AWARD NUMBER: W81XWH-19-2-0007

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

PRINCIPAL INVESTIGATOR: David Baer

CONTRACTING ORGANIZATION: Prytime Medical Devices, Inc.

REPORT DATE: June 2020

TYPE OF REPORT: Final Report

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	**2. REPORT TYPE**	**3. DATES COVERED** *(From - To)*
June 2020	Final	03/01/2019 - 02/29/2020

4. TITLE AND SUBTITLE

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

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-19-2-0007

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
David Baer

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Prytime Medical Devices, Inc.
229 N Main St, Boerne, TX 78006

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release;Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

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. This study aims to generate physiologic data on pREBOA (inflated in aortic zone I) following uncontrolled torso hemorrhage, in comparison with full REBOA and positive control (repair the arteriotomy using vascular shunt) with the ultimate goal of maintaining survival while improving outcomes for the distal organs.

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**		9	**19b. TELEPHONE NUMBER** *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

TABLE OF CONTENTS

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

   Please see slide 2 of attached presentation (Appendix A).

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.

   Phase 1, Objective 1 Milestone 1: next generation pREBOA-PRO™ design (achieved August 2019)
   Phase 1, Objective 1 Milestone 2: next generation pREBOA-PRO™ Prototype (achieved November 2019)
   Phase 1, Objective 2 Milestone 1: next generation pREBOA-PRO™ design (this includes the integrated display) (achieved November 2019)
   Phase 1, Objective 3 Milestone 1: Local IACUC approval (achieved May 2019)
   Phase 1, Objective 3 Milestone 1: ACURO approval (achieved May 2019)
   Phase 1, Objective 3 Milestone 1: Submission of final report of porcine trials for publication in DTIC. (achieved November 2019)

   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.

Please see slides 6 – 8 in the attached presentation (Appendix A). Please also see attachments 1 and 2 submitted with the Q3 report for presentation of detailed data and graphs (Appendix B and C). For methodology, please see slides 4 and 5 of the attached presentation (Appendix A).

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.

At this point in the study, we have only submitted the preliminary preclinical findings in a report submitted to DTIC (Appendix C). In the future, we will prepare the results of studies funded by this award to be presented at conferences and published in peer-reviewed journals.

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.

Phase 2 Objective 1 – Design validation of pREBOA-PRO™ will be complete including full manufacturing process and sterilization process validations. The submission of 510K package to the FDA is planned during this Phase. A commercialization plan will be developed in anticipation of 510K approval.

Phase 2 Objective 2 – A model of the miniaturized APOC will be prototyped including initial software controls for titration of balloon inflation / deflation for smooth control and ability to control titration to a targeted MAP. These prototypes will be under engineering test continuing into the following quarter.

Phase 2 Objective 3 – Iteration of prototype units of pREBOA-PRO™ with dual fluid columns and an integrated display will be built based on the prototype design developed in Phase 1. There will be continuation of design refinement based on pre-clinical and engineering bench testing results.

Phase 2 Objective 4 – Attain IACUC and ACURO approval for IACUC protocol amendment relevant to studies planned at later time point in Phase 2 Objective 4.

Phase 2 Objective 5 - Attain IACUC and ACURO approval for IACUC protocol amendment relevant to studies planned at later time point in Phase 2 Objective 5.

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

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

Please refer to slide 10 of the attached presentation (Appendix A).

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, it is likely that civilian trauma care will also be positively impacted upon commercialization of the pREBOA-PRO™.

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.*

Please refer to slide 10 of the attached presentation (Appendix A). The most likely impact of the pREBOA-PRO™ and the integrated display and controller will be on the practices of military and civilian clinicians during care of trauma patients suffering from non-compressible torso hemorrhage.

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:*

Please refer to slide 7 of the attached presentation (Appendix A).

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.

During Phase 1, there was a delay in the initiation of the sterilization testing for pREBOA-PRO™. This had the potential to push the schedule, however, the delay ended up being very short and the sterilization testing was still able to be initiated during Q3.

No further anticipated delays or problems identified at this point.

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.

  Final prototype of pREBOAPRO™ is complete and will move forward in validation testing and submission to the FDA for 510K approval before commercialization.

- **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 Attachment 2 of the Q3 report (Appendix C) 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:	INFORMATION PENDING FINAL NOVEMBER INVOICE

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:	INFORMATION PENDING FINAL NOVEMBER INVOICE
Contribution to Project:	Mr. Franklin is the project manager and lead design engineer on this project. He leads the daily planning and exaction 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:	INFORMATION PENDING FINAL NOVEMBER INVOICE
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:	INFORMATION PENDING FINAL NOVEMBER INVOICE
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.

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 COL Todd Rassmusen 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.*

PENDING FINAL NOVEMBER INVOICE

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: CCCRP Project Report Presentation
Appendix B: Attachment 1 from Phase 1, Q3 Report
Appendix C: Attachment 2 from Phase 1, Q3 Report

Appendix A: CCCRP Project Report Presentation

Advanced Partial Occlusion Controller (APOC) for pREBOA

Principal Investigator: David Baer, Ph.D.

Organization: Prytime Medical Devices, Inc.

Study Background

Problem Statement

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. To achieve REBOA, a balloon catheter is advanced into the aorta through access gained in the common femoral artery. 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.

Competing Solutions

None known.

Proposed Solutions

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.

Military Relevance

In October 2018, the Committee on Tactical Combat Casualty Care recommended that ARC be provided to soldiers with NCTH. ARC combines two important strategies: transfusion with whole blood and Zone 1 REBOA. As discussed in the ARC guideline, implementation of ARC is significantly limited by the limits on full occlusion REBOA and the complexity of implementation of intermittent REBOA. The next generation pREBOA catheter proposed here has been specifically planned to meet the needs and requirements for use in a deployed setting. The new design simplifies use by eliminating the need for external monitors to display blood pressure readings and, when paired with a controller, provides more easily manageable pREBOA. These two innovations, combined with the ability to have precision control of partial blood flow during REBOA, address the biggest hurdles for implementing REBOA in an austere environment.

Research Questions and Hypotheses

Aims / Hypotheses

- Specific aim: to optimize and complete Design Verification and Validation for FDA clearance of pREBOA-PRO™, the first REBOA catheter designed for pREBOA; develop next generation pREBOA-PRO™ which includes integrated pressure display distal and proximal MAP directly on the catheter; design miniature APOC System for pREBOA which will provide patient-centered approach to maintain physiological equilibrium in prehospital and en route care; and conduct preclinical testing of pREBOA-PRO™ catheter and APOC System.

Design and Methodology

Design

Design and development of the pREBOA-PRO™ catheter required a number of tests, including balloon optimization and verification and validation testing.

For Phase 1 preclinical studies, Yorkshire swine (70-100 kg; female) were randomly assigned into one of the 5 groups: (1) Time Control (TC; Instrumentation only, no injury or occlusion; n=5); (2) Negative Control (NC; injury, no REBOA; n=5), (3) Positive Control (PC; injury, rapid surgical repair; n=5); (4) pREBOA (PR; injury, partial occlusion with distal MAP at 30 mmHg; n=8), (5) Full REBOA (FR; injury, complete occlusion; n=8). For Phase 2 preclinical studies, Yorkshire swine (70-100 kg; female) will be randomly assigned into one of the 3 groups based on the targeted distal MAP (n=8 per group): low (< 15 mmHg); (2) moderate (15< MAP< 30 mmHg); (3) high (30< MAP< 60 mm).

Power was estimated using PROC POWER SAS 9.4. We estimated means for three groups and general standard deviation on the lactate measurement, referring to the results of Russo et al's study. For means of 3.2, 3.2 and 9.3 with a standard deviation of 0.3, we have over 99% power to detect a difference between the third group and each of the other two at a significance level corrected for multiple comparisons, p<0.017. Even if the group differences were as small as 3.2, 3.2 and 5.3, the power is still over 80%.

Methods

The hemorrhage model used in both Phase 1 and Phase 2 studies is performed in 5 phases: preparation, instrumentation, injury, intervention, monitoring. The injury phase includes induction of uncontrolled bleed hemorrhagic shock (HS) in the anesthetized animal. The common iliac artery will be surgically perforated to allow spontaneous bleeding. The intervention phase follows the injury phase by 5-10 minutes and includes insertion of the REBOA catheter and occlusion (depending on experimental group), surgical repair of the hemorrhage-inducing injury and biological sampling/monitoring.

Design and Methodology

Measures

Describe measures, spell out acronyms, and be explicit about study outcomes.

During catheter development, the design is built in iterations until the desired design is achieved, flow loop testing in our proprietary bench top testing system is used to characterize titration vs. inflation and generate curves for comparison. Standard design verification and validation processes are followed to ensure the device meets defined requirements and that there is rigor and compliance with manufacturing processes.

For preclinical studies, blood pressure will be monitored at the common carotid artery and femoral artery under anesthesia. Perivascular flow probes will be placed around the common carotid artery, left renal artery and distal to the balloon to record arterial blood flow. All physiological parameters will be recorded continuously from pre-injury baseline to the end of study. Blood samples (volume ~4 ml) will be collected from femoral artery, brachial artery or common carotid artery every 30-60 minutes throughout the experiment for complete blood count, blood chemistry, blood gas analysis and coagulation (thromboelastography). catheter. Tissue samples (lung, heart, liver, jejunum, kidney, aorta) will be fixed, processed and stained for hematoxylin and eosin for histological analysis.

Analyses

For preclinical studies, the mortality will be compared between groups using Fisher's Exact Test with statistical significance set at $p<0.05$. If there is shown to be an overall difference between groups, then we will explore the source of the differences using a series of 10 bivariate comparisons invoking a significance level of $p<0.005$ according to Bonferroni correction for multiple comparisons. Other outcomes, measured over time, will be investigated using linear mixed models with significant time by treatment interaction indicating a difference in groups. If a statistically significant difference at $p<0.05$ is found, between group, contrasts will be set up to identify the specific group differences with Tukey correction for multiple comparisons. In Phase 2 experiments, the outcome measures will be compared between groups with different targeted MAP. The critical threshold will be determined based on the following criteria: physiological outcomes are comparable to the PC or TC groups, and total injury score is the least among the groups.

Progress

Completed Tasks

- *Development of a next generation pREBOA-PRO™ (optimized balloon for partial occlusion, conducted model development and flow loop testing and implementation of rigorous design control processes – including FDA input)*
- *Produced an engineering design of the next generation pREBOA-PRO™ with the integrated pressure display (finished model development and conducted flow loop testing)*
- *Performed preclinical animal testing of the pREBOA-PRO™ catheter (Developed animal trial protocol, received IACUC and ACURO approval, conducted animal trials specified in Phase 1, performed data analysis and prepared a final report, which was submitted to DTIC).*

Ongoing Tasks

- *Design validation of the pREBOA-PRO™ catheter.*
- *Continue development of the pREBOA-PRO™ catheter with integrated display.*
- *Next phase of preclinical studies*

Recruitment Status

N/A.

Analyses

For the pREBOA-PRO™ catheter, the initial design iterations, flow loop testing and verification and validation steps have been complete. The pREBOA-PRO™ and APOC technologies are still in the early iterative testing stages, with some flow loop testing complete on each.

The Phase 1 preclinical study data has been preliminarily analyzed in order to look at data trends. A more in-depth analysis is planned once Phase 1 and Phase 2 preclinical studies have been accomplished. The data points being collected for analysis are: Mean arterial pressure (MAP) in the animals above and below the occlusion balloon over the experimental time course, blood flow rate above and below the occlusion balloon over the experimental time course, Complete Blood Counts (CBC), blood gas analysis, and electrolyte analysis in blood at pre-defined timepoints over the experimental time course. Furthermore, histologic analysis of tissues downstream of the aortic occlusion is currently being performed.

Current and Anticipated Challenges

Challenges

- *Challenges encountered in Phase 1 included schedule delays for sterilization testing for the pREBOA-PRO™ and with animal model development.*

Solutions

- *The schedule delay for sterilization was short and the testing was able to be initiated in Phase 1 as planned.*
- *The preclinical team experienced some challenges in establishing the hemorrhage animal model in the early parts of Phase 1. However, with well-informed trouble shooting and input from other experts in the field regarding this model, the team was able to successfully and consistently run the experiments with the hemorrhage model planned.*

Results and Conclusions

Results

- *Objective 1 Results:*
  - *Final design and prototype of pREBOA-PRO™ is complete as of November 2019, upon successful testing and design verification outcomes.*
  - *Regulatory strategy was successfully developed after meetings and follow-up input from FDA. Further refinement may be required as we move through the 510K process.*
- *Objective 2 Results:*
  - *Flow loop testing of the pREBOA-PRO™ with dual lumen and integrated display found that*
  - *The conclusion is that the results are acceptable for prototype level testing and warrant the project to move forward to the next phase as planned for design iteration.*
- *Objective 3 Results:*

  Analysis of the preclinical studies (hemorrhage model in which animals received either pREBOA or full occlusion REBOA) found that:
  - *Consistent target distal MAP was achieved by pREBOA-PRO™ following uncontrolled hemorrhage.*
  - *Steady and precise control of distal aortic flow was achieved using pREBOA-PRO™*
  - *There was elevated monocyte count after REBOA in both groups*
  - *Blood pH was lowered following REBOA in both groups*
  - *REBOA induced changes in potassium, glucose and lactate levels (both groups)*

  ****statistical analysis has not been performed on the data listed above – upon completion of more preclinical experiments, the data will be analyzed all together and statistical analysis performed. The results related to target Distal MAP and flow are expected based on results from our in vitro simulation testing.*

Most Important Findings

- Our data suggests that pREBOA-PRO™ is able to control the distal MAP precisely by regulating the balloon inflation/deflation.

Dissemination

Publications and/or Presentations

N publications and M presentations (that are of direct results of the study)

- *No publications generated at this point. Publications are planned for preparation once the preclinical work is complete.*

Products and Impacts

Products

- *The final design prototype of the pREBOA-PRO™ catheter is complete. This design will move forward for submission to attain 510K clearance from the FDA.*

Impacts

- *The pREBOA_PRO™ catheter is a significant advancement in REBOA technology. Once cleared for use in patients by the FDA, this catheter will allow for precision perfusion control in combat casualties (and civilians) suffering from NCTH. Case studies reporting on pREBOA (using our ER-REBOA™ device) suggest that pREBOA extends the safe occlusion time. Therefore, the pREBOA-PRO™ will allow medical personnel to more easily provide longer duration of hemorrhage control. This is especially important when evacuation times to definitive surgical care are longer than typical.*
- *We also anticipate that development of the integrated screen will give medical personnel actionable information included on the device, as opposed to needing additional medical equipment to monitor patient status. This will be a significant advantage in austere conditions.*
- *Finally, we anticipate that the development of APOC will further contribute to ease of use and achieving steady partial occlusion.*

Transition Plan

Additional Work

- *Upon receiving 510K clearance, the pREBOA-PRO™ catheter will need to be used in patients in a clinical setting and data gathered and analyzed before formal clinical practice guidelines can be developed. The scope of this project does not carry the other two products through 510K clearance, however, clinical use upon clearance will also be required in the future for these devices.*

Projected Timeline

- *We anticipate that the pREBOA-PRO™ will be on the market within the first 6 months of 2020. The transition timeline for the integrated display and APOC are less clear at this point, due to unknown regulatory processes – guidance from FDA will be essential in planning our regulatory strategy and building a transition plan.*

Considerations

- *Potential complex regulatory pathway for closed loop devices or devices that include software.*

Commercialization

- *During the period of performance covered by this funding award, we anticipate commercialization of the pREBOA-PRO™ catheter.*

Follow on Work

Next Steps

- *Current next steps are detailed in the Phase 2 section of the SOW for this funding award. Briefly, we will complete all steps needed for 510K submission for the pREBOA-PRO™, develop advanced prototypes of the pREBOA-PRO™ with integrated display and the APOC, and continue preclinical work.*
- *Upon completion of the work supported by this funding opportunity, we will pursue advanced development funding to allow us to get the additional products (integrated display catheter and controller) to market.*
- *Although Prytime Medical may not be the performing institution, it is clear that clinical studies on the use of pREBOA-PRO™ are strongly desired by clinicians and will likely be performed quickly after the catheter is on the market.*

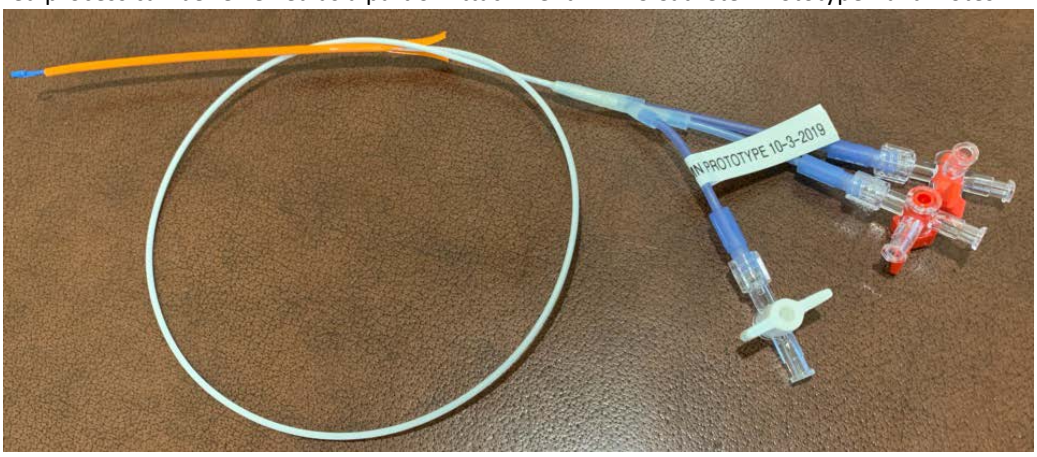
Appendix B: Attachment 1 from Phase 1, Q3 Report

1. **Purpose and Background:**

A Dual Fluid Column (DFC) Catheter has been designed by Prytime Medical in order to satisfy the need for measuring blood pressure above and below the balloon without the use of an additional device or access point to enable precision control of partial occlusion REBOA. No currently available occlusion balloon catheter product offers this ability. It is expected that the importance of this feature will enable clinicians to perform both partial and full occlusion REBOA to achieve the benefits of REBOA (control hemorrhage below the balloon and support perfusion of tissues above the balloon) while minimizing the detrimental effects (above balloon hypertension, below balloon ischemic injury). This capability may be particularly useful when paired with a device optimized for smooth transition from full flow to full occlusion.

2. **Catheter Build:**

Three test catheters were built according to processes used to build prototype catheters in the R&D center. The build process was slightly modified to allow for the incorporation of the second pressure sensing lumen. The modified process can be reviewed as a part of Attachment 1: DFC Catheter Prototype Build Notes.



Aside from the second arterial lumen, the catheter hub has a third port to allow for the extra lumen. This new hub design led the biggest challenge during the build, ensuring that the inner and outer shafts and all lumen are aligned properly and ensuring correct communication. The new hub is shown below.

During the build, one catheter had sizable crosstalk and was unable to be repaired after three attempts. A second catheter incurred a pin-hole leak in the balloon after being pulled through a damaged introducer sheath during the tortuous anatomy test. It was not known at the time of insertion that the sheath was damaged. The catheter

passed the tortuous anatomy test with ease, but since it was damaged upon removal, further data was unable to be collected on this unit.

3. Test Plan:

Testing was performed at the Prytime Medical R&D center in Denver, Colorado on October 8th, 2019. The purpose of this testing was to study the performance of the newly designed DFC Catheter and inform the development of further design modifications of the device. This testing was considered bench or prototype testing and was not governed by statistical sample sizing or formal processes although existing test processes were referenced and used when applicable.

The specific tests performed were as follows:

A. Flow Loop Testing
   - Inflation to full occlusion and full deflation
   - Partial occlusion at 30mmHg, 60 mmHg, and 90mmHg below balloon pressure
   - Inflation and deflation time, with and without the pressure relief valve

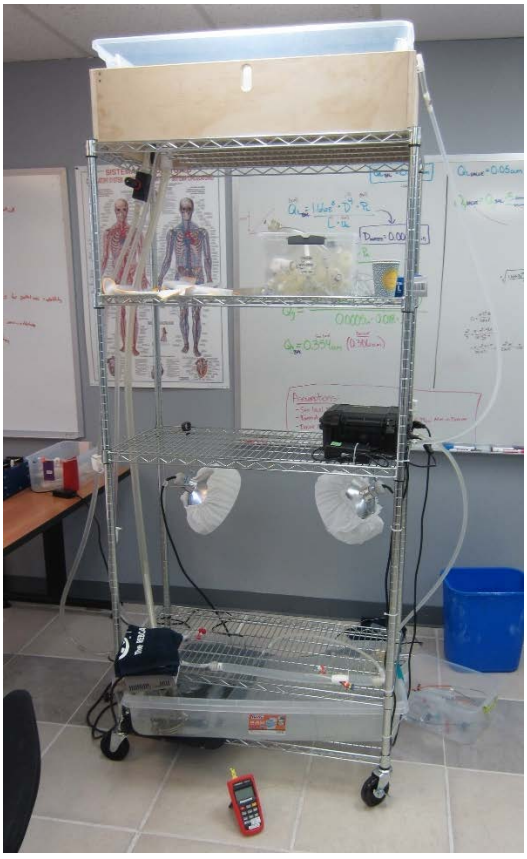
B. Tortuous Anatomy
   - Ability to traverse a simulated artery with a 90^{o} turn with a radius of 3cm

C. Engineering STAAR Testing
   - Fully occluded and un-occluded
   - Partial occlusion at 30mmHg, 60 mmHg, and 90mmHg below balloon pressure
   - Inflation and deflation time, with and without the pressure relief valve

D. General Observation

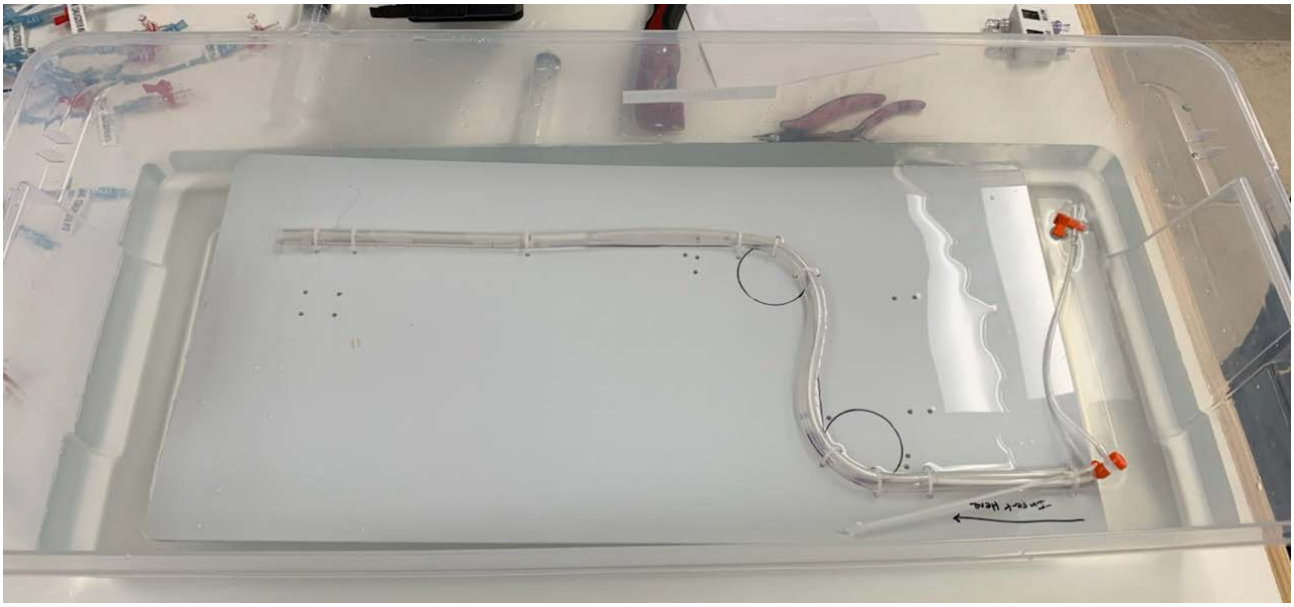
4. Equipment:

4.1 Flow Loop Tester: Located in the Denver R&D Center, this was the primary piece of equipment used for the occlusion testing.



4.2 Engineering STAAR: The engineering STAAR was used to compare occlusion pressures and test flow control.

4.3 Tortuous Anatomy Fixture: This was used for the Tortuous Anatomy test. It is intended to mimic the worst-case path that the catheter may face during placement and use.



4.4 Pressure Gauge:

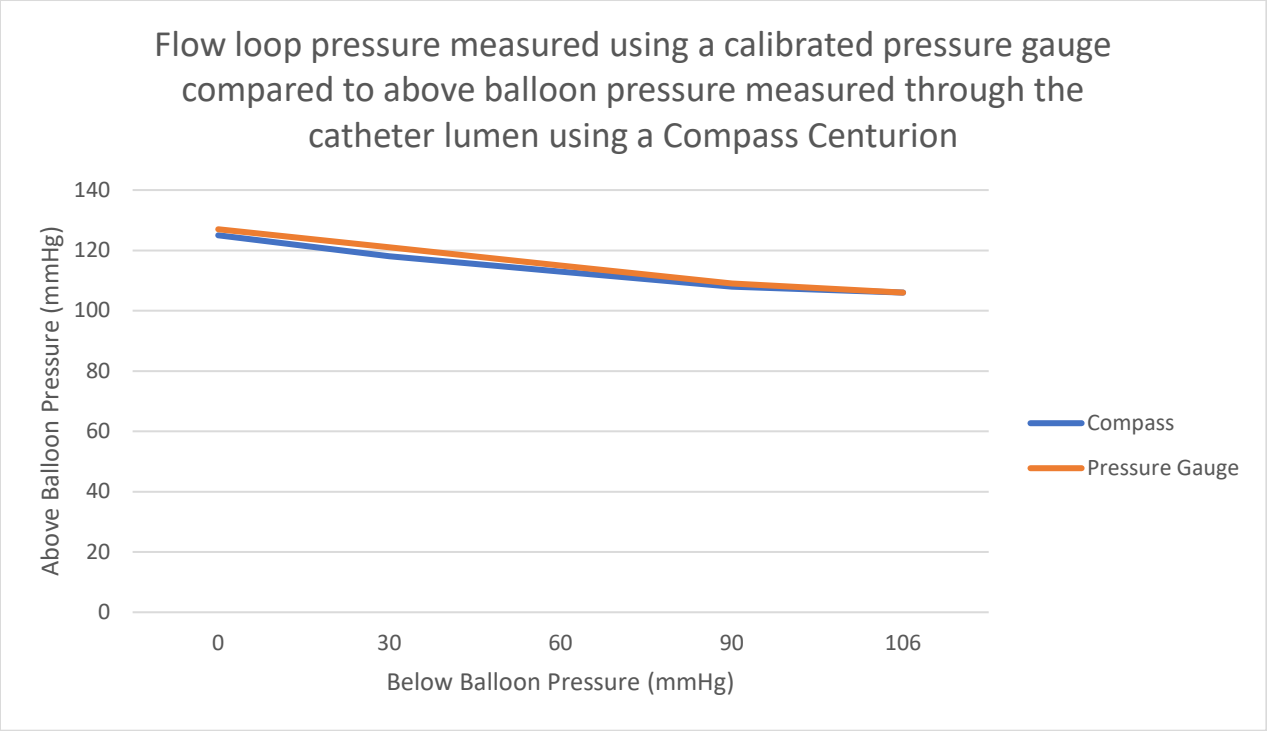
4.5 Temperature Gauge:

4.6 Stopwatch

5. Testing Results:

5.1 Flow Loop Testing: The flow-loop pressure was set at 2.25 PSI using a 24mm tubing for the simulated aorta. This tubing size is the 95th percentile of aorta size, and as larger diameter vessels are the most challenging for balloon occlusion, this represents a performance extreme. Initial un-occluded pressures with the catheter placed in the flow loop, but with the balloon deflated, were measured and recorded. These pressures were measured via the above and below balloon lumen on the catheter by attaching a Centurion® Compass pressure monitoring device to the arterial lumen extension lines, which has a rated accuracy of +/-3%. Once the pressure was measured and held steady with the Compass, it was detached, and an in-line pressure gauge was attached as a check to ensure that the Compass device was accurately measuring lumen pressure. After which, partial occlusion was measured at three different below balloon pressures and recorded. Again, at each partial pressure interval, the pressure gauge was attached to ensure accurate Compass device readings. The below balloon pressure was consistently being read from the below display on the dual compass device while the above balloon measurement switched between Compass and pressure gauge. The results of these pressure readings are shown below. The pressure gauge measurements were converted from PSI to mmHg for easier comparison.

Prototype ~~10-3~~ 03OCT2019				
Type	**Measurement**	**Method**	**mmHg**	**PSI**
Un-occluded	Catheter Below Balloon	Compass	106	-
	Catheter Above Balloon	Compass	106	-
	Catheter Above Balloon	Pressure Gauge	106	2.05
Partial 1	Catheter Below Balloon	Compass	30	-
	Catheter Above Balloon	Compass	118	-
	Catheter Above Balloon	Pressure Gauge	121	2.34
Partial 2	Catheter Below Balloon	Compass	60	-
	Catheter Above Balloon	Compass	113	-
	Catheter Above Balloon	Pressure Gauge	115	2.22
Partial 3	Catheter Below Balloon	Compass	90	-
	Catheter Above Balloon	Compass	108	-
	Catheter Above Balloon	Pressure Gauge	109	2.10
Fully Occluded	Catheter Below Balloon	Compass	0	-
	Catheter Above Balloon	Compass	125	-
	Catheter Above Balloon	Pressure Gauge	127	2.46



In all cases, the above balloon pressures measured using compass devices through the catheter lumens were within their rated accuracy. However, in all cases except for the un-occluded state, the measured compass

pressures were lower than the pressure measured using a non-medical grade pressure gauge. Possible sources of measurement difference between pressure gauge and Compass device include, but are not limited to the following:

- Centurion Compass error is ±3%
- Omega Pressure Gauge error is 0.25%
- Possible pressure loss through catheter lumen
- Difference in planar alignment of pressure transducers

The above picture shows the pressure gauge measuring the above balloon pressure with the balloon fully occluding the simulated vessel in the flow loop. The above pressure is 2.46 PSI (127 mmHg) while the below balloon compass device is showing 1 mmHg.

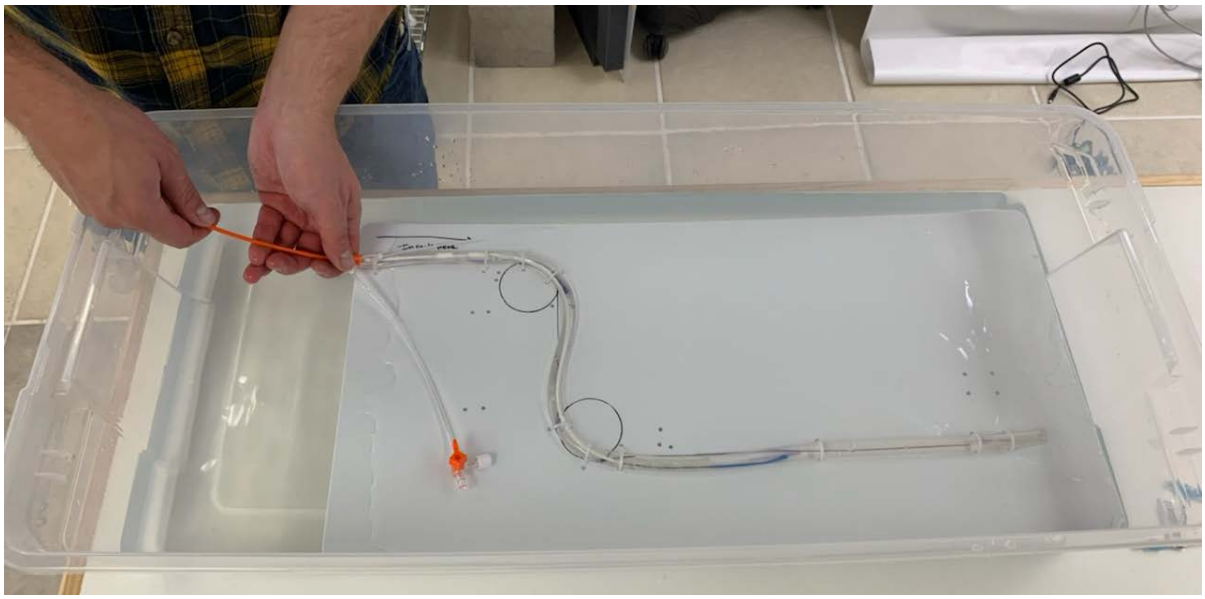
When the pressure gauge was disconnected and the compass device connected, the above balloon compass displayed 125 mmHg and the below remained at 1 mmHg. Again, the difference between the two devices may simply be due to tolerable device error. However, this shows that that the dual compass displays are comparable to that of a calibrated pressure gauge and that the additional arterial lumen in this design does not affect accurate pressure measurement.

5.2 Inflation/Deflation Time: While in the flow loop, the catheter was also tested for inflation and deflation time, both with and without a pop-off valve. These results are shown below.

Prototype 03OCT2019 - No pop-off valve	
Inflation Time (s)	Deflation Time (s)
16	17
11	12
11	10
Prototype 03OCT2019 - With pressure relief valve	
Inflation Time (s)	Deflation Time (s)
23	11
21	14
22	13

5.3 Tortuous Anatomy:

The 03OCT2019 catheter had no issue with insertion through the introducer, moving through the 90-degree bends in the tester, or removal.

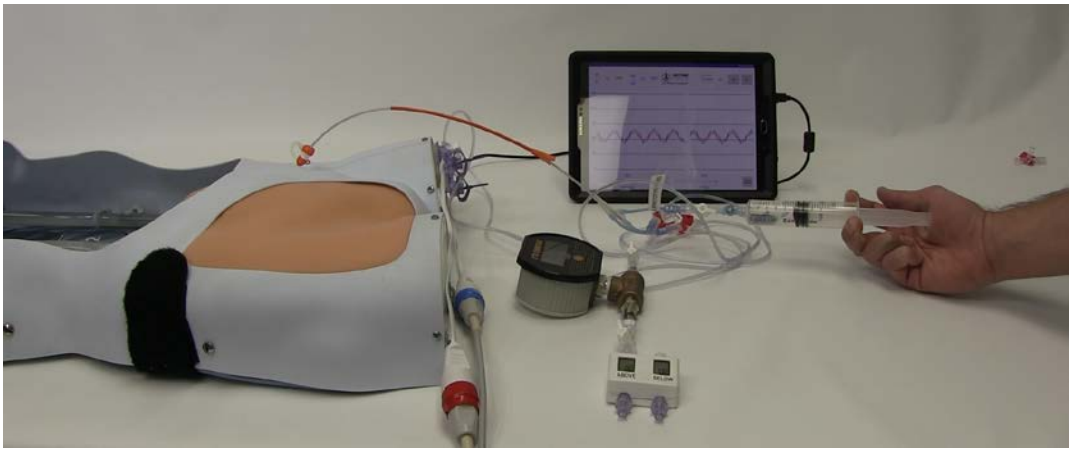


The 07OCT19 catheter was then placed in the tester. There were no issues with insertion or movement within the testing apparatus. However, during removal, the balloon was unable to move through the introducer sheath. After further inspection, it was determined that the end of the sheath was badly worn and had snagged the balloon, producing a small tear. This prototype sample was unable to be repaired, thus no further data was collected using

sample 07OCT19. Since there has been no further issues with insertion or removal of the DFC Catheters within an introducer sheath, this failure is considered closed at this time with the cause attributed to a damaged sheath.

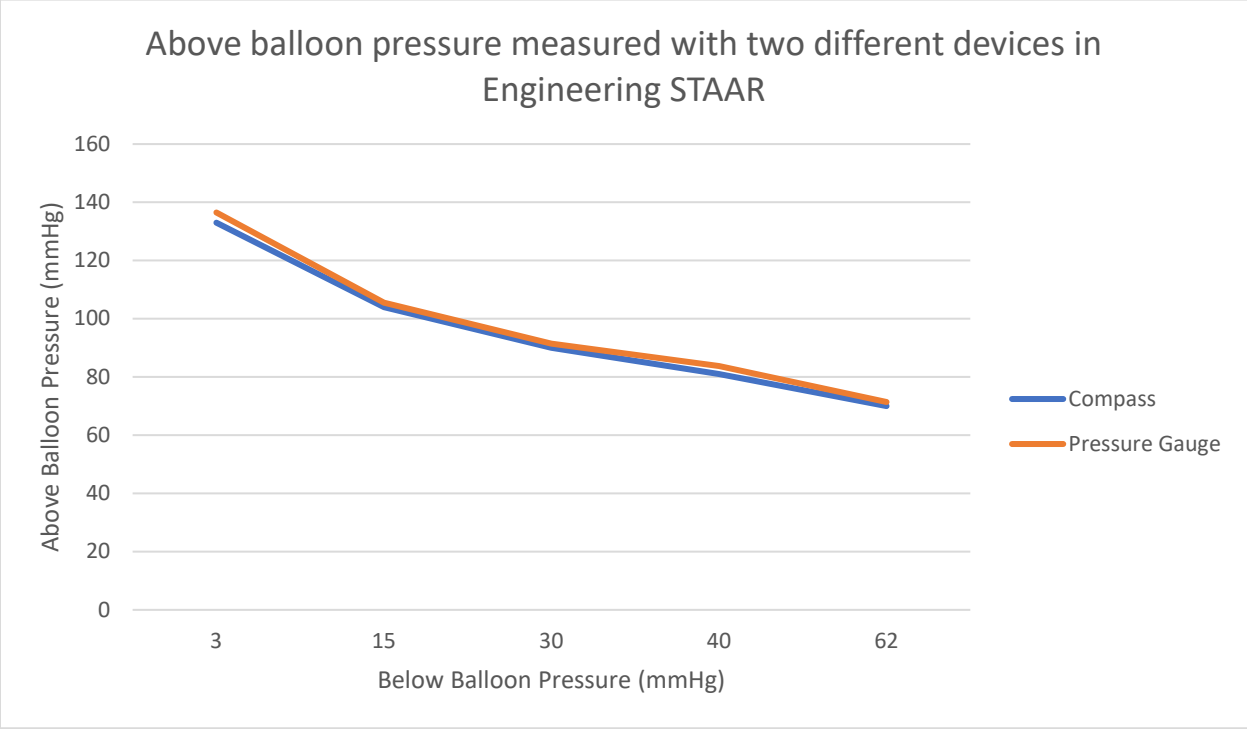
5.4 Engineer STAAR Testing:

The DFC Catheter was tested for pressure within an Engineering STAAR unit in order to more fully understand whether or not the additional lumen and dual compass display can accurately measure pressure within a simulated system.



The Engineering STAAR is setup and operates just like the regular STAAR unit except that it has an additional pressure transducer to allow the measuring and display of arterial pressure below the balloon, off the side-arm of the introducer sheath. The side-arm pressure was used for an initial check of the system to ensure that all was working properly. After which it was disconnected from the transducer and the below balloon pressure was measured with the pressure gauge and dual compass display, respectively. The pressure measurements are shown in the table below. The pressure gauge could only measure in PSI, thus the far-right column shows the conversion to mmHg for direct comparison.

Prototype 03OCT2019				
Type	**Measurement**	**Method**	**mmHg**	**PSI**
Full Occlusion	STAAR Tablet Above Balloon	-	129	-
	Catheter Below Balloon	Compass	3	-
	Catheter Above Balloon	Compass	133	-
	Catheter Above Balloon	Pressure Gauge	137	2.64
Partial 1	Catheter Below Balloon	Compass	30	-
	Catheter Above Balloon	Compass	90	-
	Catheter Above Balloon	Pressure Gauge	92	1.77
Partial 2	Catheter Below Balloon	Compass	62	-
	Catheter Above Balloon	Compass	70	-
	Catheter Above Balloon	Pressure Gauge	71	1.38
Partial 3	Catheter Below Balloon	Compass	15	-
	Catheter Above Balloon	Compass	104	-
	Catheter Above Balloon	Pressure Gauge	106	2.04
Partial 4	Catheter Below Balloon	Compass	40	-
	Catheter Above Balloon	Compass	81	-
	Catheter Above Balloon	Pressure Gauge	84	1.62



When the data from above is shown on a graph, it is demonstrated that measurements from the dual compass display are comparable with that of the pressure gauge, which is calibrated and thus accurate.

6. Discussion:

This prototype testing was conducted in order to understand how the second arterial lumen will affect inflation/deflation and to define the accuracy of the dual compass display compared to a typical pressure gauge or transducer. As shown in section 5.2, the inflation/deflation does not significantly differ with the use of a pressure-relief valve and all data points are within the pREBOA-PRO requirement of inflation time being less than 60 seconds (See UN-6, ER-019 & ER-020 in DGN-04103 Rev B). The pressure readings from the dual compass display never differed more than 4 mmHg and was usually within 1mmHg. This is acceptable at this point of the design process as it is within the design error of the compass devices and is a clinically insignificant difference. In the next design iteration, there will be a unique Prytime integrated display used and accuracy will again be assessed.

Furthermore, it was shown that the addition of the second arterial lumen and thus slight increase in outer shaft diameter did not prohibit catheter insertion into and introducer sheath, nor the catheter's ability to navigate complex anatomy pathways.

These results are acceptable for prototype level testing and warrant the project to move forward to the next phase of design iteration and planning.

7. Attachment 1: DFC Catheter Prototype Build Notes (see GAS for attachment)

Appendix C: Attachment 2 from Phase 1, Q3 Report

Objective 3: Preclinical animal testing of next generation pREBOA-PRO™.

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. This study aims to generate physiologic data on pREBOA (inflated in aortic zone I) following uncontrolled torso hemorrhage, in comparison with full REBOA and positive control (repair the arteriotomy using vascular shunt) with the ultimate goal of maintaining survival while improving outcomes for the distal organs.

METHODS

Figure 1 shows the experiment timeline.

Preparation and instrumentation phase: Briefly, Yorkshire swine (70-90 kg; N=14) were sedated, anesthetized and endotracheally intubated. Laparotomy, splenectomy and cystotomy were then performed. Electrocardiogram (ECG) was recorded using a 5-lead monitoring system (ADinstruments, Inc). The left common carotid artery and left femoral artery were cannulated for blood pressure measurement (5-Fr solid-state pressure catheter; Transonic, Inc). A 7-Fr introducer sheath was placed in the infrarenal aorta for REBOA catheter insertion. pREBOA-PRO™ catheter was advanced for zone 1 aortic deployment. Distal aortic flow rate was measured by a 12-mm flow probe (Transonic, Inc) placed at the aorta distal to REBOA catheter insertion, whereas proximal flow rate was measured at the right common carotid artery using a 4-mm flow probe (Transonic, Inc). Blood samples were collected from the brachial artery at five time points: pre-injury baseline, end of hemorrhage, end of occlusion, during ICU phase and at the end of the protocol, for complete blood count (CBC) analysis and arterial blood gases/electrolytes analysis. Serum and plasma were stored in -80^{o}C for subsequent protein analyses.

Injury phase: After instrumentation and the10-min baseline recording, the animals were subjected to uncontrolled hemorrhage for 10 minutes via arteriotomy at the external iliac artery. Shed blood in the intraperitoneal cavity was removed using a suction pump.

Intervention phase: The animals were randomly assigned into three groups – full REBOA (FR), partial REBOA (PR) and positive control (PC). In the FR group (n=6), the aorta was completely occluded using the pREBOA-PRO™ catheter for 90 minutes. Animals in PR group (n=4) received a 10-min complete occlusion of aorta, followed by 80-min partial occlusion with the target distal mean arterial pressure (MAP) of 30±5 mmHg mmHg. Instead of aortic occlusion, a temporary vascular shunt was used in the PC group (n=4) for hemorrhage control and restoring blood flow at the external iliac artery after 10-min uncontrolled hemorrhage.

Resuscitation phase: Whole blood transfusion and bolus infusion of saline were initiated 10 minutes before deflating the REBOA balloon. Pressor and calcium chloride were provided as needed. A vascular shunt was placed at the external iliac artery for revascularization.

Intensive care unit (ICU) phase: Once the resuscitation phase was underway the REBOA balloon was then completely deflated. Target MAP was maintained at 55 mmHg with fluids (saline or lactated Ringer's solution) and pressor. The animals were monitored for 2.5 hours.

All physiological parameters were acquired using PowerLab data acquisition system (ADinstruments, Inc) continuously throughout the protocol. Data was analyzed using LabChart software and averaged over 1 minute every 1 minute. Data is presented as mean± standard error of means (SEM).

Euthanasia and sample collection: At the end of the ICU phase, the animals were humanely euthanized. Tissue samples from the lung, heart, liver, small bowel, kidney and hindlimb muscle were collected for histology analysis.

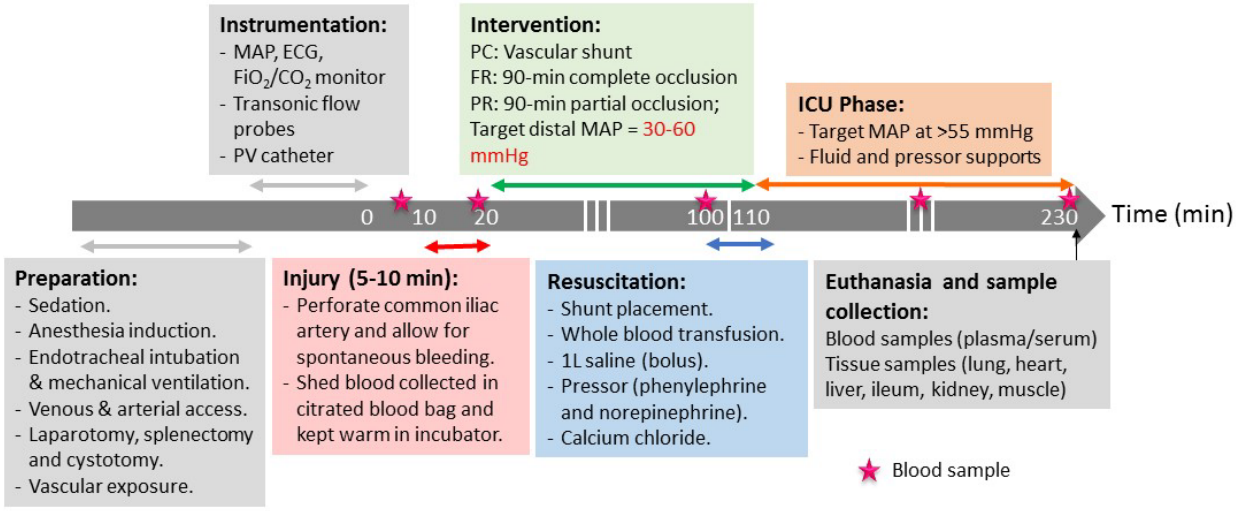


Figure 1. Experiment timeline of *in vivo* testing

RESULTS

1. Consistent target distal MAP was achieved by pREBOA-PRO™ following uncontrolled hemorrhage.

In the PR group, target distal MAP (30±5 mmHg) was achieved by partially deflating the balloon from full occlusion (Figure 1). The distal MAP in the FR group remained at 26.71±0.09 mmHg during full occlusion. Gradual increase in distal MAP was observed in both PR and FR groups during the resuscitation phase (whole blood transfusion, saline infusion, balloon deflation). Distal MAP was maintained at >55 mmHg with fluids and pressor support during the ICU phase (Figure 2, top graph).

Similar to the distal MAP, proximal MAP measured at the common aortic artery reduced during the hemorrhage phase. Complete occlusion led to an abrupt increase in proximal MAP in both REBOA groups (Figure 2, bottom graph). While the balloon was partially deflated in the PR group to allow for permissive distal perfusion, the proximal MAP dropped accordingly from

110.37±3.55 mmHg to 79.06±0.85 mmHg during the 90-min partial occlusion. A slight increase in proximal MAP was observed in the FR during the resuscitation phase, possibly due to the whole blood transfusion and bolus infusion of saline. Such effect may be dampened by the partial perfusion thus it was not detected in the PR group.

In the PC group, placement of vascular shunt prevented further reduction in distal and proximal MAP after uncontrolled hemorrhage, which remained at a level at 57.45±0.41 mmHg during the sham occlusion and ICU phases (Figure 2, top and bottom graphs, closed square).

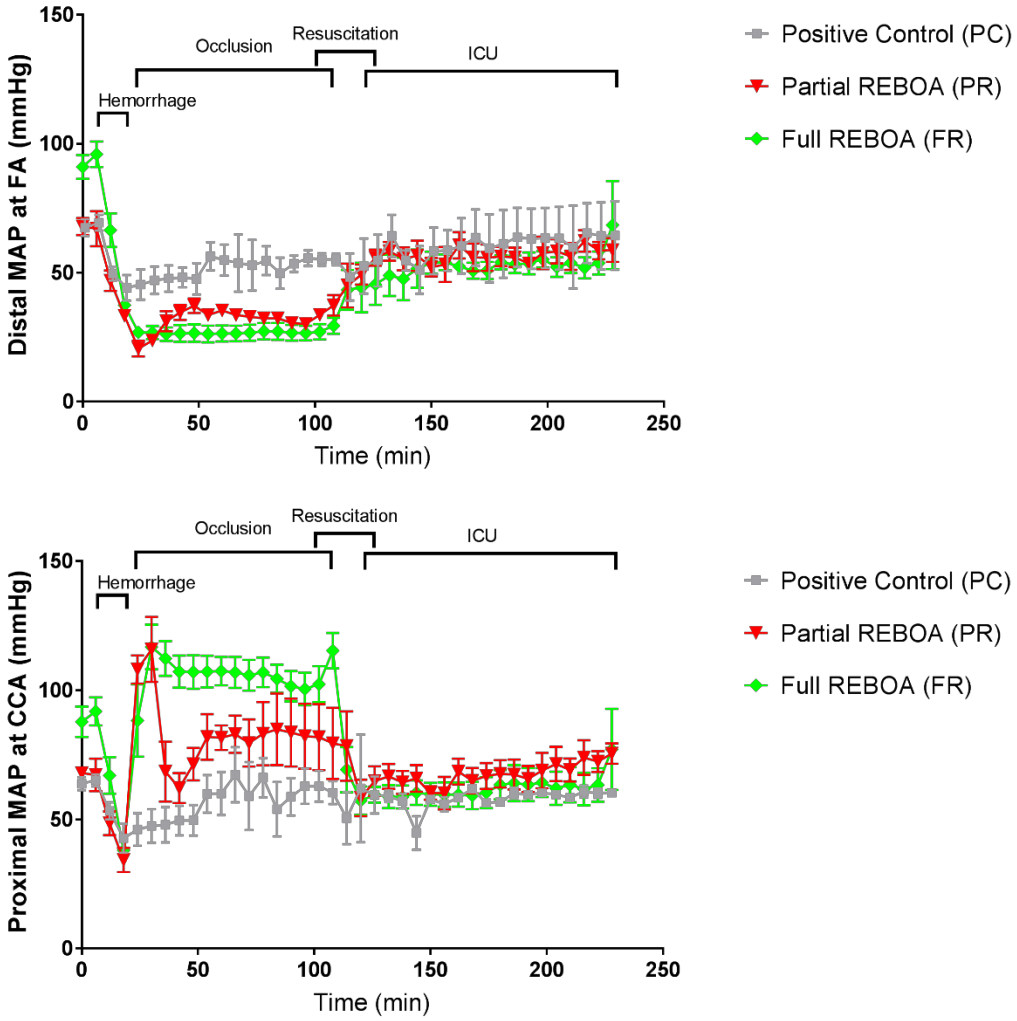


Figure 2. Mean arterial pressure (MAP) measured at the femoral artery (Top graph; FA; distal) and common carotid artery (Bottom graph; CCA; proximal)

2. Steady and precise control of distal aortic flow using pREBOA-PRO™

Figure 3 shows the flow rates measured at the infrarenal aorta (distal) and carotid artery (proximal) over time. During the hemorrhage phase, both distal and proximal aortic flow rates reduced. Distal aortic flow dropped to zero when the balloon was fully inflated. It remained zero

in the FR group whereas in the PR group, the flow rate remained at 243.92±5.03 ml/min (corresponding to the target distal MAP of 30±5 mmHg) allowing for permissive distal perfusion. Balloon deflation (i.e. reperfusion) induced a rapid spike in distal aortic flow rate in the FR group during resuscitation phase. The PR group, on the contrary, exhibited a smooth transition in distal aortic flow from partial occlusion to complete deflation of the balloon (622.23±5.34 ml/min). In the ICU phase, distal aortic flow rate in all groups remained steady (distal MAP was maintained by fluids and pressor support), in which the PR group was higher (617.71±5.89 ml/min) compared to the FR (512.82±11.48 ml/min) and the PC groups (378.45±5.99 ml/min).

Proximal flow rate exhibited a similar trend as the proximal MAP measured at the common carotid artery. It dropped during hemorrhage and then increased at complete aortic occlusion, indicating an increase in proximal perfusion induced by REBOA. In the PR group, the proximal flow rate dropped back to baseline level (537.24±7.25 ml/min) during partial occlusion. Balloon deflation/reperfusion further reduced the proximal flow rate in both REBOA groups. The proximal flow rates were comparable among the three groups during the ICU phase.

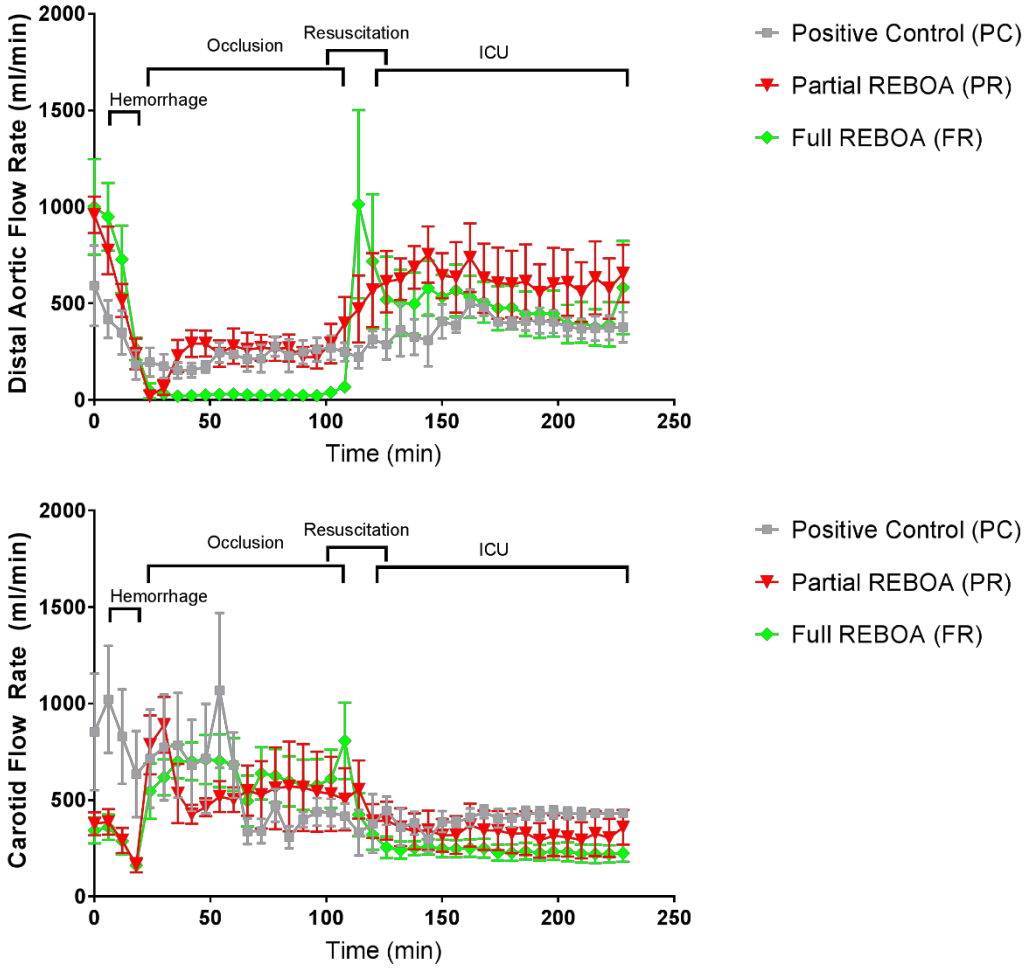


Figure 3. Flow rates measured at the infrarenal aorta (Top graph; distal) and carotid artery (Bottom graph; proximal)

3. Elevated monocyte count after REBOA

Complete blood count (CBC) test revealed an increase in circulatory monocyte percentage in the PR and FR groups at the end of aortic occlusion, which remained elevated at the end of the protocol (Figure 4, lower right graph). Such an increase may be associated with extremity ischemia induced by lack of blood flow. Other parameters including white blood cell (WBC), red blood cell (RBC), neutrophil, lymphocyte and hematocrit (HCT) were not changed dependent on treatment group..

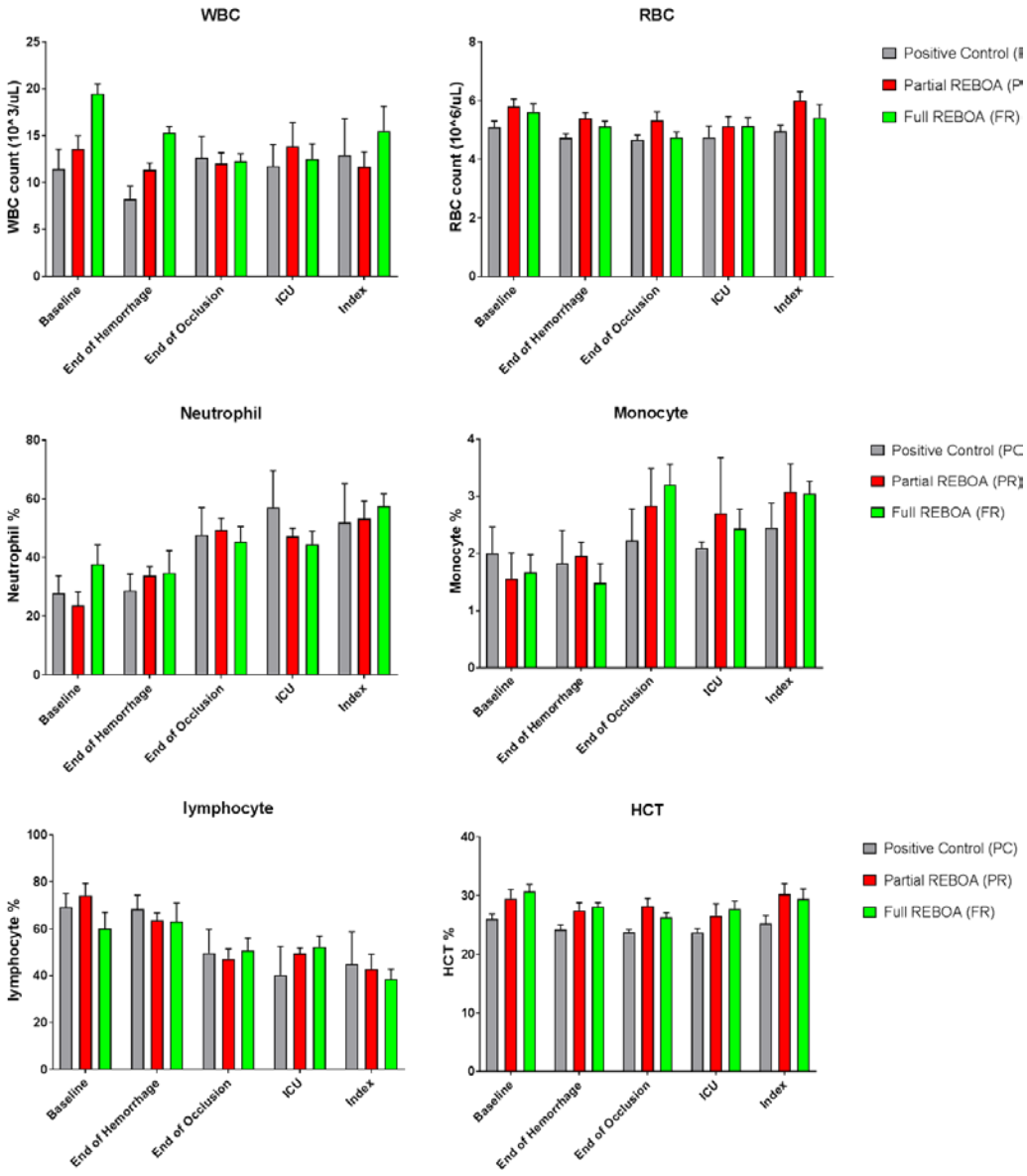


Figure 4. Complete blood count at the specified timepoints. WBC = White blood cell; RBC = Red blood cell; HCT = Hematocrit.

4. Blood pH was lowered following REBOA

As shown in Figure 5 (upper left graph), blood pH level was lowered following aortic occlusion in both REBOA groups (PR = 7.23±0.04; FR = 7.23±0.06) compared to the pre-occlusion level (PR = 7.40±0.05; FR = 7.46±0.04). It remained low until the end of the protocol, suggesting persistent acidosis induced by 90-min REBOA (both complete and partial occlusion). Partial pressure of carbon dioxide (pCO2) slightly increased after aortic occlusion but returned to baseline level at the ICU phase and at the end of the protocol. No specific changes were detected in the pO2 level. Total hemoglobin (tHb) returned to the pre-injury baseline level (baseline PR = 9.78±0.42 g/dL; baseline FR = 10.60±0.25 g/dL) at the ICU phase (PR = 9.46±0.65 g/dL; FR = 10.80±0.00), possibly due to the whole blood transfusion during the resuscitation phase. The tHb level remained high at the end of the protocol.

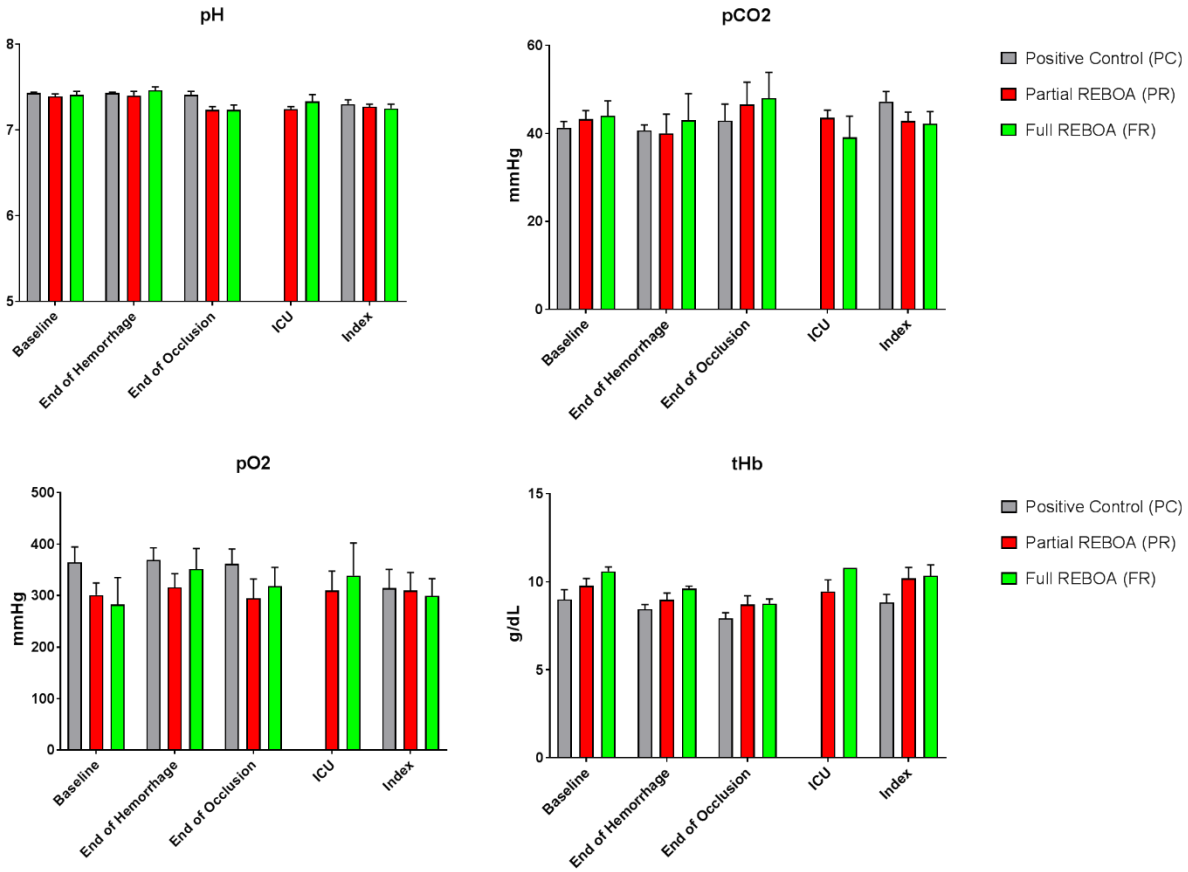


Figure 5. Blood gas analysis at the specified timepoints. pCO2 = partial pressure of carbon dioxide; pO2 = partial pressure of oxygen; tHb = total hemoglobin.

5. REBOA induced changes in potassium, glucose and lactate levels

In both REBOA groups, blood potassium levels were elevated after aortic occlusion (Figure 6, upper left graph), which may result from decreased renal excretion and potassium release from damaged cells. Glucose levels showed a distinctive pattern of change in the PR group (Figure 6, bottom left graph), in which blood glucose was increased at the end of the aortic occlusion and then returned to baseline level. On the other hand, the glucose level exhibited a decreasing trend in the FR group. Figure 6, lower right graph, shows that blood lactate level increased in both FR (6.32±0.90 mmol/L vs baseline level = 2.24±0.29 mmol/L) and PR groups (6.44±0.88 mmol/L vs baseline level = 2.22±0.20 mmol/L) following REBOA. These results indicate occlusion-induced lactate release which explains the acidosis (low pH) as mentioned in the previous section (Section 4, Figure 5) . The lactate level remained high at the end of the protocol. No changes were detected in the sodium, calcium and chloride levels following hemorrhage or REBOA.

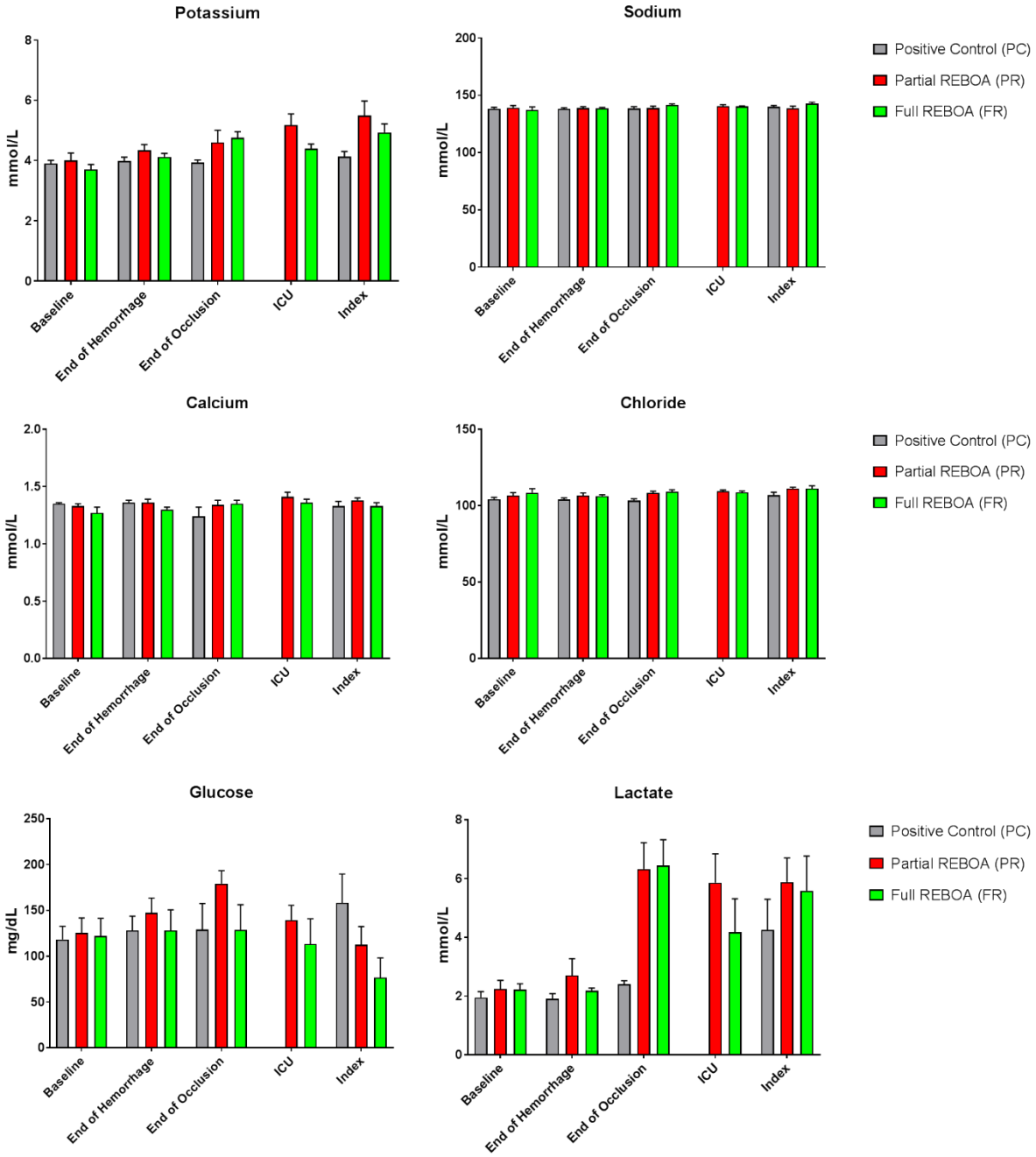


Figure 6. Electrolyte analyses at the specified timepoints.

SUMMARY

This study characterized the physiological changes following partial and complete occlusion using the pREBOA-PRO™ catheter, with the positive control group that received vascular shunt without REBOA intervention. Our data suggested that pREBOA-PRO™ was able to control the distal MAP precisely by regulating the balloon inflation/deflation. Critically, it provides a steady distal aortic perfusion, allowing for prolonged partial aortic occlusion and balancing between

hemorrhage control and distal ischemia. However, some acute complications associated with REBOA such as lactic acidosis, hyperkalemia (high potassium level) were still evident in animals subjected to partial or full REBOA. Histology analyses for ischemic tissue damages are underway.