In one case, the REBOA could not be advanced past the GROA balloon and in this case the REBOA was inflated with ~1-2 mL normal saline, and the GROA external pressure assembly was loosened just enough to allow the balloon to be advanced superior to the GROA balloon and

be properly positioned before further inflation. Hemodynamic monitoring did not indicate any additional significant hemorrhage during REBOA transition.

The hemodynamic deterioration of animals after liver laceration and the hemodynamic and perfusion improvement following application of GROA are consistent with previous studies examining GROA and REBOA as separate treatments to staunch hemorrhage. We noted no relevant hemodynamic, respiratory/airway, biochemical, coagulation, or histopathologic changes produced by GROA in this study compared to previous studies(25, 26). The noted transient increase in airway pressure is the same as in previous studies and is likely due to modest restriction of diaphragm movement during GROA activation. However, as in those previous studies, no evidence existed that either ventilation or oxygenation was impaired. Airway pressures normalized after transition to REBOA.

Limitations and future directions:

There are several limitations to this study. Given the rapid death experienced by control animals, the lethal liver laceration used in this study is likely not the most practical representation of a casualty that would be alive and salvageable by the time paramedics could reach the point of injury. However, given the ability of the tandem use of GROA and REBOA to extend survival in the present study, it could be expected that the strategy would be effective in injuries that are less rapidly lethal.

While GROA was activated during the 2-minute liver free-bleed periods, REBOA was placed during the GROA intervention through a previously placed femoral artery introducer. Our laboratory has significant experience with placement of REBOA via femoral artery exposure with placement taking 10-15 minutes. As such we did not feel a de novo percutaneous or

cutdown placement performed during the GROA activation would be representative of a point of injury placement. This would have required a study design incorporating clinical participants with various levels of REBOA experience. We do not believe this detracts from the important finding that REBOA can be placed with little or no disruption in the occlusion created by GROA indicating that a transition is feasible. This finding is also important since it will be necessary to deactivate GROA at the time of surgery. A transition to REBOA at this time would offer advantages while achieving surgical hemostasis. With the recent development of partial REBOA which allows some blood flow past the balloon, it may be worth exploring this approach with GROA in the future to mitigate the burden of total ischemia and complications of reperfusion, or as a method to extend the physiologically tolerable time of aortic occlusion which may be the primary limiting factor of the GROA devices use.

Lastly, this study was not designed to examine long term outcomes. Renewed hemorrhage combined with limited blood products for resuscitation and limited surgical repair of the liver injury, were responsible for deaths. As such we cannot comment on longer term survival rates and potential complications. Despite this, initial survival was significantly extended into a potential time window of definitive intervention compared to controls.

Conclusion:

Control of NCTH using endovascular technologies such as REBOA may present logistical challenges in point of injury implementation. The use of less invasive methods and technologies such as the GROA device may present an opportunity for more rapid control of NCTH. The subsequent transition to REBOA may be feasible as casualties move through higher

echelons of care toward definitive surgical hemostasis. Additional research and development may be warranted.

Conflicts of Interest and Source of Funding:

Authors KRW, and JSP have intellectual property associated with the device used in this study.

Authors KRW and JSP have equity shares in the company that is licensing the technology.

Author JLE is a medical advisory board member for Prytime Medical Devices Inc. He receives royalty distributions and holds stock options in the company. The remaining authors declared no conflict. This work is supported in full by a grant from the United States Department of Defense, contract number: W81XWH-18-1-0033.

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Figure legend:

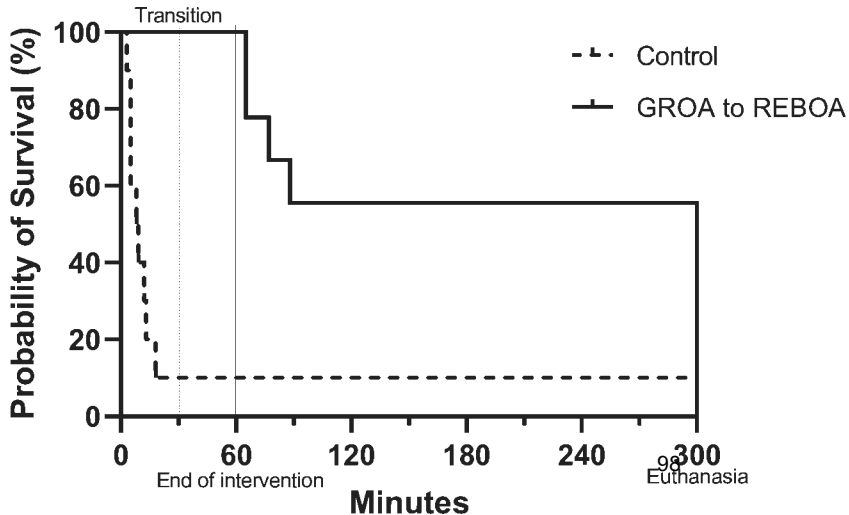
Figure 1. Kaplan-Meier survival probability curves comparing controls (dashed line) and animals receiving the 60-minute tandem interventions (solid line). Analysis demonstrated a significant survival difference between control animals and those undergoing the REBOA to GROA tandem interventions ($p < 0.01$).

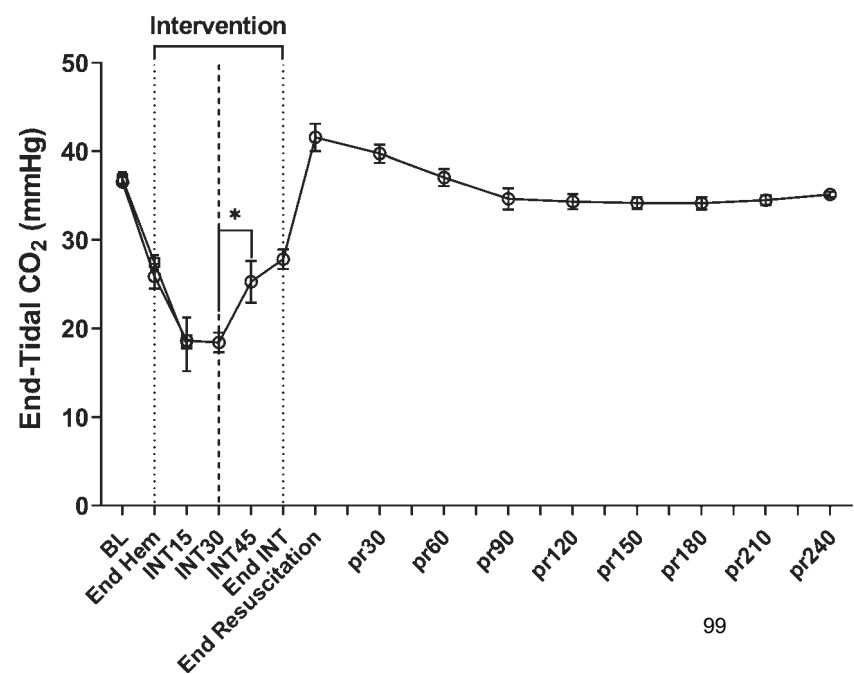
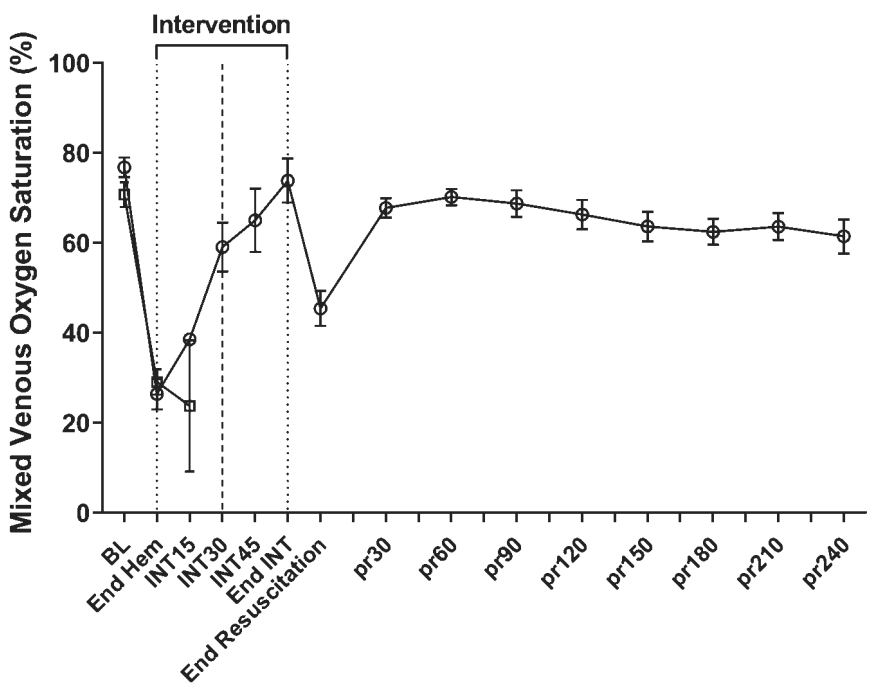
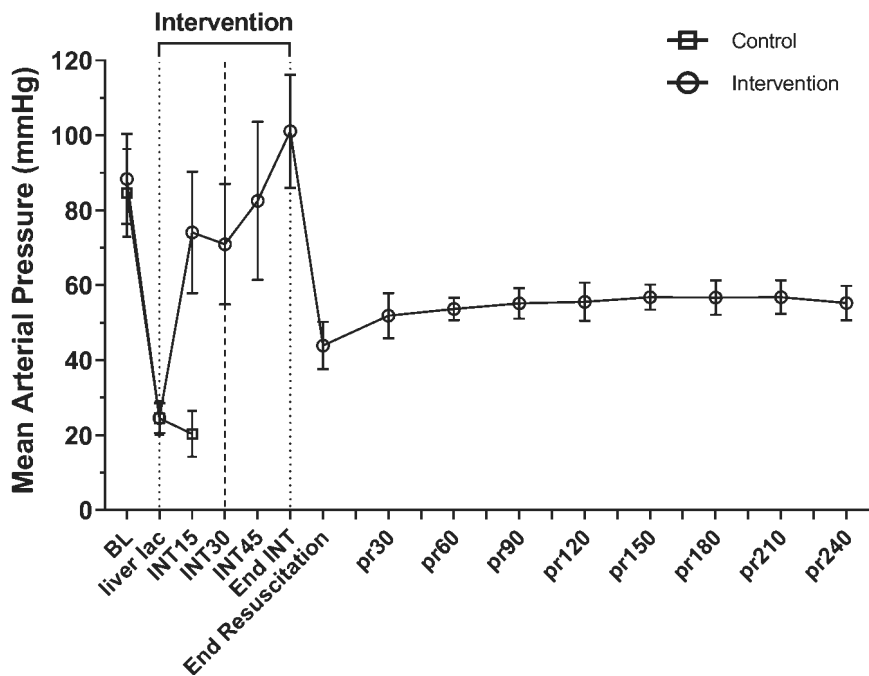
Figure 2. Average and standard error of mean arterial pressure (MAP) of the carotid artery (Top), Mixed Venous Oxygen Saturation (Middle) and End-Tidal CO₂ (Bottom). The area between the dashed lines represents the intervention period. The dotted line represents the time of transition from REBOA to GROA. BL, baseline; End Hem, End of controlled hemorrhage; liver lac, liver laceration; INT 15, 15 minutes into intervention; INT 30, 30 minutes into intervention; INT 45, 45 minutes into intervention; PR, Post Resuscitation. * Denotes statistically significant differences following transition between GROA and REBOA.

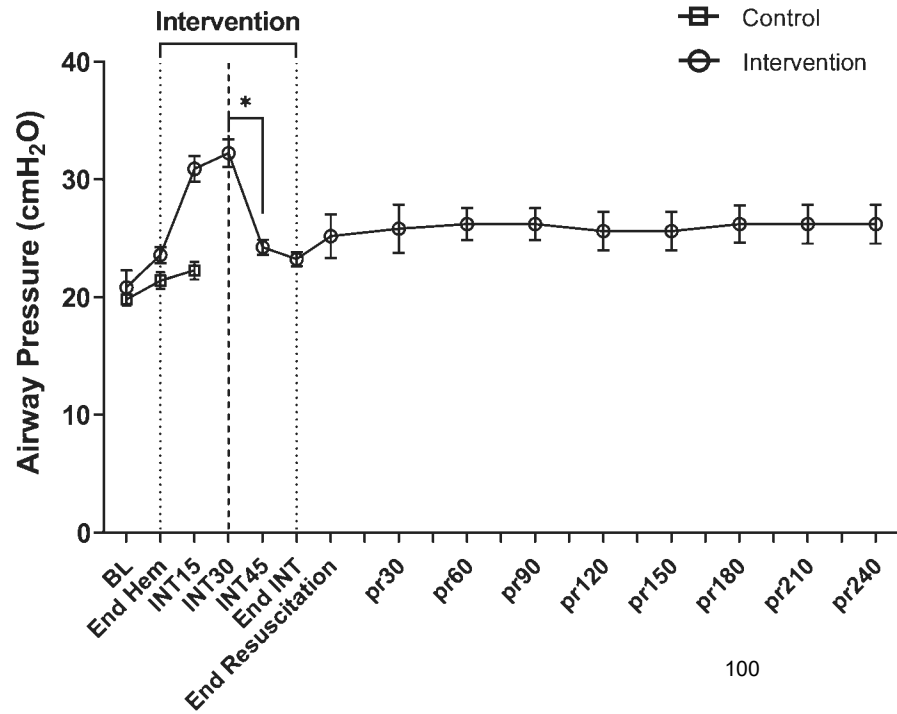
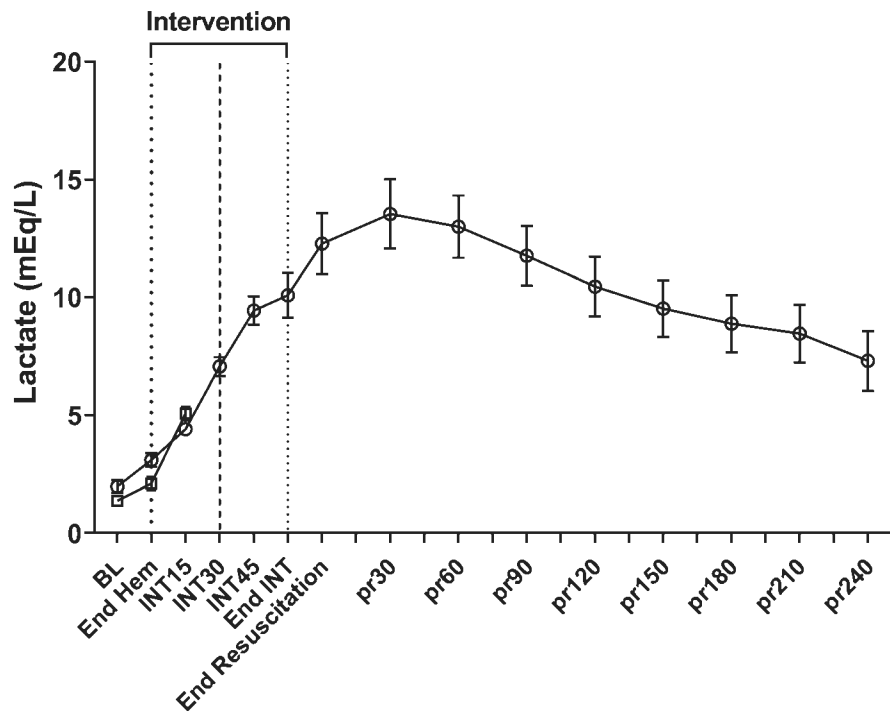
Figure 3. Average and standard error of arterial lactate concentration (Left) and Airway pressure (Right). The area between the dashed lines represents the intervention period. The dotted line represents the time of transition from REBOA to GROA. BL, baseline; End Hem, End of controlled hemorrhage; INT 15, 15 minutes into intervention; INT 30, 30 minutes into intervention; INT 45, 45 minutes into intervention; PR, Post Resuscitation. *Denotes statistically significant differences following transition between GROA and REBOA.

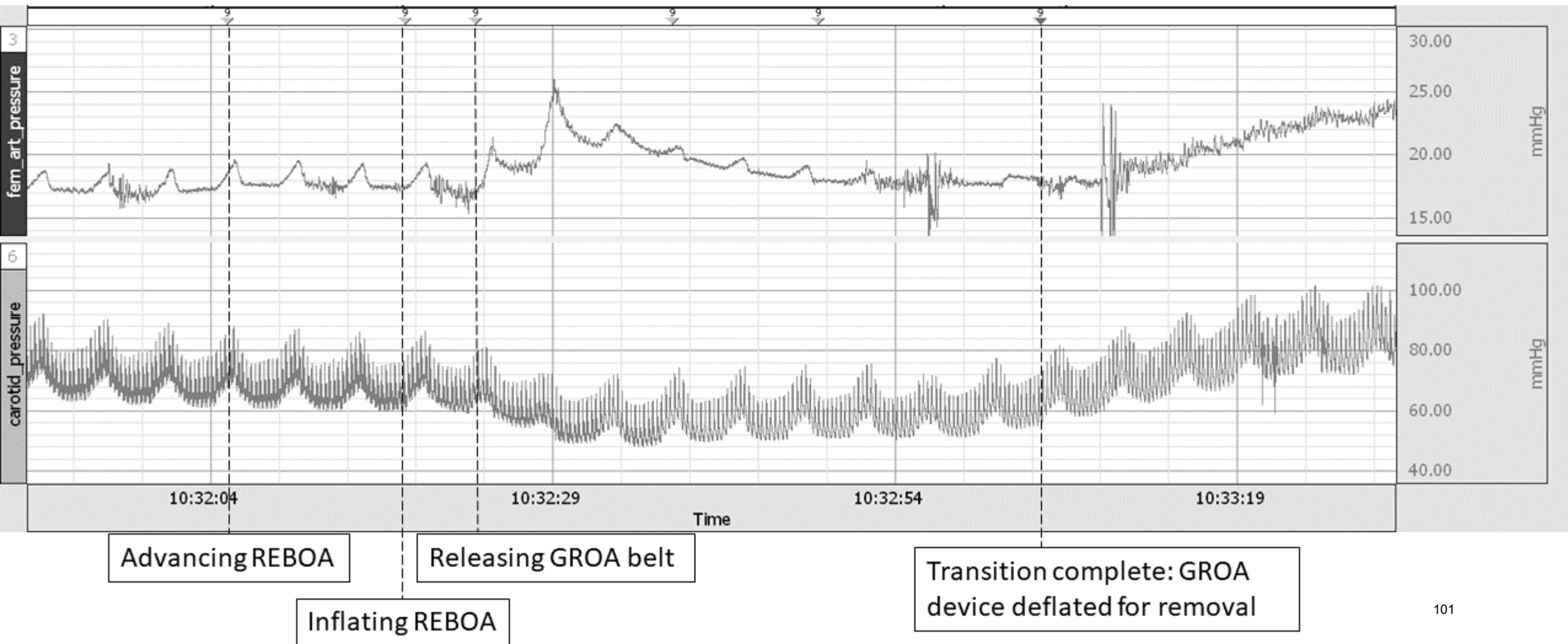
Figure 4. A representative waveform tracing of femoral arterial pressure (top) and carotid artery pressure (bottom) during a transition from aortic occlusion using GROA to REBOA. Of note is there is no return of pulsatility in the femoral artery during the transition, indicating that full aortic occlusion is maintained during the transition between interventions.

Survival time from laceration









Variable	End of GROA	15 minutes of REBOA	Percent Change	<i>p</i>-value
<i>MAP (mmHg)</i>	71 (16)	82.5 (21)	16.3%	0.4372
<i>PAP (mmHg)</i>	22 (3.5)	24 (5.2)	8.5%	0.3892
<i>CVP (mmHg)</i>	9.2 (3.5)	6.7 (1.4)	-27.2%	0.2471
<i>HR (BPM)</i>	155 (55)	157 (34)	1%	0.9960
<i>CO (L/min)</i>	1.5 (0.4)	1.8 (0.6)	18.8%	0.1325
<i>PetCO₂ (mmHg)</i>	18. (3.4)	25 (7.0)	37%	0.0183*
<i>Airway Pressure (cmH₂O)</i>	32 (3.5)	24 (2.0)	-24.8%	0.0001*
<i>PaO₂ (mmHg)</i>	182 (9.6)	188 (25.0)	3%	0.3971
<i>SmvO₂ (%)</i>	59.1 (16.4)	65.1 (21.2)	10.1%	0.2586
<i>VO₂ (mL/kg/min)</i>	4.7 (2.8)	4.11 (1.5)	-12.8%	0.6454

Data are presented as averages (SD). Statistical significance was set at $\alpha=0.05$. * Denotes statistically significant difference. MAP, Mean Arterial Pressure; PAP, Pulmonary Artery Pressure; CVP, Central Venous Pressure; HR, Heart Rate; BPM, Beats Per Minute; CO, Cardiac Output; PetCO₂, Pressure of End-Tidal CO₂; PO₂, Partial pressure of arterial oxygen; SmvO₂, Mixed venous oxygen saturation; VO₂, Oxygen consumption.

Table 2. Thromboelastography (TEG), Hematology (CBC), and Chemistry metrics reported by group and experimental timepoint.

		Control (n=10)	Intervention (n=9)
<u>TEG</u>			
R (min)	Baseline	9.81(4.463)	9.02(3.500)
	Int 45	-	8.07(3.602)
	End Res	-	10.14(5.056)
	End Exp	-	10.00(3.701)
K (min)	Baseline	2.67(1.340)	2.33(0.989)
	Int 45	-	2.02(0.781)
	End Res	-	4.00(2.884)
	End Exp	-	3.40(2.093)
MA (mm)	Baseline	71.54(4.581)	70.6(9.242)
	Int 45	-	71.9(3.399)
	End Res	-	64.5(4.494)
	End Exp	-	64.9(8.454)
TMA (min)	Baseline	30.01(10.56)	27.02(6.709)
	Int 45	-	25.22(6.563)
	End Res	-	34.10(12.06)
	End Exp	-	31.36(9.458)
CI	Baseline	3.15(1.329)	3.04(1.390)
	Int 45	-	3.44(0.598)
	End Res	-	2.07(1.438)
	End Exp	-	2.08(1.902)
<u>CBC</u>			
WBC (10⁹/L)	Baseline	13.97(3.716)	14.29(3.599)
	Int 45	-	14.95(3.116)
	End Res	-	13.38(3.201)
	End Exp	-	16.30(6.601)
Neu (10⁹/L)	Baseline	4.12(1.982)	4.64(2.166)
	Int 45	-	4.90(1.920)

	End Res	-	3.65(1.795)
	End Exp	-	11.48(6.852)
RBC (10¹²/L)	Baseline	6.56(0.696)	6.34(0.705)
	Int 45	-	6.96(0.746)
	End Res	-	6.77(1.116)
	End Exp	-	7.65(1.121)
Hgb (g/dL)	Baseline	9.68(1.067)	9.56(0.965)
	Int 45	-	10.54(1.080)
	End Res	-	10.08(1.403)
	End Exp	-	11.50(1.663)*
PLT (10⁹/L)	Baseline	315.20(66.82)	290.4(69.05)
	Int 45	-	240.6(69.80)
	End Res	-	194.0(50.25)
	End Exp	-	233.4(59.62)

Chemistry

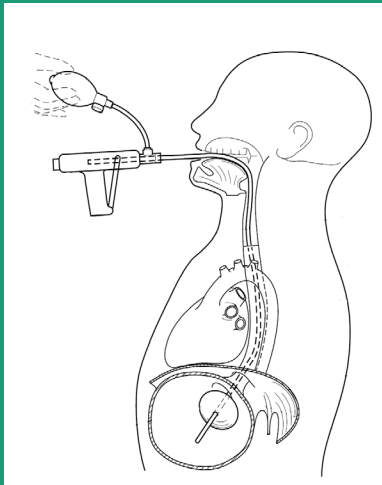
ALP (u/L)	Baseline	116.40(30.01)	104.8(38.80)
	Int 45	-	-
	End Res	-	-
	End Exp	-	148.0(63.73)*
ALT (u/L)	Baseline	45.00(13.08)	35.40(5.505)
	Int 45	-	-
	End Res	-	-
	End Exp	-	69.40(18.37)*
TBIL (mg/dL)	Baseline	0.25(0.053)	0.20(0.000)
	Int 45	-	-
	End Res	-	-
	End Exp	-	0.24(0.055)
CRE (mg/dL)	Baseline	1.24(0.190)	1.38(0.239)
	Int 45	-	-
	End Res	-	-
	End Exp	-	2.38(0.476)*

	Baseline	93.90(20.12)	96.4(26.64)
<i>GLU</i>	Int 45	-	-
<i>(mg/dL)</i>	End Res	-	-
	End Exp	-	52.6(13.28)

Data are presented as averages (SD). Statistical significance was set at $\alpha=0.05$. * Denotes statistically significant difference from baseline. WBC, White Blood Cell; Neu, Neutrophil; RBC, Red Blood Cell; Hgb, Hemoglobin; PLT, Platelet; ALP, Alkaline phosphatase; ALT, alanine aminotransferase; TBIL, total bilirubin; CRE, creatinine; GLU, Glucose; Int 45, 45 minutes of intervention; End Res, End of Resuscitation; End Exp, End of Experiment.

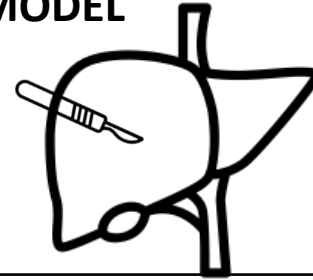
Tandem use of Gastroesophageal Resuscitative Occlusion of the Aorta followed by REBOA in a Lethal Liver Laceration Model

- GROA allows for aortic occlusion and *may prolong survival* from lethal Non-Compressible Hemorrhage.
- *Tandem application of REBOA after GROA* may be possible while *demonstrating a survival benefit* relative to controls.



PORCINE INJURY MODEL

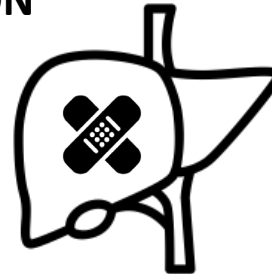
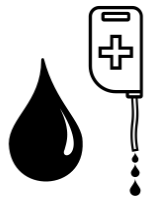
30% arterial hemorrhage
Grade-V liver laceration



INTERVENTION: 30-minutes of GROA transitioning to 30-minutes of REBOA. **Control** ($n=10$) **Treatment** ($n=9$)



RESUSCITATION



RESULTS:

- All transitions from GROA to REBOA were successful.
- No significant changes in hemodynamics.
- Significant survival benefit.

Survived % Survival

Control

1/10

10%

Treatment

9/9

100%

Conclusion: GROA transition to REBOA may be feasible and is effective at temporarily stanching lethal abdominal hemorrhage and prolonging survival.

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Gastroesophageal Resuscitative Occlusion of the Aorta (GROA)

Danielle Leander, BS^{1,2}, Brendan McCracken, BS^{1,2}, Jeffery Plott, PhD^{2,3}, Carmen Colmenero, 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}, Hakam Tiba, MD, MS^{1,2}, 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. Non-compressible torso hemorrhage (NCTH) is a challenge in critical care, and may be treated by Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA). However, this technique requires a trained trauma surgeon and is not ideal in a hostile environment. Gastroesophageal Resuscitative Occlusion of the Aorta (GROA) is a novel system to treat NCTH by occluding the aorta through the stomach.

Methods: 6 male swine (GROA $n=4$; REBOA $n=2$) with an average(SD) weight of 51(3.7) kg were used to determine the feasibility of application and removal of the GROA device. The device was placed through the oral cavity passing through the esophagus into the stomach, while an external belt was placed around the abdomen to apply external pressure. GROA or REBOA were applied to occlude the aorta for 60 minutes following a 40% controlled arterial hemorrhage to induce a low pressure hemorrhagic shock. GROA or REBOA were deflated gradually, external pressure released and animals monitored for 60 minutes.

Results: Complete occlusion of the descending aorta was confirmed by loss of femoral arterial pressure and decrease of mean(SD) hepatic artery flow from 131(12) to 0(0) mL/min. GROA application during hemorrhagic shock increased proximal aortic pressure (mean(SD)) from 33(8) to 59(SD 11) mmHg compared to REBOA 29(0) to 65(11) mmHg.

Conclusion: Preliminary results show that GROA improves hemodynamics in swine with hemorrhagic shock similar to the effect REBOA. This study is ongoing to further determine the effects of the device. GROA may be a potential treatment for a fast and effective staunching of NCTH.



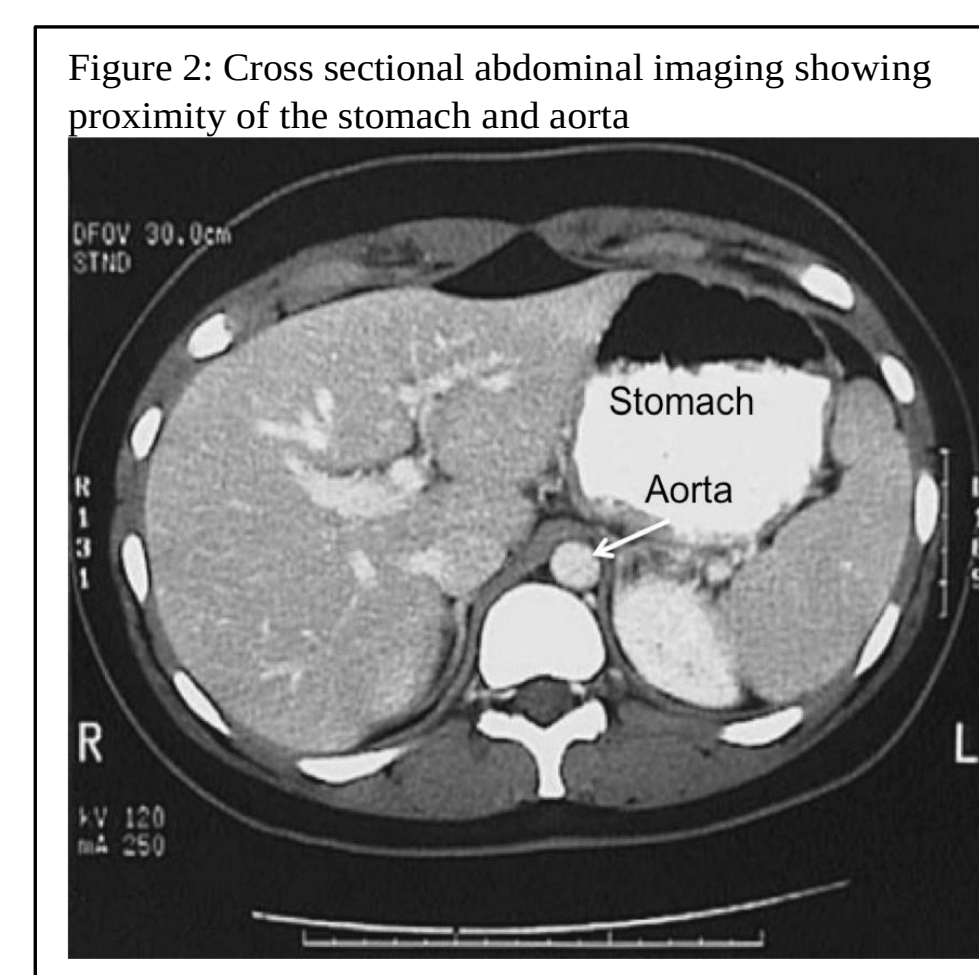
INTRODUCTION

Non-Compressible Torso Hemorrhage (NCTH)

- More than 90% of military casualties and 40% of civilian trauma deaths occur due to NCTH
- Torso and deep pelvic hemorrhage poses a large problem in the pre-hospital and PFC setting
 - Occur about every 9 out of 10 fatal injuries

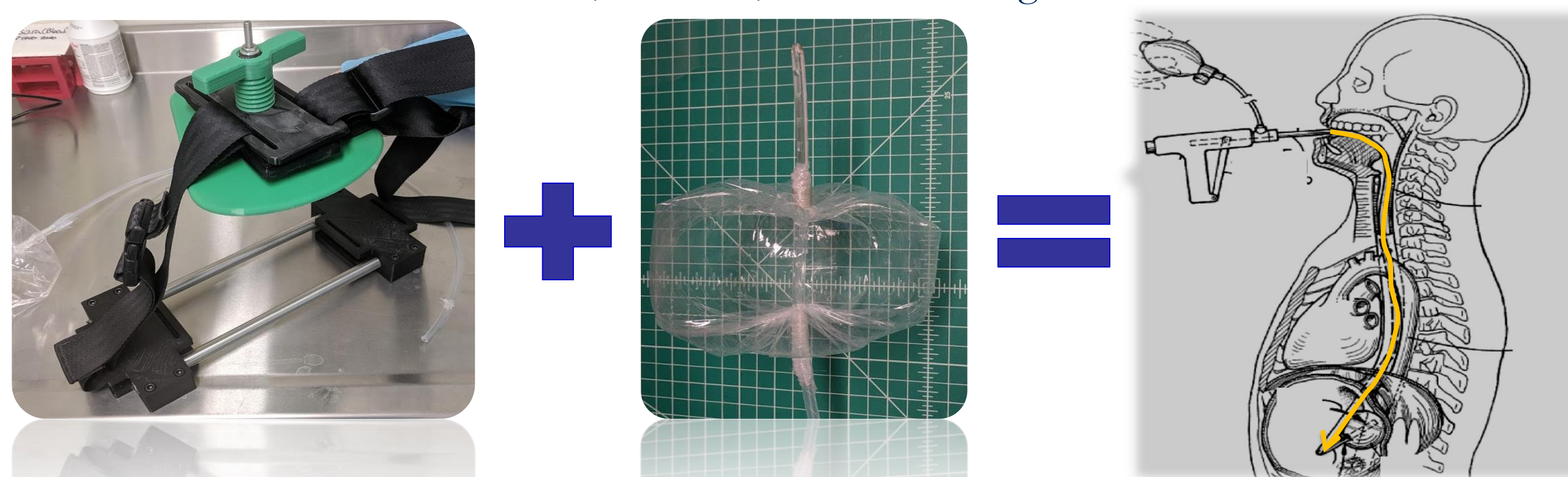
Natural Orifice Transluminal Endoscopic Surgery (NOTES)

- Technique to perform abdominal surgeries with little to no scarring
- Can use this method to occluded the aorta through the oral cavity passing through the esophagus into the lumen of the stomach



Gastroesophageal Occlusion of the Aorta (GROA)

- Bridge between REBOA and using a NOTES technique to temporarily inhibit blood flow to the lower abdomen and lower extremities during NCTH
- Orientation of the abdominal wall, stomach, and descending aorta



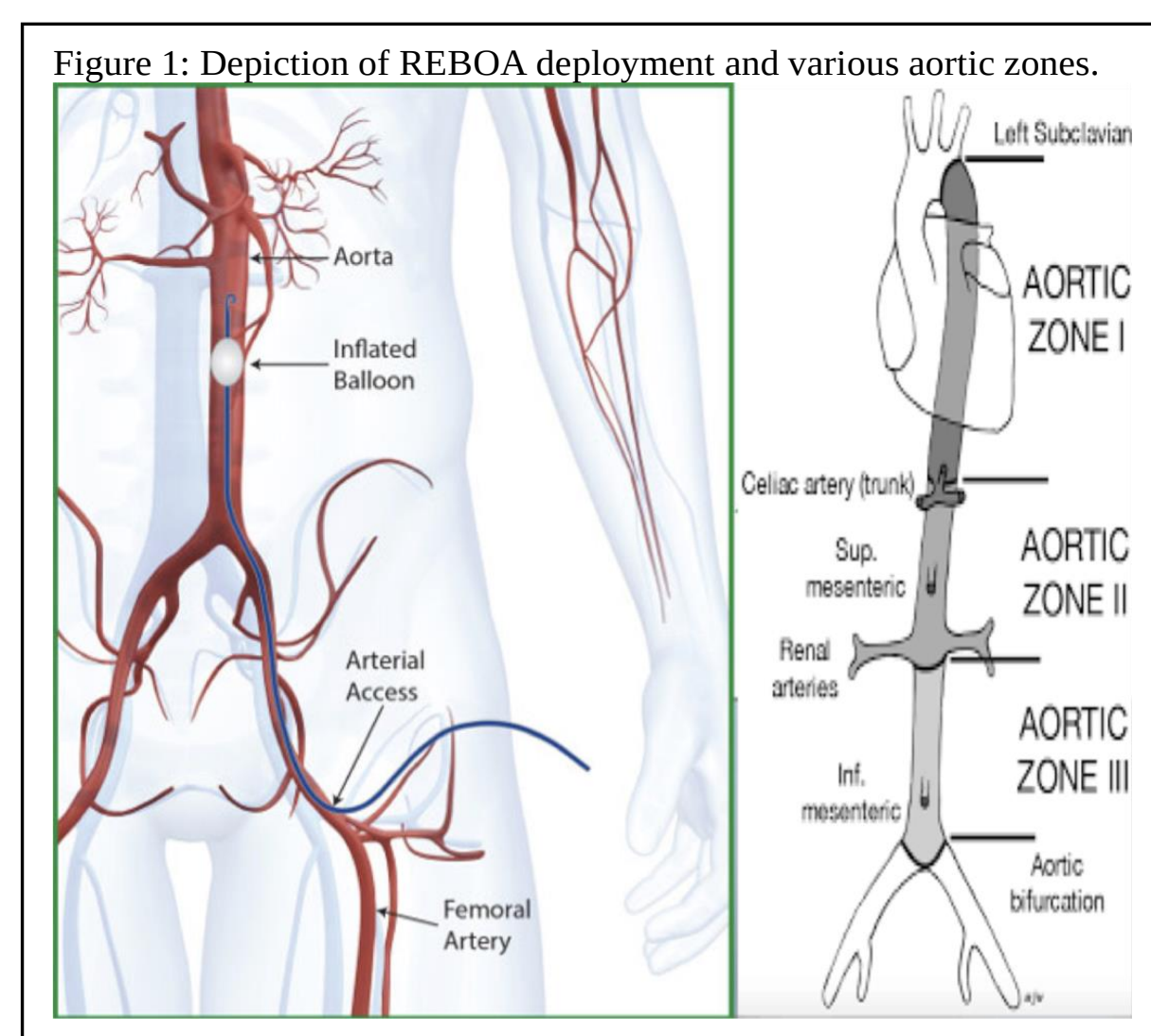
GROA Device

- Pressure Belt
 - External tourniquet to place pressure on abdominal wall for resistance
- Balloon and Catheter
 - 2.5" long flexible tip with a catheter possessing the same properties as a Salem Sump tube (used for stomach pumping)
 - Allows the device to be inserted into the stomach with minimal thrust force

Current Strategies

Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA)

- Effective tool in the treatment of hemorrhage
- 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



AIMS and Hypothesis

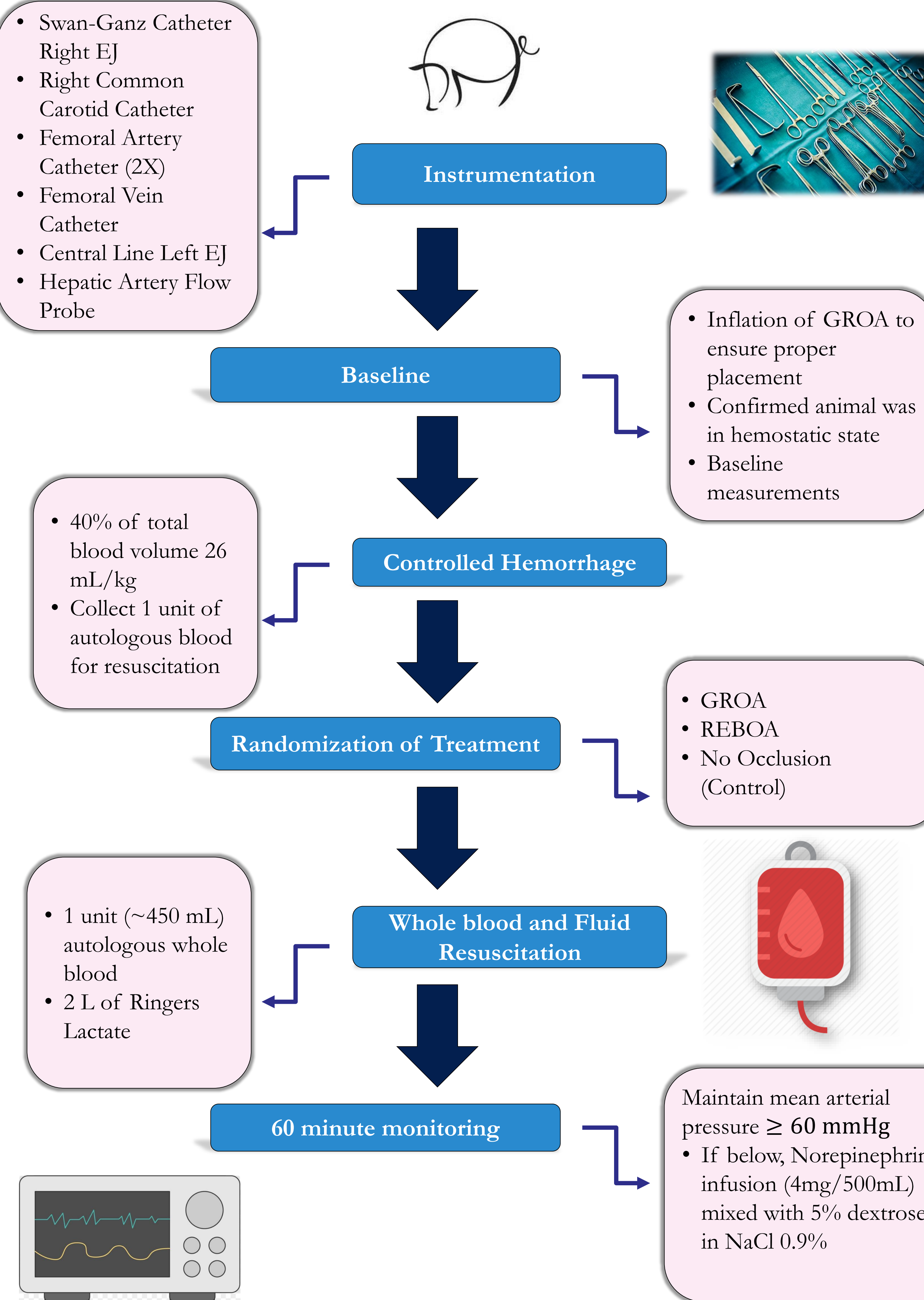
Hypothesis: The anatomical relationship between the esophagus and the stomach to the descending thoracic and abdominal aorta will allow complete mechanical occlusion of the aorta through the stomach that can prolong short-term survival of severe non-compressible abdominal hemorrhage

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



RESULTS

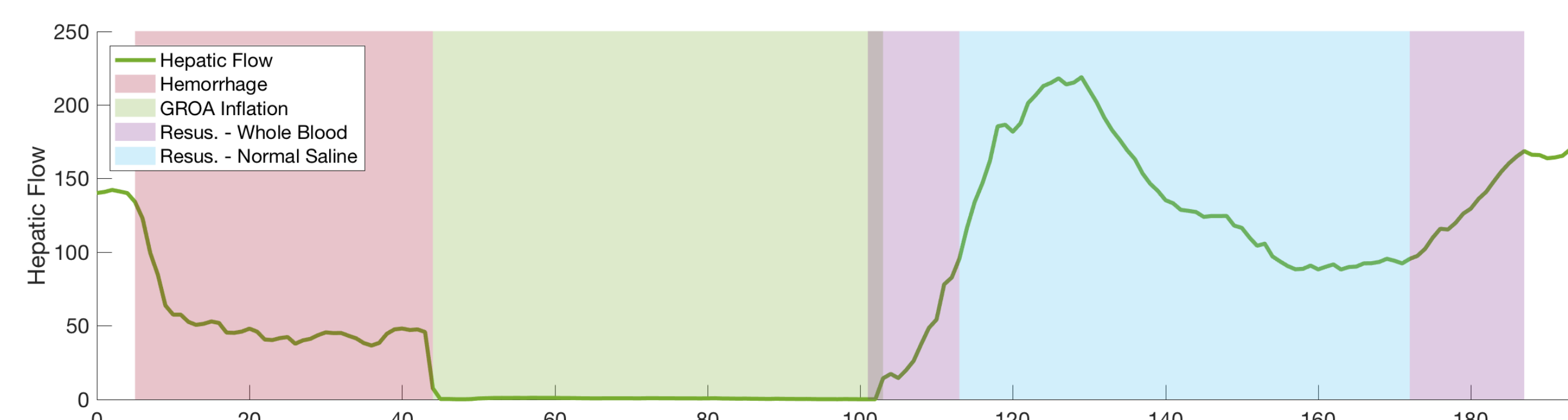
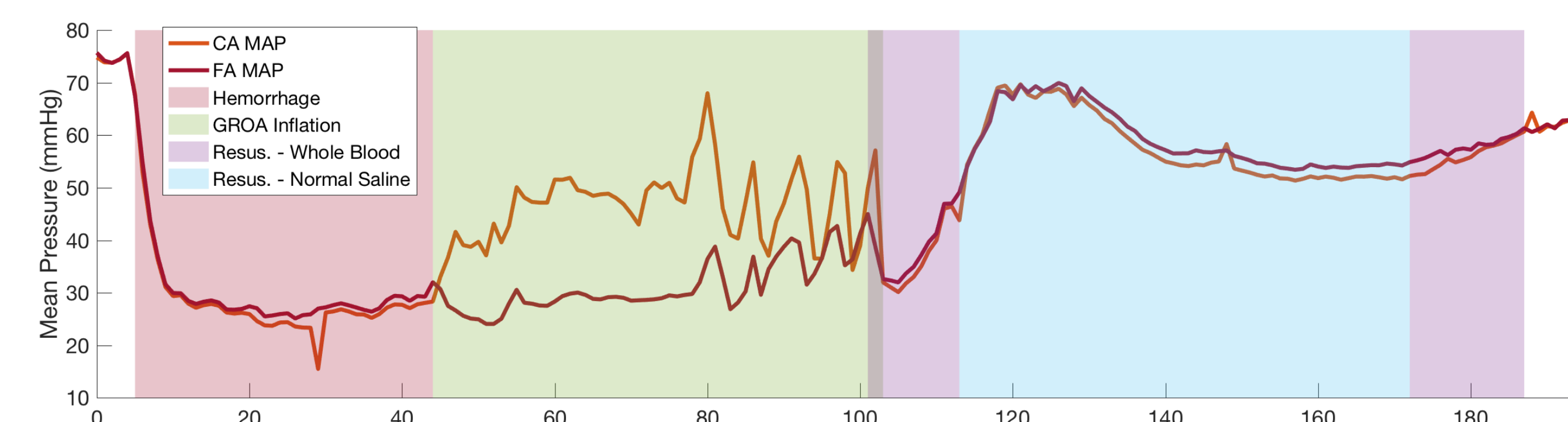


Figure 1.

- Mean carotid artery pressure rises during GROA while femoral pressure decreases
- Hepatic flow goes to 0 mL/min during inflation supporting the idea that the aorta is occluded
- Mean pressures and flow resume to hemostasis following resuscitation and GROA deflation

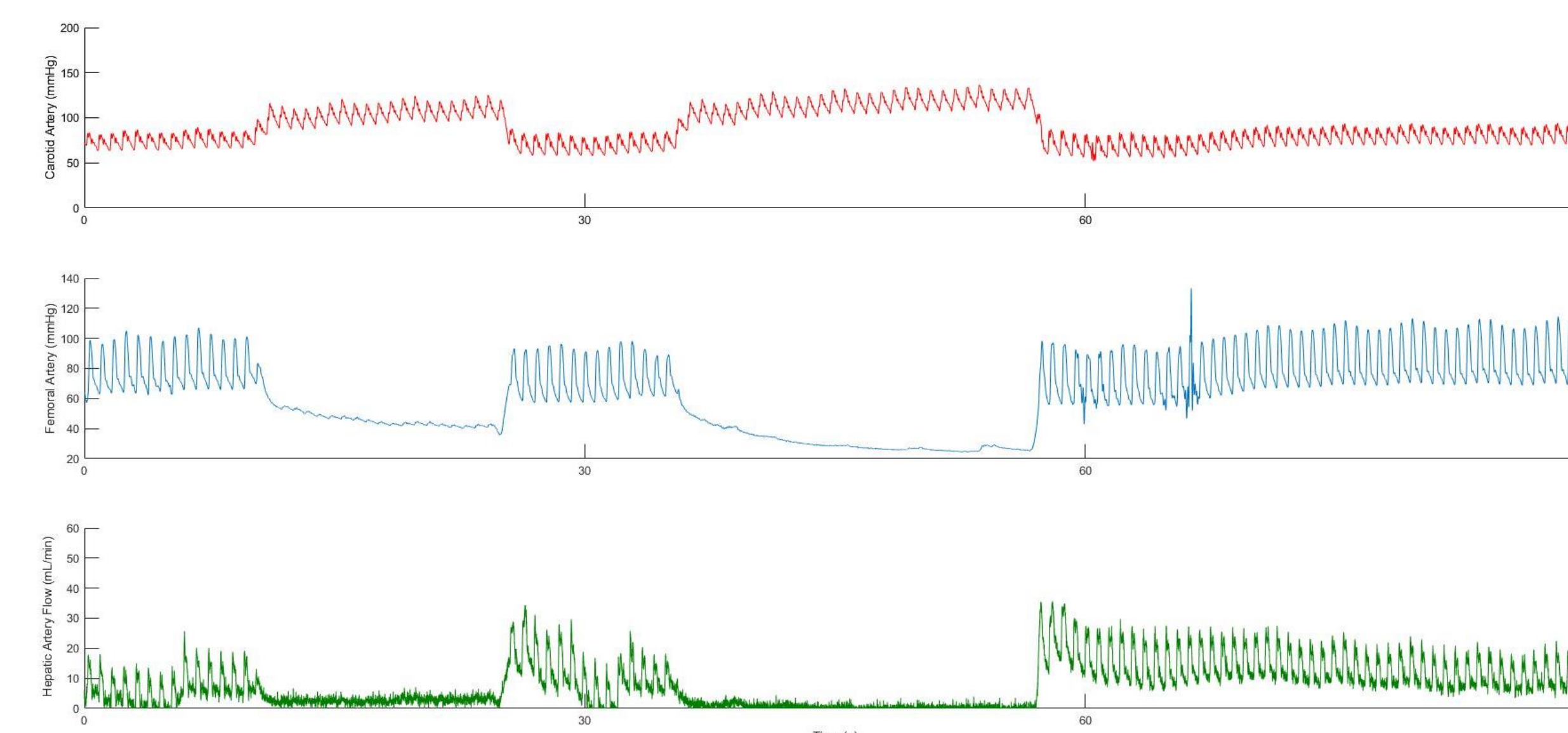


Figure 2.

- Physiological effects of full, partial, and again full occlusion of the aorta during GROA device balloon inflation
- Femoral artery pressure and hepatic flow loses all pulsatility during full occlusion
- The hepatic artery flow reduction indicates the GROA device's ability to be effective for high zone 2 hemorrhage control

CONCLUSION

Preliminary results show that GROA improves hemodynamics in swine with hemorrhagic shock similar to the effect REBOA. This study is ongoing to further determine the effects of the device. GROA may be a potential treatment for a fast and effective staunching of NCTH.

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(0) 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



INTRODUCTION

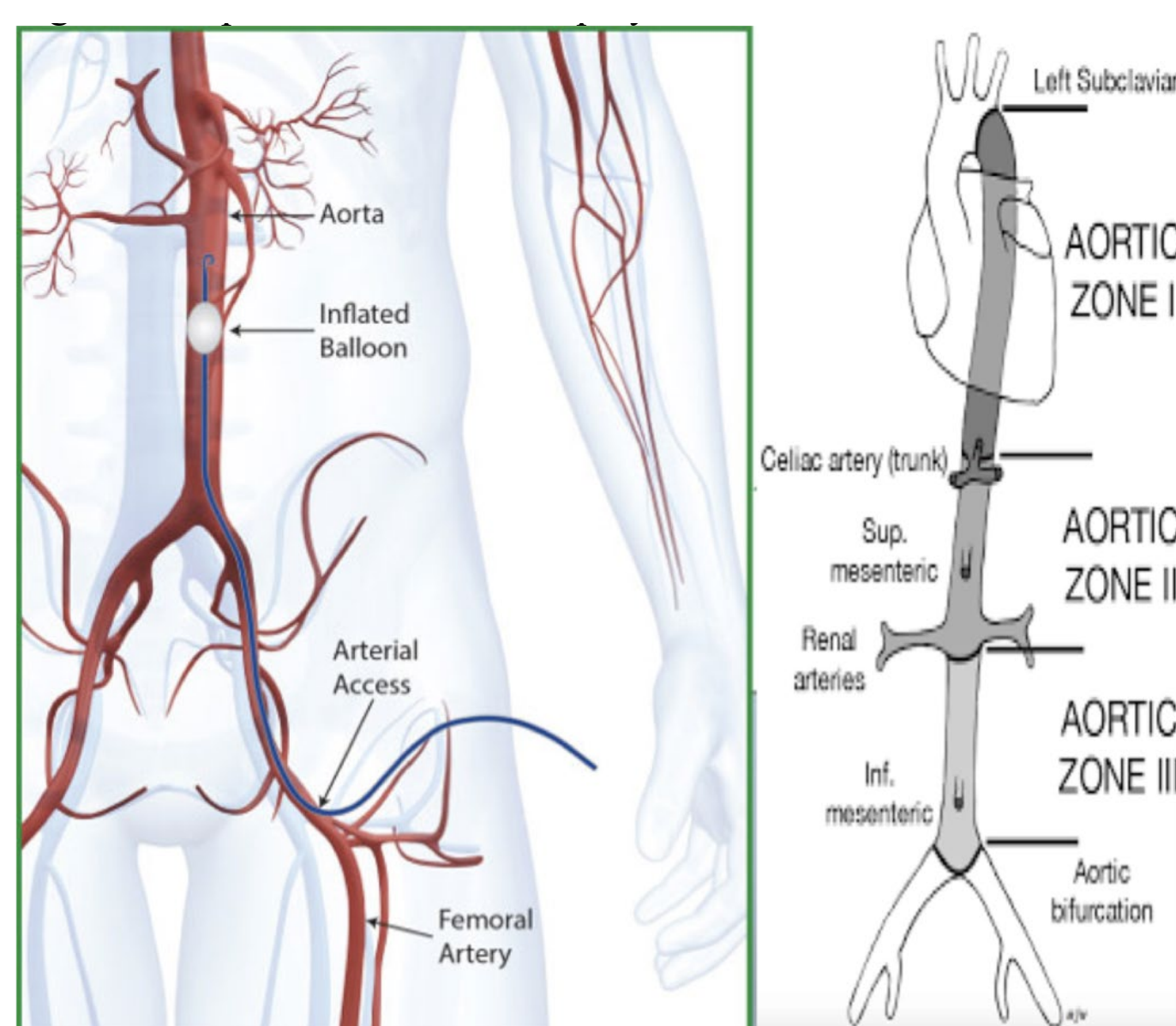
Non-Compressible Torso Hemorrhage (NCTH)

- 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)

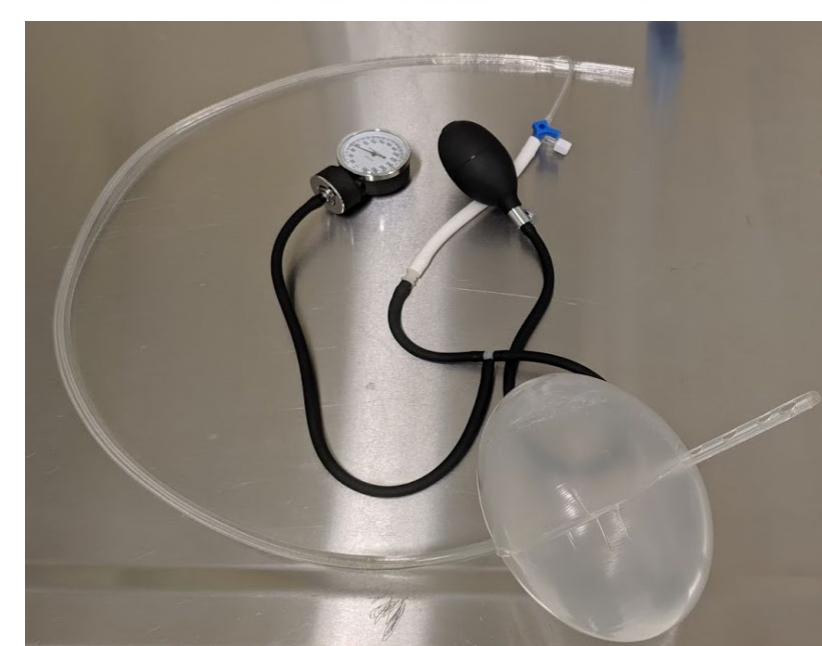
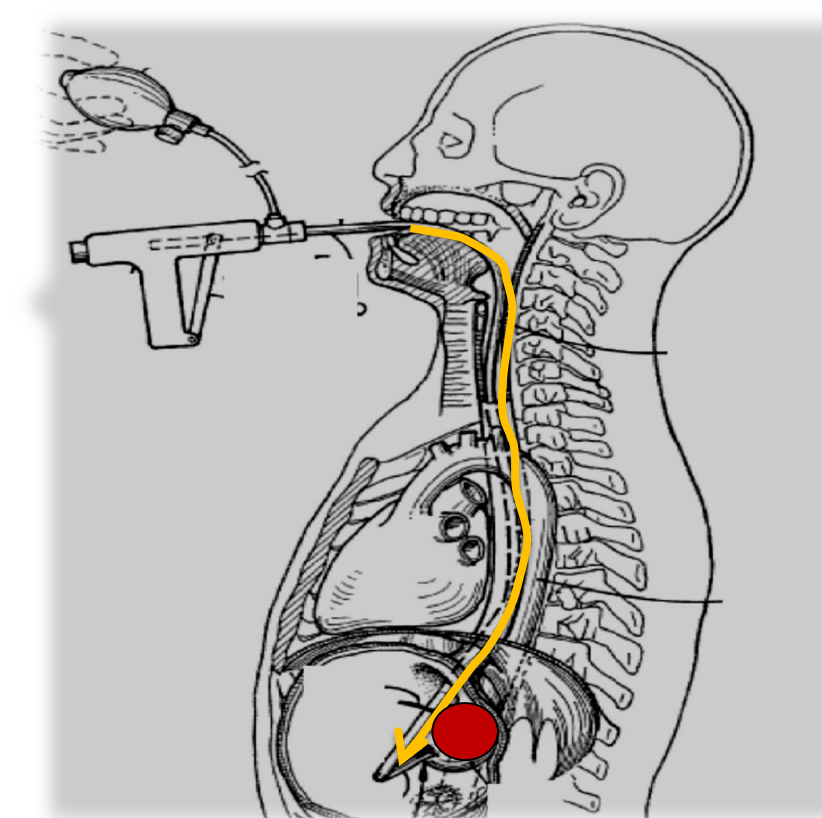
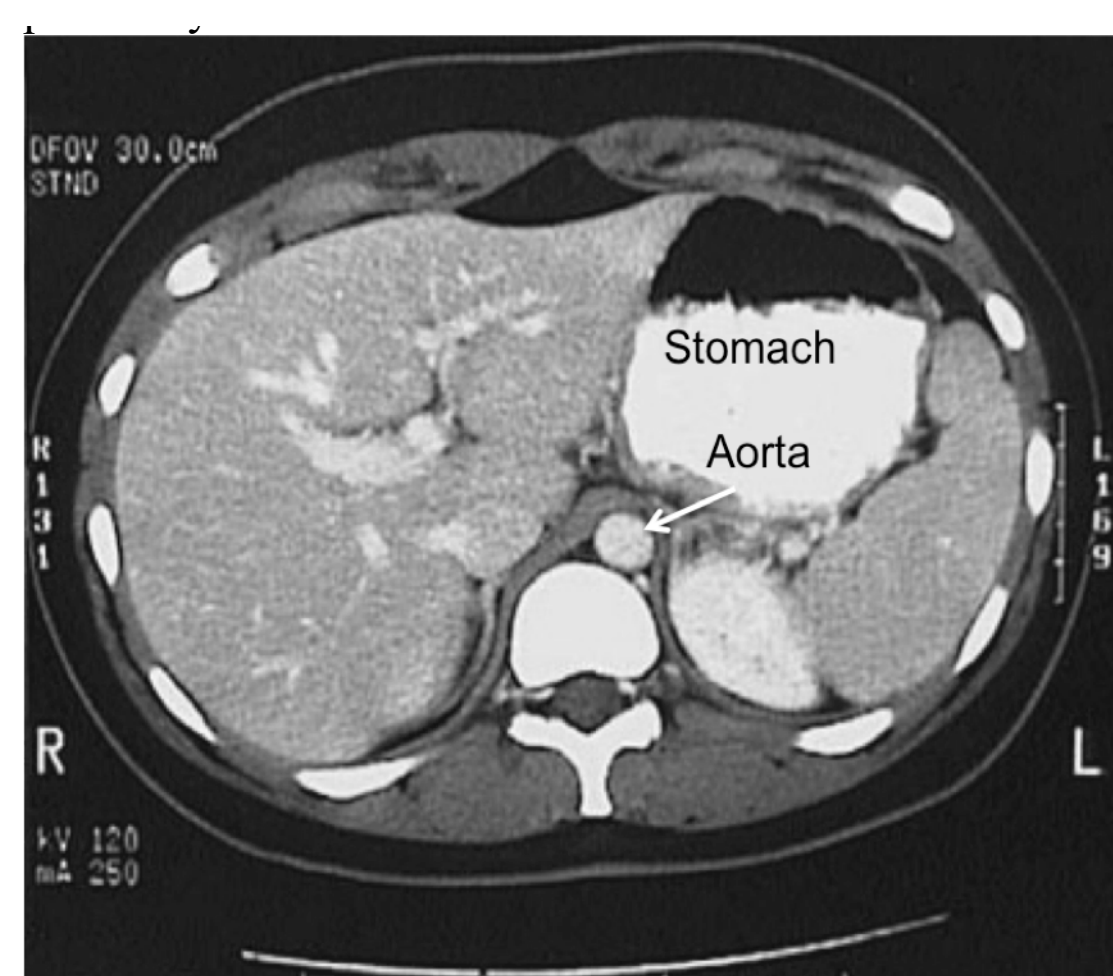
- Approved effective tool for the treatment of NCTH
- Difficult to place in hostile environments
- Zones of placement
 - Zone I: Origin at left subclavian artery to the celiac artery
 - Zone II: Origin at the celiac artery to the renal arteries
 - Zone III: Below the lowest renal artery
- No known field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

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

SPECIFIC AIMS

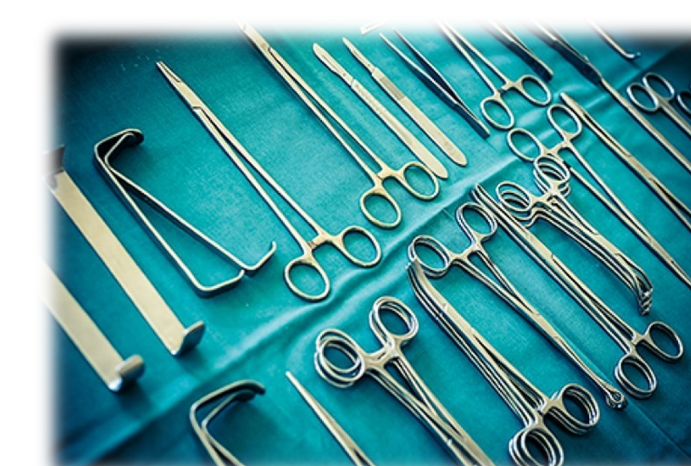
Aim 1: Design prototype GROA device that can be placed via esophagus into the stomach to produce complete occlusion of the aorta at or above the celiac artery.

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

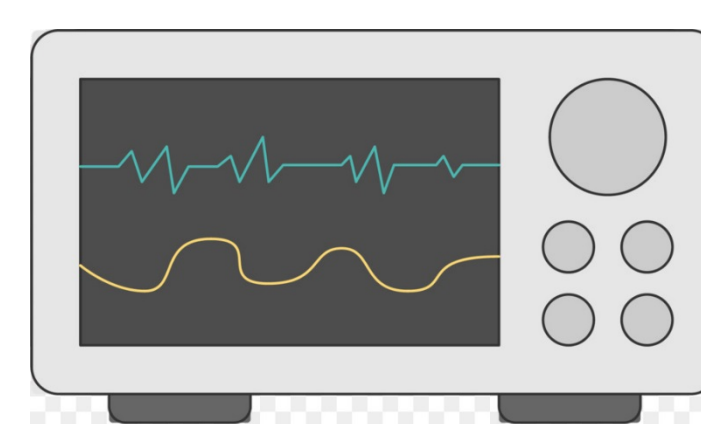
- GROA
- REBOA
- No Occlusion (Control)

Whole blood and Fluid Resuscitation

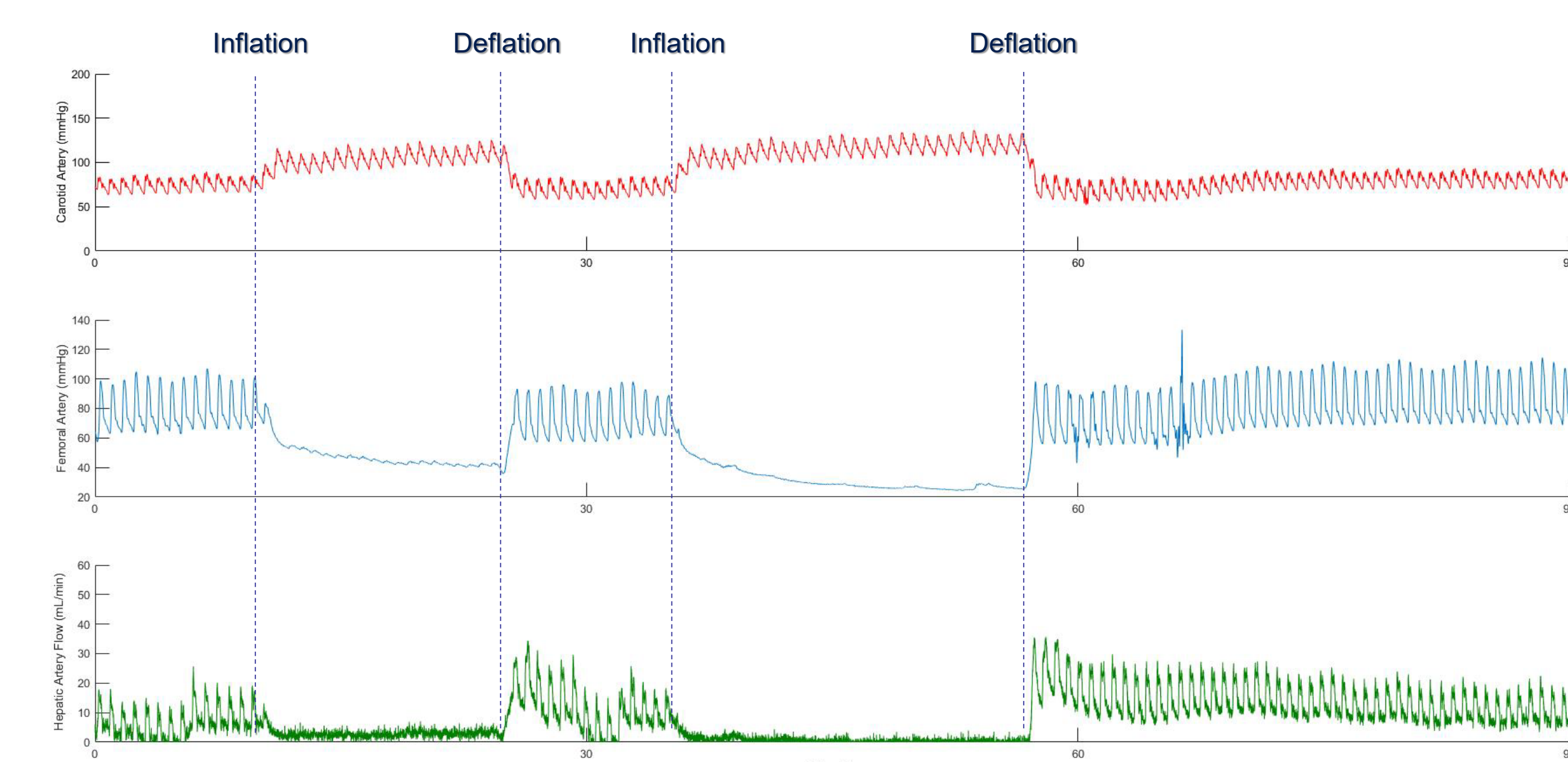
- Whole blood autologous transfusion (2 units)
- Ringer's Lactate Solution

Post Resuscitation Treatment & Monitoring

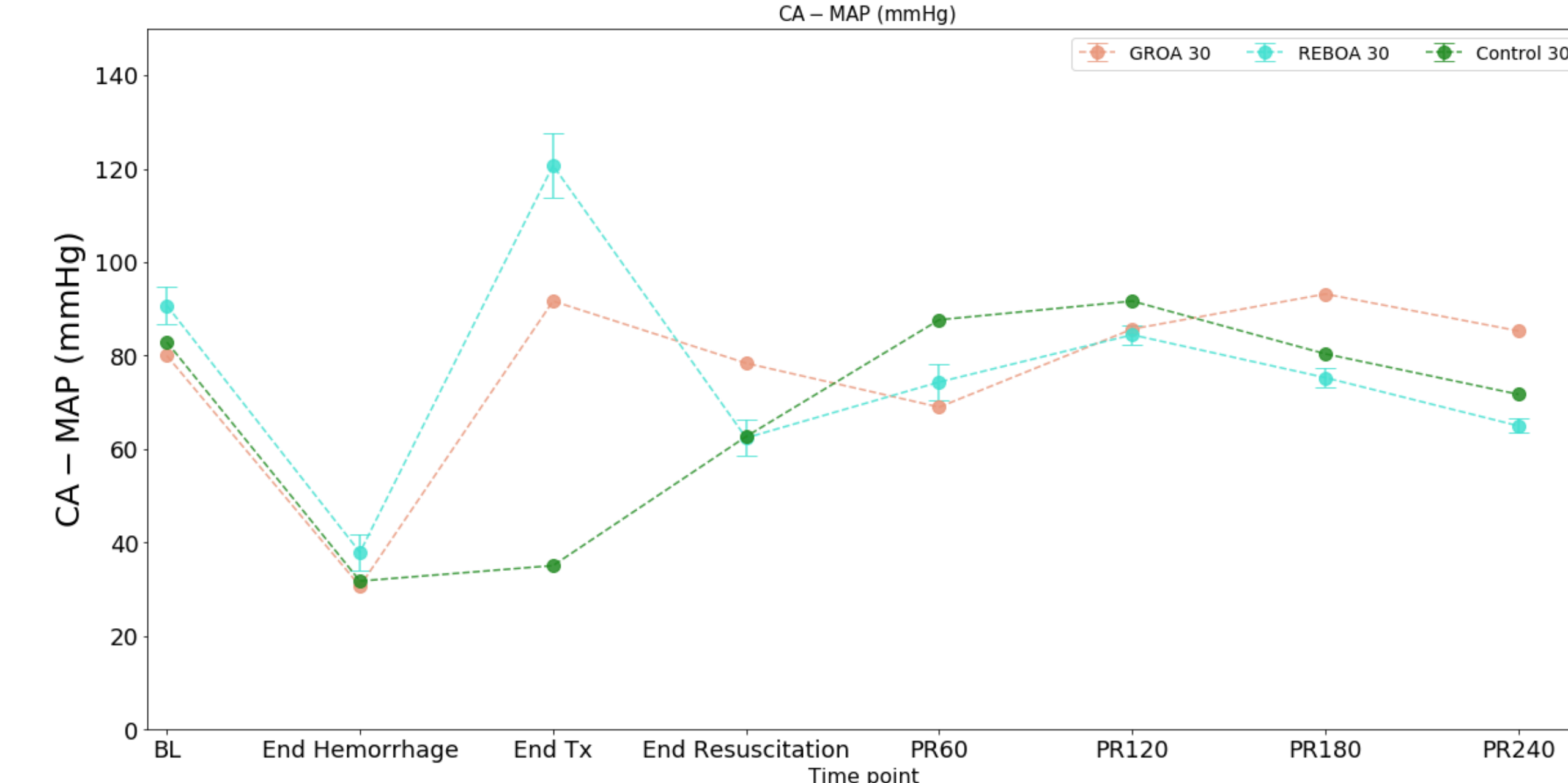
- Maintain mean arterial pressure ≥ 60 mmHg
- Norepinephrine infusion (4mg/500mL) 5% dextrose in NaCl 0.9%



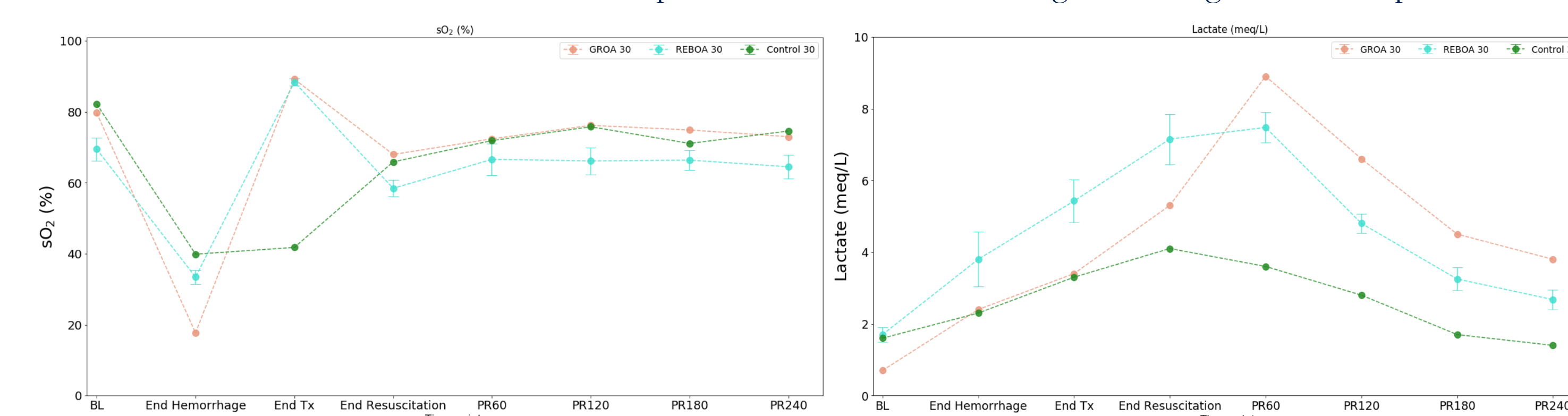
RESULTS



- 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 SvO₂ 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

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

Brendan M. McCracken^{1,2}, Mohamad Hakam Tiba^{1,2}, Carmen I. Colmenero^{1,2}, Jeffery S. Plott^{2,4}, Danielle C. Leander^{1,2}, Nicholas L. Greer^{1,2}, Stewart Wang^{2,3}, Albert Shih^{2,4}, Jonathan Eliason^{2,5}, and Kevin R. Ward^{1,2,3}

1. Emergency Medicine, 2. Michigan Center for Integrative Research in Critical Care (MCIRCC)
3. Biomedical Engineering, 4. Mechanical Engineering 5. Department of Surgery

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

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

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

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

Learning Objective 1: Describe the unmet need for field-deployable and early phase treatment strategies of non-compressible torso hemorrhage.

Learning Objective 2: Discuss the concept of aortic occlusion as a treatment strategy for non-compressible torso hemorrhage, and current strategies of aortic occlusion such as REBOA and surgical hemostasis.

Learning Objective 3: Analyze the physiological tolerance of gastroesophageal resuscitative occlusion of the aorta (GROA) compared to REBOA as treatment strategy for non-compressible torso hemorrhage.

Gastroesophageal Occlusion of the Aorta (GROA) is effective at stanching hemorrhage and prolonging survival in a swine model of lethal non-compressible abdominal hemorrhage.

Brendan M. McCracken^{1,2}, Mohamad Hakam Tiba^{1,2}, Carmen I. Colmenero^{1,2}, Jeffery S. Plott^{2,4}, Danielle C. Leander^{1,2}, Nicholas L. Greer^{1,2}, Stewart Wang^{2,3}, Albert J. Shih^{2,4}, Jonathan Eliason^{2,5}, and Kevin R. Ward^{1,2,3}

1. Emergency Medicine, 2. Michigan Center for Integrative Research in Critical Care (MCIRCC)
3. Biomedical Engineering, 4. Mechanical Engineering 5. Department of Surgery

Introduction: The pre-hospital environment is where most mortality occurs from traumatic hemorrhage continues to be the leading cause of preventable death due to trauma. Resuscitative endovascular occlusion of the aorta (REBOA) has proven to be an effective counter measure against non-compressible torso hemorrhage, however this technique is limited in its application outside of trauma centers or in the pre-hospital environment. Gastroesophageal Resuscitative Occlusion of the Aorta (GROA) is an emerging technique which has been shown to be both feasible and physiologically tolerable as an alternative to REBOA which may be more suitable for pre-hospital application. In this study, we aimed to determine if GROA is capable of temporarily stopping hemorrhage and prolonging survival in a swine model of lethal abdominal injury and compare it to REBOA and controls. We hypothesized GROA would prolong survival similar to REBOA when compared to controls.

Methods: Male Yorkshire mix swine (n=24) were anesthetized and surgically instrumented for data collection. A 30% controlled arterial hemorrhage was performed followed by a severe liver laceration. Animals were assigned to either GROA, REBOA, or control intervention groups for a period of 60-minutes. Upon completion of the intervention period, occlusion devices were deactivated, surgical repair of the injury was attempted while autologous whole blood and crystalloid fluid resuscitation was initiated. Surviving animals were monitored for up to four hours while data were collected. Animals were euthanized at the end of the monitoring period.

Results: GROA and REBOA animals experienced a significant improvement in survival compared to controls p=0.01. 7/8 Control animals died from injury prior to the end of the intervention period with a median survival time of 10.5 minutes. All GROA and REBOA animals survived the duration of the intervention period with median survival times following resuscitation of 86 and 88 minutes respectively due to renewed hemorrhage. Post-mortem histological examination of the gastric mucosa revealed mild inflammation in the GROA group.

Conclusion: The observed data suggests GROA was effective at temporarily stanching lethal abdominal hemorrhage and prolonging survival in a model of lethal non-compressible abdominal hemorrhage, similar to REBOA. The survival benefit and simple application technique of GROA indicates a high probability of success for pre-hospital aortic impingement.

Gastroesophageal Resuscitative Occlusion of the Aorta (GROA): Tandem use with REBOA for treatment of lethal abdominal hemorrhage.

Brendan M. McCracken^{1,2}, Mohamad Hakam Tiba^{1,2}, Nicholas L. Greer^{1,2}, Traci A. Cramer^{1,2}, Carmen I. Colmenero^{1,2}, Ketut B. Priambada Putra⁴, Albert J. Shih^{2,3,4}, Kevin R. Ward^{1,2,3}

1. Department of Emergency Medicine, University of Michigan, Ann Arbor, Michigan

2. The Max Harry Weil Institute for Critical Care Research and Innovation, University of Michigan, Ann Arbor, Michigan

3. Department of Biomedical Engineering, University of Michigan, Ann Arbor, Michigan

4. Department of Mechanical Engineering, University of Michigan, Ann Arbor, Michigan

Introduction: The majority of mortality events from *potentially survivable* injuries from non-compressible torso hemorrhage (NCTH) occur in the austere or pre-hospital environments. Gastroesophageal Resuscitative Occlusion of the Aorta (GROA) is an emerging technique potentially suitable for the pre-hospital treatment of NCTH. In initial pre-clinical trials, GROA has been shown to be both effective at stanching lethal abdominal hemorrhage, and physiologically tolerable for at least 60 minutes when compared to resuscitative endovascular occlusion of the aorta (REBOA). However, logistical barriers might exist to its immediate implementation of REBOA at the point of injury which might delay management of NCTH.

In this study we evaluate GROA's ability to serve as a *field-bridge* by demonstrating the feasibility of transitioning from GROA to REBOA in a swine model of rapidly lethal abdominal hemorrhage.

Methods: Twenty-one Yorkshire mix swine were anesthetized and instrumented for data collection. A controlled arterial hemorrhage was performed removing 30% of the total blood volume (approximately 20ml/kg), followed by a grade-V liver laceration. Animals were assigned to intervention groups which included 30 minutes of GROA transitioning to 30 minutes of REBOA (n=9), 60 minutes of GROA transitioning to 30 minutes of REBOA (n=2), or control (n=10) which received no intervention. Following the intervention period, surgical hemostasis was attempted while the devices were removed and shed blood with crystalloid resuscitation was initiated. Animals which survived were monitored for up to an additional 4-hours. All animals were euthanized at the end of the monitoring period, or when predetermined experimental endpoints were met.

Results: Data are presented as mean (SD) or median (interquartile). The model was rapidly lethal, and nine out of ten control animals reached exsanguination endpoints with a median survival time of 8.5 minutes (9.25 minutes) after injury. The transition from GROA to REBOA was successful in all animals receiving the intervention without loss of aortic occlusion. All animals receiving GROA transitioning to REBOA survived both the 60 and 90-minute intervention periods. The average time of transition from GROA to REBOA was 63.2 seconds (18.8 seconds) once cannulation and placement of REBOA was achieved. Hemodynamics and oxygenation metrics remained stable or improved following the transition. Animals receiving the interventions showed a significant improvement in survival compared to controls $p=0.0007$. Histopathological findings from the post-mortem tissues of intervention animals ranged from no findings to mild inflammation of the superficial gastric mucosa.

Conclusion: This study demonstrates a highly successful in-vivo transition from GROA to REBOA while maintaining aortic occlusion. The tandem interventions resulted in the rapid stabilization and improvement in hemodynamics and a significant improvement in survival relative to controls. The simple and plausible pre-hospital application of GROA suggests that GROA may be feasibly used as a field-bridge when more advanced techniques of hemostasis such as REBOA, interventional radiology, or definitive surgical repair are yet unavailable.

Disclaimer: This study is supported by a Department of Defense grant award W81XWH-18-1-0033. A patent application was submitted on 8/18/20 and assigned a United States Patent number # PCT/US2020/046796. GROA Technology is under license to Precision Trauma, LLC.

Learning Objective 1: Describe the unmet need for field-deployable and early phase treatment strategies of non-compressible torso hemorrhage.

Learning Objective 2: Discuss the concept of aortic occlusion as a treatment strategy for non-compressible torso hemorrhage, and compare current strategies of aortic occlusion including GROA, REBOA, and surgical hemostasis.

Learning Objective 3: Discuss the feasibility of transitioning from GROA to REBOA and analyze the physiological response of the tandem use of GROA to REBOA and the subsequent survival benefit relative to controls.



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(71) Applicant: **THE REGENTS OF THE UNIVERSITY OF MICHIGAN** [US/US]; Office of Technology Transfer, 1600 Huron Parkway, 2nd Floor, Ann Arbor, MI 48109-2590 (US).

(72) Inventors: **WARD, Kevin**; 6730 Fleming Creek Dr., Superior Twp., MI 48198 (US). **PLOTT, Jeffrey Stephen**; 7308 Aqua Isle Dr., Algonac, MI 48001 (US).

(74) Agent: **CHINLUND, Michael A.**; Marshall, Gerstein & Borun LLP, 233 S. Wacker Drive, 6300 Willis Tower, Chicago, IL 60606-6357 (US).

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(54) Title: GASTROESOPHAGEAL AORTIC OCCLUSION DEVICE AND METHOD

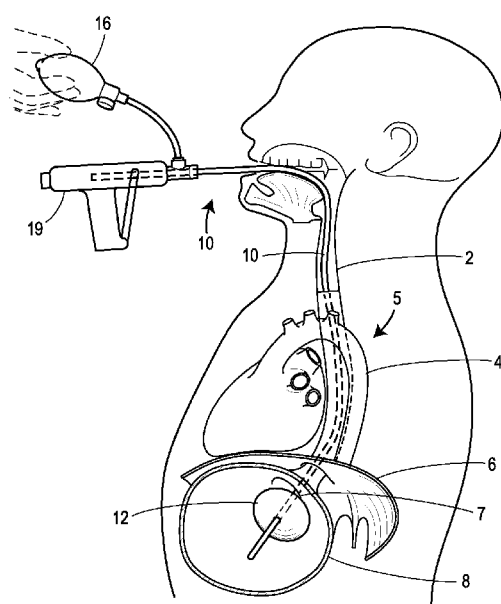


FIG. 1

(57) Abstract: A device and method for occluding the descending aorta includes inserting a gastroesophageal resuscitative aortic occlusion device into a stomach of a patient through the esophagus. The gastroesophageal resuscitative aortic occlusion device includes a catheter having a body and a first lumen, and a distal end having a first opening fluidly coupled to the first lumen. An inflatable balloon is disposed on the catheter. An interior of the inflatable balloon is fluidly coupled to the first opening. An inflation device is operably connected to the catheter and fluidly coupled to the first lumen. Activation of the inflation device forces fluid into the interior of the inflatable balloon through the first lumen and the first opening. Activating the inflation device to pressurizes the inflatable balloon with a fluid. An external pressure device applies pressure to the abdomen of the patient until blood flow through the descending aorta is reduced or stopped.

GASTROESOPHAGEAL AORTIC OCCLUSION DEVICE AND METHOD FIELD OF THE DISCLOSURE

[0001] The present disclosure relates to arterial hemorrhage occlusion devices and methods and more particularly to gastroesophageal aortic occlusion devices and methods.

BACKGROUND

[0002] Hemorrhagic shock is a leading cause of death from trauma. Many times there are delays in reaching hospitals which are qualified to take care of the complex injuries of such individuals. Many patients who die of trauma, die from multi-system involvement. Multi-system involvement may include head injury along with injuries to organs of the thoracic and abdominal cavity. Uncontrolled hemorrhage leading to hypovolemic shock is a leading cause of death from trauma especially from blunt and penetrating trauma of the abdomen. When head trauma occurs concomitantly with thoracic and abdominal hemorrhage, the brain becomes hypoperfused and, thus, becomes at greater risk for secondary injury. Currently, in the pre-hospital and emergency department setting, there are limited means to control exsanguinating hemorrhage below the diaphragm while maintaining myocardial and cerebral blood flow. Definitive control of hemorrhage is performed at surgery but this may be delayed and may not occur within the golden hour (time from injury to definitive treatment/repair) where the best opportunity lies in salvaging the patient. Survival with improved neurologic outcome might be enhanced if means were available to slow or stop ongoing hemorrhage (especially below the diaphragm) while maintaining adequate perfusion to the heart and brain until definitive treatment of the hemorrhage is available. This would be especially true of trauma victims whose transport to appropriate medical facilities would be prolonged.

[0003] One method of slowing or stopping hemorrhage is the use of a pneumatic anti-shock garment (PASG). Use of the PASG has met with varying degrees of success depending on the location of injury. This garment is placed on the legs and abdomen and is then inflated. Hemorrhage in the abdominal cavity, as well as the lower extremities, is controlled through tamponade while systemic blood pressure is raised partially through autotransfusion and by raising peripheral vascular resistance. Use of the PASG can sometimes be cumbersome and does not uniformly control hemorrhage or raise blood pressure. In addition, persons with concomitant penetrating thoracic injuries may hemorrhage more when the device is applied. The device may also raise intracranial pressure, which might detrimentally alter cerebral blood flow resulting in neurologic injury.

[0004] Other more drastic means to control abdominal bleeding prior to surgery have been the use of thoracotomy to cross-clamp the thoracic aorta and the use of balloon catheters placed into the aorta from the femoral arteries to a point above the celiac-aortic axis. These techniques have met with varying degrees of success and require a high degree of skill and cannot be performed in hospitals not equipped to care for trauma patients or by paramedical care personnel.

[0005] Deliberately keeping hemorrhaging trauma victims in a hypotensive state is currently being examined as a means to improve survival. This is done based on the premise that overall hemorrhage (especially abdominal hemorrhage) is reduced if mean arterial pressure is kept low by not aggressively volume-repleting the victim prior to surgery. Unfortunately, this may be dangerous for trauma victims with concomitant head injury or myocardial dysfunction.

[0006] An important cause of hemorrhagic shock not caused by trauma includes rupture of abdominal aortic aneurysms. These can occur suddenly and without warning. Control of bleeding even at surgery can be difficult. Temporary measures discussed above for hemorrhage secondary to trauma have been tried for hemorrhage secondary to aneurysm rupture. The same difficulties apply. Survival might be enhanced if hemorrhage could be controlled earlier while maintaining perfusion to the heart and brain.

[0007] U.S. Patent No. 5,531,776, and U.S. Patent Publication No. 2002/0016608, the disclosures of which are hereby incorporated herein by reference, each disclose non-invasive techniques for partially or completely occluding the descending aorta. While these techniques have been at least somewhat successful at reducing hemorrhagic shock, these methods and devices have not gained widespread acceptance due to some difficulty in advancing and properly placing the devices in a patient. Additionally, these methods require particular orientations of the devices for correct operation. Finding and maintaining the precise orientation can be difficult.

SUMMARY

[0008] In a first example, a gastroesophageal resuscitative aortic occlusion device includes a catheter, the catheter including a body having a first lumen, the body also having a distal end including a first opening fluidly coupled to the first lumen. An inflatable balloon is disposed on the catheter. An interior of the selectively inflatable balloon is fluidly coupled to the first opening. An inflation device is operably connected to the catheter and fluidly coupled to the first lumen.

Activation of the inflation device forces fluid into the interior of the inflatable balloon through the first lumen and the first opening.

[0009] In a second example, a gastroesophageal resuscitative aortic occlusion kit includes an occlusion device having a catheter, the catheter including a body having a first lumen. The body has a distal end including a first opening fluidly coupled to the first lumen. An inflatable balloon is disposed on the catheter. An interior of the selectively inflatable balloon is fluidly coupled to the first opening. An inflation device is operably connected to the catheter and fluidly coupled to the first lumen. Activation of the inflation device forces fluid into the interior of the inflatable balloon through the first lumen and the first opening. An external pressure device is used in conjunction with the occlusion device.

[0010] In yet another example, a method of occluding the descending aorta includes inserting a gastroesophageal resuscitative aortic occlusion device into a stomach of a patient through the esophagus. The gastroesophageal resuscitative aortic occlusion device includes a catheter having a body and a first lumen. The body also includes a distal end having a first opening fluidly coupled to the first lumen. An inflatable balloon is disposed on the catheter. An interior of the inflatable balloon is fluidly coupled to the first opening. An inflation device is operably connected to the catheter and fluidly coupled to the first lumen. Activation of the inflation device forces fluid into the interior of the inflatable balloon through the first lumen and the first opening. Activating the inflation device to pressurizes the inflatable balloon with a fluid. An external pressure device applies pressure to the abdomen of the patient until blood flow through the descending aorta is reduced or stopped.

[0011] Any of the first, second, and third examples may include any one or more of the following optional forms.

[0012] In one optional form, a first vacuum device is operably connected to the catheter, the first vacuum device activating to remove fluid from the inflatable balloon.

[0013] In another optional form, the first vacuum device is fluidly coupled to the first lumen.

[0014] In yet other optional forms, the body further includes a second lumen and the distal end further includes a second opening fluidly coupled to the second lumen, the second lumen fluidly connecting the distal end to ambient pressure.

[0015] In yet other optional forms, the body further includes a third lumen and the distal end further includes a third opening fluidly coupled to the third lumen.

[0016] In yet other optional forms, a second vacuum device is fluidly coupled to the third lumen, the second vacuum device activating to remove stomach contents when the distal end is located in a patient stomach.

[0017] In yet other optional forms, the inflatable balloon may be displaced from the distal end of the catheter by a distance, preferably by at least 20 mm.

[0018] In yet other optional forms, the inflatable balloon is displaced from the distal end of the catheter by between about 20 mm and about 150 mm, preferably between about 30 mm and about 100 mm.

[0019] In yet other optional forms, the inflatable balloon comprises a material having a shore hardness of between 70A and 70D.

[0020] In yet other optional forms, the inflatable balloon further comprises a wall having a thickness of between 0.003 in and 0.015 in.

[0021] In yet other optional forms, a pressure sensor senses internal pressure in the inflatable balloon.

[0022] In yet other optional forms, a pulsatile flow sensor senses blood pressure.

[0023] In yet other optional forms, the fluid is ambient air.

[0024] In yet other optional forms, operation of the inflation device may be reversed to remove fluid from the inflatable balloon.

[0025] In yet other optional forms, the distal end of the catheter comprises a plurality of cutouts to increase flexibility.

[0026] In yet other optional forms, the distal end of the catheter comprises a softer material than the catheter proximate the inflatable balloon.

[0027] In yet other embodiments, the distal end of the catheter comprises a smaller diameter than the catheter proximate the inflatable balloon.

[0028] In yet other optional forms, the distal end of the catheter comprises a blunt end.

[0029] In yet other optional forms, a removable sheath covers the inflatable balloon during insertion of the catheter.

[0030] In yet other optional forms, the inflatable balloon comprises an annular shape when fully inflated.

[0031] In yet other optional forms, an external pressure device is applied to the abdomen of the patient.

[0032] In yet other optional forms, the external compression device is one of a circumferential compression device and a human hand.

[0033] In yet other optional forms, a telescoping member may be at least partially slidably disposed within the catheter and the catheter may slide along the telescoping member for insertion, removal, and/or positioning within a patient.

BRIEF DESCRIPTION OF THE DRAWINGS

[0034] FIG. 1 is a schematic view of a gastroesophageal resuscitative aortic occlusion device inserted into a stomach of a patient.

[0035] FIG. 2 is a plan view of the gastroesophageal resuscitative aortic occlusion device of FIG. 1

[0036] FIG. 3 is a close up view of a balloon of the gastroesophageal resuscitative aortic occlusion device of FIG. 2 in a collapsed state.

[0037] FIG. 4A is a close up view of a distal end of a catheter of the gastroesophageal resuscitative aortic occlusion device of FIG. 2.

[0038] FIG. 4B is a cross sectional view of the catheter of FIG. 4A

[0039] FIG. 5 is a perspective view of an external pressure device applied to an abdomen of a patient and used in conjunction with the gastroesophageal resuscitative aortic occlusion device of FIG. 2.

[0040] FIG. 6 is a plan view of the external pressure device of FIG. 5.

[0041] FIGS 7A-7C are side perspective, close up perspective, and cross-sectional views, respectively, of an alternate embodiment of a gastroesophageal resuscitative aortic occlusion device, with a telescoping member at least partially deployed.

[0042] FIGS. 8A-8C are side perspective, close up perspective, and cross-sectional views, respectively, of the gastroesophageal resuscitative aortic occlusion device of FIGS. 7A-7C, with the telescoping member retracted.

[0043] FIGS. 9A and 9B are side and close up views, respectively, of another alternate embodiment of a gastroesophageal resuscitative aortic occlusion device, with a telescoping member at least partially deployed.

[0044] FIGS. 10A and 10 B are close-up and partial cross-sectional views, respectively of the gastroesophageal resuscitative aortic occlusion device of FIGS. 9A and 9B, with the telescoping member retracted.

DETAILED DESCRIPTION

[0045] The disclosed devices and techniques are based upon the fact that a majority of human beings have similar physiological relationships between the esophagus, the stomach, and the descending aorta. These methods include positioning a device, having an elongated tubular member, in a portion of the patient's stomach juxtaposed with the patient's descending aorta and displacing with the tubular member a wall of the portion of the stomach posteriorly-laterally in the direction of the descending aorta.

[0046] Turning now to FIG. 1, one embodiment of a gastroesophageal resuscitative aortic occlusion device 10 is illustrated inserted into a patient 1 through the patient's esophagus 2. The patient's descending aorta 4 is juxtaposed with the esophagus 2 throughout a significant portion of the thoracic cavity 5. However, the esophagus 2 and descending aorta 4 are most closely bound where they mutually pass in close proximity through the diaphragm 6 just above the esophageal-gastric junction 7. Below the diaphragm 6, the descending aorta 4 passes posteriorly of the stomach 8 between the stomach 8 and vertebral spinal column. Because the descending aorta 4 and esophagus 2 are tightly bound in close proximity where they pass through the diaphragm 6, manipulation of a device positioned adjacent the esophageal-gastric junction 7 may be used to deflect or expand the esophagus 2 and/or the stomach 8 to thereby at least partially occlude the descending aorta 4 against the vertebral column, which decreases or stops blood flow through the descending aorta 4.

[0047] To carry out such non-invasive partial or complete occlusion of the descending aorta 4 requires proper positioning both longitudinally and radially of a surface which is moveable laterally a sufficient distance, with a sufficient force, and having a surface of sufficient area to at least partially occlude the patient's descending aorta 4. The gastroesophageal resuscitative aortic occlusion device 10 described herein overcomes the difficulties of proper positioning of the moveable surface notwithstanding the great variety in the anatomy of a patient, as will be described in more detail below.

[0048] The gastroesophageal resuscitative aortic occlusion device 10 includes a force-producing surface, such as an inflatable balloon 12, and a positioning device in the form of an elongated member, such as a catheter 14. The catheter 14 positions the inflatable balloon 12

through the patient's esophagus 2 and into a portion of the patient's stomach 8, which is near the patient's descending aorta 4. The gastroesophageal resuscitative aortic occlusion device 10 further includes an inflation mechanism, such as a hand pump 16 which selectively inflates the inflatable balloon 12. The outer surface 18 of the inflatable balloon 12 applies pressure posteriorly-laterally in the direction of the patient's descending aorta 4 sufficient to cause either partial, or substantially complete, occlusion of the patient's descending aorta 4.

[0049] Once inflated in the patient's stomach 8, proper positioning of the inflatable balloon 12 is achieved by pulling the catheter 14, such as by pulling on a handgrip 19, which draws the inflatable balloon 12 to the wall of the stomach 8 at the esophageal-gastric junction 7. The inflatable balloon 12 is drawn upwardly and posteriorly, which is the direction necessary to impinge the descending aorta 4, thereby substantially occluding blood flow through the patient's descending aorta 4.

[0050] The descending aorta 4 is a main artery of the body. As such, it is a large vessel and it is pressurized by the heart to a pressure that may extend over 200 millimeters of mercury, or approximately four pounds per square inch in some cases. Therefore, in order to substantially occlude the descending aorta 4, the gastroesophageal resuscitative aortic occlusion device 10 must overcome pressures as great as 200 mm of mercury. Furthermore, the descending aorta 4 is a muscular structure having muscle tone which affords rigidity. Therefore, the descending aorta 4 has a stiffness which resists crushing thereof. While less than the pressure of the fluid in the descending aorta 4, this muscle tone adds appreciably to the force required to substantially occlude the descending aorta 4. In the illustrated embodiment, force sufficient to partially or completely occlude the descending aorta 4 is achieved with the inflatable balloon 12 being made of a suitable medical grade material, such as polyurethane, a polyester film, such as Mylar®, polyethylene terephthalate, or similar materials, and having a surface with an inflated diameter preferably of between approximately 3 and approximately 8 inches and most preferably between approximately 5 and approximately 7 inches. Internal balloon pressures of between 30 mm of mercury and 500 mm of mercury, preferably between 60 mm of mercury and 300 mm of mercury, advantageously allow the inflatable balloon 12 to partially or fully occlude the descending aorta and/or to reduce or stop bleeding in other areas of the abdomen. The catheter 14 is sufficiently strong to allow forces to be transmitted to inflatable balloon 12 to impart force to the surface of inflatable balloon 12 to partially or completely occlude the descending aorta 4.

[0051] As illustrated in FIGS. 2-4, the gastroesophageal resuscitative aortic occlusion device 10 comprises the catheter 14, which has a body 20 including a first lumen 22. The body 20 also includes a distal end 24 having a first opening 26 fluidly coupled to the first lumen 22.

[0052] The inflatable balloon 12 is disposed on the catheter 14 and a distal end 28 of the inflatable balloon 12 is displaced from a tip 30 of the distal end 24 of the catheter 14 by a distance. An interior 32 of the inflatable balloon 12 is fluidly coupled to the first opening 26.

[0053] In some embodiments, the distal end 28 of the inflatable balloon 12 is displaced from the tip 30 of the distal end 24 of the catheter 14 by at least 20 mm. In other embodiments, the distal end 28 of the inflatable balloon 12 is displaced from the tip 30 of the distal end 24 of the catheter 14 by between about 20 mm and about 150 mm, preferably by between about 30 mm and about 100 mm. Displacements in these ranges facilitate insertion and proper placement of the inflatable balloon 12 into the stomach 8.

[0054] In some embodiments, the inflatable balloon 12 comprises a material having a shore hardness of between 70A and 70D. In other embodiments, the inflatable balloon 12 further comprises a wall having a thickness of between 0.003 in and 0.015 in. These ranges of hardness and wall thickness produce sufficient force to occlude or partially occlude the descending aorta 4 when the inflatable balloon 12 is inflated.

[0055] The hand pump 16 is operably connected to the catheter 14 and fluidly coupled to the first lumen 22. Activation of the hand pump 16, such as by squeezing, forces fluid, such as ambient air, into the interior 32 of the inflatable balloon 12 under pressure through the first lumen 22 and through the first opening 26. The inflatable balloon 12 is thereby filled with fluid under pressure, which causes the inflatable balloon 12 to expand.

[0056] In some embodiments, an optional a first vacuum device 40 may be operably connected to the catheter 14, the first vacuum device 40 activating to remove fluid from the inflatable balloon 12, thereby causing the inflatable balloon 12 to deflate. The first vacuum device 40 may be fluidly connected to the first lumen 22. The first vacuum device 40 may be used to deflate the inflatable balloon 12 during insertion, repositioning, and/or during removal of the inflatable balloon 12 from the patient 1. In some embodiments, the hand pump 16 and the first vacuum device 40 may be combined into a single device, such as a hand pump with a reversible valve to allow fluid to be pumped or removed based on the valve position.

[0057] In some embodiments, the body 20 may further include a second lumen 52 and the distal end 24 of the catheter 14 may further include a second opening 54 that is fluidly coupled

to the second lumen 52. The second lumen 52 may allow the second opening 54 at the distal end 24 to be fluidly connected with ambient pressure, which equalizes pressure in the stomach 8 of the patient 1 when the inflatable balloon 12 is inflated, which may prevent equalization of pressure through the esophagus 2.

[0058] In some embodiments, the body 20 may further include a third lumen 56 and the distal end 24 of the catheter 14 may further include a third opening 58, which may be fluidly coupled to the third lumen 56. The third lumen 56 may be optionally fluidly connected to a second vacuum device 60. The second vacuum device 60 may be activated to remove stomach contents when the distal end 24 is located in the patient's stomach 8. In some cases, stomach contents may need to be removed to make room for the inflatable balloon 12, or to increase effectiveness of the inflatable balloon 12, and/or to reduce the risk of patient aspiration.

[0059] In some embodiments, the gastroesophageal resuscitative aortic occlusion device 10 further includes a pressure sensor 70 that senses internal pressure in the inflatable balloon 12. The pressure sensor 70 may be fluidly connected to the first lumen 22 so that internal pressure of the inflatable balloon 12 may be sensed so that a user may inflate the inflatable balloon 12 to the proper pressure.

[0060] In yet other embodiments, the gastroesophageal resuscitative aortic occlusion device 10 may further include a pulsatile flow sensor or pressure sensor 80, either embedded into the device, or that are operatively connected to the device but that are applied external to the patient distal to the point of balloon inflation, that sense blood pressure or flow emanating from the descending aorta 4 distal to the point of balloon inflation. In some embodiments, the sensors may be separate from the balloon apparatus, but part of a larger system. The sensors provide data that enhances positioning of the balloon to aid in more complete occlusion of the descending aorta. In some uses, it may be desirable to only partially occlude the descending aorta, for example, if an operator determines that blood flow should only be slowed, but not stopped for medical reasons, in which case the sensors provide data that will assist in producing the desired amount of occlusion. In some embodiments, the sensors may comprise conductive bands or other pressure sensing elements in the balloon, or optical pressure sensors or ultrasonic pressure sensors for internal sensing, or external sensing (relative to the device itself) that may be attached to other bodily structures in the patient distal to the location of balloon inflation.

[0061] In some embodiments, the distal end 24 of the catheter 14 may include a plurality of cutouts 82 that increase flexibility of the distal end 24 to ease insertion of the catheter 14 through the esophagus 2.

[0062] In yet other embodiments, the distal end 24 of the catheter 14 may comprise a softer material than the catheter 14 proximate the inflatable balloon 12.

[0063] In some embodiments, the tip 30 of the distal end 24 of the catheter 14 comprises a blunt end.

[0064] In yet other embodiments, the gastroesophageal resuscitative aortic occlusion device 10 may comprise a removable sheath (not shown) that covers the inflatable balloon 12 during insertion of the inflatable balloon 12 through the esophagus 2. The sheath may break-away or dissolve when contacted with stomach acid to free the inflatable balloon 12 for inflation.

[0065] In yet other embodiments, the inflatable balloon 12 comprises an annular shape when fully inflated.

[0066] Turning now to FIGS. 5 and 6, an external pressure device 100 may be used in conjunction with the gastroesophageal resuscitative aortic occlusion device 10 to enhance occlusion of the descending aorta 4.

[0067] In some embodiments, the external pressure device 100 may comprise a circumferential compression device 111 that includes a strap 113 and a pressure plate 115. In other embodiments, the external pressure device 100 may comprise a human hand.

[0068] In the embodiment illustrated in FIGS. 5 and 6, the circumferential compression device 111 may also include an upper plate 117 that is movably connected to the pressure plate 115. The upper plate 117 may include a pressure increasing device, such as an extending screw 121 that increases pressure of the pressure plate 115 on the abdomen of the patient 1.

[0069] Turning now to FIGS. 7-10, other optional embodiments of a gastroesophageal resuscitative aortic occlusion device are illustrated. The gastroesophageal resuscitative aortic occlusion devices of FIGS. 7-10 may include any features described above with respect to FIGS. 1-4, even if they are not expressly described with respect to FIGS. 7-10. Moreover, the embodiment described in FIGS. 7-8 has common elements listed as 100 greater than the elements of FIGS. 1-4 and the embodiment described in FIGS. 9-10 has common elements listed as 200 greater than the elements of FIGS. 1-4.

[0070] The gastroesophageal resuscitative aortic occlusion device 110 of FIGS. 7 and 8 comprises a catheter 114, which has a body 120 including a first lumen 122. The body 120 also includes a distal end 124 having a first opening located within an inflatable balloon 112 (but not illustrated in FIGS. 7 and 8) fluidly coupled to the first lumen 122.

[0071] The inflatable balloon 112 is disposed on the catheter 114 and a distal end 128 of the inflatable balloon 112 is displaced from a tip 130 of the distal end 124 of the catheter 114 by a distance. An interior of the inflatable balloon 112 is fluidly coupled to the first opening.

[0072] In some embodiments, the distal end 128 of the inflatable balloon 112 is displaced from the tip 130 of the distal end 124 of the catheter 114 by at least 20 mm. In other embodiments, the distal end 128 of the inflatable balloon 112 is displaced from the tip 130 of the distal end 124 of the catheter 114 by between about 20 mm and about 150 mm, preferably by between about 30 mm and about 100 mm. Displacements in these ranges facilitate insertion and proper placement of the inflatable balloon 112 into the stomach.

[0073] A hand pump (not shown in FIGS. 7 and 8) is operably connected to the catheter 114 and fluidly coupled to the first lumen 122 through a fluid line 186 and valve 188. Activation of the hand pump, such as by squeezing, forces fluid, such as ambient air, into the interior of the inflatable balloon 112 under pressure through the first lumen 122 and through the first opening. The inflatable balloon 112 is thereby filled with fluid under pressure, which causes the inflatable balloon 112 to expand.

[0074] In some embodiments, an optional a first vacuum device (not shown in FIGS. 7 and 8) may be operably connected to the catheter 114, also through the fluid line 186 and the valve 188. The first vacuum device may activate to remove fluid from the inflatable balloon 112, thereby causing the inflatable balloon 112 to deflate. The first vacuum device may also be fluidly connected to the first lumen 122. The first vacuum device may be used to deflate the inflatable balloon 112 during insertion, repositioning, and/or during removal of the inflatable balloon 112 from the patient. In some embodiments, the hand pump and the first vacuum device may be combined into a single device, such as a hand pump with a reversible valve to allow fluid to be pumped or removed based on the valve position.

[0075] In some embodiments, the body 120 may further include a second lumen 152 and the distal end 124 of the catheter 14 may further include a second opening(s) 154 that is fluidly coupled to the second lumen 152. The second lumen 152 may allow the second opening 154 at the distal end 124 to be fluidly connected with ambient pressure, which equalizes pressure in

the stomach of the patient when the inflatable balloon 112 is inflated, which may prevent equalization of pressure through the esophagus.

[0076] In some embodiments, the body 120 may further include a third lumen 156 and the distal end 124 of the catheter 114 may further include a third opening 158, which may be coupled to the third lumen 156. The third lumen 156 may be sized and shaped to receive a telescoping member 190. The telescoping member 190 is slidably disposed within the third lumen 156 so that a distal end of the telescoping member 190 may extend out of the distal end 124 of the catheter 114, when the telescoping member 190 is in a deployed position.

[0077] The telescoping member 190 may facilitate placement of the inflatable balloon 112. For example, the telescoping member 190 may protrude beyond the distal end 124 of the catheter 114. There is no limitation on how far the telescoping member 190 might protrude. In one embodiment, a clinician may first place the telescoping member 190 into the patient's stomach and then pass the gastroesophageal resuscitative aortic occlusion device 110 over the telescoping member 190. Alternatively, the telescoping member 190 may only protrude partially out of the distal end 124 of the catheter 114 to provide additional guidance and support for the gastroesophageal resuscitative aortic occlusion device 110 during insertion. As a result, the gastroesophageal resuscitative aortic occlusion device 110 is more easily navigated into the esophagus and into the stomach since the telescoping member 190 acts as a guide. The telescoping member 190 is preferably flexible. The telescoping member 190 may comprise, for example, PVC or a thermoplastic polyurethane (TPU), but other flexible materials may be used as well. The telescoping member 190 may optionally include a first lumen 192 and a second lumen 194. The first and second lumens 192, 194 may be utilized, for example, for the removal of stomach contents. More specifically, the first lumen 192 may be used for vacuuming out stomach contents while the second lumen 194 may be used for venting the stomach to atmosphere. A distal end 196 of the telescoping member 190 may include one or more fenestrations 198. These fenestrations 198 fluidly connect the first and second lumens 192, 194 the outside of the telescoping member 190, for example, to the stomach of a patient and any contents therein. Further the distal end 196 is preferably rounded to minimize trauma to the patient during insertion and removal.

[0078] When the telescoping member 190 is no longer needed, the clinician may partially or completely remove the telescoping member 190 by pulling on a proximal end 199. The telescoping member 190 then slides out (partially or completely) of the third lumen 156.

[0079] Turning now to FIGS. 9 and 10, another alternate embodiment of a gastroesophageal resuscitative aortic occlusion device 210 is illustrated. The gastroesophageal resuscitative aortic occlusion device 210 of FIGS. 9 and 10 is the same as the embodiment illustrated in FIGS. 7 and 8, with the exception of the inflatable balloon 212 placement on the catheter 214. In the embodiment of FIGS. 9 and 10, the inflatable balloon 112 may be mounted near or at the distal end 224 of the catheter 214. A telescoping member 290 may also be used to assist in placement of the inflatable balloon 212. Then, once the inflatable balloon 212 is positioned within the stomach, the telescoping member 290 can be removed as described above, and the inflatable balloon 212 may be inflated. Once the inflatable balloon 212 is fully inflated, it acts to shield the stomach from the distal end 224 of the catheter 214. As a result, trauma to the stomach is reduced, which could occur from prolonged force of a more pointed object pressed up against the stomach wall.

[0080] In some embodiments, a gastroesophageal resuscitative aortic occlusion kit may include the gastroesophageal resuscitative aortic occlusion device 10 and external pressure device 100 described above.

[0081] The gastroesophageal resuscitative aortic occlusion device 10 and external pressure device 100 described above may be used in a method of occluding the descending aorta 4.

[0082] The gastroesophageal resuscitative aortic occlusion device 10 may be inserted into the stomach 8 of a patient through the esophagus 2. The hand pump 16 may be activated to pressurize the inflatable balloon 12 with a fluid. External pressure is applied to the abdomen of the patient 1 with the external pressure device 100 until blood flow through the descending aorta 4 is reduced or stopped.

[0083] The disclosed gastroesophageal resuscitative aortic occlusion device, external pressure device, and methods of using the gastroesophageal resuscitative aortic occlusion device and the external pressure device provide hemorrhage control for the management of trauma and an inhibition of blood flow below the diaphragm to enhance coronary and cerebral perfusion. Studies have shown that, although over half of the tissue beds are below the diaphragm, approximately two-thirds of bleeding that leads to hemorrhagic shock occurs below the diaphragm. Therefore, the ability to control bleeding below the diaphragm provides a significant advantage particularly in management of trauma. This is particularly useful in treating patients who have suffered abdominal injuries from knives and guns, blunt trauma from falls, explosions, motor vehicle accidents, complications due to the delivery of babies from subdiaphragmatic hemorrhaging and other vascular catastrophes below the diaphragm such as

ruptured abdominal aortic aneurysms. The disclosed gastroesophageal resuscitative aortic occlusion device and external pressure device are particularly useful in battlefield applications in which it is essential to be able to rapidly control life-threatening hemorrhage in a non-invasive manner in order to avoid immediate death and complications from infections and the like until definitive repair of injuries can take place. Additionally, the ability to perform this procedure rapidly and effectively reduces the exposure of the medical personnel to battlefield injuries.

[0084] Changes and modifications in the specifically described embodiments can be carried out without departing from the principles of the invention. For example, electrodes can be applied to stomach balloons for use in cardiac pacing and defibrillation. Although balloons and cuffs may be inflated using air, other techniques involving hydraulic fluids and mechanical actuators may suggest themselves to those skilled in the art. Although inflatable devices are illustrated as spherical or annular, other shapes could be used such as cylindrical, pill-shaped, and the like. Also, the various elements of each illustrated embodiment of the invention can be combined and substituted with other of the embodiments. The embodiments are provided in order to illustrate the invention and should not be considered limiting. The described methods and devices are to be limited only by the scope of the appended claims.

CLAIMS

1. A gastroesophageal resuscitative aortic occlusion device comprising:
a catheter, the catheter including a body having a first lumen, the body also having a distal end including a first opening fluidly coupled to the first lumen;
an inflatable balloon disposed on the catheter, an interior of the inflatable balloon being fluidly coupled to the first opening; and
an inflation device operably connected to the catheter and fluidly coupled to the first lumen,
wherein activation of the inflation device forces fluid into the interior of the inflatable balloon through the first lumen and the first opening.
2. The gastroesophageal resuscitative aortic occlusion device of claim 1, further comprising a first vacuum device operably connected to the catheter, the first vacuum device activating to remove fluid from the inflatable balloon.
3. The gastroesophageal resuscitative aortic occlusion device of claim 2, wherein the first vacuum device is fluidly coupled to the first lumen.
4. The gastroesophageal resuscitative aortic occlusion device of any one of claims 1-3, the body further including a second lumen and the distal end further including a second opening fluidly coupled to the second lumen, the second lumen fluidly connecting the distal end to ambient pressure.
5. The gastroesophageal resuscitative aortic occlusion device of claim 4, the body further including a third lumen and the distal end further including a third opening fluidly coupled to the third lumen.
6. The gastroesophageal resuscitative aortic occlusion device of claim 3, further comprising a second vacuum device fluidly coupled to a second lumen, the second vacuum device activating to remove stomach contents when the distal end is located in a patient stomach.
7. The gastroesophageal resuscitative aortic occlusion device of any one of claims 1-6, wherein the inflatable balloon is displaced from the distal end of the catheter, preferably by at least 20 mm.

8. The gastroesophageal resuscitative aortic occlusion device of claim 7, wherein the inflatable balloon is displaced from the distal end of the catheter by between about 20 mm and about 150 mm, preferably between about 30 mm and about 100 mm.

9. The gastroesophageal resuscitative aortic occlusion device of any one of claims 1-8, wherein the inflatable balloon comprises a material having a shore hardness of between 70A and 70D.

10. The gastroesophageal resuscitative aortic occlusion device of any one of claims 1-9, wherein the inflatable balloon further comprises a wall having a thickness of between 0.003 in and 0.015 in.

11. The gastroesophageal resuscitative aortic occlusion device of any one of claims 1-10, further comprising a pressure sensor that senses internal pressure in the inflatable balloon.

12. The gastroesophageal resuscitative aortic occlusion device of any one of claims 1-11, further comprising a pulsatile flow sensor.

13. The gastroesophageal resuscitative aortic occlusion device of any one of claims 1-12, wherein the fluid is ambient air.

14. The gastroesophageal resuscitative aortic occlusion device of any one of claims 1-13, wherein operation of the inflation device may be reversed to remove fluid from the inflatable balloon.

15. The gastroesophageal resuscitative aortic occlusion device of any one of claims 1-15, wherein the distal end of the catheter comprises a plurality of cutouts to increase flexibility.

16. The gastroesophageal resuscitative aortic occlusion device of any one of claims 1-15, wherein the distal end of the catheter comprises one of a softer material than the catheter proximate the inflatable balloon or the distal end of the catheter comprises a smaller diameter than the catheter proximate the inflatable balloon.

17. The gastroesophageal resuscitative aortic occlusion device of any one of claims 1-16, wherein the distal end of the catheter comprises a blunt end.

18. The gastroesophageal resuscitative aortic occlusion device of any one of claims 1-17, further comprising a removable sheath that covers the inflatable balloon.

19. The gastroesophageal resuscitative aortic occlusion device of any one of claims 1-18, wherein the inflatable balloon comprises an annular shape when fully inflated.

20. The gastroesophageal resuscitative aortic occlusion device of any one of claims 1-19, further comprising an external pressure device.

21. The gastroesophageal resuscitative aortic occlusion device of claim 20, wherein the external pressure device is one of a circumferential compression device and a human hand.

22. The gastroesophageal resuscitative aortic occlusion device of any one of claims 1-21, further comprising a telescoping member that is at least partially slidably disposed within the catheter.

23. The gastroesophageal resuscitative aortic occlusion device of any one of claims 1-22, wherein inflatable balloon is capable of containing internal pressures of between 30 mm of mercury and 500 mm of mercury, preferably between 60 mm of mercury and 300 mm of mercury.

24. A gastroesophageal resuscitative aortic occlusion kit, comprising:
an occlusion device comprising a catheter, the catheter including a body having a first lumen, the body also having a distal end including a first opening fluidly coupled to the first lumen; an inflatable balloon disposed on the catheter, an interior of the inflatable balloon being fluidly coupled to the first opening; and an inflation device operably connected to the catheter and fluidly coupled to the first lumen, wherein activation of the inflation device forces fluid into the interior of the inflatable balloon through the first lumen and the first opening; and
an external pressure device.

25. A method of occluding the descending aorta, the method comprising:
inserting a gastroesophageal resuscitative aortic occlusion device into a stomach of a patient through the esophagus, the gastroesophageal resuscitative aortic occlusion device comprising a catheter, the catheter including a body having a first lumen, the body also having a distal end including a first opening fluidly coupled to the first lumen; an inflatable balloon disposed on the catheter, an interior of the inflatable balloon being fluidly coupled to the first opening; and an inflation device operably connected to the catheter and fluidly coupled to the first lumen, wherein activation of the inflation device forces fluid into the interior of the inflatable balloon through the first lumen and the first opening;

activating the inflation device to pressurize the inflatable balloon with a fluid; and

applying external pressure to the abdomen of the patient until blood flow through the descending aorta is reduced or stopped.

26. The method of claim 25, further comprising inserting a telescoping member within the catheter and sliding the catheter along the telescoping member.

27. The method of claim 25, wherein pressurizing the inflatable balloon with a fluid includes producing an internal pressure in the inflatable balloon of between 30 mm of mercury and 500 mm of mercury, preferably between 60 mm of mercury and 300 mm of mercury.

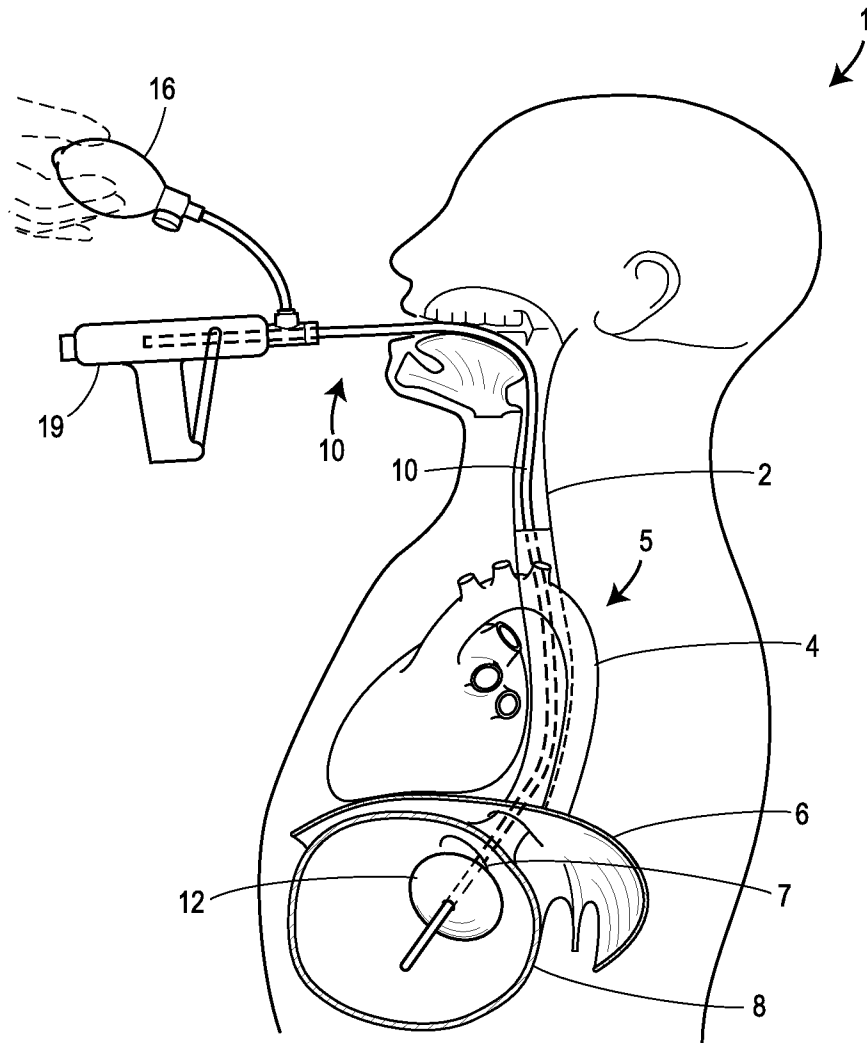


FIG. 1

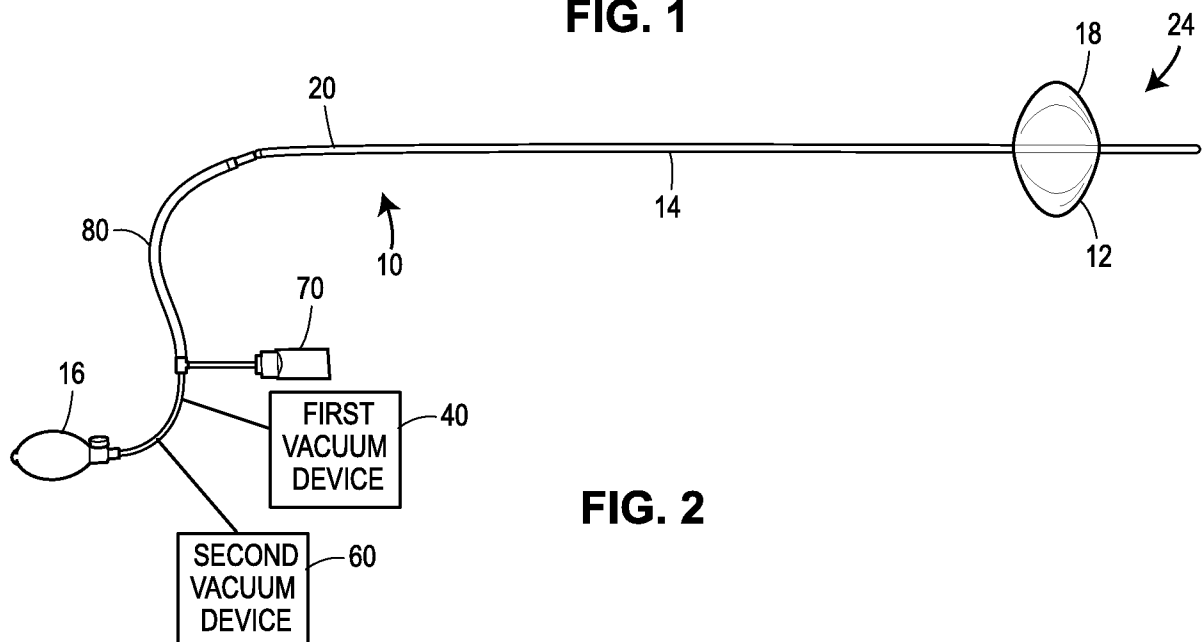


FIG. 2

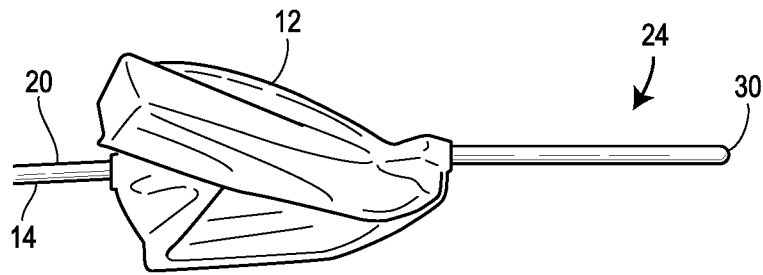


FIG. 3

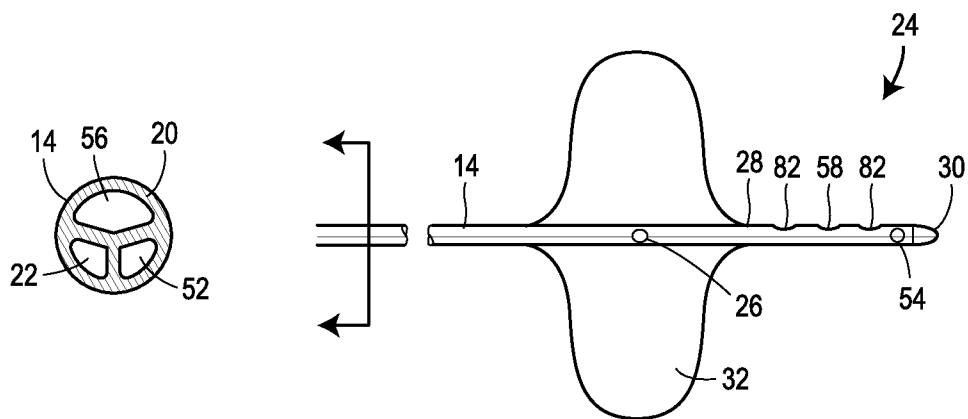


FIG. 4

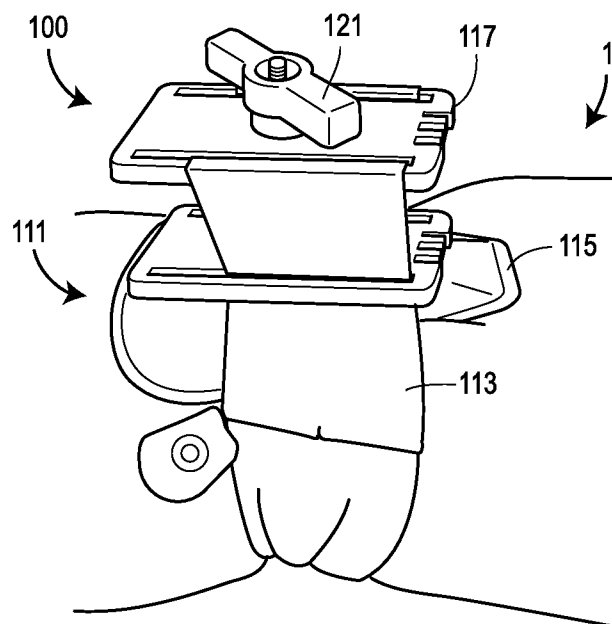


FIG. 5

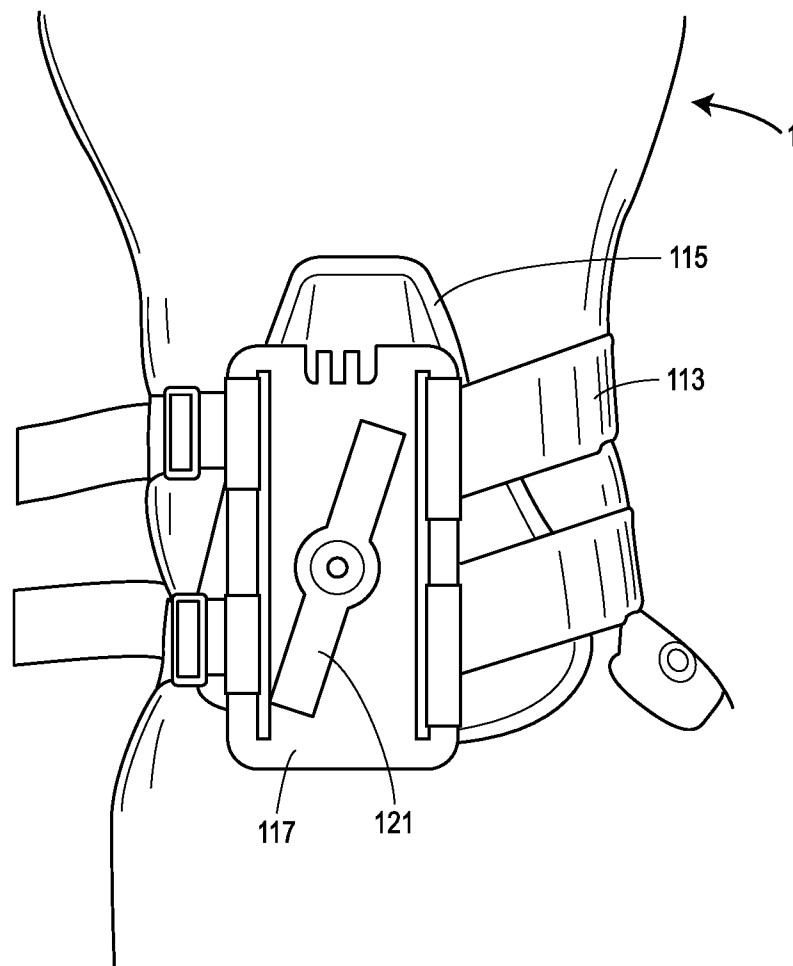
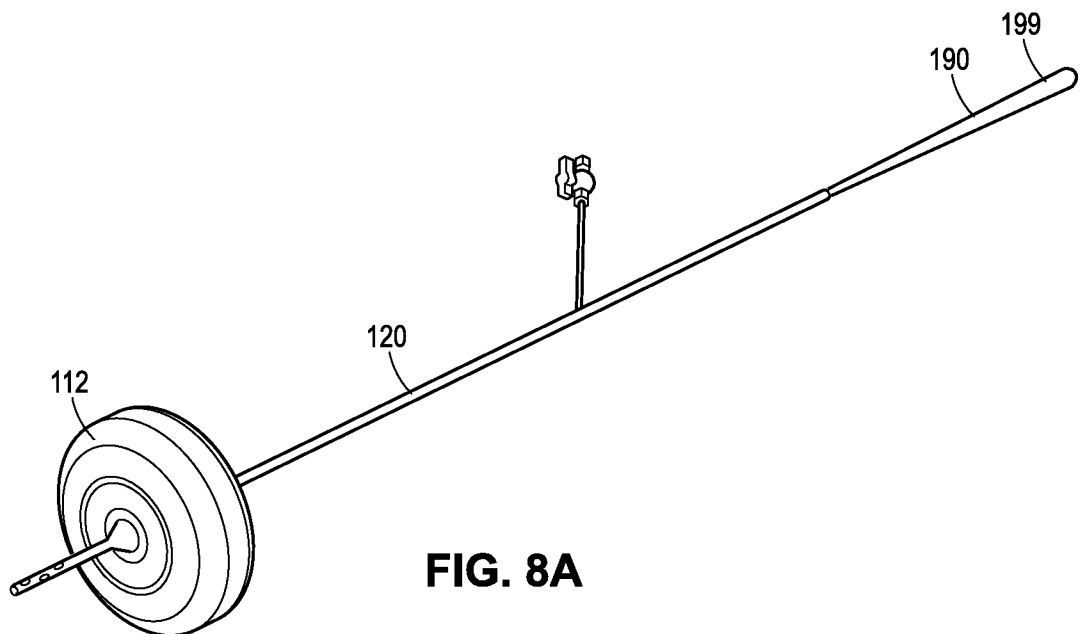
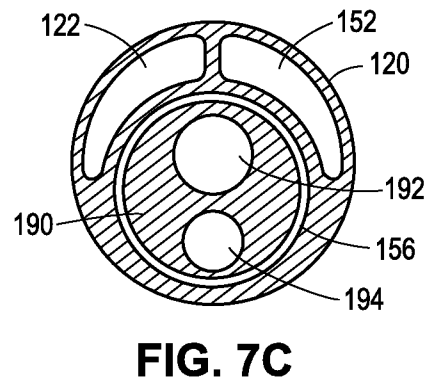
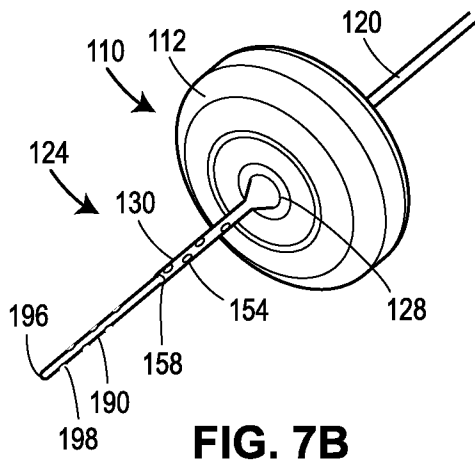
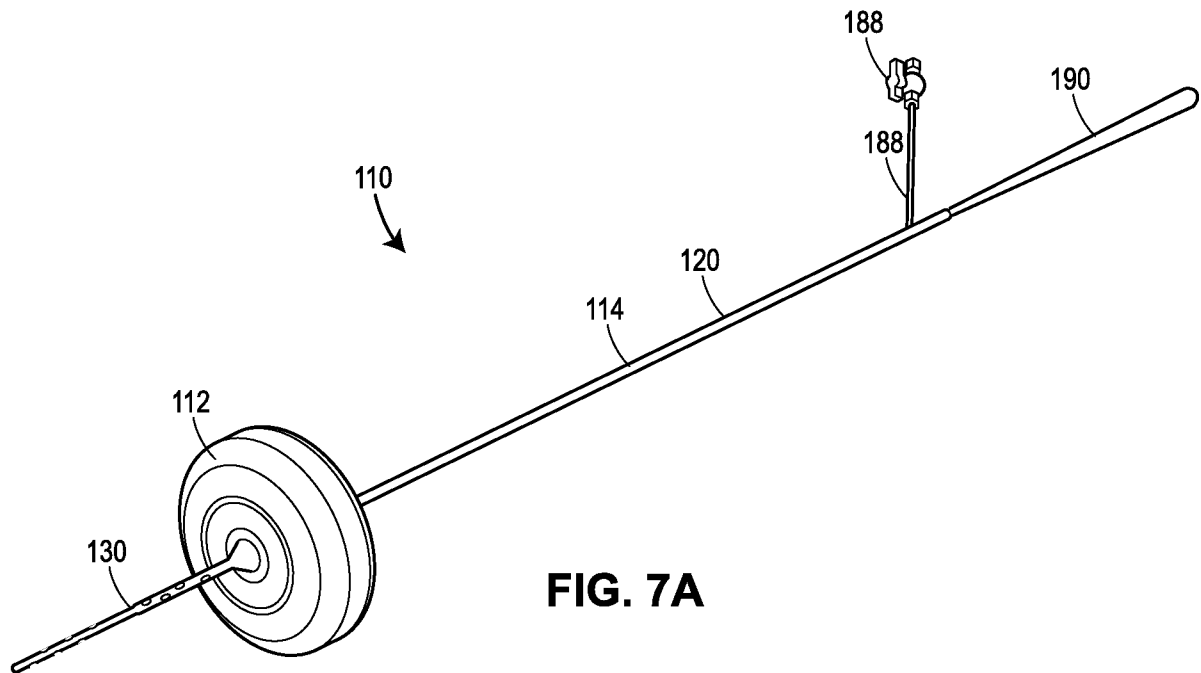
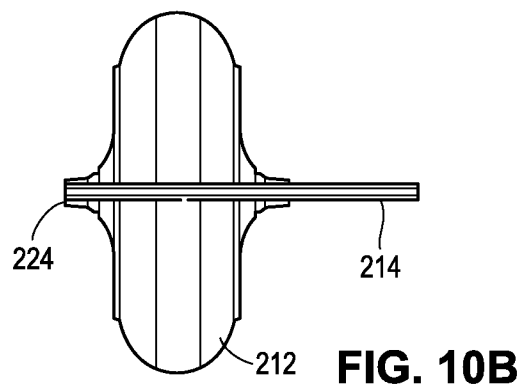
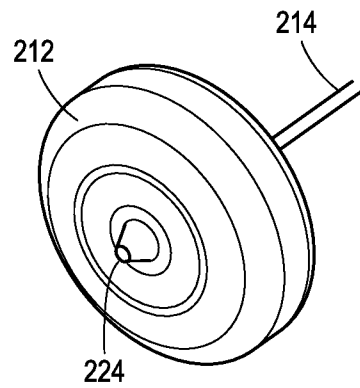
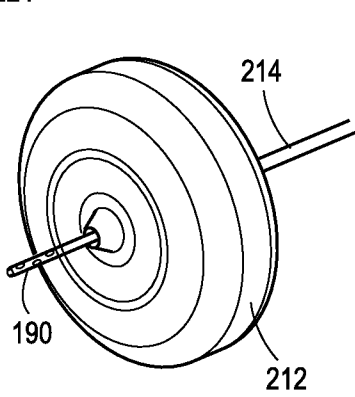
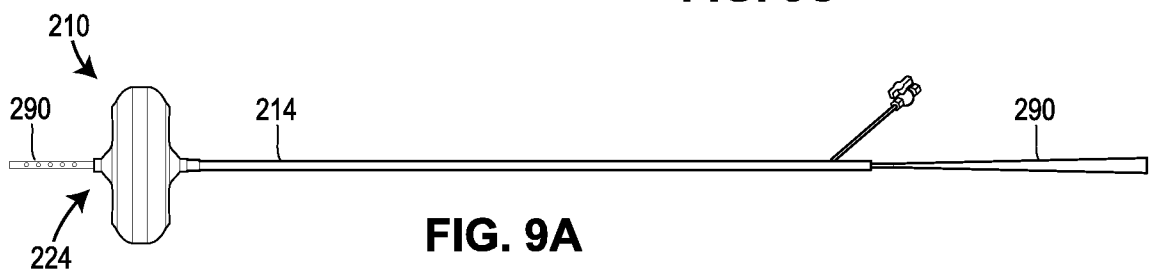
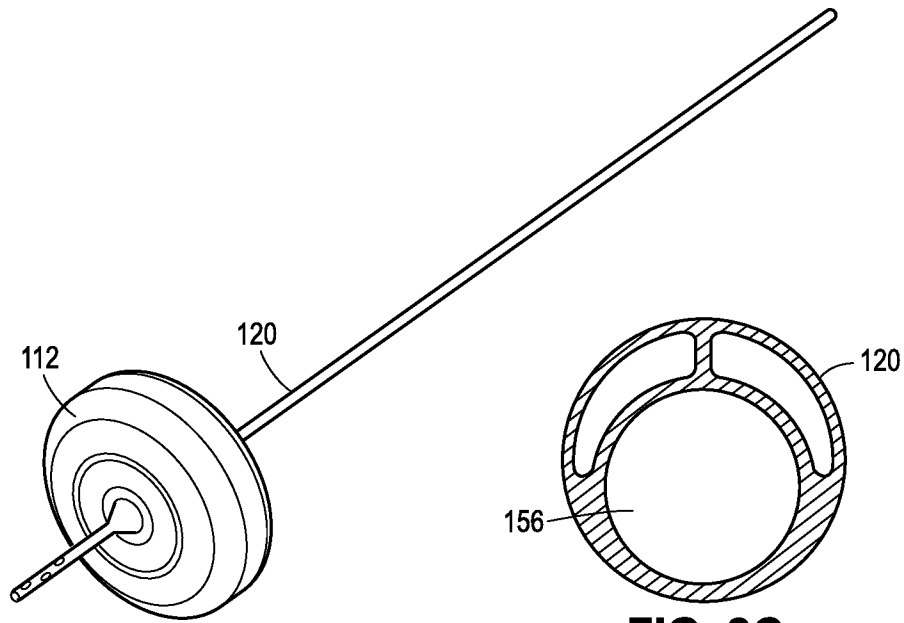


FIG. 6





INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 20/46796

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61B 17/12, A61B 17/135, A61M 1/00, A61M 25/10 (2020.01)

CPC - A61B 17/12136, A61B 17/12022, A61B 17/12131, A61M 25/10, A61M 25/1018, A61M 25/10181, A61M 1/0003, A61B 5/42, A61B 5/4238, A61B 2017/00818

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- A	WO 2019/018362 A1 (FRACTYL LABORATORIES, INC.) 24 January 2019 (24.01.2019) entire document.	1-6, 24 ----- 25-27
A	US 4,326,507 A (Barkalow) 27 April 1982 (27.04.1982) entire document.	25-27
A	US 2018/0133105 A1 (ZOLL Medical Corporation) 17 May 2018 (17.05.2018) entire document.	25-27
A	US 2002/0016608 A1 (Ward) 07 February 2002 (07.02.2002) entire document.	1-6, 24-27
A	US 2011/0245665 A1 (Nentwick) 06 October 2011 (06.10.2011) entire document.	1-6, 24-27
A	US 2018/0093080 A1 (Hotspur Technologies, Inc.) 05 April 2018 (05.04.2018) entire document.	1-6, 24-27

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

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"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

26 October 2020

Date of mailing of the international search report

18 NOV 2020

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Facsimile No. 571-273-8300

Authorized officer

Lee Young

Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 20/46796

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 7-23
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.



(51) International Patent Classification:

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(71) Applicant: **THE REGENTS OF THE UNIVERSITY OF MICHIGAN** [US/US]; Office of Technology Transfer, 1600 Huron Parkway, 2nd Floor, Ann Arbor, MI 48109-2590 (US).

(72) Inventors: **PLOTT, Jeffery, Stephen**; 7308 Aqua Isle Dr., Algonac, MI 48001 (US). **WARD, Kevin, R.**; 6730 Fleming Creek Dr., Superior Township, MI 48198 (US).

(74) Agent: **CHINLUND, Michael, A.**; Marshall, Gerstein & Borun LLP, 233 S. Wacker Drive, 6300 Willis Tower, Chicago, IL 60606-6357 (US).

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(54) Title: ANTI-HEMORRHAGE DEVICE WITH RIGID BACK PLATE

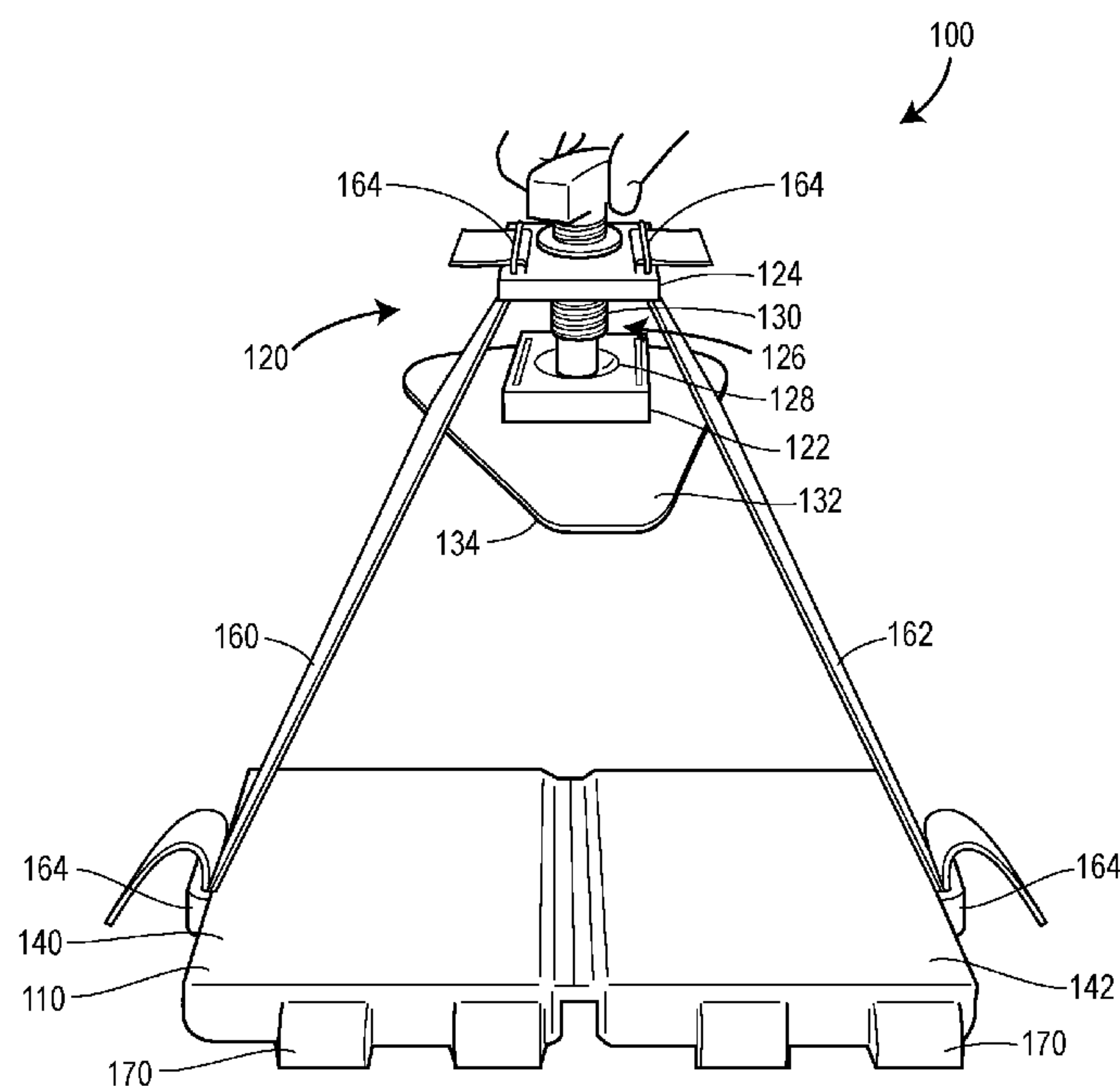


FIG. 5

(57) Abstract: An anti-hemorrhage device, and an anti-hemorrhage kit, includes a rigid platform and a compression device adjustably secured to the rigid platform. The kit also includes a gastroesophageal aortic occlusion device.

Published:

— *with international search report (Art. 21(3))*

ANTI-HEMORRHAGE DEVICE WITH RIGID BACK PLATE

FIELD OF THE DISCLOSURE

[0001] The present disclosure relates to hemorrhage occlusion devices and methods and more particularly to an anti-hemorrhage device or kit with a rigid back plate and a compression device.

BACKGROUND

[0002] Hemorrhagic shock is a leading cause of death from trauma. Many times there are delays in reaching hospitals that are qualified to take care of the complex injuries of such individuals. Many patients who die of trauma, die from multi-system involvement. Multi-system involvement may include head injury along with injuries to organs of the thoracic and abdominal cavity. Uncontrolled hemorrhage leading to hypovolemic shock is a leading cause of death from trauma especially from blunt and penetrating trauma of the abdomen. When head trauma occurs concomitantly with thoracic and abdominal hemorrhage, the brain becomes hypoperfused and, thus, becomes at greater risk for secondary injury. Currently, in the pre-hospital and emergency department setting, there are limited means to control exsanguinating hemorrhage below the diaphragm while maintaining myocardial and cerebral blood flow. Definitive control of hemorrhage is performed at surgery but this may be delayed and may not occur within the golden hour (time from injury to definitive treatment/repair) where the best opportunity lies in salvaging the patient. Survival with improved neurologic outcome might be enhanced if means were available to slow or stop ongoing hemorrhage (especially below the diaphragm) while maintaining adequate perfusion to the heart and brain until definitive treatment of the hemorrhage is available. This would be especially true of trauma victims whose transport to appropriate medical facilities would be prolonged.

[0003] One method of slowing or stopping hemorrhage is the use of a pneumatic anti-shock garment (PASG). Use of the PASG has met with varying degrees of success depending on the location of injury. This garment is placed on the legs and abdomen and is then inflated. Hemorrhage in the abdominal cavity, as well as the lower extremities, is controlled through tamponade while systemic blood pressure is raised partially through autotransfusion and by raising peripheral vascular resistance. Use of the PASG can sometimes be cumbersome and does not uniformly control hemorrhage or raise blood pressure. In addition, persons with concomitant penetrating thoracic injuries may hemorrhage more when the device is applied. The device may also raise intracranial pressure, which might detrimentally alter cerebral blood flow resulting in neurologic injury.

[0004] Other more drastic means to control abdominal bleeding prior to surgery have been the use of thoracotomy to cross-clamp the thoracic aorta and the use of balloon

catheters placed into the aorta from the femoral arteries to a point above the celiac-aortic axis. These techniques have met with varying degrees of success, require a high degree of skill, and cannot be performed in hospitals not equipped to care for trauma patients or by paramedical care personnel.

[0005] Deliberately keeping hemorrhaging trauma victims in a hypotensive state is currently being examined as a means to improve survival. This is done based on the premise that overall hemorrhage (especially abdominal hemorrhage) is reduced if mean arterial pressure is kept low by not aggressively volume-repleting the victim prior to surgery. Unfortunately, this may be dangerous for trauma victims with concomitant head injury or myocardial dysfunction.

[0006] An important cause of hemorrhagic shock not caused by trauma includes rupture of abdominal aortic aneurysms. These can occur suddenly and without warning. Control of bleeding even at surgery can be difficult. Temporary measures discussed above for hemorrhage secondary to trauma have been tried for hemorrhage secondary to aneurysm rupture. The same difficulties apply. Survival might be enhanced if hemorrhage could be controlled earlier while maintaining perfusion to the heart and brain.

[0007] U.S. Patent No. 5,531,776, and U.S. Patent Publication No. 2002/0016608, the disclosures of which are hereby incorporated herein by reference, each disclose non-invasive techniques for partially or completely occluding the descending aorta. While these techniques have been at least somewhat successful at reducing hemorrhagic shock, these methods and devices have not gained widespread acceptance due to some difficulty in advancing and properly placing the devices in a patient. Additionally, these methods require particular orientations of the devices for correct operation. Finding and maintaining the precise orientation can be difficult.

[0008] Finally, in some cases, external pressure may be necessary to stop internal or external hemorrhages. In some areas of the body, for example in the abdomen, external pressure is normally applied by hand. Hand pressure can be cumbersome and in the case where there is only one person to help, hand pressure removes one hand available to accomplish other tasks. Tourniquets may be used in some cases, but tourniquets can result in limb complications and cannot be used on the trunk of the body.

SUMMARY

[0009] In a first example, an anti-hemorrhage device includes a rigid platform and a compression device adjustably secured to the rigid platform.

[0010] In a second example, an anti-hemorrhage kit includes an anti-hemorrhage device including a rigid platform and a compression device adjustably secured to the rigid platform, and a gastroesophageal aortic occlusion device.

[0011] In yet another example, a method of stopping or slowing a hemorrhage includes placing a body part on a rigid platform, attaching a first strap to a first side of the rigid platform, attaching a second strap to a second side of the rigid platform, connecting the first and second straps to a compression device, locating the compression device over an area of hemorrhage, and operating the compression device to apply pressure to the area of hemorrhage. The first and second straps are at least partially spaced from the torso so that the torso is not fully constricted circumferentially when the compression device is operated.

[0012] Any of the first, second, and third examples may include any one or more of the following optional forms.

[0013] In one optional form, the compression device includes a pressure plate carriage and a strap carriage that is linearly translatable relative to the pressure plate carriage.

[0014] In another optional form, the pressure plate carriage and the strap carriage are connected by a screw.

[0015] In yet another optional form, the screw comprises a first screw nested within a second screw.

[0016] In yet another optional form, a pressure plate is removably attached to the pressure plate carriage.

[0017] In yet another optional form, the pressure plate has one of a generally triangular shape, a generally rectangular shape, a generally circular shape, a generally oval shape, or any combination thereof.

[0018] In yet another optional form, the rigid platform includes a first rigid housing and a second rigid housing that are pivotably connected to one another.

[0019] In yet another optional form, each of the first rigid housing and the second rigid housing include a perimeter rim that surrounds a central pocket.

[0020] In yet other optional forms, the compression device is adjustably secured to the rigid platform with a first adjustable strap and a second adjustable strap.

[0021] In yet other optional forms, the first adjustable strap is connected to the first rigid housing and the second adjustable strap is connected to the second rigid housing.

[0022] In yet other optional forms, a plurality of pressure plates is adapted to be removably secured to the compression device.

[0023] In yet other optional forms, the compression device includes a pressure plate carriage and a strap carriage that is linearly translatable relative to the pressure plate carriage.

[0024] In yet other optional forms, the pressure plate carriage and the strap carriage are connected by a screw.

BRIEF DESCRIPTION OF THE DRAWINGS

[0025] FIG. 1 is a schematic view of a gastroesophageal resuscitative aortic occlusion device inserted into a stomach of a patient.

[0026] FIG. 2 is a plan view of the gastroesophageal resuscitative aortic occlusion device of FIG. 1

[0027] FIG. 3 is a close up view of a balloon of the gastroesophageal resuscitative aortic occlusion device of FIG. 2 in a collapsed state.

[0028] FIG. 4A is a close up view of a distal end of a catheter of the gastroesophageal resuscitative aortic occlusion device of FIG. 2.

[0029] FIG. 4B is a cross sectional view of the catheter of FIG. 4A

[0030] FIG. 5 is a perspective view of an external pressure device including a rigid back plate.

[0031] FIG. 6 is perspective view of the external pressure device of FIG. 5 stored and placed within a cavity of the rigid back plate, together with a gastroesophageal device, which forms an anti-hemorrhage kit.

[0032] FIG. 7 is a perspective view of the external pressure device of FIG. 6 with the rigid back plate folded, thereby enclosing the external pressure device of FIG. 5 within the cavity.

[0033] FIG. 8 is a perspective view of the external pressure device of FIG. 5 wrapped around a body part, the body part being placed on the rigid back plate.

DETAILED DESCRIPTION

[0034] Initially, a gastroesophageal device will be described that may be used in conjunction with an external pressure device, which will be discussed further below. The gastroesophageal device and external pressure device may be used together to slow or stop bleeding in the lower part of the body. However, each device may also be used separately to stop other types of bleeding.

[0035] Turning now to FIG. 1, one embodiment of a gastroesophageal resuscitative aortic occlusion device 10 is illustrated inserted into a patient 1 through the patient's esophagus 2.

The patient's descending aorta 4 is juxtaposed with the esophagus 2 throughout a significant portion of the thoracic cavity 5. However, the esophagus 2 and descending aorta 4 are most closely bound where they mutually pass in close proximity through the diaphragm 6 just above the esophageal-gastric junction 7. Below the diaphragm 6, the descending aorta 4 passes posteriorly of the stomach 8 between the stomach 8 and vertebral spinal column. Because the descending aorta 4 and esophagus 2 are tightly bound in close proximity where they pass through the diaphragm 6, manipulation of a device positioned adjacent the esophageal-gastric junction 7 may be used to deflect or expand the esophagus 2 and/or the stomach 8 to thereby at least partially occlude the descending aorta 4 against the vertebral column, which decreases or stops blood flow through the descending aorta 4.

[0036] To carry out such non-invasive partial or complete occlusion of the descending aorta 4 requires proper positioning both longitudinally and radially of a surface which is moveable laterally a sufficient distance, with a sufficient force, and having a surface of sufficient area to at least partially occlude the patient's descending aorta 4. The gastroesophageal resuscitative aortic occlusion device 10 described herein overcomes the difficulties of proper positioning of the moveable surface notwithstanding the great variety in the anatomy of a patient, as will be described in more detail below.

[0037] The gastroesophageal resuscitative aortic occlusion device 10 includes a force-producing surface, such as an inflatable balloon 12, and a positioning device in the form of an elongated member, such as a catheter 14. The catheter 14 positions the inflatable balloon 12 through the patient's esophagus 2 and into a portion of the patient's stomach 8, which is near the patient's descending aorta 4. The gastroesophageal resuscitative aortic occlusion device 10 further includes an inflation mechanism, such as a hand pump 16 that selectively inflates the inflatable balloon 12. The outer surface 18 of the inflatable balloon 12 applies pressure posteriorly-laterally in the direction of the patient's descending aorta 4 sufficient to cause either partial, or substantially complete, occlusion of the patient's descending aorta 4.

[0038] Once inflated in the patient's stomach 8, proper positioning of the inflatable balloon 12 is achieved by pulling the catheter 14, such as by pulling on a handgrip 19, which draws the inflatable balloon 12 to the wall of the stomach 8 at the esophageal-gastric junction 7. The inflatable balloon 12 is drawn upwardly and posteriorly, which is the direction necessary to impinge the descending aorta 4, thereby substantially occluding blood flow through the patient's descending aorta 4.

The descending aorta 4 is a main artery of the body. As such, it is a large vessel and it is pressurized by the heart to a pressure that may extend over 200 millimeters of mercury, or

approximately four pounds per square inch in some cases. Therefore, in order to substantially occlude the descending aorta 4, the gastroesophageal resuscitative aortic occlusion device 10 must overcome pressures as great as 200 mm of mercury. Furthermore, the descending aorta 4 is a muscular structure having muscle tone, which affords rigidity. Therefore, the descending aorta 4 has a stiffness which resists crushing thereof. While less than the pressure of the fluid in the descending aorta 4, this muscle tone adds appreciably to the force required to substantially occlude the descending aorta 4. In the illustrated embodiment, force sufficient to partially or completely occlude the descending aorta 4 is achieved with the inflatable balloon 12 being made of a suitable medical grade material, such as polyurethane, a polyester film, such as Mylar®, polyethylene terephthalate, or similar materials, and having a surface with an inflated diameter preferably of between approximately 3 and approximately 8 inches and most preferably between approximately 5 and approximately 7 inches. The catheter 14 is sufficiently strong to allow forces to be transmitted to inflatable balloon 12 to impart force to the surface of inflatable balloon 12 to partially or completely occlude the descending aorta 4.

[0039] As illustrated in FIGS. 2-4, the gastroesophageal resuscitative aortic occlusion device 10 comprises the catheter 14, which has a body 20 including a first lumen 22. The body 20 also includes a distal end 24 having a first opening 26 fluidly coupled to the first lumen 22.

[0040] The inflatable balloon 12 is disposed on the catheter 14 and a distal end 28 of the inflatable balloon 12 is displaced from a tip 30 of the distal end 24 of the catheter 14 by a distance. An interior 32 of the inflatable balloon 12 is fluidly coupled to the first opening 26.

[0041] In some embodiments, the distal end 28 of the inflatable balloon 12 is displaced from the tip 30 of the distal end 24 of the catheter 14 by at least 20 mm. In other embodiments, the distal end 28 of the inflatable balloon 12 is displaced from the tip 30 of the distal end 24 of the catheter 14 by between about 20 mm and about 150 mm, preferably by between about 30 mm and about 100 mm. Displacements in these ranges facilitate insertion and proper placement of the inflatable balloon 12 into the stomach 8.

[0042] In some embodiments, the inflatable balloon 12 comprises a material having a shore hardness of between 70A and 70D. In other embodiments, the inflatable balloon 12 further comprises a wall having a thickness of between 0.003 in and 0.015 in. These ranges of hardness and wall thickness produce sufficient force to occlude or partially occlude the descending aorta 4 when the inflatable balloon 12 is inflated.

[0043] The hand pump 16 is operably connected to the catheter 14 and fluidly coupled to the first lumen 22. Activation of the hand pump 16, such as by squeezing, forces fluid, such

as ambient air, into the interior 32 of the inflatable balloon 12 under pressure through the first lumen 22 and through the first opening 26. The inflatable balloon 12 is thereby filled with fluid under pressure, which causes the inflatable balloon 12 to expand.

[0044] In some embodiments, an optional a first vacuum device 40 may be operably connected to the catheter 14, the first vacuum device 40 activating to remove fluid from the inflatable balloon 12, thereby causing the inflatable balloon 12 to deflate. The first vacuum device 40 may be fluidly connected to the first lumen 22. The first vacuum device 40 may be used to deflate the inflatable balloon 12 during insertion, repositioning, and/or during removal of the inflatable balloon 12 from the patient 1. In some embodiments, the hand pump 16 and the first vacuum device 40 may be combined into a single device, such as a hand pump with a reversible valve to allow fluid to be pumped or removed based on the valve position.

[0045] In some embodiments, the body 20 may further include a second lumen 52 and the distal end 24 of the catheter 14 may further include a second opening 54 that is fluidly coupled to the second lumen 52. The second lumen 52 may allow the second opening 54 at the distal end 24 to be fluidly connected with ambient pressure, which equalizes pressure in the stomach 8 of the patient 1 when the inflatable balloon 12 is inflated, which may prevent equalization of pressure through the esophagus 2.

[0046] In some embodiments, the body 20 may further include a third lumen 56 and the distal end 24 of the catheter 14 may further include a third opening 58, which may be fluidly coupled to the third lumen 56. The third lumen 56 may be optionally fluidly connected to a second vacuum device 60. The second vacuum device 60 may be activated to remove stomach contents when the distal end 24 is located in the patient's stomach 8. In some cases, stomach contents may need to be removed to make room for the inflatable balloon 12, or to increase effectiveness of the inflatable balloon 12k, and/or to reduce the risk of patient aspiration.

[0047] In some embodiments, the gastroesophageal resuscitative aortic occlusion device 10 further includes a pressure sensor 70 that senses internal pressure in the inflatable balloon 12. The pressure sensor 70 may be fluidly connected to the first lumen 22 so that internal pressure of the inflatable balloon 12 may be sensed so that a user may inflate the inflatable balloon 12 to the proper pressure.

[0048] In yet other embodiments, the gastroesophageal resuscitative aortic occlusion device 10 may further include a pulsatile flow sensor or pressure sensor 80, either embedded into the device, or that are operatively connected to the device but that are applied external to the patient distal to the point of balloon inflation, that sense blood pressure or flow emanating from the descending aorta 4 distal to the point of balloon

inflation. In some embodiments, the sensors may be separate from the balloon apparatus, but part of a larger system. The sensors provide data that enhances positioning of the balloon to aid in more complete occlusion of the descending aorta. In some uses, it may be desirable to only partially occlude the descending aorta, for example, if an operator determines that blood flow should only be slowed, but not stopped for medical reasons, in which case the sensors provide data that will assist in producing the desired amount of occlusion. In some embodiments, the sensors may comprise conductive bands or other pressure sensing elements in the balloon, or optical pressure sensors or ultrasonic pressure sensors for internal sensing, or external sensing (relative to the device itself) that may be attached to other bodily structures in the patient distal to the location of balloon inflation.

[0049] In some embodiments, the distal end 24 of the catheter 14 may include a plurality of cutouts 82 that increase flexibility of the distal end 24 to ease insertion of the catheter 14 through the esophagus 2.

[0050] In yet other embodiments, the distal end 24 of the catheter 14 may comprise a softer material than the catheter 14 proximate the inflatable balloon 12.

[0051] In some embodiments, the tip 30 of the distal end 24 of the catheter 14 comprises a blunt end.

[0052] In yet other embodiments, the gastroesophageal resuscitative aortic occlusion device 10 may comprise a removable sheath (not shown) that covers the inflatable balloon 12 during insertion of the inflatable balloon 12 through the esophagus 2. The sheath may break-away or dissolve when contacted with stomach acid to free the inflatable balloon 12 for inflation.

[0053] In yet other embodiments, the inflatable balloon 12 comprises an annular shape when fully inflated.

[0054] Turning now to FIGS. 5-8, an external pressure device 100 may be used alone, or in conjunction with the gastroesophageal resuscitative aortic occlusion device 10, to stop hemorrhages in various locations, both internal and external, on a body.

[0055] The external pressure device 100, also referred to as an anti-hemorrhage device 100, includes in one embodiment, a rigid platform 110 and a compression device 120 adjustably secured to the rigid platform 110. The compression device 120 includes a pressure plate carriage 122 and a strap carriage 124 that is linearly translatable relative to the pressure plate carriage 122. The pressure plate carriage 122 may also be considered to be linearly translatable relative to the strap carriage 124.

[0056] In some embodiments, the pressure plate carriage 122 and the strap carriage 124 are connected by a screw 126. More specifically, the pressure plate carriage 122 is connected to one end of the screw 126 so that when the screw 126 is rotated in a first direction, the pressure plate carriage 122 translates away from the strap carriage 124, and when the screw is rotated in a second direction, the pressure plate carriage translates towards the strap carriage 124. In some embodiments, the screw 126 comprises a first screw 128 nested within a second screw 130.

[0057] A pressure plate 132 is removably attached to the pressure plate carriage 122. The pressure plate 132 may have various shapes. For example, the pressure plate 132 may have any one of a generally triangular shape, a generally rectangular shape, a generally circular shape, a generally oval shape, or any combination thereof. A bottom surface of the pressure plate 132 may be shaped to fit a certain portion of the human body. For example, the bottom surface of the pressure plate 132 may be convex shaped, for example to compliment the groin area, the bottom surface of the pressure plate 132 may be concave shaped, for example to compliment a side of the leg or arm, or the bottom surface of the pressure plate 132 may be angled with respect to the pressure plate carriage 122, for example to compliment a side of the torso. In yet other embodiments, the bottom surface of the pressure plate 132 may combine any of the aforementioned shapes to better complement a location on the body having a hemorrhage. In some embodiments, the bottom surface of the pressure plate may include an absorbent layer 134 and/or may include a clotting agent to enhance blood clotting. By form fitting the bottom surface of the pressure plate 132 to the hemorrhage location, the pressure plate 132 can slow or stop bleeding more quickly, for example, by providing targeted pressure at the hemorrhage location. Additionally, the removable attachment of the pressure plate 132 to the pressure plate carriage 122 makes changing of the pressure plate 132 quick and easy. The pressure plate 132 may be removably attached to the pressure plate carriage 122 by any removable connection that provides stability to the pressure plate 132 when connected while allowing quick and easy removal from the pressure plate carriage 122. Some example removable connections include, but are not limited to, a snap-fit connection, a magnetic connection, and a removable fastener connection. A plurality of pressure plates 132 may be included in a kit with the external pressure device 100, each pressure plate 132 having a different shape, to give a user many options for selecting an optimal shape for a particular bleeding location. In some embodiments, the pressure plate 132 may include movable sections that allow the overall shape of the pressure plate 132 to be changed to better fit a bleeding location.

[0058] The rigid platform 110 comprises a first rigid housing 140 and a second rigid housing 142 that are pivotably connected to one another, for example by a hinge. Each of

the first rigid housing 140 and the second rigid housing 142 may comprise a perimeter rim 144a, 144b that surrounds a central pocket 146a, 146b (FIG. 6). The central pockets 146a, 146b form an enclosure when the first rigid housing 140 and the second rigid housing 142 are pivoted to a closed position (FIG. 7). The central pockets 146a, 146b are large enough to receive the pressure plate 132, the screw 126, the pressure plate carriage 124 and a plurality of straps 150. The central pockets 146a, 146b are also sized and shaped to receive other optional components, such as the gastroesophageal resuscitative aortic occlusion device 10 of FIGS. 1-4, and/or a plurality of pressure plates 132 having different shapes.

[0059] In an open and deployed position (FIG. 5), the first rigid housing 140 and the second rigid housing 142 form a stable platform for a portion of a body having a hemorrhage. In a closed position (FIG. 7), the first rigid housing 140 and the second rigid housing 142 form an enclosed container that protects components and devices that may be used for hemorrhage control. The enclosed container is compact and easy to carry as well as rugged and damage resistant and waterproof. The enclosed container may include one or more handles 148 to facilitate carrying of the device.

[0060] The compression device 120 is adjustably secured to the rigid platform 110 with a first adjustable strap 160 and a second adjustable strap 162. The first adjustable strap 160 is connected to the first rigid housing 140 and the second adjustable strap 162 is connected to the second rigid housing 142. The first adjustable strap 160 and the second adjustable strap 162 facilitate gross or large adjustments in the compression device 120 during initial placement of the compression device 120. The first adjustable strap 160 and the second adjustable strap 162 may include adjustment loops 164 located on the rigid platform 110 and on the strap carriage 124.

[0061] A plurality of interlocking teeth 170 may be formed on the outer side surfaces of the first rigid housing 140 and on the second rigid housing 142. The interlocking teeth 170 form stabilizing buttresses with the ground when the first rigid housing 140 and the second rigid housing 142 are in the open and deployed position (FIG. 5), and the interlocking teeth 170 align the first rigid housing 140 and the second rigid housing 142 when moving towards a closed position (FIG. 7) by interlocking with one another.

[0062] As illustrated in FIG. 6, an anti-hemorrhage kit 200 may be formed that includes the anti-hemorrhage device having the rigid platform 110 and the compression device 120, as discussed above. In some embodiments, the anti-hemorrhage kit 200 may include the gastroesophageal aortic occlusion device 10. In other embodiments, the anti-hemorrhage kit 200 may include the plurality of pressure plates 132.

[0063] One method of slowing or stopping a hemorrhage on body includes procuring the kit 200 of FIG. 6 and opening the kit 200 by pivoting the first rigid housing 140 relative to the second rigid housing 142 until the central pockets 146a, 146b are exposed, thereby exposing contents stored in the central pockets 146a, 146b. The contents are removed and the rigid platform 110 is flipped over so that the central pockets 146a, 146b are facing downward, which results in a stable platform being formed for a body or body part having a hemorrhage. The first and second straps 160, 162, if not already attached, are secured to the rigid platform 110 at the adjustment loops 164, as illustrated in FIG. 5. A pressure plate 132 is then chosen based on the hemorrhage location and the pressure plate 132 is removably secured to the pressure plate carriage 122, which results in the configuration illustrated in FIG. 5.

[0064] A body part, such as a torso 300 is placed on the rigid platform 110, as illustrated in FIG. 8. The compression device 120 is located proximate an area of hemorrhage 310. The compression device 120 is operated, for example, by turning the screw 126 to move the pressure plate 132 away from the strap carriage 124, which applies pressure to the area of hemorrhage 310. The first and second straps 160, 162 are advantageously at least partially spaced from the torso 300 near the rigid platform 110 so that the torso 300 is not fully constricted circumferentially when the compression device 120 is operated. The first and second straps 160, 162 are held away from the torso by the rigid platform 110. As a result, targeted pressure is applied to the area of hemorrhage 310 while allowing blood to flow in other regions of the torso 300 not affected by the hemorrhage. In the same manner, other body parts may be placed on the rigid platform 110 to reduce or stop hemorrhages.

[0065] In one embodiment, the gastroesophageal resuscitative aortic occlusion device 10 and external pressure device 100 described above may be used in a method of occluding the descending aorta 4.

[0066] The gastroesophageal resuscitative aortic occlusion device 10 may be inserted into the stomach 8 of a patient through the esophagus 2. The hand pump 16 may be activated to pressurize the inflatable balloon 12 with a fluid. External pressure is applied to the abdomen of the patient 1 with the external pressure device 100 until blood flow through the descending aorta 4 is reduced or stopped.

[0067] The disclosed gastroesophageal resuscitative aortic occlusion device and external pressure device provide hemorrhage control for the management of trauma and an inhibition of blood flow below the diaphragm to enhance coronary and cerebral perfusion. Studies have shown that, although over half of the tissue beds are below the diaphragm, approximately two-thirds of bleeding that leads to hemorrhagic shock occurs below the

diaphragm. Therefore, the ability to control bleeding below the diaphragm provides a significant advantage particularly in management of trauma. This is particularly useful in treating patients who have suffered abdominal injuries from knives and guns, blunt trauma from falls, explosions, motor vehicle accidents, complications due to the delivery of babies from subdiaphragmatic hemorrhaging and other vascular catastrophes below the diaphragm such as ruptured abdominal aortic aneurysms. The disclosed gastroesophageal resuscitative aortic occlusion device and external pressure device are particularly useful in battlefield applications in which it is essential to be able to rapidly control life-threatening hemorrhage in a non-invasive manner in order to avoid immediate death and complications from infections and the like until definitive repair of injuries can take place. Additionally, the ability to perform this procedure rapidly and effectively reduces the exposure of the medical personnel to battlefield injuries. Finally, the devices described herein may be used to elevate coronary and cerebral perfusion pressure and blood flow during cardiopulmonary resuscitation in the setting of cardiac arrest by allowing redirection of blood flow produced by chest compression to the heart and brain and away from the abdomen. Increasing coronary perfusion pressure advantageously aids in returning spontaneous circulation during cardiopulmonary resuscitation.

[0068] Changes and modifications in the specifically described embodiments can be carried out without departing from the principles of the invention. For example, electrodes can be applied to stomach balloons for use in cardiac pacing and defibrillation. Although balloons and cuffs may be inflated using air, other techniques involving hydraulic fluids and mechanical actuators may suggest themselves to those skilled in the art. Although inflatable devices are illustrated as spherical or annular, other shapes could be used such as cylindrical, pill-shaped, and the like. Also, the various elements of each illustrated embodiment of the invention can be combined and substituted with other of the embodiments. The embodiments are provided in order to illustrate the invention and should not be considered limiting. The described methods and devices are to be limited only by the scope of the appended claims.

CLAIMS

1. An anti-hemorrhage device comprising:
a rigid platform; and
a compression device adjustably secured to the rigid platform.
2. The anti-hemorrhage device of claim 1, wherein the compression device comprises a pressure plate carriage and a strap carriage that is linearly translatable relative to the pressure plate carriage.
3. The anti-hemorrhage device of claim 2, wherein the pressure plate carriage and the strap carriage are connected by a screw.
4. The anti-hemorrhage device of claim 3, wherein the screw comprises a first screw nested within a second screw.
5. The anti-hemorrhage device of claim 2, further comprising a pressure plate removably attached to the pressure plate carriage.
6. The anti-hemorrhage device of claim 5, wherein the pressure plate has a generally triangular shape.
7. The anti-hemorrhage device of claim 1, wherein the rigid platform comprises a first rigid housing and a second rigid housing, the first rigid housing and the second rigid housing being connected to one another by one of a pivotable connection, a slide connection, and a snap-fit connection.
8. The anti-hemorrhage device of claim 7, wherein each of the first rigid housing and the second rigid housing comprise a perimeter rim that surrounds a central pocket.
9. The anti-hemorrhage device of claim 8, wherein the compression device is adjustably secured to the rigid platform with a first adjustable strap and a second adjustable strap.
10. The anti-hemorrhage device of claim 9, wherein the first adjustable strap is connected to the first rigid housing and the second adjustable strap is connected to the second rigid housing.
11. An anti-hemorrhage kit comprising:
an anti-hemorrhage device including a rigid platform, and a compression device adjustably secured to the rigid platform; and
a gastroesophageal aortic occlusion device.

12. The kit of claim 11, further comprising a plurality of pressure plates that are adapted to be removably secured to the compression device.

13. The kit of claim 11, wherein the compression device comprises a pressure plate carriage and a strap carriage that is linearly translatable relative to the pressure plate carriage.

14. The kit of claim 13, wherein the pressure plate carriage and the strap carriage are connected by a screw.

15. The kit of claim 11, wherein the rigid platform comprises a first rigid housing and a second rigid housing.

16. A method of stopping or slowing a hemorrhage, the method comprising:
placing a torso on a rigid platform;
attaching a first strap to a first side of the rigid platform;
attaching a second strap to a second side of the rigid platform;
connecting the first and second straps to a compression device;
locating the compression device over an area of hemorrhage;
operating the compression device to apply pressure to the area of hemorrhage,
wherein the first and second straps are at least partially spaced from the torso so that the torso is not fully constricted circumferentially when the compression device is operated.

17. The method of claim 16, wherein operating the compression device includes turning a screw that separates a pressure plate carriage from a strap carriage.

18. The method of claim 16, further comprising selecting a first pressure plate from a plurality of pressure plates, and removably attaching the first pressure plate to the compression device, wherein the first pressure plate is selected based on the location or shape of the area of hemorrhage.

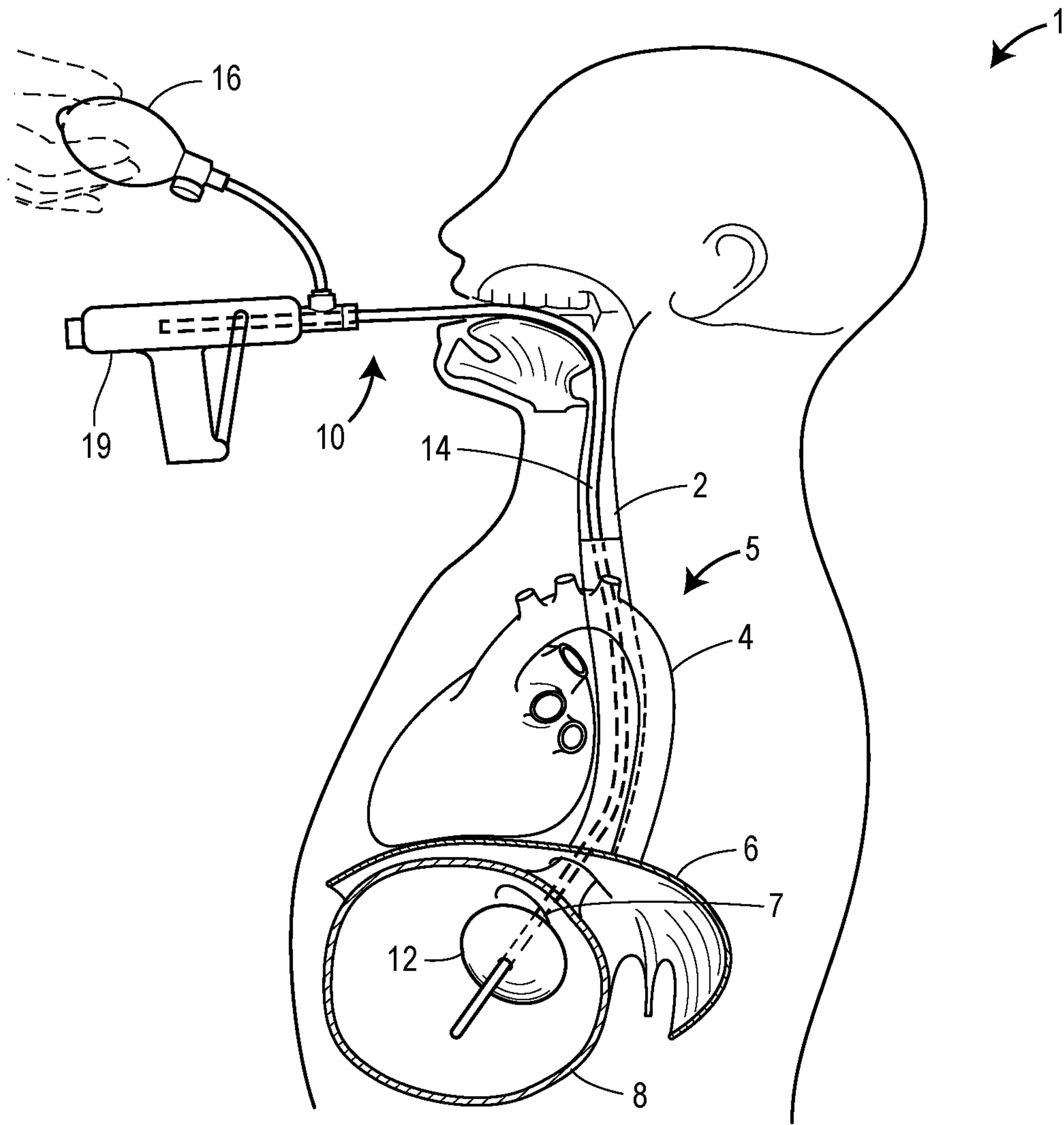


FIG. 1

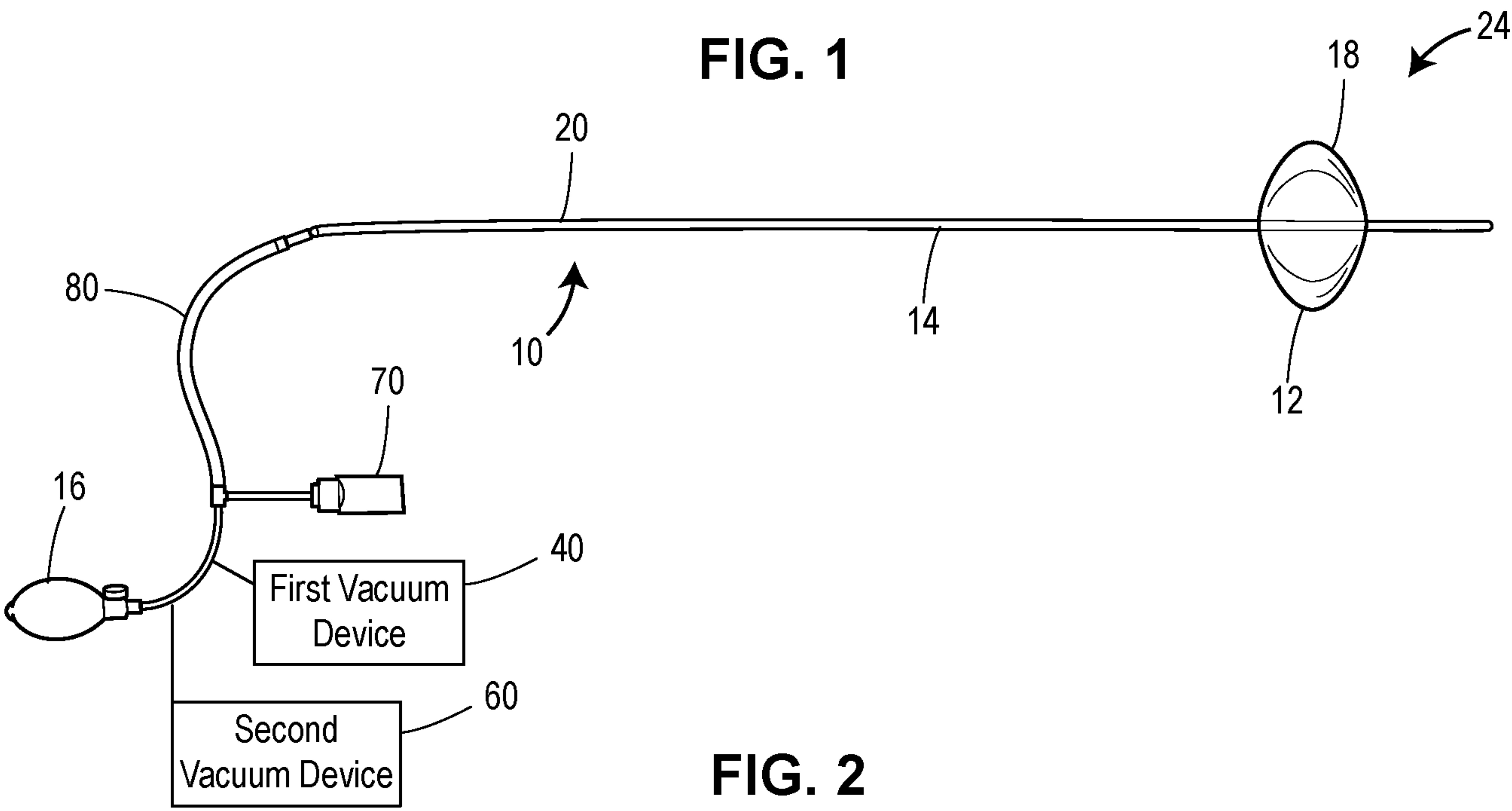


FIG. 2

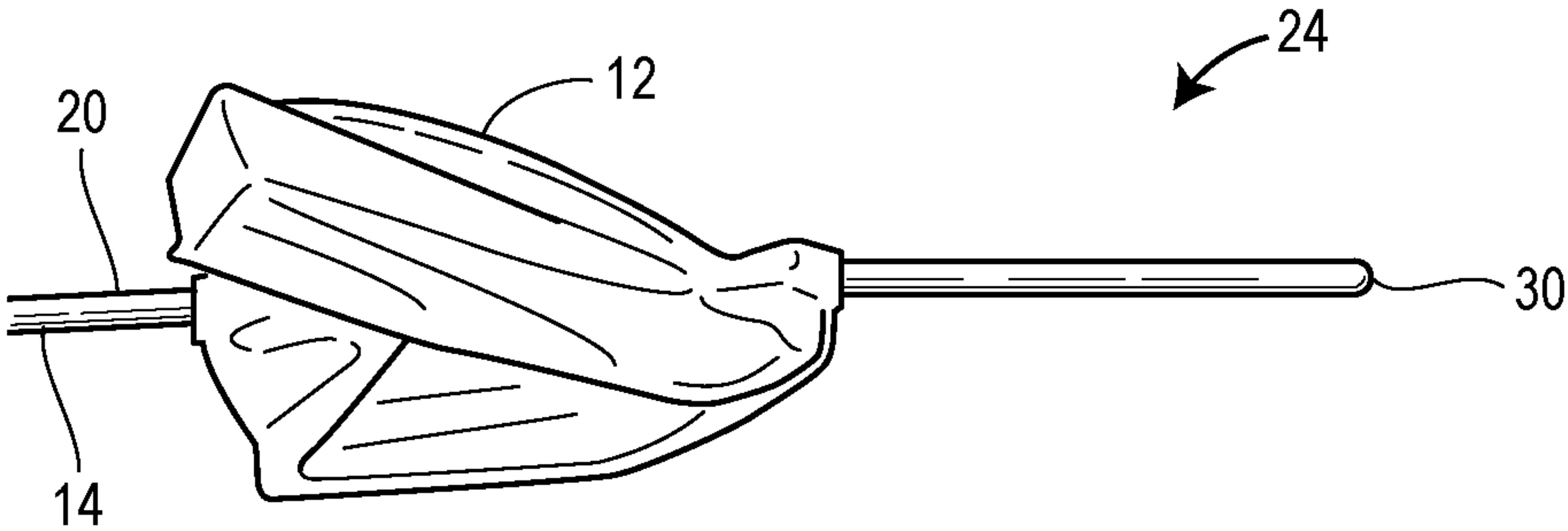


FIG. 3

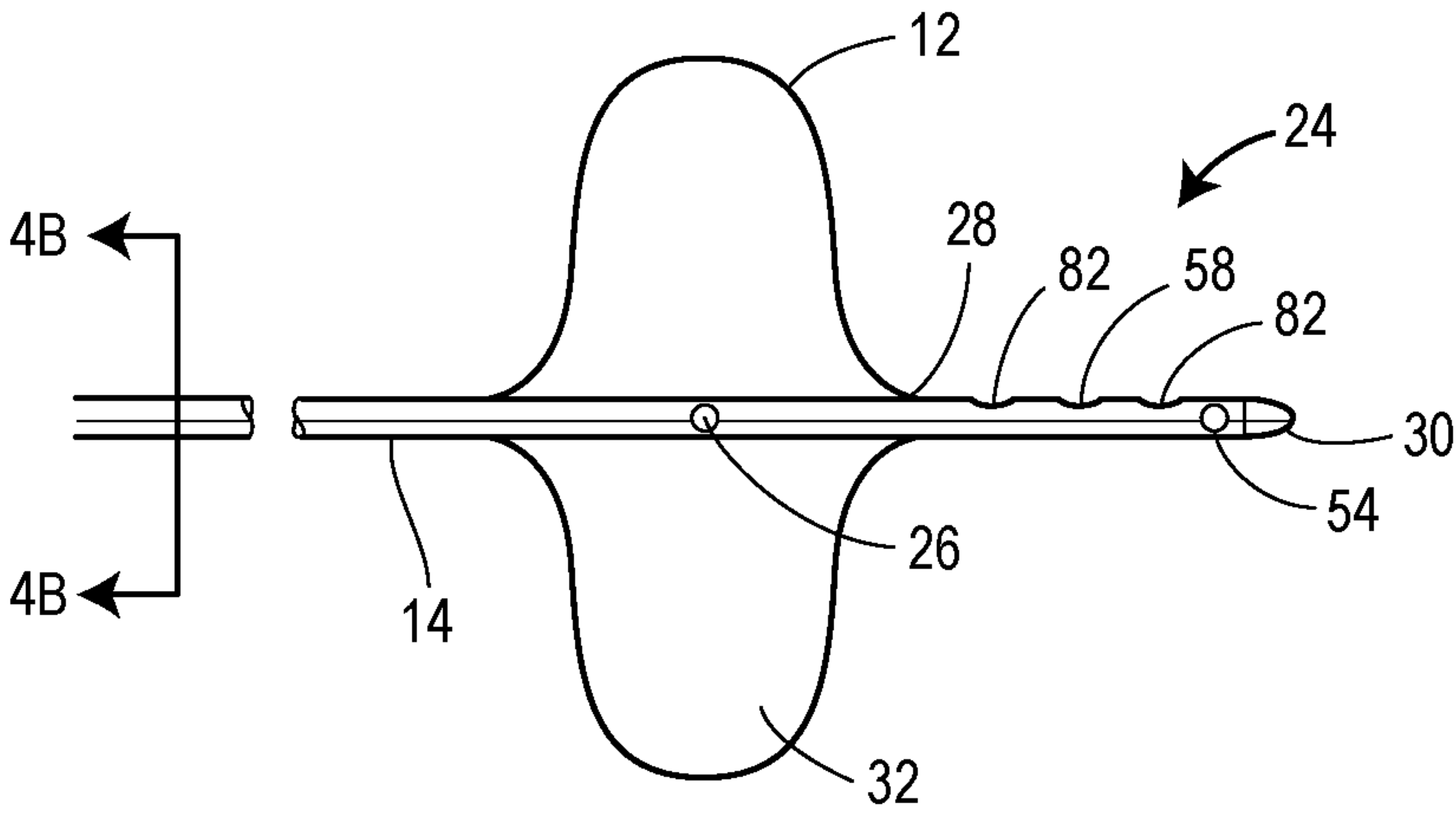


FIG. 4A

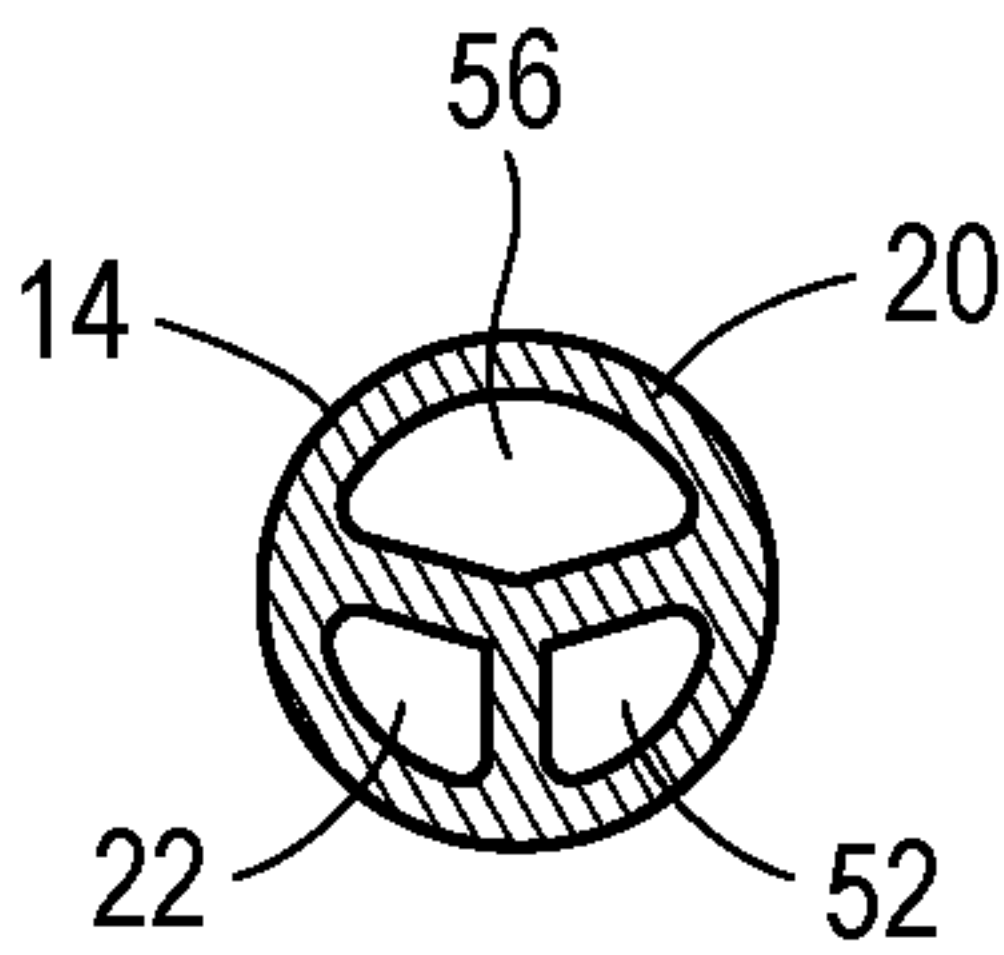


FIG. 4B

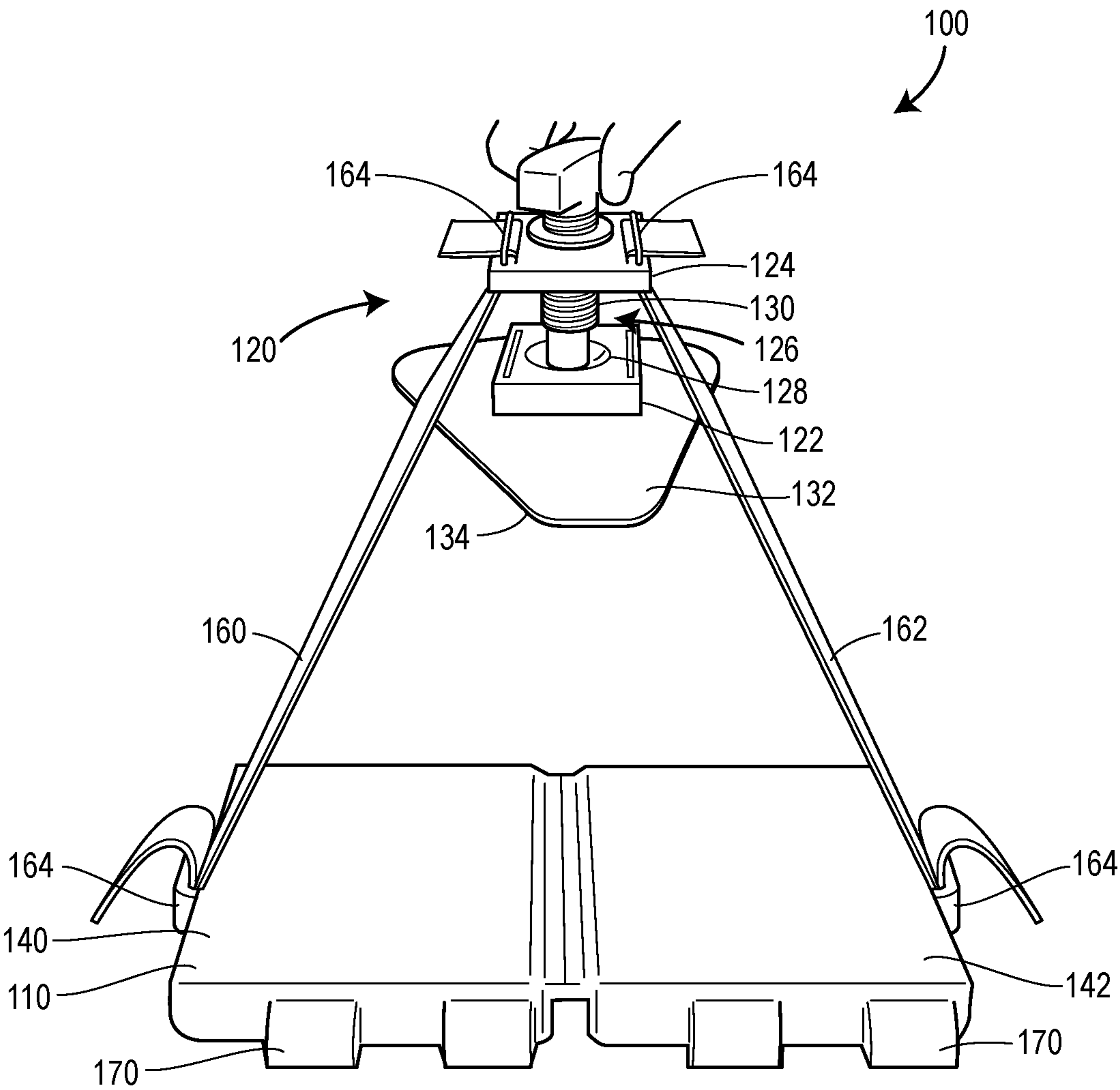


FIG. 5

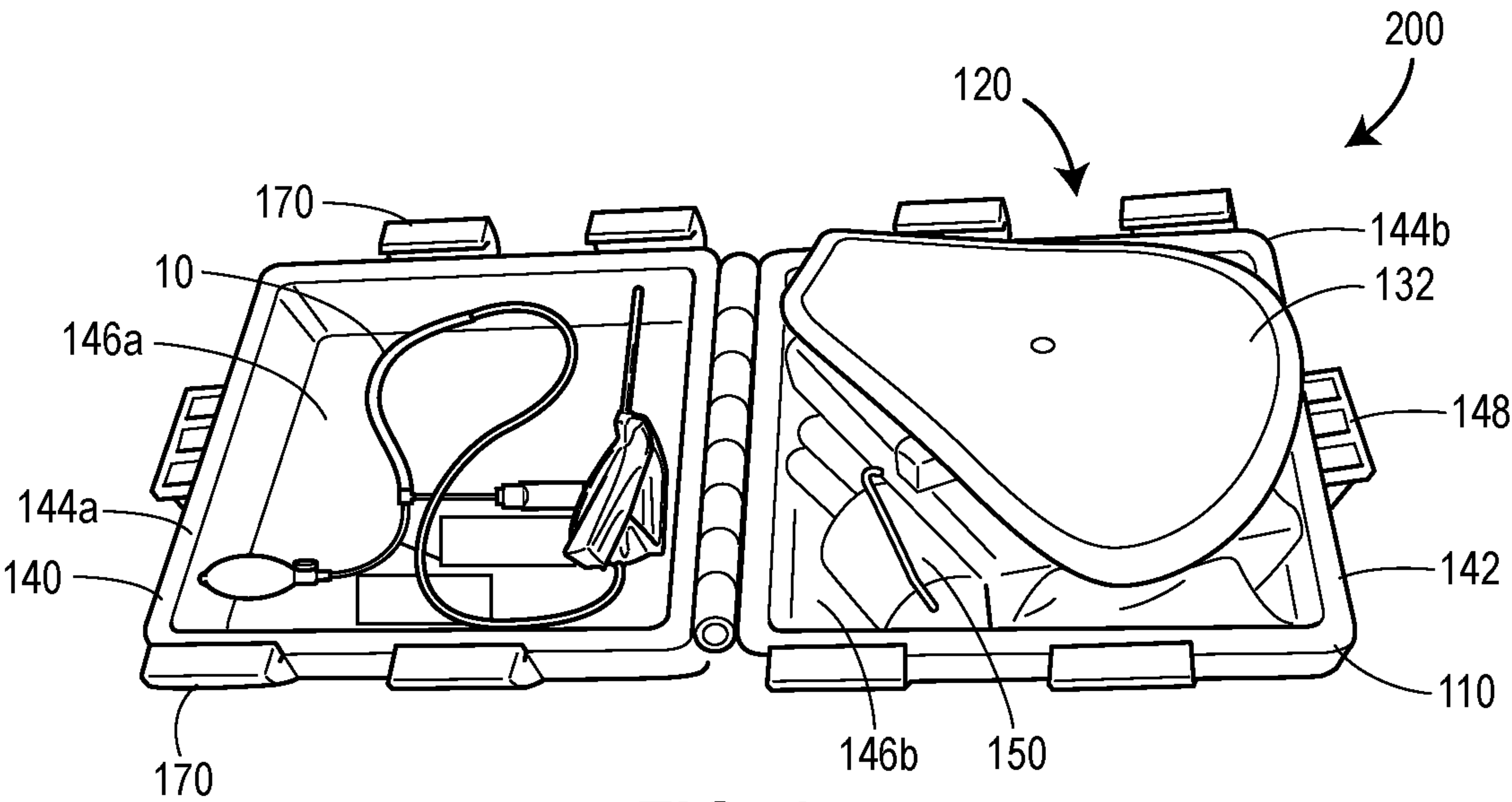


FIG. 6

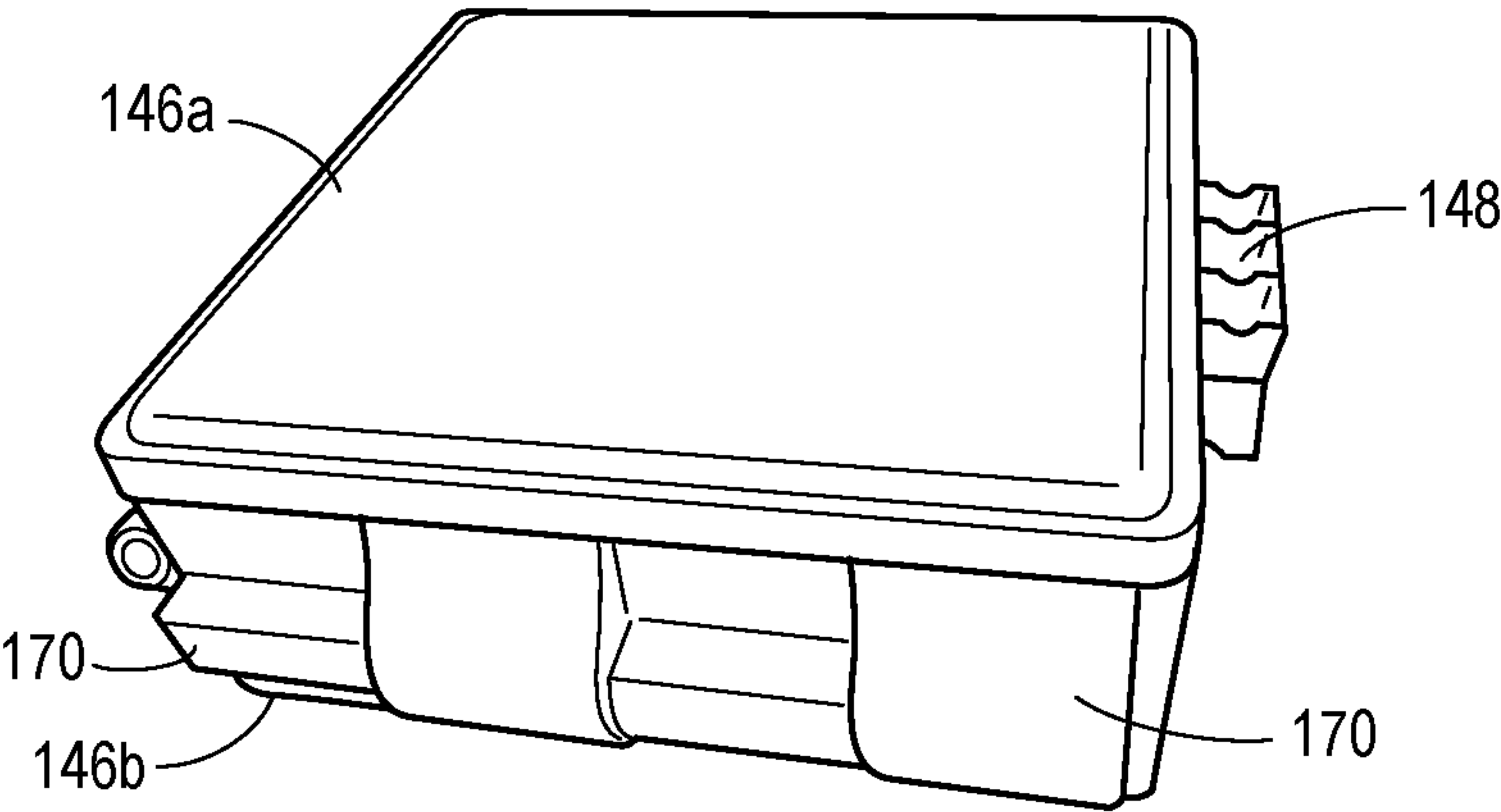


FIG. 7

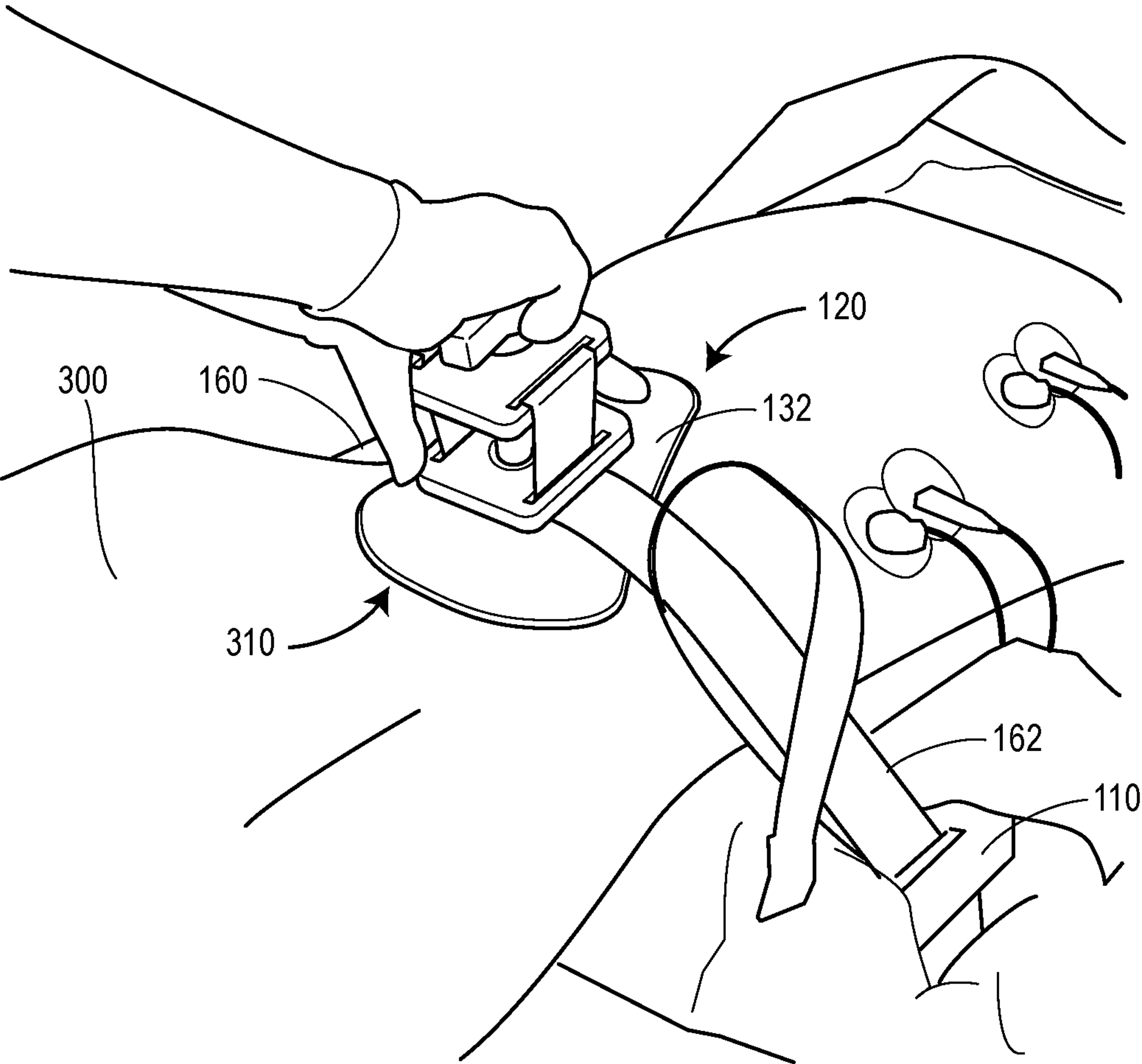


FIG. 8

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 20/67247

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61B 17/00, A61B 17/12, A61B 17/132 (2021.01)

CPC - A61B 17/1325, A61B 17/132, A61B 17/00, A61B 17/12, A61B 2017/12004

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- A	US 2018/0193030 A1 (Regents of the University of Michigan) 12 July 2018 (12.07.2018), entire document	1-4 --- 7-10
X --- Y --- A	US 4,742,825 A (Freund et al.) 10 May 1988 (10.05.1988), entire document	1-3, 5-6 --- 11-18 --- 7-10
Y	US 2002/0016608 A1 (Ward) 07 February 2002 (07.02.2002), entire document	11-15
Y	US 2019/0290288 A1 (6:8 Medical Solutions LLC) 26 September 2019 (26.09.2019), entire document	16-18
A	US 6,454,097 B1 (Blanco) 24 September 2002 (24.09.2002), entire document	7-10
A	US 2007/0198052 A1 (Ben-David) 23 August 2007 (23.08.2007), entire document	1-18

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

09 MARCH 2021

Date of mailing of the international search report

MAR 25 2021

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Lee Young

Telephone No. PCT Helpdesk: 571-272-4300

FY22 JOINT WARFIGHTER MEDICAL RESEARCH PROGRAM PRE-APPLICATION TEMPLATE

Describe the research or product development effort that establishes the basis for the proposed follow-on effort.

1. Title of Project / Principal Investigator / Institution:

Title: Development of Gastroesophageal Resuscitative Occlusion of the Aorta (GROA) for Treatment of Noncompressible Torso Hemorrhage

Principle Investigator: Kevin R. Ward

Institution: University of Michigan

2. Contract or assistance agreement number:

W81XWH-18-1-0033

3. Funding agency and POC for prior effort:

Department of the Army, USA MED Research Acquisition Activity (USAMRAA)

Congressionally Directed Medical Research Programs (CMDRP)

Science Officer: Ms. Rene Smith

Science Officer Email: rene.k.smith.civ@mail.mil

US Army Medical Research Acquisition Activity (USAMRAA)

Grants Specialist/Contract Specialist: Ms. Raven Conner

Grants Specialist/Contract Specialist Email: raven.n.conner.civ@mail.mil

4. Award start date, end date, total value, balance of unexpended funds, option years remaining on the award:

Award Start and End Date: 02/01/2018-01/31/2022

Total Award Value: \$2,995,616

Balance of unexpended funds: \$0.00

Option years remaining on the award: none

5. Products or deliverables accomplished / expected:

The overall goal of the project was to develop a less invasive alternative to Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) for temporary treatment of noncompressible torso hemorrhage of the abdomen and pelvis. The project leveraged the anatomical relationship of the esophagus and stomach to the abdominal aorta and the vertebral bodies to allow for compressive occlusion of the aorta between the posterior wall of the stomach and the anterior surface of the thoracic vertebral bodies. The less invasive device and method is called Gastroesophageal Resuscitative Occlusion of the Aorta or GROA. GROA is performed by placing a special oro-gastric balloon catheter into the stomach. Once placed the balloon is inflated followed by the application of external pressure to the epigastric area with the use of special adjustable plate to occlude the aorta. GROA is viewed as a minimally invasive point of injury device that will serve as a bridge to REBOA and definitive surgical hemostasis, allowing medics to rapidly stabilize a casualty and control noncompressible torso hemorrhage in austere settings when REBOA is not available. We accomplished the following during our initial product development effort:

- a. Expected Deliverable: Development of a prototype gastroesophageal balloon catheter device and system capable of rapid insertion and producing gastroesophageal resuscitative occlusion

FY22 JOINT WARFIGHTER MEDICAL RESEARCH PROGRAM PRE-APPLICATION TEMPLATE

of the aorta (GROA) at a zone II level of occlusion in a large animal (swine) model.

Accomplishment: GROA placement and activation within 2 minutes resulting in Zone II occlusion at the level of the celiac axis confirmed with hepatic artery blood flow monitoring.

- b. Expected Deliverable: Comparison of the physiologic tolerance and short-term survival to Zone II aortic occlusion by GROA versus REBOA at 30-, 60-, and 90-minute time periods.

Accomplishment: No significant difference found in short term physiologic tolerance and survival between GROA and REBOA in a large animal (swine) model.

See: Tiba MH, McCracken BM, Colmenero CI, Plott JS, Leander DC, Greer NL, Wang SC, Shih AJ, Eliason JL, Ward KR. Gastroesophageal resuscitative occlusion of the aorta: Physiologic tolerance in a swine model of hemorrhagic shock. J Trauma Acute Care Surg. 2020 Dec;89(6):1114-1123. PMID: 33112534.

- c. Expected Deliverable: Comparison of GROA to REBOA on ability to increase short-term survival in a large animal (swine) model of lethal liver laceration and hemorrhage.

Accomplishment: Both GROA and REBOA significantly increased short-term survival with no significant difference in performance between GROA and REBOA when compared to control animals receiving no intervention.

See: McCracken BM, Tiba MH, Colmenero Mahmood CI, Leander DC, Greer NL, Plott JS, Shih AJ, Wang SC, Eliason JL, Ward KR. Gastroesophageal resuscitative occlusion of the aorta prolongs survival in a lethal liver laceration model. J Trauma Acute Care Surg. 2022 May 1;92(5):880-889. doi: 10.1097/TA. Epub 2021 Oct 27. PMID: 34711792.

- d. Expected Deliverable: Feasibility trial to transition GROA application to REBOA in a large animal (swine) model of lethal liver laceration and hemorrhage.

Accomplishment: Successfully demonstrated ability to initially use GROA to control life-threatening hemorrhage followed by ability to insert and activate REBOA for subsequent hemorrhage control without any additional hemorrhage.

See: Tiba MH, McCracken BM, Geer NL, Cramer TA, Mahmood CI, Priambada Putra KB, Plot JS, Shih AJ, Wang SC, Eliason JL, Ward KR. Tandem use of gastroesophageal resuscitative occlusion of the aorta followed by REBOA in a lethal liver laceration model. J Trauma Acute Care Surg 2022: Accepted.

6. Challenges to providing products or deliverables related to this effort:

All specific aims of the previous effort were accomplished as the focus was on early-stage feasibility. However, as is common in all early-stage technology development, funding levels restricted the ability to:

- a: Perform longer term outcome studies to examine for complications from the GROA device.
- b: Perform more intense iterative design and manufacturing of the GROA product.
- c: Use and de-risk GROA in human cadavers.

7. Estimated Technology Readiness Level (TRL) or Knowledge Readiness Level (KRL) of your current or previous research or product development effort:

The previously funded project above resulted in the GROA product reaching a Technology Readiness Level of 3.

FY22 JOINT WARFIGHTER MEDICAL RESEARCH PROGRAM PRE-APPLICATION TEMPLATE

Describe the proposed follow-on research or product development effort for consideration under the FY22 Joint Warfighter Medical Research Program.

1. Title of Proposal / Principal Investigator / Institution:

Title: Refinement and Testing of Gastroesophageal Resuscitative Occlusion of the Aorta (GROA) for Treatment of Noncompressible Torso Hemorrhage

Principal Investigator: Kevin R. Ward

Institution: University of Michigan

2. Describe the proposed follow-on effort and explain how it is a logical continuation of the previously funded, prior year research or product development effort:

To logically build on the results of the previously funded effort, we propose to conduct additional GROA testing and design optimization required for near-term translation:

- a. Test GROA and compare to REBOA in a large animal (swine) longer term (72 hour) survival model of lethal hemorrhage to define pathologic and histopathologic complications of aortic occlusion. This is an important next step because prior testing only occurred over periods of 30 to 90 minutes with a four-hour recovery period, which did not allow us to examine for potential complications as needed for translation.
- b. Test GROA in comparison to REBOA for the ability to occlude the aorta in a perfused human cadaver model of hemorrhage. This will be an important next step to ensure that GROA can routinely and effectively occlude the aorta in humans.
- c. Obtain combat casualty care provider feedback on the use and design of the GROA system to optimize design and utility allowing its future use in combat settings.
- d. Lock in design and components of the GROA system to support the regulatory process for future phase I clinical safety testing.

3. Indicate the FY22 JWMP Focus Area(s) to be addressed by the proposed effort:

Combat casualty care: Novel solutions for non-compressible torso hemorrhage.

4. Major milestones:

- a. Completion of large animal (swine) lethal hemorrhage models comparing GROA to REBOA on 72-hour outcomes and tissue histopathology.
- b. Completion of efficacy studies in human perfused cadaver models comparing GROA to REBOA efficacy, implementation differences, and characteristics in aortic occlusion.
- c. Completion and incorporation of user design features and characteristics from diverse combat casualty care providers to produce prototypes suitable for future phase I clinical testing.

5. Projected period of performance and proposed cost / budget per year:

Project Period of Performance: March 1, 2023 - April 30, 2026

Total Proposed Cost: \$4,050,000

Year 1 March 1, 2023-April 30, 2024: \$1,350,000 (total cost)

Year 2 March 1, 2024-April 30, 2025: \$1,350,000 (total cost)

Year 3 March 1, 2025-April 30, 2026: \$1,350,000 (total cost)

6. Describe how the proposed effort will augment and/or accelerate clinical, technical, or materiel/knowledge product development with a clear benefit to military medicine:

All activities of the proposed effort are meant to de-risk and optimize the GROA system for FDA evaluation, preparing it for a future phase I clinical safety trial and commercialization.

The results generated will inform the regulatory and commercialization strategy including

FY22 JOINT WARFIGHTER MEDICAL RESEARCH PROGRAM PRE-APPLICATION TEMPLATE

locking in designs and identifying manufacturers and other efforts to advance the GROA system from a TRL of 3 to a TRL of 5. The product is envisioned to address a severe limitation in the combat casualty care field treatment of noncompressible torso hemorrhage since REBOA is invasive and requires special training not widely available in the battlefield. GROA will overcome these issues and serve as a bridge to REBOA since it is minimally invasive and easier to implement.

7. Expected products or deliverables:

We expect the proposed work to produce the following:

- a. Evidence supporting no long-term complications of GROA use in a swine 72-hour survival model of lethal hemorrhage in comparison to REBOA.
- b. Evidence from perfused human cadaver models supporting the ability of GROA to occlude the aorta similar to REBOA.
- c. Critical feedback using perfused human cadaver models from military combat casualty care providers (special operators, combat medics, early role 1 and 2 emergency/trauma physicians) on form factors, ergonomics, and other use characteristics.
- d. A refined prototype GROA device and system with completed design files and testing in animals and human cadavers that supports pre-submission communications with the FDA that would support future Phase I clinical testing and commercialization.

8. Major challenges anticipated:

The major anticipated challenges for this proposed effort include:

- a. Obtaining adequate efficacy testing and user feedback from perfused cadaver models to lock in designs and performance to support moving the technology to a TRL of 5 and to discussions with the FDA. The use of perfused cadaver models for product design and testing is relatively new. However, we will be collaborating with a DoD partner with significant experience in the use of perfused cadavers to address this potential challenge.
- b. Identifying and engaging an OEM partner to create and manufacture the final GROA balloon system given recent supply chain challenges created by the COVID pandemic. Despite previous supply chain challenges, we feel confident given the current status of the COVID pandemic that we will be able to engage one or more OEM partners to succeed.

9. Specify whether this work will involve collaboration with a DoD activity:

This work will involve collaboration with the following DoD activity:

Madigan Army Medical Center – Points of Contact:

- a. MAJ Jason Bingham, MD – General Surgery Department Chair, General Surgery Residency Associate Program Director – Jason.r.bingham4.mil@mail.mil
- b. LTC Erik Roedel, MD – Madigan Army Medical Center Trauma Surgeon – erik.q.roedel.mil@mail.mil
- c. MAJ John McClellan, MD – Madigan Army Medical Center Trauma Surgeon, Special Forces Surgeon – john.m.mcclellan18.mil@mail.mil

10. Specify whether the effort involves animal use, and if so whether the proposed research is covered under an existing animal use protocol:

This effort does involve animal use. Part of the proposed research is covered by an existing animal use protocol (PRO00009566). Prior to funding, we will make amendments to update the current protocol to include additional procedures and the longer monitoring period. We do not anticipate challenges in receiving approval for these given our previous experience.

11. Specify whether the effort involves human subjects use, and if so whether the proposed research is covered under an existing human use protocol:

This does not involve living human subjects. The project will utilize perfused human cadavers.

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12. Specify whether the effort will be a clinical trial (i.e., a research study in which one or more human subjects are prospectively assigned to one or more interventions, which may include placebo or other control, to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes):

This effort is not a clinical trial.

13. Specify whether prior federally-funded Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR) data supports the follow-on effort, and if so explain active SBIR/STTR data rights:

No federally-funded Small Business Innovation Research or Small Business Technology Transfer grants have been or will be used to support the research.

14. Transition Potential

14a. Describe the regulatory strategy, including whether the anticipated product/outcome will require FDA approval, and if so list interactions with the FDA to date:

The GROA device will require FDA clearance prior to marketing for sale. While we have not had any interactions with the FDA regarding the GROA device, we anticipate that it may follow a similar regulatory pathway to the REBOA device, which is regulated as a Class II device as a vascular clamp.

We will create the design history file, design review, and a device master record initiated to support either a 510(k) or Premarket Approval (PMA). Once a design freeze is achieved for the GROA system—which will be a primary endpoint of this grant application—we plan to work with regulatory experts and the FDA to create alignment on the final testing needed for an FDA submission and subsequent clearance as a Class II Medical Device (TLR 4 activities). Furthermore, we will strive to have all component suppliers identified and qualified for critical components and audited for cGMP/QSR compliance. A design history and testing file coupled with any DME review will be created and verified. A product development plan will be drafted. We will intensely investigate and determine substantially equivalent devices and their classification for a 510K. It is also anticipated that a Pre-Investigational Device Exemption (IDE) meeting will be held with the Center for Devices and Radiologic Health (CDRH) to determine device classification. As a part of this we will validate data and readiness with manufacturing partners for cGMP inspection.

14b. Specify whether there is a commercialization strategy for the product/outcome, and if so briefly describe:

Following the conclusion of this grant, we expect to have achieved a design freeze for the GROA device with sufficient verification testing as indicated above showing that GROA is safe and efficacious to a degree to support a Phase I clinical safety trial. During the performance period we will be working to interest companies in the trauma space, such as Precision Trauma, to commercialize GROA. We fully anticipate that the GROA system will be licensed to a commercial entity near the time of completion of the proposed project.

14c. Estimated TRL or KRL of the product/outcome at the end of the proposed follow-on effort:

We anticipate that the GROA technology will achieve a TRL of 5 by the end of the 3-year performance period.