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TITLE: Hypothermia for Patients Requiring Evacuation of Subdural Hematoma: Effect on Spreading Depolarizations

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14. ABSTRACT
This report describes Year 4 progress in clinical studies to determine the impact of temperature management on spreading depolarizations (SD) and outcomes in severe traumatic brain injury (TBI), following SOW revision in Year 3. In this year, ethical approvals were obtained to address research questions using existing clinical databases from the W81XWH-08-2-0016 (Objective 1) and TRACK-TBI (NIH U01; Objective 2)studies. Statistical approaches and custom programs were developed for Obj.1. In analysis of hourly physiologic data (n=2229), results demonstrated significant effects of increased temperature (>36 C), lower blood pressure, and lower heart rate to increase risk of SDs as recorded from the brains of TBI patients. Each variable showed an independent effect in multivariate logistic regression. The model predicted the occurrence of SDs with 80% accuracy, 40% sensitivity, and 80% specificity on a naïve test data set. Results suggest a simple physiologic model of SD prediction to generalize principles of SD for patient care. Obj. 2 will be pursued in the next period.

15. SUBJECT TERMS
traumatic brain injury; subdural hematoma; electroencephalography; spreading depression; spreading depolarization; therapeutic hypothermia; craniotomy

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1. INTRODUCTION:

The ***hypothesis of the originally funded study*** was that a mechanism of therapeutic benefit of hypothermia in TBI patients is through suppression of mass neuronal spreading depolarizations (SD) in cerebral cortex. The ***objective*** was to determine whether very early cooling in the HOPES trial is associated with reduced incidence of spreading depolarizations compared to normothermia treatment. The HOPES trial was a separately funded, prospective, randomized trial to determine the effects of very early cooling in the specific pathoanatomic subgroup of TBI patients undergoing surgical evacuation of acute subdural hematomas (ASDH).

As communicated in the Year 2 Annual Report, completion of the proposed study was not possible since (1) Office of the Secretary of the Army review of the study protocol, which utilized Exception from Informed Consent, was never accomplished, and (2) during this period, at a scheduled interim review on August 27, 2018, the Data Safety and Monitoring Board of the HOPES study recommended to end the trial due futility.

In Year 3, alternate research plans were developed to address the original hypothesis concerning the role of hypothermia and SD as a mechanistic target for improving outcome from TBI. A revised statement of work and revised contract were executed at the start of Quarter 4, Year 3. ***This report describes progress in Year 4 in alignment with milestones of the revised statement of work.***

2. KEYWORDS:

traumatic brain injury; subdural hematoma; electroencephalography; spreading depression; spreading depolarization; therapeutic hypothermia; normothermia; controlled normothermia; temperature management; mass lesion; craniotomy;

3. ACCOMPLISHMENTS:

Major goals of the project

It is recognized that fever contributes to secondary injury after TBI and should be avoided. However, it is uncertain how aggressively therapy should be applied, and whether there is benefit to controlled normothermia, targeted temperature management, or hypothermia. Hypothermia, for instance, remains attractive as a treatment for elevated intracranial pressure, despite mixed results and several failures in clinical trials.

Under the revised SOW, we aim to refine understanding of optimal practices for temperature management in TBI by examining patient temperatures and temperature management therapies and their relationship to functional and cognitive outcomes in a large national, observational TBI cohort. In a more focused study, we will further investigate spreading depolarizations (SDs) as a hypothesized neuronal mechanism for the adverse effects of fever. SDs are pathologic waves in cerebral cortex that recur for days following TBI and are an independent factor in worse patient outcomes. We hypothesize that temperature management is effective due to suppression of SDs, and that the limit and extent of outcome benefit of lower patient temperatures is similar to the impact of temperature on SD risk.

OBJECTIVE 1: Determine the impact of patient temperature and temperature management practices on the variable incidence and timing of SDs after severe TBI.

Specific Aim 1A: Determine the impact of patient temperature on SD probability.
Specific Aim 1B: Determine whether patients without SDs (n=55) differ from those with SDs (n=83) in temperature values and temperature management practices.
Specific Aim 1C: Determine the impact of temperature management on 6-month clinical outcomes.

OBJECTIVE 2: Determine the impact of patient temperature on long-term functional and cognitive outcomes in a large national cohort.

Specific Aim 2A: Determine the impact of patient temperature on functional outcomes.
Specific Aim 2B: Determine the impact of patient temperature on cognitive outcomes.
Specific Aim 2C: Determine the impact of temperature mangement practices on 6-month clinical outcomes.

Accomplishments toward these goals in Year 4, aligned with SOW Milestones

Objective 1

Preparatory Work

1. It was determined that Objective 1 will be accomplished using a deidentified data set that was determined by the University of Cincinnati IRB to meet requirements for exemption from IRB review in accordance with 45 CFR 45.104 (secondary research on data or specimens; no consent required). The protocol and IRB determination were submited to HRPO on December 4, 2019. Clarification was requested and re-submitted to HRPO on January 9, 2020. HRPO approval was obtained on January 31, 2020.

2. Biostatistics doctoral student Koffi Wima was identified to assist in the analysis of Aims 1A-1C. However, after 6 weeks of working with him, it was determined that he did not have sufficient skills and background to accomplish the MATLAB programming needed for data analysis (tasks 2-3), as described in the Year 3 annual report. In the second quarter quarter, we identified a another biostatistics student, Xinyu Cong, to perform the custom programming and statistical analysis for Objective 1 under direction of the PI and Roman Jandarov, PhD, professor of biostatistics.

Milestones

1. Write MATLAB code for import of hourly physiologic values and SD times - *100% Complete*

Progress: Xinyu Cong completed writing of MATLAB programs for import of hourly physiologic values as well as spreading depolarization (SD) times for the database of n=138 patients.

2. Write MATLAB code to analyze SD rates in relation to physiologic values - *100% Complete*

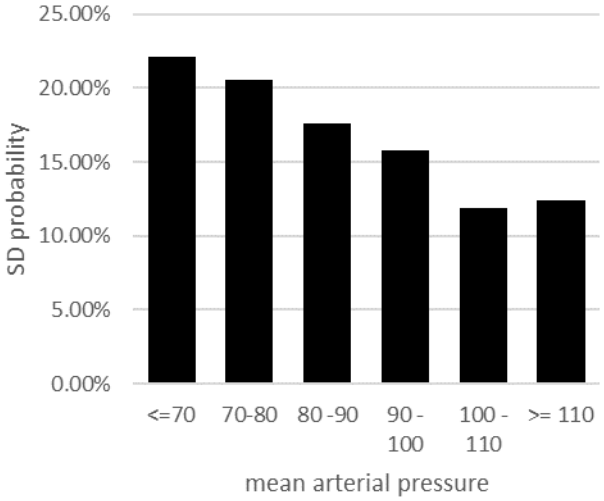
Progress: Xinyu Cong completed writing of MATLAB programs for analysis of hourly physiologic values in relation to spreading depolarization (SD) times for the database of n=138 patients.

3. Perform analysis of Aim 1A: Determine the impact of patient temperature on SD probability – *100% Complete*

Progress:

A. General Methods and Mean Arterial Pressure. Initial comparisons of physiologic values (mean arterial pressure, temperature, etc.) between patients with and without SDs, with statistical testing, were accomplished. We also compared values between (a) times when SDs occurred, (b) times when no SDs occurred, and (c) all values recorded. Results from n=138 patients were consistent with results reported in a prior publication based on ~15 patients, thus confirming accuracy of our present analysis and programming routines.

We further calculated the impact of individual variables on SD probability. The graph below shows the impact of varying mean arterial pressure (MAP) on SD probability.



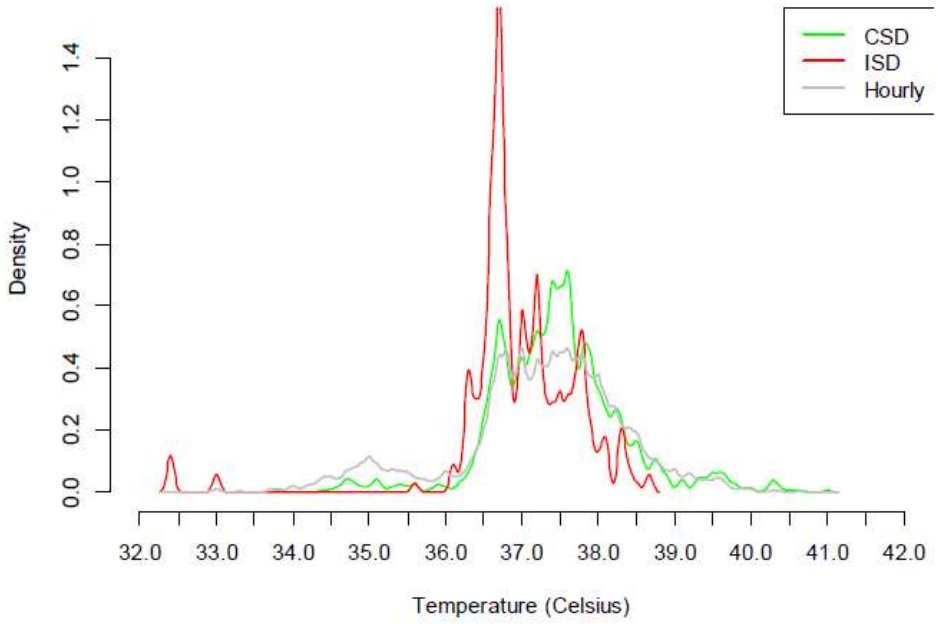
Results of a regression model were highly significant, as follows:

β = -1.25804 - 0.09526*MAP(70 -80) - 0.28724*MAP(80 - 90) - 0.41898*MAP(90 -100) - 0.74329*MAP(100 -110) - 0.69368*MAP(>110), where Pr(having SD) = exp(β)/1+exp(β) and Pr(no SD) = 1/1+exp(β).

B. Temperature. When all SDs were considered together, we found that patient temperatures during hours with SDs were significantly higher compared to hours with no SD (average value = 37.35 vs. 37.25, resp.). In Poisson regression accounting for the number of SDs observed in the hour, this effect of higher temperature to increase SD risk was highly significant at $p<0.001$).

The density plot below shows that the main effect occurs for temperatures <36 C. The gray traces shows the distribution of temperature values in the entire data set of 3,856 hours in 83 patients. The red and green traces show the distribution of temperature values during SDs (two subtypes: CSD and ISD). Below 36 C, the probability of SDs is low compared to

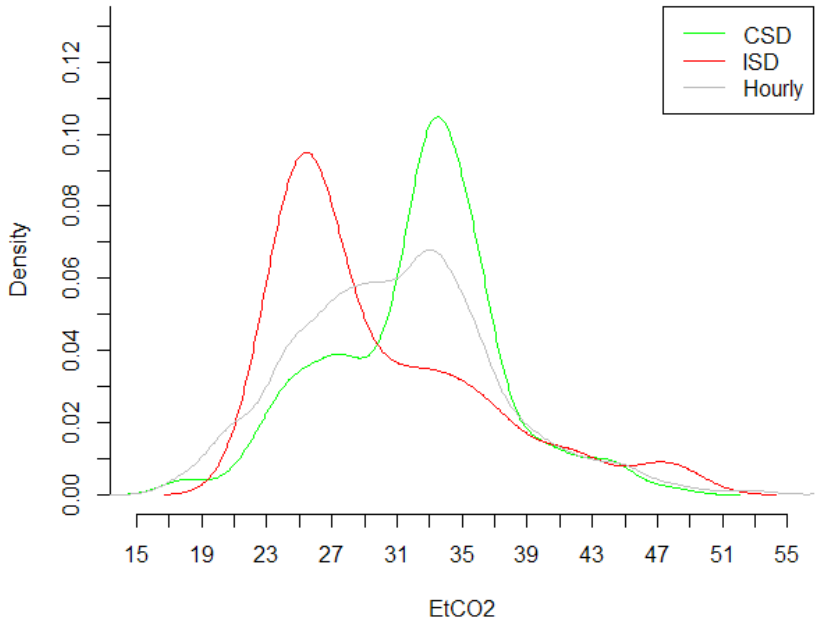
the probability of temperatures in this range, indicating that SDs are suppressed by low temperature. By contrast, probabilities are similar in the range of 37-38 C. These results suggest that maintaining patient temperature below 36 C may be an effective therapeutic strategy to suppress SDs.



C. End-tidal CO_2. We also we undertook a detailed, rigorous analysis of a subset of data to determine the impact of CO_2 levels on SDs. This analysis was spurred by results from a separate, smaller study suggesting that low end-tidal CO_2 (E_TCO_2) may increases the risk of SD, and that higher levels may prevent SD. Data on hourly E_TCO_2 and SDs were available from 38 patients, comprising a total of 1760 hours of patient monitoring. A total of 619 SDs occurred in this time.

To our surprise, we found that SD rate was not significantly impacted by E_TCO_2. However, we did find that low E_TCO_2 is associated with increased rates of *isoelectric* SDs (ISDs). ISD are a subset of SDs in which brain activity remains suppressed to a flatline state, in contrast to transient depression during CSDs. ISDs are a poor prognostic sign, associated with worse patient outcomes.

The graph below shows hourly E_TCO_2 values from the whole dataset (gray), in comparison to values during CSDs and ISDs. Most ISDs occur at E_TCO_2 values <30 mmHg, while the median E_TCO_2 in patients is 33.



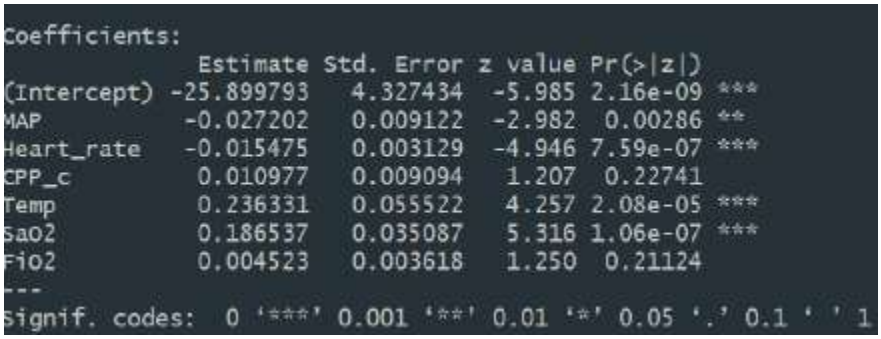
In the same subset of patients, we examined whether ISDs were associated with potential confounding variables of hyperventilation, mean arterial pressure (MAP), cerebral perfusion pressure (CPP), and intracranial pressure (ICP). Only ICP was significantly associated with SDs in univariate analysis. In multivariate regression, both ICP and E_TCO_2 were significant independent predictors of ISD occurrence. Results of both logistic and poisson regression are shown below. Importantly, this is the first demonstration that E_TCO_2 impacts the occurrence of SDs, likely due to an effect of low CO_2 to decrease cerebral blood flow and exacerbate ischemia. This result highlights the importance of ventilatory parameters to maintain eucapnia (CO_2 > 35 mmHg) to prevent secondary brain injury.

ISD		
Logistic Reg	**Coefficients**	**p-value**
Intercept	0.41	0.633
EtCO2	-0.063	0.0206
ICP	-0.044	0.0331
Poisson Reg		
Intercept	0.68	0.171
EtCO2	-0.05	0.00193
ICP	-0.036	0.003

While this exercise did not directly address the impact of temperature, it validated an additional variable for which we need to control in the analysis of temperature effects. As importantly, it allowed our team to work through and document the precise steps, data sorting, reporting, and statistical methods to address the objective's aims in multivariate analysis.

D. Multivariate Analysis. We then used multivariate analysis to determine the independent impact of temperature on SD occurrence. For this analysis, we used only hours (n=2229) in which complete data were available for all variables in the model, including MAP, heart rate, temperature, cerebral perfusion pressure, and oxygen saturation (SaO2). The result of

logistic regression are shown below. In this model, MAP, heart rate, temperature, and SaO2 had significant independent effects. Temperature was signficant at p<0.0001.



```
Coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) -25.899793   4.327434  -5.985 2.16e-09 ***
MAP          -0.027202   0.009122  -2.982  0.00286 **
Heart_rate   -0.015475   0.003129  -4.946 7.59e-07 ***
CPP_c         0.010977   0.009094   1.207  0.22741
Temp          0.236331   0.055522   4.257 2.08e-05 ***
SaO2          0.186537   0.035087   5.316 1.06e-07 ***
FiO2          0.004523   0.003618   1.250  0.21124
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

The model was then applied to a test data set (239 hours) that was not used in model development. Results showed that the model has an accuracy of predicting hours with SDs of 79.9%. The sensitivity is 40% and specificity is 80%.

Importantly, these results suggest that a very simple model of basic vital signs can be used to predict the risk of SDs (and thus secondary brain injury) in patients.

4. Perform analysis of Aim 1B: Determine whether patients without SDs (n=55) differ from those with SDs (n=83) in temperature values and temperature management practices – *50% Complete*

Progress: Research thusfar has focused on predictors of SD in patients that have SD (n=83), i.e. when does it occur. The next step will be to analyze factors, including temperature management, that predict which patients have SDs (n=83 vs. n=55). All methods have been developed to conduct this analysis, which will be straightforward.

5. Perform analysis of Aim 1C: Determine the impact of temperature management on 6-month clinical outcomes – *Not started*

6. Manuscript preparation and publication – *20% Complete*

Progress: We have initiated writing of the results reported above in a manuscript for publication.

Objective 2

Preparatory Work

Objective 2 will be accomplished using data from the study, TRACK-TBI ("Transforming Research and Clinical Knowledge in TBI"). All sites have IRB-approved TRACK-TBI protocols. The protocol for Objective 2 was submitted to HRPO on January 14, 2020. On March 10, HRPO notified the investigators that protocol submitted, including TRACK-TBI IRB approvals for all investigators and TRACK-TBI Executive Committee approval, was not acceptable. A standalone protocol with limited research activities reviewed by the UC IRB was requested. A conference call was held to discuss and clarify this determination, which was upheld. Thereafter, we submitted a stand-alone protocol for this objective to the UC IRB and received an "Exempt Determination" on June 11, 2020. A Use of Data/Specimens form was then submitted to HRPO along with UC IRB determination and associated documents on June 24, 2020. HRPO approval was received on July 27, 2020.

Milestones

1. Completion of data entry – *100% Complete*

2. Data cleaning and extraction – *100% Complete*

   Progress: Data for the 1083 adult patients admitted to the ICU in the TRACK-TBI study were reviewed for completeness of hourly data entry. Missing data points were confirmed as not be available or were completed by the local study team.

3. Adapt MATLAB code for data import and analysis – *Not started*

4. Perform analysis of Aim 1A – *Not started*

5. Perform analysis of Aim 1B – *Not started*

6. Perform analysis of Aim 1C – *Not started*

   Progress: No significant progress on Tasks 4-6 beyond that reported in the Year 3 Annual Report.

7. Manuscript preparation and publication – *Not started*

Opportunities for training and professional development
Nothing to Report

Dissemination of results to communities of interest
Nothing to Report

Next reporting period

In the next quarter, for Objective 1, we will focus on consolidating the results to date on hourly data in patients with SDs, in a manuscript for publication. Thereafter, we will conduct analyses of patients with vs. without SDs to complete an SD prediction model. Finally, we will add analysis of impact on outcome.

For Objective 2, we will review data analysis objectives with the study team, prepare the cleaned data for MATLAB import, and apply developed statistical approaches to initiate data analysis.

4. IMPACT

Impact on the development of the principal discipline(s) of the project
Our results are significant in developing a simple physiologic data model to predict the occurrence of SD in patients with severe TBI. The gold-standard measurement of SDs requires placement of invasive electrode strips on the brain of patients undergoing neurosurgery. This method limits generalization and application of SD-based knowledge (prognostication and treatment) to patients who are not eligible for these procedures and at medical centers that do not have this capability.

A physiological model for SD prediction, on the other hand, could overcome this limitation by identifying which patients, and at which times, are at high risk for SDs. Furthermore, identification of the risk factors that cause SDs (high temperature, low MAP, etc.) will suggest effective therapeutic interventions to mitigate these risks and possibly improve patient outcomes.

Impact on other disciplines
The impact described above applies broadly to the field of neurocritical care.

Impact on technology transfer
Nothing to report

Impact on society beyond science and technology
Nothing to report

5. CHANGES/PROBLEMS

Changes in approach and reasons for change
Nothing to report since the contract modification was executed

Actual or anticipated problems or delays and actions or plans to resolve them
Nothing to report since the contract modification was executed

Changes that had a significant impact on expenditures
Nothing to report since the contract modification was executed

Significant changes in use or care of human subjects
Nothing to report since the contract modification was executed

Significant changes in use or care of vertebrate animals
Not applicable

Significant changes in use of biohazards and/or select agents
Not applicable

6. PRODUCTS

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
A DOD grant application, based in part on SD risk factors identified in the present study (EtCO2, MAP, temperature), has been recommended for funding. The proposed INDICT trial would aim to treat SDs by adjustment of these variables according to thresholds presently identified to decrease SD risk and reduce secondary brain injury.

Title: Improving neurotrauma by depolarization inhibition with combination therapy (INDICT): a Phase 2 randomized feasibility trial
PI: Hartings, Jed A.
Funding Agency: Joint Warfighter Medical Research Program
Period: 2021-2024

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?
Name: Jed Hartings, PhD
Project Role: Principal Investigator
Nearest person month worked: 2
Contribution to Project: Corresponded with DOD and all collaborating partners to obtain ethical approvals. Organized the initiation of work and planning of objectives, and directed and supervised data analysis. Supervised budget and establishment of subawards.

Name: Xinyu Cong
Project Role: Data Analyst
Nearest person month worked: 3
Contribution to Project: Developed all custom programming for data handling and statistical analysis. Performed all data cleaning, summary, and analyses.

Changes in other support of the PD/PI(s) or senior/key personnel since the last reporting period
Nothing to report

Other organizations involved as partners
Organization Name: University of Texas at Houston
Location of Organization: Houston, TX
Partner's contribution to the project: Data curation, analysis, writing, and intellectual contribution in approach to Objective 2
Financial support to project: None
In-kind support: None
Facilities, Collaboration, or Personnel Exchange outside contribution noted above: None

Organization Name: University of Pittsburgh
Location of Organization: Pittsburgh, PA
Partner's contribution to the project: Data curation, analysis, writing, and intellectual contribution in approach to Objective 2
Financial support to project: None
In-kind support: None
Facilities, Collaboration, or Personnel Exchange outside contribution noted above: None

Organization Name: University of California San Francisco
Location of Organization: San Francisco, CA
Partner's contribution to the project: Data management, curation, and extraction in support of Objective 2
Financial support to project: None
In-kind support: None
Facilities, Collaboration, or Personnel Exchange outside contribution noted above: None

8. SPECIAL REPORTING REQUIREMENTS

Quad Chart is submitted separately.

9. APPENDICES

None