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TITLE: Evaluation of Partial Flow Strategies in Hemorrhage and Traumatic Brain Injury with Endovascular Variable Aortic Control

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CONTRACTING ORGANIZATION: Wake Forest School of Medicine, Winston-Salem, NC

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14. ABSTRACT

Both iREBOA and pREBOA are partial flow strategies, building upon the success of REBOA (complete aortic occlusion) to achieve hemorrhage control and restore hemodynamics in patients with exsanguinating non-compressible truncal hemorrhage. These techniques aim to extend the duration of intervention and minimize ischemia to distal tissue beds prior to definitive surgical hemostasis, particularly in austere military environments. An ideal strategy balances hemodynamic stability to the heart, lungs and brain, while minimizing downstream ischemia. This is especially important in the context of traumatic brain injury (TBI), where brain hypoperfusion is known to result in worse neurologic outcomes. In preliminary studies, pREBOA promotes improved hemodynamic stability through continuous low level downstream blood flow, whereas iREBOA can result in pronounced hemodynamic shifts at the time of balloon deflation. We hypothesize that hemodynamic stability, cerebral perfusion and blood loss utilizing automated pREBOA will be superior to iREBOA.

15. SUBJECT TERMS
None listed.

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TABLE OF CONTENTS

1. INTRODUCTION:

Both iREBOA and pREBOA are partial flow strategies, building upon the success of REBOA (complete aortic occlusion) to achieve hemorrhage control and restore hemodynamics in patients with exsanguinating non-compressible truncal hemorrhage. These techniques aim to extend the duration of intervention and minimize ischemia to distal tissue beds prior to definitive surgical hemostasis, particularly in austere military environments. An ideal strategy balances hemodynamic stability to the heart, lungs and brain, while minimizing downstream ischemia. This is especially important in the context of traumatic brain injury (TBI), where brain hypoperfusion is known to result in worse neurologic outcomes. In preliminary studies, pREBOA promotes improved hemodynamic stability through continuous low level downstream blood flow, whereas iREBOA can result in pronounced hemodynamic shifts at the time of balloon deflation. We hypothesize that hemodynamic stability, cerebral perfusion and blood loss utilizing automated pREBOA will be superior to iREBOA.

2. KEYWORDS:

Automated Critical Care, Precision Medicine, Partial Aortic Occlusion, Intermittent Aortic Occlusion, Hemorrhagic Shock, Traumatic Brain Injury, Prolonged Field Care, Systemic Perfusion, Patient Management, Trauma, Blood Pressure

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Spec Aims/Tasks/Subtasks	Description	Progress
Specific Aim 1 (Hemorrhage without Traumatic Brain Injury):	To compare pREBOA and iREBOA in a highly lethal arterial/venous swine injury model without TBI. This will run concurrent with specific aim two.	
Major Task 1		
Subtask 1: Local IACUC and ACURO submission and approval	Experimental protocol for large animal experimentation will be generated utilizing key personnel from Wake Forest and U of Utah, with submission to Wake Forest IACUC for approval. Following local approval, the approved protocol will be submitted to the ACURO for final approval prior to in-animal model development.	**100%**

***Milestone # 1*: ACURO approval obtained**		**100%**
Subtask 2: EVAC Software development	Computer-controlled Endovascular Variable Aortic Control to perform both partial and intermittent Resuscitative Endovascular Balloon Occlusion of the Aorta is utilized in this experiment. Existing software will be adapted to this specific model to enable reproducibility across experiments.	**100%**
Subtask 3: Benchtop verification and validation of EVAC experimental protocol	Using an existing benchtop flow model and a custom digital simulation environment, all algorithms will be extensively tested and validated prior to large animal experimentation.	**100%**
Subtask 4: Large animal model development (n=16 animals total max; 8 animals for model development, 8 animals for donor blood)	In-animal model development will be performed to refine the vascular injury and timing of all critical events, particularly the extent and onset of vascular injury as well as timing and rates of whole blood resuscitation. Model development for specific aims 1 and 2 will occur simultaneously, with a total of 8 model development studies across both spec aims.	**50%**
Subtask 5: Large animal study: iREBOA vs pREBOA with hemorrhage alone (3 arms: iREBOA, pREBOA, control; n=8 experimental animals per arm; n=8 donor animals per arm)	Randomized experimentation comparing partial and intermittent Resuscitative Endovascular Balloon Occlusion of the Aorta utilizing automated EVAC technology with hemorrhage alone.	0%
***Milestone # 2*: Completion of large animal study**		0%
Subtask 6: Data analysis	Physiologic data including real-time hemodynamics and laboratory assays will be extracted, compiled, and analyzed.	0%
Subtask 7: Histologic analysis	Prescribed histologic processing and analysis will be performed on tissue collected at the time of necropsy, to be led by a clinical veterinary pathology.	0%
***Milestone #3*: Completion of data analysis**		0%
Subtask 8: Reporting and manuscript development	All key personnel will participate in preparation of scholarly publications based on the analyzed data obtained from the large animal study.	0%
***Milestone #4*: Publication and presentation of results**		0%

Specific Aim 2 (Hemorrhage with Traumatic Brain Injury):	To compare pREBOA and iREBOA in a highly lethal arterial/venous swine injury model with TBI. This will run concurrent with specific aim one.	
Major Task 2		
Subtask 1: Local IACUC and ACURO submission and approval	Experimental protocol for large animal experimentation will be generated utilizing key personnel from Wake Forest and U of Utah, with submission to Wake Forest IACUC for approval. Following local approval, the approved protocol will be submitted to the ACURO for final approval prior to in-animal model development.	**100%**
***Milestone # 1*: ACURO approval obtained**		**100%**
Subtask 2: EVAC Software development	Computer-controlled Endovascular Variable Aortic Control to perform both partial and intermittent Resuscitative Endovascular Balloon Occlusion of the Aorta is utilized in this experiment. Existing software will be adapted to this specific model to enable reproducibility across experiments.	**100%**
Subtask 3: Benchtop verification and validation of EVAC experimental protocol	Using an existing benchtop flow model and a custom digital simulation environment, all algorithms will be extensively tested and validated prior to large animal experimentation.	**100%**
Subtask 4: Large animal model development (n=16 animals total max; 8 animals for model development, 8 animals for donor blood)	In-animal model development will be performed to refine the vascular injury and timing of all critical events, particularly the extent and onset of vascular injury as well as timing and rates of whole blood resuscitation, reproducibility of the blood instillation induced traumatic brain injury, and finalizing the imaging protocol. Model development for specific aims 1 and 2 will occur simultaneously, with a total of 8 model development studies across both spec aims.	**50%**
Subtask 5: Large animal study: iREBOA vs pREBOA with hemorrhage *AND* traumatic brain injury (2 arms; n=8 experimental animals per arm; n=8 donor animals per arm)	Randomized experimentation comparing partial and intermittent Resuscitative Endovascular Balloon Occlusion of the Aorta utilizing automated EVAC technology with hemorrhage AND traumatic brain injury.	0%
***Milestone # 2*: Completion of large animal study**		0%
Subtask 6: Data analysis	Physiologic data including real-time hemodynamics and laboratory assays will be extracted, compiled, and analyzed.	0%

Subtask 7: Histologic analysis	Prescribed histologic processing and analysis will be performed on tissue collected at the time of necropsy, to be led by a clinical veterinary pathology.	0%
***Milestone #3*: Completion of data analysis**		0%
Subtask 8: Reporting and manuscript development	All key personnel will participate in preparation of scholarly publications based on the analyzed data obtained from the large animal study.	0%
***Milestone #4*: Publication and presentation of results**		0%

What was accomplished under these goals?

During grant year 1 we completed tasks needed to begin in-animal model development. The initial local IACUC protocol was reviewed and approved by both Wake IACUC and ACURO, software/algorithm development was completed, benchtop testing of the catheter and associated software algorithms was completed, disposables for model development were procured, and data acquisition hardware were procured and assembled. Following these activities and development of SOPs, study checklists, REDCap database, and other associated documents needed for data acquisition and to satisfy regulatory requirements (Appendix A), animal model development began to refine surgical procedures, TBI creation, and timing of critical events (Appendix B). The study team began interfacing with the Wake Translational Imaging Program (TIP) to coordinate MRI for the TBI cohort of this study. In addition, discussions began between the Wake and Utah grant investigator team and the Section Chief of Neuroradiology to collaborate on MRI scan interpretation and results. An amendment to the local IACUC protocol to add MRI was submitted and approved by the Wake IACUC and ACURO. Collaborators at the University of Utah developed a MRI sequence protocol for a swine TBI model that will be utilized for this study at Wake (Appendix C). During Y1Q4, two Wake general surgery residents were onboarded and trained to work in our research lab and have contributed to the work completed during quarter 4.

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

Wake resident research year – A professional development opportunity is available for interested Wake residents to spend 1+ dedicated research years in an area of interest. Recruitment usually occurs at least one year in advance of the start of their anticipated research year. In July 2021, two 3rd year General Surgery residents began their resident research year, funded by the Howard Holt Bradshaw Fellowship, as part of our research team with close mentorship provided by the investigators of this grant and other shared grants. During grant year 1 quarter 4 they contributed to completion of benchtop verification of the EVAC experimental protocol algorithms and *in vivo* model development. During their research year they will continue to work with our research team with involvement in completing model development, execution of randomized experimentation, data analysis, abstract/poster presentations and publication.

How were the results disseminated to communities of interest?

Nothing to report.

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

During the next reporting period we will continue working with our imaging core TIP to finalize imaging capabilities at Wake. Once we are approved by the TIP to begin scheduling MRI scans (approval expected to be received in October), we will execute the final model development procedures to finalize surgical procedures, TBI creation, timing of critical events, MRI transport/anesthesia logistics and MRI sequence protocol execution. Following completion of model development, randomized experimentation will commence during the next reporting period.

4. **IMPACT:**

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

Nothing to report.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

During this reporting period, the method for inducing TBI was changed from a mechanical cortical impact model to a blood instillation model. The updated method is modeled after a TBI protocol utilized by investigators and collaborators at the University of Utah. We also added end of study brain MRI to the TBI cohort. Funds for the cortical impactor will be reallocated to cover MRI costs. These changes are reflected in the approved IACUC and ACURO protocol for this grant.

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

Significant delays were encountered for this award during grant year 1 due to extended periods of downtime for our laboratory and our Animal Resources Program (ARP). Downtime experienced due to COVID was a result of complete cessation of laboratory activity which led to accumulation of delays in ongoing protocols under other awards, which in turn prevented execution of work towards this current award. Additionally, our vivarium, under the management of the ARP underwent renovations to the air handling and HVAC systems, which limited the ability to house large animals on campus to 2 animals at a time for all investigators utilizing swine on the Bowman Gray campus. Full operations within the lab were able to resume after renovations were competed in July 2021.

Changes that had a significant impact on expenditures

Efforts paid towards faculty and staff were delayed in grant year 1, as work on this grant was delayed due to reasons described in the previous section. We plan to increase throughput of animal experiments during grant year two. Personnel efforts will be adjusted within budget to appropriately cover the increased rate of experimentation, including funds that will be allocated to cover efforts on this project assigned to a second laboratory technician currently employed in the Wake investigator's department.

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

Significant changes in use or care of human subjects

Not applicable.

Significant changes in use or care of vertebrate animals

During grant year 1 quarter 4 we submitted an amendment to the IACUC approved protocol (local Wake protocol # A21-010) to add MRI brain imaging at the end of the study in the traumatic brain injury cohorts to better delineate the impact of the intervention on brain injury and function beyond just the histologic analysis. Approval was obtained from the Wake Forest IACUC on 8/4/21, approval from the ACURO was received on 9/9/21.

Significant changes in use of biohazards and/or select agents

Not applicable.

6. PRODUCTS:

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

Journal publications.

Nothing to report.

Books or other non-periodical, one-time publications.

Nothing to report.

Other publications, conference papers and presentations.

Nothing to report.

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

Nothing to report.

- **Technologies or techniques**

Nothing to report.

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

Nothing to report.

- **Other Products**

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Timothy K Williams, MD
Project Role:	Principle Investigator
Researcher Identifier (e.g. ORCID ID):	https://orcid.org/0000-0002-9186-3818
Nearest person month worked:	1
Contribution to Project:	Generated local IACUC protocol and developed initial algorithms for the conduct of the study. Completed acquisition of critical equipment purchases for the conduct of the study. Completed software development for the execution of the study. Assisted in developing the SOP, MRI setup, and associated documentation required for the study. Direct involvement with animal experimentation.

Name:	Lucas P Neff, MD
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	0
Contribution to Project:	Assisted in developing the experimental design, MRI setup, SOP and associated documentation required for the study. Direct involvement with animal experimentation.

Name:	James Jordan, PhD
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	0
Contribution to Project:	Assisted in developing the experimental design, SOP and associated documentation required for the study. Direct involvement with animal experimentation.

Name:	Austin Johnson, MD
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	0
Contribution to Project:	Assisted in developing the experimental design, MRI, SOP and associated documentation for the study.

Name:	Magan Lane
Project Role:	Research Technician
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Assisted in regulatory activities, generation of required documents for the conduct of the study and procurement of disposables. Direct involvement in with animal experimentation.

Name:	James Cranfill
Project Role:	Research Technician
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	
Contribution to Project:	Assisted in generation of required documents for the conduct of the study and procurement of disposables. Direct involvement in with animal experimentation.

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

Active support began during grant year 1 quarter 4. Updates made to efforts in grant year 2 will be reported once the rate of experimentation and appropriate effort has been determined with a goal to increase rate of experimentation to make up for unanticipated delays experienced in grant year 1. Efforts will not exceed total funds budgeted for personnel between year 1 and year 2 and will accurately reflect work being performed towards the aims of this grant.

What other organizations were involved as partners?

- **University of Utah**
  Salt Lake City, Utah
  Austin Johnson, MD, PhD and Guillaume Hoareau, DVM, PhD provide general support for experimental design, development of the TBI model, and will be involved in data analysis and publication following completion of experimentation.
- **University of California Davis**
  Sacramento, California
  UC Davis Department of Veterinary Pathology will be providing support for histopathologic analysis in the latter portions of the study. They have not been actively involved to date.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

9. APPENDICES: