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TITLE: Emergency Preservation and Resuscitation for Cardiac Arrest from Trauma (EPR-CAT)

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CONTRACTING ORGANIZATION:
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14. ABSTRACT Cardiopulmonary resuscitation (CPR) can save victims of normovolemic cardiac arrest (CA), e.g., ventricular fibrillation. During exsanguination CA from trauma, however, CPR, even with an emergency department (ED) thoracotomy and open chest CPR, results in unacceptably low survival rates. Emergency Preservation and Resuscitation (EPR) was developed to rapidly preserve the organism during ischemia, using hypothermia, drugs, and fluids, to "buy time" for transport and resuscitative surgery. The purpose of this study is to test the feasibility of rapidly inducing profound hypothermia (< 10°C) with an aortic flush in trauma victims that have suffered CA and failed standard resuscitative efforts to enable resuscitative surgery and delayed resuscitation with cardiopulmonary bypass. The primary outcome variable will be survival to hospital discharge with minimal neurologic dysfunction.					
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1. INTRODUCTION:

Cardiopulmonary resuscitation (CPR) can save victims of normovolemic cardiac arrest (CA), e.g., ventricular fibrillation. During exsanguination CA from trauma, however, CPR, even with an emergency department (ED) thoracotomy and open chest CPR, results in unacceptably low survival rates. Emergency Preservation and Resuscitation (EPR) was developed to rapidly preserve the organism during ischemia, using hypothermia, drugs, and fluids, to “buy time” for transport and resuscitative surgery. The purpose of this study is to test the feasibility of rapidly inducing profound hypothermia ($< 10^{\circ}\text{C}$) with an aortic flush in trauma victims that have suffered CA and failed standard resuscitative efforts to enable resuscitative surgery and delayed resuscitation with cardiopulmonary bypass. The primary outcome variable will be survival to hospital discharge with minimal neurologic dysfunction.

2. KEYWORDS:

Trauma, hemorrhagic shock, cardiac arrest, hypothermia, cardiopulmonary bypass, resuscitation

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 major goal of this project has been to test the hypothesis that emergency preservation and resuscitation (EPR) by rapid induction of profound hypothermia in a trauma patient who has suffered a cardiac arrest from presumed exsanguination is feasible and safe. The specific hypotheses are:

1. Aortic arch cold flush can be initiated within 5 min of pulselessness in victims of trauma.
2. Aortic arch cold flush can decrease tympanic membrane temperature to less than 34°C within 5 min of initiation and less than 20°C within 15 min.
3. EPR by aortic arch cold flush can allow survival without brain damage from otherwise lethal injuries.

Specific Aims

1. To rapidly identify potential candidates for EPR who have almost no chance of survival with current therapy.
2. To rapidly place a large-bore catheter into the proximal, descending aorta via a thoracotomy and rapidly infuse ice-cold saline into the aortic arch to cool vital organs and produce global profound hypothermia (10°C).
3. To use survival as the primary outcome variable and the Glasgow Outcome Score Extended (GOSE) and the development of multiple organ dysfunction syndrome (MODS), as secondary endpoints in survivors.

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.

Regulatory activities

The first regulatory step for proceeding with this study was to obtain an Investigational Device Exemption (IDE) from the Food and Drug Administration (FDA). Our trial is complicated by the fact that both fluids and equipment are to be used for an application that is not currently approved by the FDA. We obtained an investigator-sponsored IDE from the FDA Center for Devices and Radiological Health Office of Device Evaluation.

With the approval of the IDE, we were able to obtain approval for the proposal from the University of Pittsburgh Institutional Review Board (IRB) as both the coordinating center and participating site. Similarly, the University of Maryland IRB has approved the study. Both IRB approvals requiring completion of the community consultation process.

To begin the community consultation process in Pittsburgh, we met with the Pittsburgh Human Relations Commission. They made suggestions regarding the involvement of minorities in the community consultation process. We placed a survey instrument in trauma clinic and completed a phone survey for the community to comment on the study. A summary of the community consultation and public disclosure process was submitted to the IRB and was approved. The study was subsequently approved by the USAMRMC and the Secretary of the Army.

The community consultation process in Baltimore was conducted in a similar fashion to the process in Pittsburgh. Surveys were conducted in trauma clinic, multiple community events, and online. The summary of results were approved by the University of Maryland IRB.

Conflict of Interest

Because Drs. Tisherman and Kochanek are co-authors of a submitted patent for EPR Methods, the University of Pittsburgh Conflict of Interest Committee reviewed the plans for the trial and approved a plan to resolve the conflict so that these researchers could still be involved in the study. The University of Maryland Conflict of Interest Officer also approved the conflict of interest plan.

Clinical Accomplishments

Before initiating enrollment in both Pittsburgh and Baltimore, we completed animal and simulation training with trauma surgeons, cardiac surgeons, anesthesiologists, and perfusionists for the EPR process. We have also worked with the Emergency Department in Pittsburgh, the Trauma Resuscitation Unit in Baltimore, Operating Room, and Perfusion staff to have all of the necessary equipment available.

The study has been regularly discussed with the Independent Data Safety Monitoring Board. They recommended standardization of the transfusion protocols across sites, elimination of blunt trauma victims, and the use of Seldinger technique for aortic cannulation. They have also asked for more prolonged follow-up of subjects (to 12 months), including additional functional outcome using the SF-36 form.

The study opened for enrollment in Pittsburgh in early 2014. This site was subsequently suspended later that year because necessary faculty left the institution. During that time, the investigators observed that there were some patients who were in profound shock in the Emergency Department and subsequently suffered a cardiac arrest in the Operating Room. We therefore revised the enrollment criteria to include such patients. No subjects were enrolled in Pittsburgh.

In 2016, the study opened for enrollment at the Shock Trauma Center of the University of Maryland Medical Center. We have enrolled 7 subjects (4 EPR and 3 controls) between Nov 2016 and September 2017. For all of the EPR subjects, the cannulation and cooling processes went well. The surgical procedures were conducted expeditiously and the subjects went on cardiopulmonary bypass. In the first case, the subject developed a spontaneous pulse, but suffered massive, lethal intravascular clotting and a consumptive coagulopathy after liberation from cardiopulmonary bypass and administration of protamine. In the second case, the subject could not be liberated from cardiopulmonary bypass, likely because of a constellation of injuries that were not survivable. In the third case, the subject was coagulopathic and could not be liberated from cardiopulmonary bypass. Once placed on extracorporeal membrane oxygenation and given protamine very slowly, he developed intravascular clotting and could be supported. In the fourth case, the subject was liberated from cardiopulmonary bypass and was transferred to the intensive care unit. He subsequently succumbed to intractable coagulopathic bleeding.

The first control subject died in the operating room from exsanguinating hemorrhage. The second control subject survived the initial resuscitation, but later died from multiple organ system failure, despite the use of extracorporeal membrane oxygenation. The third control subject died of exsanguinating hemorrhage and a direct cardiac injury.

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.

Nothing to report as we have not reached our goal of 20 subjects (10 EPR and 10 control).

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.

We will continue the study under new funding.

- 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).

Nothing to report

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.

Nothing to report

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.*

Nothing to report

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.*

Nothing to report

- 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:

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.

Nothing to report.

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

Given the finding of unusual intravascular clotting during liberation from cardiopulmonary bypass (CPB), we have adjusted our approach to administration of heparin and protamine to provide anti-coagulation during CPB yet appropriate clotting after liberation from CPB. As the dosing of these drugs were not proscribed in the IRB protocol, the IRB did not feel that a change in the protocol was necessary. It was also noted that coagulopathy and clotting complications were already noted as potential complications in the protocol and consent form.

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.

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).*

Tisherman SA, Alam HB, Rhee PM, Scalea TM, Drabek T, Forsythe RM, Kochanek PM: Development of the Emergency Preservation and Resuscitation for Cardiac Arrest from Trauma (EPR-CAT) clinical trial. J Trauma Acute Care Surg, 2017;83(5):803-809.

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.

The following website was used for disseminating information about the study in Baltimore as part of the public disclosure process:
www.eprstudy.com

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

Nothing to report

- **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.

Nothing to report.

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: Patrick Kochanek, MD
Project role: Principal investigator
Nearest person month worked: 1
Contribution to project: Provided research oversight and administrative support

Name: Samuel A. Tisherman, MD
Project role: Co-investigator
Nearest person month worked: 6
Contribution to project: Developed the protocol, conducted training sessions, and obtained regulatory approvals. He has also been the local principal investigator in Pittsburgh and, later, Baltimore.

Name: Leslie Sult, RN
Project role: Research coordinator
Nearest person month worked: 5
Contribution to project: Served as research coordinator in Baltimore, participated in the community consultation process, managed the equipment, assisted with training, and assisted with the conduct of the research protocol.

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.

Dr. Tisherman obtained new funding as PI for “Emergency Refreshing of Combat Surgical Skills” from the US Army Medical Research & Materiel Command. Total costs: \$1,471,317.

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.*

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: N/A

QUAD CHARTS: N/A

9. APPENDICES: N/A