

AWARD NUMBER: W81XWH-19-2-0007

TITLE: Development of Advanced Occlusion Controller (APOC) for pREBOA to Include Development of Next-Generation pREBOA-PRO

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CONTRACTING ORGANIZATION: Prytime Medical Devices, Inc.

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1) INTRODUCTION: *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

For combat-injured Soldiers, non-compressible torso hemorrhage (NCTH) is the largest cause of potentially-preventable deaths on the battlefield. Resuscitative Endovascular Balloon Occlusion of the AORTA (REBOA) is a technique to control NCTH in the abdomen and pelvis. As observed in both animal studies and clinical use, safe occlusion time for Zone 1 REBOA is limited. Exceeding the occlusion time that is recommended in the current Joint Trauma System (JTS) REBOA Clinical Practice Guideline of 30-60 minutes risks serious injury or death. In order to extend safe occlusion time with REBOA, the partial REBOA (pREBOA) strategy has been developed. Prytime Medical developed the pREBOA-PRO™ catheter, capable of achieving pREBOA and needs to continue development in order for the catheter to be available on the market for clinical use. The catheter will allow clinicians ease of use in achieving pREBOA and extending possible occlusion time. In addition to the new catheter design, Prytime Medical has developed a controller for automated maintenance of pREBOA. However, the controller needs to be miniaturized and refined for use in a deployed setting. We are addressing the problems listed above by optimizing the balloon for partial REBOA (pREBOA) and submission of a 510k for pREBOA-PRO™ to FDA. Development of the next generation ≤7Fr guidewire free, single access point, pREBOA-PRO™ catheter with integrated digital display designed specifically to work standalone or in conjunction with a miniaturized Advanced Partial Occlusion Controller (APOC) will provide precision perfusion control to medical personnel working in austere conditions. This next generation catheter builds upon the technology of our flagship catheter, the ER-REBOA™, but is unique in the fact that it has the only balloon specifically designed for partial REBOA. This will allow for extended occlusion times, which, in turn, allows for longer transport times for combat wounded soldiers suffering from NCTH to reach definitive surgical care.

2) KEYWORDS: *Provide a brief list of keywords (limit to 20 words).*

REBOA, non-compressible torso hemorrhage, hemorrhage, partial REBOA, prolonged field care, controller, precision perfusion control

3) ACCOMPLISHMENTS: *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

The goal of this effort is to optimize the balloon for partial REBOA (pREBOA) and submit 510k for pREBOA-PRO™ to FDA, develop the next generation ≤7Fr guidewire free, single access point, pREBOA-PRO™ catheter with integrated digital display designed specifically to work standalone or in conjunction with an Advanced Partial Occlusion Controller (APOC). In addition, rigorous animal data relative to ischemia, reperfusion, throughput, and neuro and vascular safety endpoints will be developed.

The Phase 2 Objectives and Milestones are as follows:

Phase 2, Objective 1 Milestone 1: Production Quality Prototype of next generation pREBOA-PRO™ (achieved June 2020)

Phase 2, Objective 2 Milestone 1: Prototype APOC design (achieved Aug 2020)

Phase 2, Objective 3: Development of Integrated Pressure Display (achieved June 2020)

Phase 2, Objective 4 Milestone 1: Local IACUC approval (achieved May 2019)

Phase 2, Objective 4 Milestone 2: ACURO approval (achieved May 2019)

Phase 1, Objective 4 Milestone 3: Submission of final report of porcine trials for publication in DTIC. (achieved concurrent with submission of this report)

Phase 2, Objective 5 Milestone 1: Local IACUC approval (achieved May 2019)

Phase 2, Objective 5 Milestone 2: ACURO approval (achieved May 2019)

Phase 2, Objective 5 Milestone 3: Submission of final report of porcine trials for publication in DTIC. (achieved concurrent with submission of this report)

Phase 2, Objective 6 Milestone 1: Optimized APOC (achieved May 2021)

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

1) Major activities included completion of design validation for pREBOA-PRO™ and preparation and submission of the pREBOA-PRO™ 510(k) package to the FDA. Design work was completed for the integrated display electronic mechanisms, user interface and the APOC. We received FDA clearance for the pREBOA-PRO™ catheter and finished final release of product and labeling to production and commercialization. The first integrated display prototype and controller (APOC) for use in preclinical studies was finalized, and subsequent iterative updates were made based on feedback and data from the preclinical studies. All preclinical experiments were complete and the final APOC prototype was optimized. Additionally, Phase 1 Preclinical manuscript was prepared and submitted to the Journal of Trauma and Acute Care Surgery and Phase 2 preclinical experiments, preliminary data analysis and manuscript drafting was finished. Submission and acceptance of an abstract to the AAST Conference was completed with the Phase 2 data. Finally, we engaged FDA with respect to building our regulatory strategy for gaining approval for a partial REBOA controller.

2) Specific Objectives during Phase 2 were:

Objective 1: Design Validation of next generation pREBOA-PRO™

Objective 2: Development of miniature APOC for pREBOA

Objective 3: Development of next generation pREBOA-PRO that includes integrated pressure display

Objective 4: Preclinical animal testing of next-generation pREBOA-PRO™

Objective 5: Preclinical animal testing of APOC semi-open and closed loop controller

Objective 6: Optimize APOC Prototype using Prytime's formal design control process including FDA oversight and interaction

1. Significant Results/Key Outcomes:

a. Objective 1:

- i. Objective 1 is complete. The pREBOA-PRO™ received FDA clearance on June 5th, 2020.
- ii. Milestone Achieved: Final regulatory clearance and production release achieved

b. Objective 2 is complete.

- i. Subtask 1: Development of miniature APOC
 1. Subtask 1 is complete. The miniature APOC has been developed and lab tested in preparation for preclinical studies.
- ii. Subtask 2: Optimize technique for smooth titration control
 1. Subtask 2 is complete – smooth control of balloon inflation/deflation confirmed in bench testing.
- iii. Subtask 3: Optimize control of proximal or central aortic pressure within “dialed in” range.
 1. Subtask 3 is complete – APOC is capable of achieving specific blood pressure target confirmed in bench testing.

Milestone Achieved: The Prototype APOC is designed.

c. Objective 3 is complete.

- i. Subtask 2: Optimize Digital bar representation of occlusion
 1. Subtask 2 is complete. Upon receiving feedback from Trauma surgeons, the display information was shifted from degree of occlusion to including SBP/DBP and MAP, plus pressure waveforms for above and below balloon pressure.
 2. Integrated display prototype has been developed and tested and is ready for preclinical experiments.

d. Objective 4:

- i. All approvals that are needed to start this study are in place.
- ii. Conduct Animal Trials – all preclinical work has been accomplished and preliminary review of the data confirmed that no repeat experiments are needed. Analysis is underway and is expected to be complete in June 2020. The resulting report will be included in the Phase 2 Final report and also submitted to DTIC.

e. Objective 5:

- i. All approvals that are needed to start this study are in place.
- ii. Conduct Animal Trials – all preclinical work has been accomplished and preliminary review of the data confirmed that no repeat experiments are needed. Analysis is underway and is expected to be complete in June 2020. The resulting report will be included in the Phase 2 Final report and submitted to DTIC.

- f. Objective 6 is complete:
 - i. Subtask 1: Optimization of APOC based on animal study results
 - 1. Subtask 1 is complete – iterative adjustments to the APOC were performed based on feedback from the preclinical testing team. Final controller iteration was achieved mid-way through the preclinical testing and the APOC performed as desired for the remaining portion of the study.
 - ii. Subtask 2: Conduct model development and flow loop testing
 - 1. Subtask 2 is complete – iterative development and testing was performed over the course of the preclinical studies as described above.
 - iii. Subtask 3: Implement a rigorous design control process, including FDA oversight and interaction.
 - 1. Subtask 3 is complete – design control process was based on our existing quality management system.
 - 2. System specifications and performance characteristics of APOC controller have been compiled and reviewed for potential commercial configuration. Based on interaction and feedback from FDA it is expected that this project will proceed with baseline requirements from APOC but with updated design for blood pressure measurement to meet risk management and performance expectations.

Milestone Achieved: Optimized APOC

- 4) Other achievements
 - a. Manuscript describing the preclinical outcomes for Phase 1 was submitted for consideration for publication. Reviewer comments were received and are currently being addressed before resubmission. An abstract describing Phase 2 preclinical results was submitted and selected for a presentation at the American Association for the Surgery of Trauma (AAST) Conference. The conference will take place in the last week of September 2021. The Phase 2 preclinical work was also developed into a manuscript and submitted for consideration to Journal of Trauma.

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

If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. “Training” activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. “Professional development” activities result in increased knowledge or skill in one’s area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to report.

How were the results disseminated to communities of interest?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

In addition to submitting the preclinical results to DTIC, the results from Phase 2 were disseminated to the scientific and medical communities of interest via presentation at conferences and through submission for publication to journals that are indexed in Pubmed. The manuscripts are still under review/revision, but once published, will reach a large relevant readership. (see details in section above)

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

If this is the final report, state “Nothing to Report.”

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

Nothing to report.

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

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

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

The preclinical studies found that the Automated Partial Occlusion Controller (APOC) is equivalent or superior to manual control of partial REBOA in achieving a blood pressure target distal to the REBOA occlusion balloon. This suggests that the APOC for REBOA could alleviate clinical personnel during the care of a combat wounded service member and allow for additional resources to be applied towards patient care. These promising results will drive our next stage of development, with the goal of having the APOC controller developed within the cube/weight limitations to be included in a medic pack and be commercialized for military and civilian use.

What was the impact on other disciplines?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Though the next generation REBOA catheter (pREBOA-PRO™) was designed to allow for ease of use of partial REBOA in combat casualties and for military use, since commercialization, the civilian trauma care community is also adopting its use and will also be positively impacted by this new technology. We anticipate that the same will hold true when the APOC is commercialized.

What was the impact on technology transfer?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

The pREBOA-PRO™ catheter is already changing how civilian trauma physicians deliver REBOA. The ability to easily achieve partial REBOA has led to adoption of the partial REBOA practice in several Trauma Centers and numerous trauma physicians. They are able to extend safe occlusion time in badly wounded patients without causing distal ischemia that is characteristic of extended full occlusion REBOA.

What was the impact on society beyond science and technology?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Currently, the regulatory pathway for approval of the APOC is not well-defined. As we continue through the process of development and regulatory approval for this device, we will learn (along with the FDA) about the regulatory pathway and data needed for submission to receive clearance on a product of this nature (semi-closed loop or closed loop controller for REBOA).

- 5. CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, “Nothing to Report,” if applicable:*

We experienced delay in being able to conduct the preclinical experiments due to Covid-19 closure of the USU vivarium. This led to the need to receive a no-cost extension for the project. However, once the facility resumed operations, we were able to fully accomplish the study well within the new POP.

Changes in approach and reasons for change

Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to report.

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

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

We experienced delay in being able to conduct the preclinical experiments due to Covid-19 closure of the USU vivarium. This led to the need to receive a no-cost extension for the project. However, once the facility resumed operations, we were able to fully accomplish the study well within the new POP.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to report.

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

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

N/A

Significant changes in use or care of vertebrate animals

A few changes to the animal protocol were developed during the animal model development. Changes were described in an amendment to the original IACUC-approved protocol; the amendment also received IACUC approval. The amendment and IACUC approval were both submitted to the ACURO office.

Significant changes in use of biohazards and/or select agents

N/A

6. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state “Nothing to Report.”*

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

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

Nothing to report.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume; year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report.

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report.

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to report.

- **Website(s) or other Internet site(s)**

List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to report.

- **Technologies or techniques**

Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

The pREBOA-PRO™ catheter received FDA clearance in June 2020, Health Canada clearance, and is currently in civilian clinical use in both countries.

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

Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to report.

- **Other Products**

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- *data or databases;*
- *physical collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Data was collected from the preclinical studies – preliminary results are described in Appendix A and also submitted to DTIC for unrestricted publishing.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate “no change”.

Example:

Name: Mary Smith
Project Role: Graduate Student
Researcher Identifier (e.g. ORCID ID): 1234567
Nearest person month worked: 5

Contribution to Project: Ms. Smith has performed work in the area of combined error-control and constrained coding.
Funding Support: The Ford Foundation (Complete only if the funding support is provided from other than this award.)

Name: David Baer
Project Role: PI
Researcher Identifier: N/A
Nearest person month worked: 75 hours
Contribution to Project: Dr. Baer has served as PI of this research effort, providing broad oversight and feedback.

Name: Curtis Franklin
Project Role: Project Manager and Senior Engineer
Researcher Identifier: N/A
Nearest person month worked: 3
Contribution to Project: Mr. Franklin is the project manager and lead design engineer on this project. He leads the daily planning and execution of the project, including requirement development and specification development. He provides direction to the contract manufacturer and coordinates use of prototypes in the pre-clinical studies associated with this project.

Name: Jeremy Reynolds
Project Role: Biomedical Engineer
Researcher Identifier: N/A
Nearest person month worked: 3
Contribution to Project: Mr. Reynolds is the primary designer on this project, creating detail design and specifications for the product. He executes preliminary iterations for development and testing of alternatives for design decisions, creating documentation for production of the device.

Name: Eric Pointer
Project Role: Quality and Regulatory Engineer
Researcher Identifier: N/A
Nearest person month worked: 1

Contribution to Project: Mr. Pointer serves as the quality engineer assuring the overall quality of the product. He is responsible for the risk management activities, test planning and execution in support of regulatory design control requirements.

Name: Greg Schmid
Project Role: Senior Software Engineer
Researcher Identifier: N/A
Nearest person month worked: 7
Contribution to Project: Mr. Schmid is the lead software engineer on this project. He leads the software programming and user interface design for the integrated display and APOC. He also works with the preclinical team to receive user feedback and perform iterative updates to the devices.

Name: Julie Burgett
Project Role: SVP New Product Development
Researcher Identifier: N/A
Nearest person month worked: 1
Contribution to Project: Ms. Burgett is the engineering team lead and ensures the project is being executed per the product plan, budget and timeline.

Name: Matt Pickering
Project Role: Senior Engineer
Researcher Identifier: N/A
Nearest person month worked: 4
Contribution to Project: Mr. Pickering is a senior mechanical engineer. He is responsible for design activities for integrated display and controller.

Name: Rico Jaeger
Project Role: Senior Engineer
Researcher Identifier: N/A
Nearest person month worked: 2
Contribution to Project: Mr. Jaeger is a senior engineer and contributes to the design iterations of the APOC controller.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to report.

What other organizations were involved as partners?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:

Organization Name:

Location of Organization: (if foreign location list country)

Partner’s contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner’s facilities for project activities);*
- *Collaboration (e.g., partner’s staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner’s staff use each other’s facilities, work at each other’s site); and*
- *Other.*

Organization Name: Uniformed Services University of the Health Sciences

Location of Organization: Bethesda, MD

Partner’s contribution to the project: The lab of LTC Joseph White performed all activities associated with the preclinical work funded under this award. This includes all supplies, facilities, personnel and reporting associated with the preclinical work.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to <https://ers.amedd.army.mil> for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on <https://www.usamraa.army.mil>) should be updated and submitted with attachments.*

Submitted with attachments

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.*

Appendix A: Preclinical Results Report

Appendix A: Preclinical Results Report

Objective 4 and 5: Preclinical animal testing of next-generation pREBOA-PRO™ with integrated display and the APOC semi-open and closed loop controller

pREBOA-PRO™ is designed to permit precise management of the blood pressure above and/or below the balloon, in order to (1) provide adequate perfusion of the heart and brain; (2) stop lower-body bleeding and (3) permit some perfusion of vital organs such as the kidneys, gut, and liver. The objective of this study was to assess the technical feasibility of the novel advanced partial occlusion controller (APOC) in achieving partial REBOA at multiple distal mean arterial pressures in a porcine model of hemorrhage.

Methods:

Approvals

This study was approved by the Institutional Animal Care and Use Committee (IACUC) at the Uniformed Services University of the Health Sciences (USUHS), Bethesda, Maryland. This study was conducted by the Battlefield Shock and Organ Support (BSOS) Program at USUHS, Bethesda, Maryland. All animal care and use was in strict compliance with the Guide for the Care and Use of Laboratory Animals, and the National Institutes of Health guide for the care and use of Laboratory Animals (NIH Publications No. 8023, revised 1978) in a facility accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International. This study was awarded funding by Prytime Medical Devices, Inc. (Boerne, TX) as a subaward to the Henry M. Jackson Foundation for the Advancement of Military Medicine.

Study Design

This study was a prospective, randomized, pre-clinical swine study with six experimental groups. Animals were randomized to either manual (MAN) or automated (CON) titration at a target distal MAP of 25, 35, or 45 mmHg (n=8 swine per group). In order to establish noninferiority of APOC, manual titration groups were considered controls. The phases of the protocol included: animal preparation, baseline evaluation, hemorrhage, complete occlusion, targeted regional optimization (TRO), surgical control, and critical care (CC) (**Figure 1A**). Animals were excluded from final analysis if they did not survive to the CC phase.

Animal Acquisition

Healthy, adult, nonpregnant female Yorkshire-cross swine (*Sus scrofa*) (average weight 68.1±0.7 kg), obtained from Animal Biotech 106 Industries Inc. (Dolyestown, Pennsylvania) were acclimated for a minimum of three days while housed at the USU animal vivarium.

Animal Preparation

Sedation: Animals were premedicated with 6.6 mg/kg tiletamine/zolazepam (Telazol, Fort Dodge Animal Health, Fort Dodge, Iowa) intramuscularly prior to transportation to the operating room (OR). On arrival to the OR, peripheral intravenous access was obtained via an 18-gauge peripheral cannula in each ear. Maintenance intravenous fluids (normal saline) were initiated at a rate of 5 mL/kg/hr to account for insensible losses. Lidocaine at 25 mcg/kg/hr was also initiated for the prevention of tachyarrhythmias. Anesthesia was induced with Telazol and endotracheal intubation performed. Maintenance anesthesia consisted of 1-5% isoflurane in 100% oxygen with the following mechanical ventilation parameters: tidal volumes of 7-10 mL/kg, respiratory rate of 10 to 15 breaths per minute, and positive end-expiratory pressure

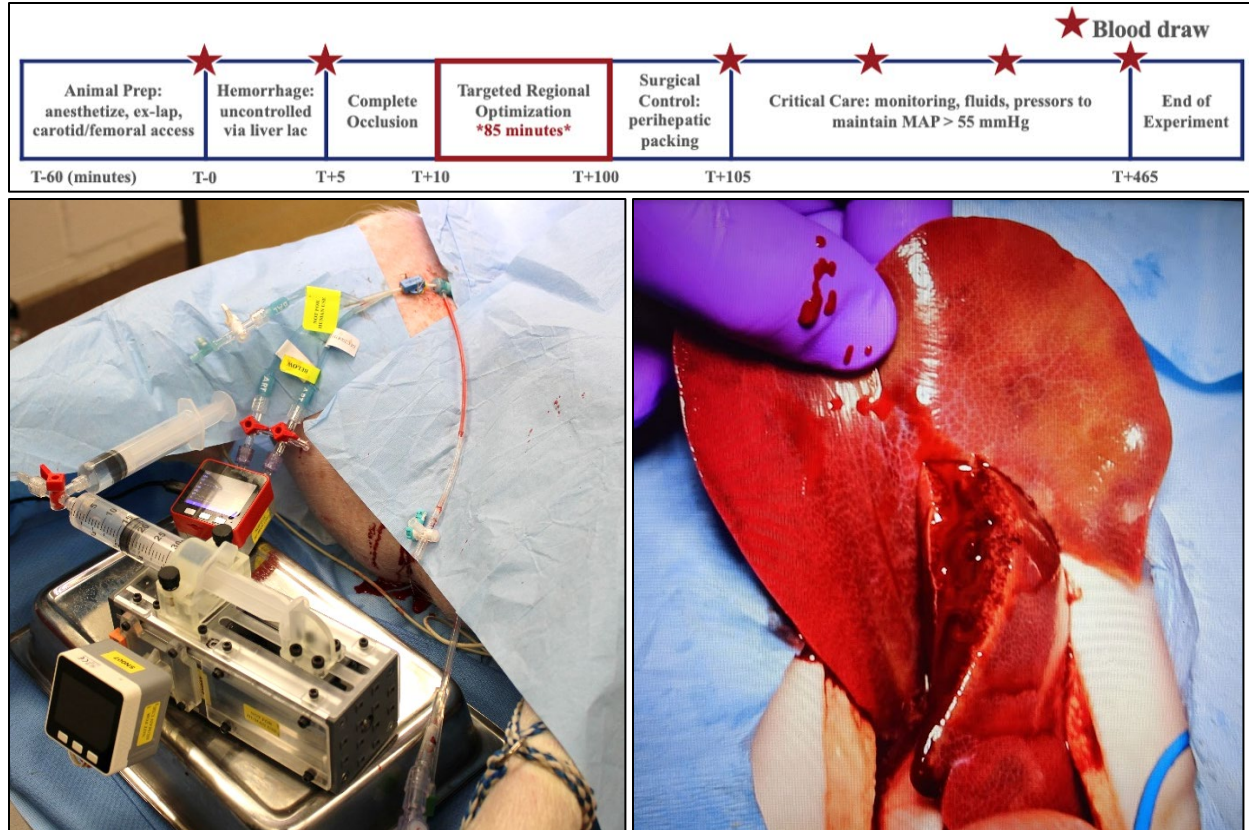


Figure 1: Experimental Protocol. A) Phases of experimental protocol and timing of blood draws B) Experimental setup during the 85-minute partial occlusion (PO) phase demonstrating the Advanced Partial Occlusion Controller (APOC) and partial REBOA catheter inserted into the right common femoral artery. C) Hepatic laceration at approximately 6 cm from the left lateral liver edge.

(PEEP) of 5, to maintain end-tidal carbon dioxide (CO₂) of 40 ± 5 mmHg. Warming blankets were applied to maintain a body temperature of approximately 38 °C.

Surgical Procedures and Instrumentation: A midline laparotomy was performed and a foley catheter (Medline Industries, Northfield, Illinois) was inserted into the bladder via open cystotomy. The left renal artery was circumferentially isolated near its origin and a 4 millimeter (mm) Basic Vascular Flowprobe (Transonic Systems Inc., Ithaca, New York) was placed. The suprarenal aorta was circumferentially isolated and a 12-16 mm Confidence Cardiac Output Flowprobe (Transonic Systems Inc., Ithaca, New York) was placed. The abdomen was then temporarily closed and animals received a 1 liter (L) normal saline bolus. A midline neck dissection was performed isolating the bilateral cervical common carotid arteries. A 4 mm Basic Vascular Flowprobe (Transonic Systems Inc., Ithaca, New York) was placed around the left common carotid artery. The right common carotid artery was cannulated with a 7 French (Fr) arterial sheath, facilitating placement of a Solid-State Pressure Catheter (Transonic Systems Inc., Ithaca, New York) for continuous measurement of proximal MAP as well as laboratory draws throughout the protocol.

Using ultrasound guidance and standard Seldinger technique, percutaneous access was performed at the bilateral common femoral arteries (CFA). A 7 French (Fr) sheath was placed in

the left CFA for insertion of a Solid-State Pressure Catheter (Transonic Systems Inc., Ithaca, New York) in order to collect continuous measurement of distal aortic MAP. An 8Fr sheath was placed in the right CFA and the next-generation pREBOA-PRO™ (Partial Resuscitative Endovascular Balloon Occlusion of the Aorta - Pressure Regulated Occlusion) (Prytime Medical Inc., Boerne, Texas) catheter with integrated pressure display (IPD) was inserted to aortic Zone 1 (**Figure 1B**). The IPD and APOC controller were calibrated, and in APOC groups, the controller was pre-set for desired distal MAP.

Baseline Evaluation

Hemodynamic parameters (proximal and distal arterial flow rates and MAP) were recorded for a 10-minute baseline evaluation. Blood samples for baseline laboratory values were also obtained.

Hemorrhage

Uncontrolled hemorrhage was initiated with a 6-cm liver laceration approximately 6 cm from the left lateral liver edge (**Figure 1C**). Five minutes of free bleeding was allowed, unless greater than 20% estimated blood volume loss (EBL) occurred, or MAP dropped below 40 mmHg, at which point complete occlusion was initiated. End of hemorrhage blood samples were obtained.

Complete occlusion

Using the APOC interface, the balloon was manually inflated until full occlusion was achieved – defined by loss of distal aortic flow and diminished distal MAP. Complete occlusion was sustained for 5 minutes. 1 L normal saline bolus was administered.

Targeted regional optimization (TRO)

Following complete occlusion, an 85-minute TRO phase was initiated, using either manual or APOC titration of balloon volume to achieve target distal MAP of 25, 35, or 45 mmHg per randomization. If proximal MAP dropped below 40 mmHg a rescue maneuver was applied in which the balloon was reinflated to full occlusion for 5 minutes. In the first rescue a 1 L normal saline bolus was also administered. In the second rescue, a second 1 L normal saline bolus was administered in addition to the initiation of vasoactive medications (phenylephrine 0.5 milligrams per milliliter (mg/mL) or norepinephrine 0.05 mg/mL).

Surgical Control

At the end of the 85-minute TRO phase, surgical control was obtained via perihepatic packing with 10 laparotomy pads. Following packing, the pREBOA-PRO™ was deflated and removed from the animal over a 5-minute period. Blood samples were obtained.

Critical Care

Following balloon deflation, animals entered a 6-hour CC phase. Upon initiation of CC, animals received a 1L normal saline bolus as well as 7 mg/kg of Calcium Chloride and Lidocaine infusion was stopped. Vasoactive medications were administered as needed to maintain proximal MAP greater than 50 mmHg. At the conclusion of the CC portion animals were humanely euthanized with an overdose of pentobarbital-based euthanasia solution. Blood samples were obtained at 2 (CC1) and 4 (CC2) hours into the CC portion, as well as immediately prior to euthanasia. Necropsy was performed including samples of the hindlimb muscle, left kidney (inferior lobe), myocardium (apex) and lung (left lower lobe).

Data Collection

Blood samples were obtained at the timepoints described above and depicted in Figure 1C for arterial blood gas and biochemical analyses to include markers of renal and hepatic function (ABL 800 FLEX; 201 Radiometer America, Brea, California). Hemodynamic and

physiologic data were continuously monitored and recording using PowerLab data acquisition system (AD Instruments, Colorado Springs, Colorado) at a sampling rate of 1 kilo Samples per second (kS/s). Data was analyzed using LabChart software (V8.0; AD Instruments, Colorado Springs, Colorado) as 1-minute averages taken at 1-minute intervals across the whole recording period.

Statistical Analysis

All data were expressed as mean ± standard error of mean (SEM). Graphpad Prism software (Version 9.1.1; San Diego, California). One sample t-tests were performed to compare average distal MAP achieved during TRO phase in each group compared to the target (i.e. 25, 35 or 45 mmHg). One-way ANOVA models were used to compare average distal MAP achieved as well as percent deviance from target MAP during TRO phase by MAN and CON regulation. Two-way repeated measures ANOVA or mixed effects models were performed to test for significant differences between groups and interactions between groups and time points in hemodynamic, biochemical and blood gas data. For hemodynamic and biochemical analyses, the MAN and CON groups were combined into a single cohort for each target MAP (n=16 per group for 25, 35, and 45 mmHg). Tukey’s post-hoc test was used for pairwise multiple comparisons. $P < 0.05$ was considered statistically significant.

Results

There were no significant differences in total hemorrhage volume, crystalloid administered, urine output, or vasoactive medications administered between the six experimental groups or when comparing combined cohorts at distal target MAP of 25 vs 35 vs 45 mmHg. There were no rescue maneuvers required in 25 mmHg groups. A total of 7 rescue maneuvers were required in both the 35 mmHg and 45 mmHg groups. Two swine died prior to initiation of the CC phase (1 in MAN35 and one in MAN45 group) and were not included in the final analysis.

When comparing mean distal MAP attained to goal distal MAP (25, 35 or 45 mmHg) in all groups, there were no significant differences in mean MAP attained, There were no significant differences in the average MAP achieved by APOC as compared to manual titration (Table 1).

Table 1: Differences in distal mean arterial pressure (MAP) and average percent deviance from target between manual (MAN) and APOC (CON) groups during the 85-minute targeted regional optimization (TRO) phase

	Mean MAP ±SEM (mmHg)	P (mean MAP compared to CON)	Avg % Deviance ±SEM	P (% Dev compared to CON)
MAN25	26.1 ± 1.78	p>0.9999	14.9 ± .466	P<0.0001
MAN35	33.7 ± 1.05	p>0.9999	10.4 ± .594	P=.8770
MAN45	45.2 ± 1.31	p>0.9999	11.9 ± .579	P<0.0001
CON25	26.2 ± 1.05		10.9 ± .366	
CON35	34.6 ± 1.30		9.95 ± .370	
CON45	44.0 ± .900		9.34± .602	

When comparing the average percent deviance of distal MAP attained compared to target distal MAP, there was statistically less deviance from the target in CON25 and CON45 as compared to MAN25 and MAN45 (**Table 1 and Figure 2**). Within manual groups, there was significant variability in the level of precision based on the target MAP (MAN25 vs MAN35 $p < .0001$, MAN25 vs MAN45 $p = .0028$, MAN35 vs MAN45 $p = .001$) whereas the CON groups maintained comparable levels of precision at each target MAP (i.e. no statistically significant differences between CON groups regardless of distal target). The APOC made on average 77 balloon volume adjustments per experiment (measured on a minute-to-minute basis throughout the 85-minute TRO phase) as compared to 29 adjustments by manual titration (**Figure 3**).

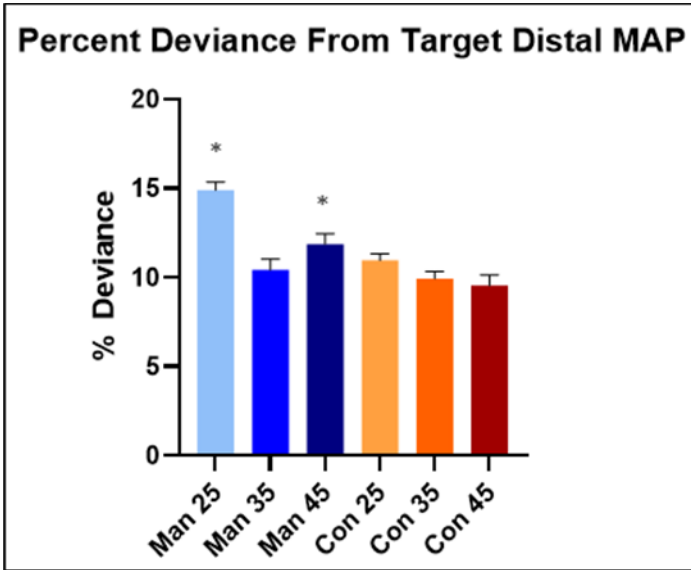


Figure 2: Average percent deviance from target distal MAP

most restrictive distal MAP target (25) when compared to the 35 and 45 groups. The impact on distal flow was less pronounced between the 35 and 45 groups. (25 vs. 35 and 25 vs. 45 $p < .0001$) (**Figure 4**).

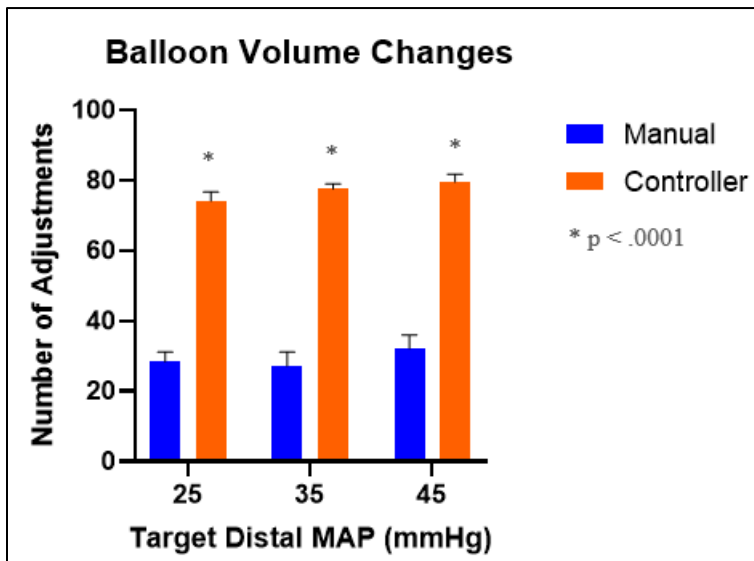


Figure 3: Average number of balloon volume adjustments across experimental groups

The APOC made on average 77 balloon volume adjustments per experiment (measured on a minute-to-minute basis throughout the 85-minute TRO phase) as compared to 29 adjustments by manual titration (**Figure 3**).

More restrictive distal MAP targets (i.e. lower target distal MAP) resulted in significantly higher proximal MAP and proximal flow ($p < .0001$ for each comparison). Flow distal to the balloon was significantly lower in the

lower. The

lower. The impact on distal flow was less pronounced between the 35 and 45 groups. (25 vs. 35 and 25 vs. 45 $p < .0001$) (**Figure 4**).

Creatinine was higher in the distal MAP 25 mmHg groups at surgical control (SC): 25 vs. 45 $p = .0065$, CC1: 25 vs. 35 $p = .0079$, 25 vs. 45 $p = .0016$, and CC2: 25 vs 45 $p = .0084$. Potassium was significantly higher in distal MAP 25 mmHg groups at CC1: 25 vs 35 $p = .0068$, 25 vs 45 $p = .0198$. (**Figure 5**).

Neutrophil gelatinase-associated lipocalin (NGAL), a highly sensitive biomarker for early acute kidney injury, trended higher in the most restrictive distal target (25 mmHg). This difference was significant between 25 and 35 and 25 and 45 mmHg groups. NGAL levels were comparable between

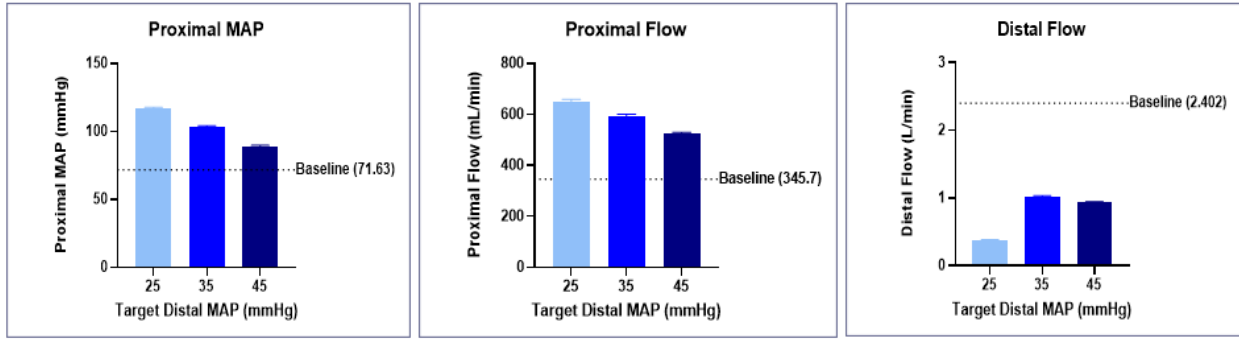


Figure 4: Proximal MAP, proximal flow, and distal flow across target distal MAPs. Mean baseline values for each measurement are indicated by the horizontal dotted lines

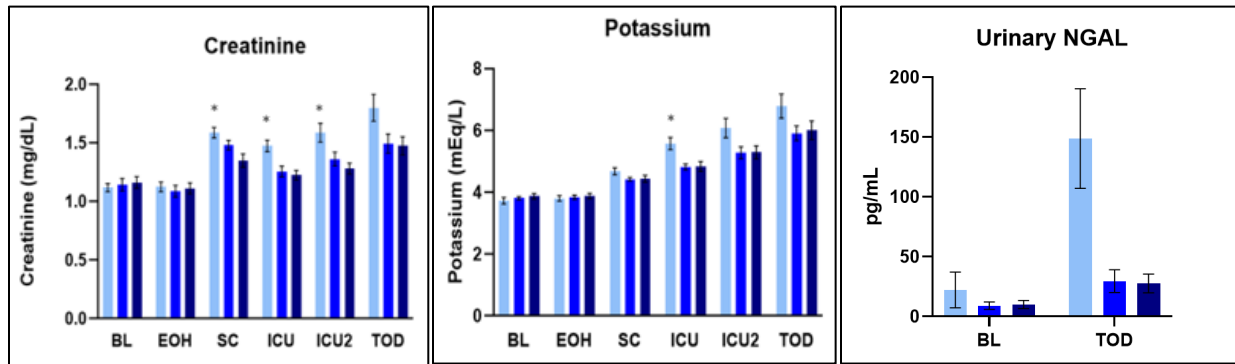


Figure 5: Creatinine, potassium and neutrophil gelatinase-associated lipocalin (NGAL) levels among target distal MAP groups at various timepoints throughout experiments

the 35 and 45 mmHg groups.

Conclusion

This is the first preclinical study examining the functionality of a novel, automated advanced partial occlusion controller in achieving TRO. This study demonstrated both technical feasibility and accuracy of the device in achieving specific, targeted distal MAP across a spectrum of distal pressures. The APOC provides precise and consistent regulation of TRO compared to manual titration, which may allow for less resource-intensive implementation of TRO strategies. TRO likely exists across a spectrum of distal pressures, where the optimal strategy is to allow as much distal flow as is clinically tolerated, while noting that highly restrictive applications may be less optimal.