Biologic Mechanisms of Early Exercise After Intracerebral Hemorrhage

NCT04027049

7/10/2020

JHM IRB - eForm A – Protocol

- **Use the section headings to write the JHM IRB eForm A, inserting the appropriate material in each. If a section is not applicable, leave heading in and insert N/A.**
- **When submitting JHM IRB eForm A (new or revised), enter the date submitted to the field at the top of JHM IRB eForm A.**

****

1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

While recent advances in the treatment of acute ischemic stroke (AIS) have dramatically improved functional recovery for many patients, the burden of disability from ischemic stroke remains and more than half of patients with spontaneous intracerebral hemorrhage (sICH) remain disabled at one year post-stroke.[4,14,36-37] There is an urgent need to develop interventions aimed at reducing the burden of severe disability in patients with ischemic and hemorrhagic stroke.

The innate immune response is triggered by an ischemic or hemorrhagic insult initiating a cascade of biochemical processes activating white blood cells, macrophages and microglia.[3,15,17,29-30] The expression of the pro-inflammatory M1 cytokine phenotype predominates in the early period after AIS and sICH and is thought to worsen secondary brain injury. The anti-inflammatory M2 phenotype, including brain derived neurotrophic factor, demonstrates a slower ascent to peak and is associated with tissue repair.[9,18,55] Intervening to effect a balancing of M1 and M2 cytokines and accelerated expression of BDNF may increase the capacity for tissue repair.

Animal and human studies have demonstrated that moderate intensity exercise when compared to exertional exercise or strength training result in shifting of cytokine expression toward anti-inflammation and diminished markers of oxidative stress.[7,16,24,35,45] The benefit of early exercise in AIS and sICH in decreasing pro-inflammatory factors has been demonstrated in animal models when exercise is introduced between 24 hours and three days in AIS and at three or four days in sICH.[40,53-55] An exercise intervention that is standardized in frequency with measureable intensity and duration is necessary to explore the effects of an exercise intervention in acutely ill patients with AIS and sICH. We hypothesize that a balancing of the inflammatory response after sICH can occur with the application of moderate exercise in the acute period.

Objectives (include all primary and secondary objectives)

Primary Objective: to determine the effects of twice-daily, lower extremity CE of 20 minutes duration plus usual care, compared to usual care alone, on the trajectories of M1 versus M2 cytokine phenotypes in the serum and cerebrospinal fluid (CSF).

Secondary Objectives:

(i) To determine the effects of twice-daily, lower extremity CE of 20 minutes duration plus usual care compared to usual care alone and a third retrospective cohort of patients receiving usual care during the COVID-19 pandemic on, the immediate and sustained physical impairment, disability scores and relevant coavriates such as delirium and hospital acquired infections at NCCU discharge and 30 days after hemorrhage.

(ii) To determine the correlation between serum and cerebrospinal fluid cytokines in patients with external CSF drainage as part of their care.

(iii) To explore the relationship between pre-morbid physical function and quality of life and changes in inflammatory factors among all participants.

(iv) To determine the effects of twice-daily, lower extremity CE of 20 minutes duration plus usual care alone on hemispatial neglect as measured by the Sunnybrook Neglect Assessment Procedure on day 1 of the study at transfer from the ICU or discharge from the hospital and 30 days after hemorrhage.

2. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

There is an urgent need to develop interventions aimed at reducing the burden of severe disability in patients with sICH and AIS. Outcomes for patients with sICH have remained relatively stagnant and while outcomes after acute ischemic stroke have improved over the past several years with the widening of treatment windows for thrombolysis and use of thrombectomy the burden of disability after stroke in general remains high.[4,14,36-37]

The innate immune response is triggered by the insult initiating a cascade of biochemical processes activating white blood cells, macrophages and microglia after a hemorrhagic ischemic insult.[48-49,53] The initial immune response results in increased permeability of the blood brain barrier, cytokine expression, programmed neuronal death or apoptosis and culminates in brain tissue damage and loss of brain function. Cerebral inflammation likely contributes to morbidity and mortality through cerebral edema, cytokine and chemokine induced neuronal injury and thrombin associated toxicity.[45-46] The expression of the pro-inflammatory M1 cytokine phenotype predominates in the early period after sICH and is thought to worsen secondary brain injury. The anti-inflammatory M2 phenotype demonstrates a slower ascent to peak and is associated with tissue repair and hematoma degradation in sICH.[45-46,55] Additionally, BDNF was been shown in animals to be produced in lesser amounts after sICH, potentially impeding repair and recovery.[9,18] Intervening to effect a balancing among M1 cytokines and M2 cytokines may increase the capacity for tissue repair.

Animal and human studies have demonstrated that moderate intensity exercise when compared to exertional exercise or strength training result in a balancing of cytokine production and diminished markers of oxidative stress.[16,24,35,40] An added benefit of early exercise in sICH was suggested by Takamatsu whose work demonstrated a decrease in IL1β and IL-6 and an increase in IL-10 with treadmill running within 4 days of sICH in rats.[40] Enhanced motor recovery was thought to be explained in part by enhanced neuronal plasticity using dendritic length as an endpoint.[23] Zhang and colleagues demonstrated a reduction in pro-inflammatory factors and anxiety behaviors in animal models with induced AIS.[53]

An adaptable exercise intervention that is standardized in frequency with measureable intensity and duration is necessary to explore the effects of an exercise intervention in critically ill stroke patients. Accessibility of the intervention to patients with severe disability and altered levels of consciousness presents a challenge that can be overcome with in-bed cycle ergometry (CE) (see figure 1). Cycle ergometry is provided to patients by nurses or rehabilitation therapists with patients lying supine in bed by securing the lower extremities into supported pedals while motor driven rotations of the cycle move the legs passively. Active cycling can occur as a patient attempts to move their legs in a pedaling motion. Two recent trials of lower extremity CE reporting 963 sessions in critically ill medical patients cited a 0.6-2% rate of adverse events requiring termination of a cycling session, none requiring further intervention after

cessation of cycling.[25-27,43] Cycle ergometry in critically ill patients with brain injury has been undertaken in a recent observational cohort study reporting no clinically significant changes in intracranial pressure or systemic hemodynamics.[43] Further, our Neurocritical Care mobility group has compiled an unpublished dataset, consisting of 39 CE sessions in 39 patients with intracranial pressure monitoring that demonstrates no clinically significant changes in intracranial pressure, hemodynamics or neurologic status.[28] Studies of cycle ergometry to date have reported on rehabilitation therapist delivery of cycle ergometry in durations of 20-30 minutes, which due to resource constraints is usually delivered once per day.[6,25-27,43,] Our unit has established a practice where nurses also deliver this intervention while closely monitoring neurologic and hemodynamic status allowing for more than one session to be delivered. Recent studies of CE in critically ill patients, including patients with neurologic illness, reported that cycling did not adversely affect hemodynamics or intracranial pressure.[6,8,25-27]

Enrollment of subjects within the original study framework was put on hold beginning on March 16, 2020 due to the necessary hospital response to prevent further spread of COVID-19 and to maximize reosurces to treat hospitalized patients. Adding a second control group where all variables except for biologic and survey data will allow comparison of three different care conditions, intervention plus usual care, usual care only and usual care only during a pandemic. Usual care in terms of study visit timing, number, and length may be different than pre-pandemic care paradigms due to staff redeployment and restructuring are care areas to support care during a disaster.

3. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

This pilot study uses a randomized parallel group design to determine the difference in the expression of pro- and anti-inflammatory cytokines in response to this specific exercise intervention plus usual care versus usual care only. Patients will be enrolled on day 3 of illness and data will be collected for seven consecutive days. We seek to enroll a convenience sample of up to 100 consecutive patients with supratentorial sICH and acute ischemic stroke admitted to the Johns Hopkins Hospital Neurosciences Critical Care Unit (NCCU). Patients will be screened within 24-48 hours of arrival for eligibility according to the inclusion and exclusion criteria listed below. Informed consent will be obtained from the patient or legally authorized representative (LAR). The consenting process will be performed remotely via videoconference when possible.

Patients will be randomly assigned to the intervention plus usual care or usual care only group using a standard randomization schema generated by STATA 14.0 (College Station, Texas). The AIS and sICH cohorts will have separate randomization schemas.

After enrollment, the Patient-Reported Outcomes Measurement Information System (PROMIS) Glabal Measure of Health v1.2 questionnaire for (pre-morbid health) will be administered to the patient or their LAR depending on the patient's ability to complete the form. At the last follow-up visit the patient or LAR will complete the Stroke Impact Survey. Additionally, the Sunnybrook Neglect Assessment Procedure will be administered to the patient on day 1 of the study, on transfer from the ICU or discharge from the hospital and at 30 days after the hemorrhage.[31] If the patient is assessed as not having neglect at the time of enrollment or is found not to have neglect as measured by the assessment procedure then they will not have to complete this measure at subsequent time points.

The intervention group will receive two CE sessions per day after randomization with a unit owned cycle (Reck Motomed Letto, Germany). Sessions will be held at least 2hours apart to allow for patient rest and activities of patient care. The clinician will set the device to an automatic program where passive cycling will be initiated and the device will provide resistance if the patient attempts to actively cycle. Vital signs (e.g., heart rate, blood pressure, pulse oximetry, intracranial pressure) will be monitored continuously by a study team member present at the bedside during the CE session, if an

Figure 1: Supine cycle ergometer

arterial line is not available the non-invasive cuff will be cycled every 5 minutes. Continuous vital signs will be extracted from the Sickbay software application, which collects physiologic data on all NCCU (see IRB00132987 Multimodality Neuromonitoring in the Neurocritical Care Unit). A clinician will observe the patient at all times during the session for signs of pain and discomfort and will administer the behavioral or visual analog pain scale every 5 minutes during the session depending on the patient's level of consciousness. Patient tolerance will be defined as the absence of the following: decline in neurological examination; sustained change in intracranial pressure, blood pressure, heart rate or oxygen saturation outside of prescribed goals per established patient specific plan of care; an increase in pain as measured by the behavioral pain scale or numeric pain rating scale not easily ameliorated by position change by the clinician; and accidental tube/device/catheter removal.[22,34] Manual muscle strength testing using the Medical Research Council Sum Score will be performed by a clinician before the first session on days three and seven for patients in the control group. General strength will be assessed using a hand-held dynamometer for patients able to follow simple commands before the first session on days three and seven for patients in the control group. Other relevant covariates will be extracted from the medical record such as delirium screening, hospital acquired infections, volume of hematoma and cerebral edema on routine CT scans and body temperature.

The second control group, retrospective observational cohort, will consist of ischemic and hemorrhagic stroke patients admitted to the NCCU on the Johns Hopkins Hospital and Johns Hopkins Bayview campuses from March 16, 2020 through the end of the prohibition of tier II and III studies declared by the Johns Hopkins University Institutional Review Board. All data collection will be accomplished through retrospective chart abstraction. Face-to-face contat will not be required. The same clinical variables will be collected for this cohort to the extent that they are recorded in the medical record from admission to 90 days after the initial ischemic or hemorrhagic stroke.

The following samples will be obtained for the intervention + usual care group and the control group, usual care only:

a) A 2 teaspoon sample of the patient's serum on the day of enrollment and two additional times during the seven day study period timed with routine collection of blood, when possible, for daily blood tests while the patient is in the hospital. Blood samples will be collected from an existing arterial or central line or via venipuncture. The initial blood sample will be collected on study day 1 prior to cycling in the intervention group and between 8 am-12 pm in the control group. Subsequent samples will be drawn after the second cycling session and between 2 pm and 6 pm in the control group.
b) A 4-5 mL sample of saliva on the day of enrollment and two additional times during the seven day study period. Saliva will be collected between 8 am-10 am in all participants and prior to the first cycling session of the day for the intervention group.
c) A 4 mL sample of cerebrospinal fluid (CSF) on the day of enrollment and two additional times during the seven day study period timed with collection of other sampling, when an external ventricular drain is in place as a part of care. CSF sampling will occur in patients with an external ventricular drain inserted as part of their care and will end after 3 samples or when the drain is discontinued. Efforts will be made to time CSF sampling with planned sampling, if possible and sampling will be performed by a nurse or physician study team member trained in the skill as part of their job using aspetic technique. The initial CSF sample will be collected on study day 1 prior to cycling in the intervention group and between 8 am-12 pm in the control group. Subsequent samples will be drawn after the second cycling session and between 2 pm and 6 pm in the control group.

All samples will be placed on dry ice, centrifuged and stored in a -70 degree Celsius freezer within 1 hour of obtaining the sample. Samples will be labeled with de-identified data (patient study number and date only).

Usual care in the NCCU consists of evaluation and treatment by physical and occupational therapists assigned to the neurosciences service when an order for evaluation and treatment is entered by medical providers. Patients may be seen up to 5 times per week depending on their level of participation and intensity of therapy required, however many patients with sICH particularly those in coma are treated by therapists 2 times per week. Nursing staff in the NCCU provide passive range of motion and progressive a patient's mobility from supine to upright positioning, sitting at the side of bed, transferring to chair, lift assisted transfer to chair and ambulation as the patient's condition allows. All usual care activities will be recorded by the study team via extraction from the medical record. Usual care during the pandemic is similar to the care described above however, due to resource constraints it is possible that care focused on mobility and recovery was reprioritized in order to provide acute and intensive care for other patients.

Table 1. Study Activities Schedule for the intervention and prospective control group

	Admission day 1-2	Study day 1 = hospital day 3	Study day 2 = hospital day 4	Study day 3 = hospital day 5	Study day 4 = hospital day 6	Study day 5 = hospital day 7	Study day 6 = hospital day 8	Study day 7= hospital day 9	Day of ICU transfer	30 days after hemorrhage (-10, +30 days)
Screening, Inclusion/ Exclusion, Consent	X									
Intervention and monitoring										
Cycle ergometry 20 minute sessions (twice each study day)		XX	XX	XX	XX	XX	XX	XX		
Vital signs (BP, HR, RR, SpO^2, ICP)		X	X	X	X	X	X	X		
Pain scores		X	X	X	X	X	X	X		
Physiologic outcomes for the intervention and control groups										
Blood draw (IL1-β, IL-6, TNF-α, IL-10, CRP, BDNF)		X		X				X		
Saliva sample for cortisol		X		X				X		
CSF sampling, if a external ventricular		X		X				X		

drain is in place										
Outcome measures										
Medical Research Council Sum Score (strength testing)[21]		X		X				X	X	X
Grip strength		X		X				X	X	X
Modified Rankin scale score	X								X	X
Barthel Index[12]									X	X
Sunnybrook Neglect Assessment Procedure (SNAP)[31]		X							X *This battery will only be completed if the patient was found to have neglect on the initial assessment.*	X *This battery will only be completed if the patient was found to have neglect on the initial assessment.*
Questionnaires										
Promis Global Measure of Health v1.2 to patient or legally authorized representative (LAR)		X								
Stroke										X

Impact Survey to patient or LOR										

b. Study duration and number of study visits required of research participants.

The study will enroll patients for approximately two years. Each patient will receive study interventions or procedures depending on group assignment for 7 days, assessment of motor function and physical/cognitive functioning on transfer from the NCCU or 1 day after the last study day if the patient completed study activities outside of the NCCU and 30 days (-10 days, +30 days) after occurrence of sICH. We will allow a 30 day time period in which to contact the patient if they are not able to be contacted on the 30th day for a total study period of 60 days. If a patient is seen in clinic prior to the 30 day period after the hemorrhage, follow-up assessments will be performed at that time. The stroke service currently collects a modified Rankin score for all ischemic and hemorrhagic stroke patients at 90 days via phone as a standard of care. We will record this value for all patients in this study. If a patient is not scheduled for an in-person visit after discharge, only the 90 day modified Rankin scale will be collected as an outcome measure.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

This pilot trial cannot be blinded because of the use of the supine cycle ergometer which is a large piece of equipment introduced into the patients' rooms in the intervention group twice per day during the initial study period, however outcome measures at NCCU transfer and 30 days will be obtained by a study team member blinded to the participant's group assignment.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

Current therapy will not be stopped. Participants will receive the study intervention in addition to usual care.

e. Justification for inclusion of a placebo or non-treatment group.

In order to detect a signal of cytokine modulation with the intervention regimen of supine cycle ergometry, a control group not receiving the intensive intervention regimen is necessary for comparison.

f. Definition of treatment failure or participant removal criteria.

If a patient meets the following stopping criteria on >2 consecutive sessions the patient will be withdrawn from the study: change in neurological examination, sustained change in intracranial pressure, blood pressure, heart rate, or oxygen saturation that is outside of provider-prescribed range, significant pain exacerbated by mobilization.[22,34]

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

Upon study procedure completion participants will continue to receive usual care.

4. Inclusion/Exclusion Criteria

Inclusion criteria:	**Rationale:**
Age ≥18 years	Spontaneous intracerebral hemorrhage and acute ischemic stroke is typically a disease of the adult.
Supratentorial intracerebral hemorrhage with or without intraventricular hemorrhage	Only patients with a supratentorial ICH will be included due to the fact that patients with infratentorial ICH often require surgery, introducing an overlay of inflammation above that which is caused by the ICH itself. It is known that intraventricular hemorrhage increases severity of illness and mortality, however it is a common co-occurring process in patients with ICH and should be studied concurrently.[13]
Acute ischemic stroke with a Medical Research Council Sum Score (MRCSS) of <27.	Patients with a clinical diagnosis of stroke and motor weakness as identified by the MRCSS as less than 27.[21]
Pre-morbid modified Rankin Score of 0-2	The modified Rankin Score (mRS) is a commonly

	used tool to quantify disability after stroke and is scored from 0 to 6 with higher scores describing increased disability including death. The mRS will be used to characterize a patient's pre-morbid functional status correlating with a patient's potential for recovery after stroke as well as an outcome measure at discharge and 30 days after hemorrhage.[5,13] Patients with a mRS >2 prior to admission have poor potential for recovery.
Patient must be able to provide informed consent or have a legally authorized representative to provide consent on their behalf	
Exclusion criteria:	
Patients with known inflammatory conditions, infection requiring antibiotics or pregnancy	Underlying inflammatory disorders such as, but not limited to, rheumatoid arthritis, Lupus and fibromyalgia and pregnancy will impact interpretation of inflammatory biomarkers. Patients with a diagnosed infection requiring antibiotics (e.g., bacteremia, pneumonia, urinary tract infection) at the time of screening will be excluded due to associated systemic inflammation.
Patients receiving daily anti-inflammatory medications including but not limited to prednisone, methotrexate, non-steroidal anti-inflammatory medications (ibuprofen, naproxen, indomethacin, celecoxib) and aspirin >325mg.	These anti-inflammatory medications will adversely impact our ability to interpret inflammatory markers.
Glasgow Coma Score (GCS) 3 48 hours after admission.	A GCS of 3 represents the deepest form of coma wherein no response can be elicited from the patient in terms of eye opening, verbal output and motor response. A GCS of 3 on admission portends a poor outcome.[41]
Patients in whom withdrawal of life support is being considered by surrogate decision makers.	These patients are likely to die prior to or shortly after randomization. In the event that a surrogate elects not to withdraw life support, the patient will be reassessed for eligibility once more within 72 hours of the ictus.
Injury to the lower extremities, hips or pelvis, weight >250 kg (weight limit of cycle), or body habitus precluding normal function of cycle.	These injuries or physical characteristics may make the cycling activity unsafe.

5. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

The cycle ergometer (CE) is capable of facilitating movement of the upper and lower extremities regardless of the participant's ability to participate, therefore making it possible for use in patients with varying levels of consciousness and physical impairment. The CE is currently used by Rehabilitation Therapists and nurses as part of rehabilitative therapy in some NCCU patients.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

No medications will be administered.

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

No medications will be administered.

Study Statistics

a. Primary outcome variable.

Pro-inflammatory cytokines: IL-1β, TNFα, IL-6; Anti-inflammatory/repair factors: IL-10, BDNF

b. Secondary outcome variables will be measured at discharge and 30 days post-intracerebral hemorrhage or acute ischemic stroke.

- Modified Rankin Scale (mRS)
- Barthel Index will be measured at discharge and 30 days
- Medical Research Council Sum Score and dynamometry to measure muscle strength
- Discharge location (e.g., home, nursing facility), although not well studied, is commonly associated with physical function at discharge.
- SF-12
- Vital signs (e.g., heart, rate, blood pressure, respiratory rate)
- Delirium positive days
- Hospital acquired infections (e.g., catheter associated urinary tract infection and central line associated blood stream infection)
- CSF cytokines and repair factors
- Stroke Impact Survey

c. Statistical plan including sample size justification and interim data analysis.

Sample size was calculated for a fully powered trial and 9% of this sample size will be used for this pilot according to Cocks' methodology.[10] An effect size of 0.28 was used, based on a published single group observational study in critically ill patients with a primary outcome of cytokine change.[47] Detection of an effect size of 0.28 with power of 80% and an α of 0.05 requires a sample size of 400 for a full trial and 9% represents a pilot sample size of 36 participants. Due to the enrollment of two stroke phenotypes, ischemic and hemorrhagic, we will analyze each cohort separately, therefore 40 participants per cohort are required. Accounting for attrition, up to 100 participants may be consented in order to enroll up to 40 participnats per cohort. Each cohort will have 20 participants in each of two arms, intervention and control. It is estimated that at least 3-5 patients will be enrolled per month over 18 months.

Descriptive statistics will be used to report sociodemographic variables. Baseline characteristics will be compared between the two groups. If they are found to be similar, post-intervention outcomes will be compared between the groups. If the baseline characteristics are found to be different, an adjusted analysis as described below will be conducted. Mean (SD) or median (IQR) will be used to describe continuous variables, and frequency (%) will be used for categorical variables. Mean differences in cytokines between the three time points (baseline, day 3 and day 7) will be calculated for each participant in the intervention and control groups. We will also plot data over time by group. Assumptions of normality will be checked and appropriate parametric or non-parametric tests will be used to detect absolute mean differences due to the small sample size, with an a priori significance level of 0.05, although the primary aim of this study is to estimate effect size. Data quality will be ensured by analyzing all samples in duplicate and procurement of samples will be performed by the same investigator. Statistical analysis will be performed using Stata 14.0 (College Station, Texas).

Primary aim (1): To determine whether a regimen of twice daily 20-minute sessions of CE plus usual care administered to patients with sICH and AIS (n=20) increases cytokines of the M2 phenotype and decreases cytokines of the M1 phenotype within 10 days of sICH when compared to a similar group of patients with sICH receiving usual care only (n=20).

The effect size, absolute difference between the two groups and the standard error of the difference will be estimated. The standardized difference will be estimated using Cohen's d. A two-sample t-test will be used to detect differences between post-test outcomes. If the baseline outcome is different, an analysis of covariance (ANCOVA) will be used to compare the outcomes between the two groups adjusting for the baseline difference as a covariate.

Hypothesis: Patients in the CE group will demonstrate an increase in cytokines of the M2 phenotype and a decrease in the M1 phenotype when compared to the group receiving usual care only.
Aim 2: To determine the effects of twice-daily, lower extremity CE of 20 minutes duration plus usual care compared to usual care alone and a third retrospective cohort of patients receiving usual care during the COVID-19 pandemic on, the immediate and sustained physical impairment and disability scores at NCCU discharge and 30 days after hemorrhage.

Data from this aim will be analyzed in the same fashion as described above.
Hypothesis: The CE group will demonstrate decreases in 90-day modified Rankin Scale score, increases in the Medical Research Council sum score (muscle strength) and grip strength, less delirium positive days and hospital acquired infections.

d. Early stopping rules.

If a patient meets the following stopping criteria on >2 consecutive sessions the patient will be withdrawn from the study: change in neurological examination, sustained change in intracranial pressure, blood pressure, heart rate, or oxygen saturation that is outside of provider-prescribed range or significant pain exacerbated by mobilization.

6. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

The risks of this study are designed to be minimal. Potential risks to the participant include the following: hemodynamic instability, increased intracranial pressure, skin breakdown associated with the supine cycle ergometer, pain, muscle spasm and musculoskeletal injury.

b. Steps taken to minimize the risks.

Patients are continuously monitored on a cardiorespiratory monitor with oxygen saturation, heart rate, intracranial pressure (when applicable) and blood pressure, measured by arterial catheter or non-invasive cuff. Blood pressure, heart rate, oxygen saturation, respiratory rate and intracranial pressure will be measured and recorded continuously using the Medical Informatics, Sickbay software application currently installed in the NCCU and collecting data from all cardiorespiratory monitors. Pain will be measured and documented every 5 minutes visual analog scale or behavioral pain scale in patients unable to report pain level.

The NCCU is staffed 24 hours per day by a dedicated team of Neuro Intensivists, fellows and resident physicians assigned exclusively to the unit who can respond immediately to physiologic changes or adverse events when notified. A chain of command is followed when a primary provider is not available to respond due to other emergent patient care duties.

Administration of cycle ergometry will be performed by the Principal Investigator or trained registered nurses (RN) who currently perform this therapy in the NCCU and have been trained in current personal protective equipment standards in the setting of the novel Coronavirus pandemic. These clinicians are in possession of reusable face shields and masks as part of their routine work. All clinicians performing the intervention will have documented competency using a standardized competency checklist including physiologic monitoring considerations, positioning and alignment of the patient in the cycle ergometer and considerations for the management of lines and tubes to mitigate risk of dislodgement. The applicant will observe the application and performance of CE performed by unit RNs during 10% of sessions to assure correct procedure. All procedures for applying the CE to the patient will be explained to the patient or family member(s) in attendance. A physical therapist is part of our study team and will provide consultation as needed regarding cycle ergometry. Standard disinfection of the ergometer, inclusive of current guidelines for prevention of Coronavirus transmission, will be performed at the conclusion of each session by the study team.

A recent prospective safety and feasibility study of supine cycle ergometry in critically ill patients found only one adverse event in 541 sessions (181 patients), dislodgement of a radial arterial line. Another recent prospective study of 20 patients in an NCCU with intracranial pressure monitoring, 3 of which had a diagnosis of sICH, found no significant increases in intracranial pressure. Since, cycle ergometry is currently available in the NCCU, we performed an internal retrospective evaluation of 23 patients with an

intraventricular catheter (intracranial pressure monitor) over 32 sessions receiving supine lower extremity cycle ergometry. This evaluation revealed no peripheral oxygen desaturation, hemodynamic instability and no increases in intracranial pressure requiring an end to the session or further treatment.

Procurement of blood specimens will occur in tandem with standard of care blood draws (phlebotomy or arterial line) when possible and will be drawn by the applicant or the registered nurse caring for the patient. CSF specimens will be obtained using a protocol developed by the sponsor for a previous clinical trial requiring CSF sampling from an external ventricular drain.

Plan for reporting unanticipated problems or study deviations.

c. Legal risks such as the risks that would be associated with breach of confidentiality.

Breaches in confidentiality will be reported to the IRB immediately by the PI. All data will be stored in files on secured servers of the Johns Hopkins Hospital.

d. Financial risks to the participants.

There are no financial risks to participants.

7. Benefits

a. Description of the probable benefits for the participant and for society

There is no direct benefit to participants but participation may help future patients. Participants in the intervention arm of the study may benefit from increased attention by the study team during twice-daily visits for the 7-day duration of the intervention period. The proposed study has the potential to lead to further investigations, which may be associated with improved functional outcome in this devastating disease process.

8. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

There will be no remuneration to participants or their legally authorized representatives and withdrawal from the study will not affect the participant's care or legally authorized representatives in any way.

9. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

There will be no cost of participation to the participant. Study assays and administration of the intervention will be supported by a foundation grant from the Zach Sowers Brain Injury Research Fund, The Scholl Foundation and in kind support of investigator time from the Johns Hopkins Hospital.

References

1. Amidei C, Sole ML. Physiological responses to passive exercise in adults receiving mechanical ventilation. American Journal of Critical Care 2013;22(4):337-48.

2. Arafah BM, Nishiyama FJ, Tlaygeh H, Hejal R. Measurement of salivary cortisol concentration in the assessment of adrenal function in critically ill subjects: A surrogate marker of the circulating free cortisol. J Clin Endocrinol Metab 2007;92(8):2965-71.

3. Barr TL, VanGilder RL, Seiberg R, Petrone A, Chantler PD, Huang C-C. Systemic Transcriptional Alterations of Innate and Adaptive Immune Signaling Pathways in Atherosclerosis, Ischemia Stroke, and Myocardial Infarction. Journal of Bioanalysis and Biomedicine. 2015;7(2): 029–034. doi:10.4172/1948-593X.1000120.

4. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. Heart disease and stroke statistics--2017 update: A report from the american heart association. Circulation 2017;135(10):e146-e603.

5. Burn JP. Reliability of the modified rankin scale. Stroke 1992;23(3):438.

6. Burtin C, Clerckx B, Robbeets C, et al. Early exercise in critically ill patients enhances short-term functional recovery. Critical Care Medicine 2009;37(9):2499-505. doi:10.1097/CCM.0b013e3181a38937

7. Calabrese EJ. Pre- and post-conditioning hormesis in elderly mice, rats, and humans: Its loss and restoration. Biogerontology 2016;17(4):681-702.

8. Camargo Pires-Neto R, Fogaca Kawaguchi YM, et al. Very early passive cycling exercise in mechanically ventilated critically ill patients: physiological and safety aspects- a case series. PloS One 2013;8(9):e74182.

9. Chen J, Qin J, Su Q, Lie Z, Yang J. Treadmill rehabilitation treatment enhanced BDNF-TrkB but not NGF-TrKA signaling in a mouse intracerebral hemorrhage model. Neuroscience letters. 2010; 529:28-32.

10. Cocks K, Torgerson DJ. Sample size calculation for pilot randomized trials: a confidence interval approach. Journal of Clinical Epidemiology 2013;66:197-201.

11. Di Napoli M, Godoy DA, Campi V, et al. C-reactive protein in intracerebral hemorrhage: Time course, tissue localization, and prognosis. Neurology 2012;79(7):690-9.

12. Duffy L, Gajree S, Langhorne P, Stott DJ, Quinn TJ. Reliability (Inter-rater Agreement) of the Barthel Index for Assessment of Stroke Survivors: Systematic Review and Meta-Analysis. Stroke. 2013;44:462-468.

13. Fearon P, McArthur KS, Garrity K, et al. Prestroke modified rankin stroke scale has moderate interobserver reliability and validity in an acute stroke setting. Stroke 2012;43(12):3184-8.

14. Fogelholm R, Murros K, Rissanen A, Avikainen S. Long term survival after primary intracerebral haemorrhage: A retrospective population based study. J Neurol Neurosurg Psychiatry 2005;76(11):1534-8.

15. Gao Z, Wang J, Thiex R, Rogove AD, Heppner FL, Tsirka SE. Microglial activation and intracerebral hemorrhage. Acta Neurochir Suppl 2008;105:51-3.

16. Giraldo E, Garcia JJ, Hinchado MD, Ortega E. Exercise intensity-dependent changes in the inflammatory response in sedentary women: Role of neuroendocrine parameters in the neutrophil phagocytic process and the pro-/anti-inflammatory cytokine balance. Neuroimmunomodulation 2009;16(4):237-44.

17. Gomez-Cabrera MC, Domenech E, Viña J. Moderate exercise is an antioxidant: upregulation of antioxidant genes by training. Free Radical Biology & Medicine. 2008;44(2):126-31. doi:10.1016/j.freeradbiomed.2007.02.001

18. Guo YC, Song XK, Xu YF, Ma JB, Zhang JJ, Han, PJ. The expression and mechanism of BDNF and NGB in perihematomal tissue in rats with intracerebral hemorrhage. European Review for Medical and Pharmacological Sciences. 2017;21:3452-3458.

19. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support, J Biomed Inform. 2009;42(2):377-81. doi: 10.1016/j.jbi.2008.08.010

20. Hemphill JC 3rd, Farrant M, Neill TA Jr. Prospective validation of the ICH Score for 12-month functional outcome. Neurology. 2009;73(14):1088-94.

21. Hermans G, Cerckx B, Vanhullebusch T, et al. Interobserver agreement of medical Research Council sum-score and handgrip strength in the intensive care unit. Muscle Nerve. 2012;45(1):18-25.

22. Hodgson CL, Stiller K, Needham DM, et al. Expert consensus and recommendations on safety criteria for active mobilization of mechanically ventilated critically ill adults. Crit Care 2014;18:658-667.

23. Ishida A, Misumi S, Ueda Y, et al. Early constraint-induced movement therapy promotes functional recovery and neuronal plasticity in a subcortical hemorrhage model rat. Behavioural Brain Research. 2015;284:158-166.

24. Ji LL, Gomez-Cabrera MC, Vina J. Exercise and hormesis: Activation of cellular antioxidant signaling pathway. Ann N Y Acad Sci 2006;1067:425-35.

25. Kimawi I, Lamberjack B, Nelliot A, et al. Safety and feasibility of a protocolized approach to in-bed cycling exercise in the intensive care unit: Quality Improvement Project. Phys Ther 2017;97. doi:10.1093/ptj/pzx034

26. Kho ME, Martin RA, Toonstra AL, Zanni JM, Mantheiy EC, Nelliot A, Needham DM. Feasibility and Safety of in-bed cycling for physical rehabilitation in the Intensive Care Unit. J Crit Care 2017;30(6):1419e1-5. doi:10.1016/j.jcrc.2015.07.025

27. Kho ME, Molloy AJ, Clarke FJ, et al. TryCYCLE: A prospective study of the safety and feasibility of early in-bed cycling in mechanically ventilated patients. PLOS One 2016;11(12):e0167561. doi: 10.1371/journal.pone.0167561

28. Kumble S. [Cycle ergometry in patients with external ventricular drainage] 2017. Unpublished Raw Data.

29. Lasek-Bal A, Jedrzejowska-szypulka H, Student S, Warsz-Wianecka A, Zareba K, Puz P, Bal W, Pawletko K, Lewin-Kowalik, J. The Importance of Selected Markers of Inflammation and Blood-Brain Barrier Damage for Short-Term Ischemic Stroke Prognosis. Journal of Physiology and Pharmacology. 2019;70(2): 209-217.

30. Lei C, Lin S, Zhang C, et al. High-mobility group box1 protein promotes neuroinflammation after intracerebral hemorrhage in rats. Neuroscience 2013;3(228):190-9.

31. Leibovitch FS, Vasquez BP, Ebert PL, Beresford KL, Black SE. A short bedside battery for visuoconstructive hemispatial neglect; Sunnybrook Neglect Assessment Procedure (SNAP). Journal of Clinical and Experimental Neuropsychology. 2017;34(4):359-368.

32. Li F, Pendy JT, Ding JN, Peng,C, Li X, Shen J, Wang S, Geng X. Exercise Rehabilitation Immediately following Ischemic Stroke Exacerbates Inflammatory Injury. Neurological Research;2017:39(6):530-537.

33. Mello RC, Sad EF, Andrade BC, et al. Serum and salivary cortisol in the diagnosis of adrenal insufficiency and as a predictor of the outcome in patients with severe sepsis. Arq Bras Endocrinol Metabol 2011;55(7):455-9.

34. Needham DM. Monitoring & Documentation System for Physiological Changes & Potential Safety Events for ICU Rehabilitation [Online], Johns Hopkins University Outcomes After Critical Illness & Surgery (OACIS) Group. Available: http://www.mobilization-network.org/Network/Documents [Accessed: August 1, 2017]

35. Ortega E. The "Bioregulatory effect of exercise" on the innate/inflammatory responses. J Physiol Biochem 2016;72(2):361-9.

36. Ovbiagele, B, Goldstein,LB, Higashida, RT, et al. 2013. Forecasting the future of stroke in the United States: A policy statement from the American Heart Association and American Stroke Association. Stroke 2013;44 (8): 2361-75.

37. Poon MT, Fonville AF, Al-Shahi Salman R. Long-term prognosis after intracerebral haemorrhage: Systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 2014;85(6):660-7.

38. Quinn TJ, Dawson J, Walters MR, Lees KR. Reliability of the modified rankin scale: A systematic review. Stroke 2009;40(10):3393-5.

39. Steins Bisschop CN, Courneya KS, Velthuis MJ, et al. Control group design, contamination and drop-out in exercise oncology trials: A systematic review. PLOS One 2015;10(3):e0120996. doi:10.1371/journal.pone.0120996

40. Takamatsu Y, Tamakoshi K, Waseda Y, Ishida K. Running exercise enhances motor functional recovery with inhibition of dendritic regression in the motor cortex after collagenase-induced intracerebral hemorrhage in rats. Behav Brain Res 2016;300:56-64.

41. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet. 1974;2(7872):81-4.

42. Tenorio de Franca EE, Ribeiro LC, Lamenha GG, et al. Oxidative stress and immune system analysis after cycle ergometer use in critical patients. Clinics 2017;72(3):143-149.

43. Thelandersson A, Nellgard B, Ricksten SE, Cider A. Effects of early bedside cycle exercise on intracranial pressure and systemic hemodynamics in critically ill patients in a neurointensive care unit. Neurocrit Care 2016;25(3):434-439.

44. Wang P, Li CG, Qi Z, Cui D, Ding S. Acute exercise stress promotes Ref1/Nrf2 signalling and increases mitochondrial antioxidant activity in skeletal muscle. Exp Physiol 2016;101(3):410-20.

45. Wang XM, Zhang YG, Li AL, et al. Expressions of serum inflammatory cytokines and their relationship with cerebral edema in patients with acute basal ganglia hemorrhage. Eur Rev Med Pharmacol Sci 2016;20(13):2868-71.

46. Wei P, You C, Jin H, Chen H, Lin B. Correlation between serum IL-1beta levels and cerebral edema extent in a hypertensive intracerebral hemorrhage rat model. Neurol Res 2014;36(2):170-5.

47. Winkelman C. Investigating activity in hospitalized patients with chronic obstructive pulmonary disease: A pilot study. Heart Lung 2010;39(4):319-330.

48. Wu J, Yang S, Xi G, et al. Microglial activation and brain injury after intracerebral hemorrhage. Acta Neurochir Suppl 2008;105:59-65.

49. Xue M, Del Bigio MR. Comparison of brain cell death and inflammatory reaction in three models of intracerebral hemorrhage in adult rats. J Stroke Cerebrovasc Dis 2003;12(3):152-9.

50. Yang X, Ren W, Zu H, Dong Q. Evaluate the serum cortisol in patients with intracerebral hemorrhage. Clin Neurol Neurosurg 2014;123:127-130.

51. Yang Z, Yu A, Liu Y, et al. Regulatory T cells inhibit microglia activation and protect against inflammatory injury in intracerebral hemorrhage. Int Immunopharmacol 2014;22(2):522-5.

52. Yong MS, Hwangbo K. Skilled Reach training Influences Brain Recovery Following Intracerebral Hemorrhage in Rats. J Phys Ther Sci. 2014;26:405-407.

53. Zhang P, Zhang Q, Pu H, Wu Y, Bai Y, Vosler PS, Chen J, Shi H, Gao Y, Hu Y. Very early-initiated physical rehabilitation protects against ischemic brain injury. Frontiers in Bioscience Elite. 2012;2476-2489.

54. Zhang Q, Zhang J, Yan Y, Zhang P, Zhang W, Xia R. Proinflammatory cytokines correlate with early exercise attenuating anxiety-like behavior after cerebral ischemia. Brain and Behavior. 2017;7:e00854.

55. Zhao X, Sun G, Ting SM, et al. Cleaning up after ICH: The role of Nrf2 in modulating microglia function and hematoma clearance. J Neurochem 2015;133(1):144-52.