The burden of brain hypoxia and optimal mean arterial pressure in patients with hypoxic ischemic brain injury after cardiac arrest

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Abstract

Objectives: In patients at risk of hypoxic ischemic brain injury following cardiac arrest, we sought to (i) characterize brain oxygenation and determine the prevalence of brain hypoxia, (ii) characterize autoregulation using the pressure reactivity index (PRx) and identify the optimal mean arterial pressure (MAP_{OPT}), and (iii) assess the relationship between MAP_{OPT} and brain tissue oxygenation ($PbtO_2$).

Design: Prospective interventional study.

Setting: Quaternary intensive care unit.

Patients: Adult patients with return to spontaneous circulation (ROSC) greater than 10 minutes and a post-resuscitation Glasgow Coma Score under 9 within 72 hours of cardiac arrest.

Interventions: All patients underwent multimodal neuromonitoring which included: (i) $PbtO_2$, (ii) intracranial pressure; (iii) jugular venous continuous oximetry ($SjvO_2$); (iv) regional saturation of oxygen (rSO_2) using near-infrared spectroscopy, and (iv) PRx based determination of MAP_{OPT}, lower and upper limit of autoregulation. We additionally collected MAP, end tidal carbon dioxide ($ETCO_2$) and temperature. All data were captured at 300 Hz using ICM+® brain monitoring software.

Measurements and Main Results: Ten patients (7 males) were included with a median age 47 (range 20 – 71) and ROSC 22 minutes (12 – 36). The median duration of monitoring was 47 hours (15 - 88) and median duration from cardiac arrest to inclusion was 15 hours (6 - 44). The mean $PbtO_2$ was 23 mmHg (SD 8) and the mean percentage of time with a $PbtO_2$ below 20 mmHg was 38% (6 – 100). The mean PRx was 0.23 (0.27) and the percentage of time with a PRx greater than 0.3 was 50% (12 – 91). The mean MAP_{OPT}, lower and upper of autoregulation were 89 mmHg (11), 82mmHg (8) and 96 mmHg (9), respectively. There was marked between-patient variability in the relationship between MAP and indices of brain oxygenation. As the patients' actual MAP approached MAP_{OPT}, $PbtO_2$ increased ($p<0.001$). This positive relationship did not persist when the actual MAP was above MAP_{OPT}.

Conclusions: Episodes of brain hypoxia in HIBI are frequent and perfusion within proximity of MAP_{OPT} is associated with increased $PbtO_2$. PRx can yield MAP_{OPT}, lower and upper limit of autoregulation in patients following cardiac arrest.

Introduction

The pathophysiology of hypoxic ischemic brain injury (HIBI) emanates from a primary insult during cardiac arrest and secondary injury that results partially from an inadequate balance between cerebral oxygen delivery (CDO_2) and utilization following return of spontaneous circulation (ROSC)(1). Secondary injury is increasingly recognized as a significant determinant of neurological outcome, and mitigating its deleterious effects is a mainstay of post cardiac arrest management (1, 2).

Following ROSC, brief hyperemia is followed by prolonged hypoperfusion, termed *'no-reflow'* (1, 3, 4) which causes inadequate CDO_2 and secondary injury (1, 5). Observational studies demonstrate that perturbations in CDO_2 from hypotension (6, 7) and hypocapnia (8) after ROSC during no-reflow are associated with worse neurological outcome. Animal models have confirmed the no-reflow phenomenon (9) and demonstrate that increasing CDO_2 with mean arterial pressure (MAP) augmentation results in improved thalamic and subcortical brain tissue oxygenation ($PbtO_2$) (10, 11). A recent systematic review suggests increased MAP is associated with improved neurologic outcome following cardiac arrest (12). Intuitively, uniform MAP augmentation seems like a plausible therapeutic intervention, however, a *'one size fits all'* approach fails to account for individual physiologic differences between patients and may expose patients to adverse effects of exogenous vasopressors. Hence, recent efforts have been targeted at identifying personalized perfusion targets in HIBI (13).

Cerebral autoregulation is the inherent capacity of the cerebrovasculature to undergo cyclical cerebral vasoconstriction and vasodilation to protect the brain from ischemia and hyperemia (14), respectively. In health, cerebral autoregulation maintains stable cerebral blood flow (CBF) over a wide range of MAP(14–16). After cardiac arrest, the preserved range of

autoregulation is often narrowed and right shifted (17). Pressure reactivity index (PRx), a moving Pearson's correlation coefficient between MAP and intracranial pressure (ICP), can monitor autoregulation in real time and identify individualized MAP thresholds after brain injury (18). Importantly, PRx is an indirect measure of autoregulation. Fluctuations in MAP will lead to either cerebral vasoconstriction or vasodilation with resultant subsequent changes in cerebrovascular blood volume and therefore ICP. Dysfunctional autoregulation is characterized by a positive correlation between MAP and CBF, owing to pressure passive vasodilation of the cerebrovasculature (19). Increased CBF results in increased cerebrovascular volume which itself leads to elevated ICP (20). With intact autoregulation, increasing MAP is countered by vasoconstriction, which reduces cerebrovascular blood volume and ICP, thereby producing a negative or near zero PRx (19). By plotting PRx against MAP, a U-shaped curve is formed with the nadir denoted as the optimal MAP (MAP_{OPT}) (21). After traumatic brain injury, perfusion within 5 mmHg of the optimal cerebral perfusion pressure results in improved $PbtO_2$ (22) and improved neurological outcome (21). It is unknown whether proximity to MAP_{OPT} results in improved $PbtO_2$ in humans with HIBI.

As such, we conducted a prospective study of invasive neuromonitoring in patients with HIBI. The objectives of our study were: (1) characterize $PbtO_2$ and brain hypoxia over time and its relationship to MAP, (2) characterize cerebral autoregulation as assessed by PRx over time, (3) characterize MAP_{OPT}, Lower Limit of Autoregulation (LLA) and Upper Limit of Autoregulation (ULA) over time, (4) determine the relationship between the difference in patients' actual MAP and MAP_{OPT} (termed MAP difference [MAP_{DIFF}]) and $PbtO_2$, (5) characterize the relationship between both $PbtO_2$ and PRx and two potential confounders – temperature and end-tidal carbon dioxide ($ETCO_2$).

Methods

We conducted a prospective study in 10 patients following cardiac arrest with HIBI using multimodal neuromonitoring. The University of British Columbia Clinical Research Ethics Board approved the study (August 23, 2016 - H16-00466) and written informed consent was obtained from the temporary substitute decision maker. The study was registered at clinicaltrials.gov (NCT03609333).

Study population and hospital

The Vancouver General Hospital intensive care unit (ICU) is a quaternary closed 34 bed mixed medical-surgical unit affiliated with the University of British Columbia. The ICU provides quaternary neurotrauma care for the province of British Columbia and conducts invasive multimodal neuromonitoring in approximately 40 neurologically injured patients annually.

Patients were included if they sustained a cardiac arrest and fulfilled the following criteria: 1) time to ROSC of greater than 10 minutes with greater than 20 minutes of sustained circulation, 2) post ROSC un-confounded Glasgow coma score of less than 9, and 3) inclusion within 72 hours of cardiac arrest. We excluded patients who had any of the following criteria: 1) concurrent coagulopathy (INR > 1.5, prothrombin time > 40 seconds, platelet count < 100 x 10^9/L), 2) likely cardiac catheterization within 7 days, 3) current or anticipated anticoagulant or antiplatelet therapy during the study period, 4) therapeutic hypothermia targeting a temperature under 35^{o}C, 5) prior history of severe TBI, intracranial hemorrhage or stroke, 6) anticipated withdrawal of life-sustaining therapy within 72 hours.

Neurophysiologic Monitoring & Data Collection

ICP (Camino®, Integra Lifesciences, New Jersey, USA) and $PbtO_2$ (Licox®, Integra Lifesciences, New Jersey, USA) catheters were inserted through a dual lumen bolt in the non-dominant frontal lobe by the attending neurosurgeon or designate. We also inserted a continuous oximetric jugular venous bulb ($SjvO_2$) catheter (Pediasat®, Edwards Lifesciences, USA). The $SjvO_2$ catheter was placed in the dominant internal jugular vein identified by ultrasonography, and positioned at the level of the mastoid process on skull base x-ray. Near-infrared spectroscopy (NIRS) pads (INVOS®, Medtronic, Minneapolis, MN, USA) were affixed to the forehead bilaterally. The following data were recorded at 300 Hz using ICM+® brain monitoring software (Cambridge Enterprise, United Kingdom): ICP, MAP, $PbtO_2$, rSO_2, $SjvO_2$, temperature, and $ETCO_2$).

We also collected information relating to the cardiac arrest: etiology of the cardiac arrest, initial rhythm, whether the arrest was witnessed or unwitnessed, administration of bystander cardiopulmonary resuscitation, duration until ROSC, doses of epinephrine administered, and number of defibrillation attempts. We also collected multiple daily arterial blood gas samples.

We defined brain tissue hypoxia as a $PbtO_2$ below 20 mmHg, as extrapolated from patients with traumatic brain injury (23, 24). We defined dysfunctional cerebral autoregulation as a PRx greater than 0.3 (14). Neurologic outcomes were recorded at 6 months by telephone interview using the Glasgow Outcome Scale: (1) death, (2) persistent vegetative state, (3) severe disability - conscious but disabled, (4) moderate disability – independent for daily activities but with disabilities, and (5) good recovery – normal activities although may have minor deficits. An independent intensive care physician reviewed each subject to assess for any complications related to the invasive monitoring.

Patient Management

Our ICU uses targeted temperature management guideline for post cardiac arrest care of patients with HIBI targeting a goal temperature of 36^{o}C using external surface cooling techniques and anti-pyrexial medications. Core body temperature is monitored using a continuous esophageal, rectal or urinary bladder temperature probe. Patients are sedated with intravenous propofol infusions during targeted temperature management and hemodynamic targets are set in accordance with international guidelines at the attending physician's discretion(25). All patient care decisions were left to the discretion of the attending physician and they were allowed to use the neuromonitoring data for clinical decisions as per usual practice.

Our ICU uses a tier based algorithm in patients with multimodal neuromonitoring in situ which utilizes increasing intensity of therapy aimed at keeping ICP < 25 mmHg and with titration of MAP / CPP to target $PbtO_2$ > 20 mmHg (26) using intravenous norepinephrine as the primary vasopressor. Strict adherence to arterial normoxemia (PaO_2 80 to 100mmHg) was maintained for the duration of the monitoring period in each study subject to allow delineations of the physiologic relationships with $PbtO_2$.

Statistical Analysis

A sample of 10 was chosen as the number of patients we could enroll within the time available for the study. Data collected by ICM+® brain monitoring software were exported at 10-sec averaged values into Microsoft Excel (Redmond, WA, USA). The data were then subsequently imported into Stata 15.0 (StataCorp, Texas, USA), which was used for all analyses. ICM+® software calculates PRx in real-time as a moving Pearson correlation coefficient between 30 consecutive, 10 s averaged values of MAP and ICP signals(27). MAP_{OPT} is determined as a secondary derivative by plotting PRx (y-axis) against the MAP range (x-axis) in

5 mmHg bins. An automatic multi-window curve-fitting methodology was used to estimate MAP_{OPT} (*OptimalValueFlex* function in ICM+). The LLA and ULA were also determined using this methodology (28), adopting a PRx optimal threshold of 0.25. We calculated the difference between actual MAP and MAP_{OPT} for each time point MAP_{DIFF}. We then collapsed the 10-second data over 10-minutes using mean values. All analyses were two-sided and we considered $p<0.05$ to be statistically significant.

Characterization of brain oxygenation and hypoxia over time and its relationship to MAP. $PbtO_2$ and MAP were first assessed visually by plotting both over time for each individual. To characterize the degree of brain tissue hypoxia, we calculated the number of 10-minute periods where $PbtO_2$ was below 20 mmHg for each individual. In order to estimate the average profiles of $PbtO_2$ and MAP over time, we fitted a linear mixed model specifying 'patient' as a random-effect (STATA command *xtreg*) to account for the within-subject correlation of the data structure.

We then visually assessed the relationship of each variable of brain hypoxia ($PbtO_2$, rSO_2 and $SjvO_2$) by plotting each against MAP. We overlaid the scatterplot with ten locally weighted scatterplot smooths, one for each individual. For each measure of brain hypoxia ($PbtO_2$, rSO_2 and $SjvO_2$) we fit a linear mixed model that included MAP as a fixed effect and 'patient' as a random effect (STATA command *xtreg*). For modelling, we calculated the marginal and conditional R^2 as a measure of the variance explained.

Characterization of cerebral autoregulation (PRx) over time. We plotted PRx over time for each individual. We determined average PRx by 10-minute periods to determine the percentage of time each patient demonstrated dysfunctional autoregulation, i.e. average PRx > 0.3.

Characterization of MAP_{OPT}, LLA and ULA over time and the relationship between MAP_{DIFF} and $PbtO_2$. We first plotted MAP_{OPT}, LLA and ULA over time. In order to link brain tissue oxygenation to cerebral autoregulation, we sought to assess the relationship between $PbtO_2$ and MAP_{DIFF}, which is a measurement of how far away the patients actual MAP is from their MAP_{OPT}. One would expect that $PbtO_2$ would be low when MAP_{DIFF} is below zero. We plotted $PbtO_2$ vs. MAP_{DIFF} for each patient and overlaid the scatterplot with ten locally weighted scatterplot smooths, one for each individual. Because of the non-linear relationship between $PbtO_2$ and MAP_{DIFF}, we modelled this relationship using fractional polynomial regression specifying 'patient' as a random-effect. To numerically describe this relationship, we calculated the mean (SD) of $PbtO_2$ stratified by quartiles of MAP_{DIFF}.

Characterize the relationship between both $PbtO_2$ and PRx with temperature and end-tidal carbon dioxide ($ETCO_2$). We plotted $PbtO_2$ and PRx against temperature and $ETCO_2$ and overlaid the scatterplot with ten locally weighted scatterplot smooths for each individual.
As part of an exploratory analysis, we compared PRx in survivors and non-survivors and how this changed over time. This latter analysis was performed by fitting a linear mixed model specifying 'patient' as a random-effect (STATA command *xtreg*) and included an interaction variable of time (hours) and favourable neurologic outcome (modeled as a dichotomous variable).

Results

Twenty-two consecutive patients were screened between November 2016 and January 2018, of which 10 met inclusion criteria and were enrolled. Individual demographics of the patients are shown in Table 1. The median age of the cohort was 47 and seven were male. The initial rhythm was pulseless electrical activity in 9 patients and 1 patient had ventricular fibrillation. The median duration from time of cardiac arrest to insertion of multimodal neuromonitoring was 15 hours and the median duration of multimodal monitoring was 47 hours. Over the entire cohort and duration of monitoring the mean (SD) of MAP, ICP and CPP were 88 (15) mmHg, 14 (15) mmHg and 75 (7) mmHg, respectively. The mean $ETCO_2$ was 32 (6) mmHg and mean core body temperature was 35.7 ^oC (0.8). There were no serious adverse events related to the monitoring (intracranial hemorrhage or infection) during or after the study period.

Characterization of brain oxygenation and hypoxia over time and relationship to MAP. The mean $PbtO_2$ in the entire cohort was 23 (8) mmHg. Of the 1944 10-minute averaged periods, 743 (38%) had a $PbtO_2$ under 20 mmHg. On an individual patient level, the mean percentage of time that patients in the cohort experienced a $PbtO_2$ under 20 mmHg was 38% (range 6 – 100). During the study period, the mean rSO_2 was 67 (14) % and mean $SjvO_2$ was 74% (11). Relationships between $PbtO_2$ and MAP in individual patients over time during the monitoring period are presented in Figure 1. Both $PbtO_2$ (0.20 mmHg, 95% CI: 0.18 – 0.22) and MAP (0.16 mmHg, 95% CI: 0.12 – 0.19) increased per hour during the monitoring period. Figure 2 demonstrates the relationship between MAP and indices of oxygenation. MAP was linearly related to both $PbtO_2$ and $SjvO_2$ but not rSO_2. The large difference between the conditional and marginal R^2 values observed indicates marked between-patient variability in the effects of MAP on the indices of oxygenation.

Characterization of cerebral autoregulation (PRx) over time. The overall mean PRx was 0.23 (0.27). Out of the 2409 10-minute averaged PRx measurements, 1148 (48%) were greater than 0.3. On an individual patient level, the median percentage of time with a PRx of greater than 0.30 was 50% (range 12 – 91). Figure 3 presents the change of PRx over time for each patient.

Characterization of MAP_{OPT}, LLA and ULA over time and determine the relationship between MAP_{DIFF} and $PbtO_2$. The mean (SD) $MAP_{OPT,}$ LLA and ULA were 89 (11) mmHg, 82 (8) mmHg and 96 (9) mmHg, respectively. MAP_{OPT}, LLA and ULA over time are presented for each patient in Figure 4. The median time spent of actual MAP within 5 mmHg of MAP_{OPT} was 42% (range 10 – 78). The percentage of time spent below -5 mmHg was 32% (range 12 – 74) and above +5 mmHg from the MAP_{OPT} was 27% (range 4 – 54). Please see the eTable 1 for mean values of MAP, ICP, CPP, PRx, MAP_{OPT}, LLA, ULA, $ETCO_2$ and temperature over time during the monitoring period.

In order to link brain tissue oxygenation and cerebral autoregulation, we assessed the relationship between relationship between $PbtO_2$ and MAP_{DIFF} (Figure 5). Fractional polynomial regression demonstrated a non-linear relationship between $PbtO_2$ and MAP_{DIFF} ($p<0.001$). $PbtO_2$ increased as the difference between MAP and MAP_{OPT} approached zero. $PbtO_2$ leveled off as MAP_{DIFF} went above zero. To numerically describe this relationship, we divided MAP_{DIFF} into quartiles and calculated the associated $PbtO_2$. Quartile 1 ($MAP_{DIFF} \leq$ -5mmHg) had a mean $PbtO_2$ of 19 (9) mmHg; quartile 2 (MAP_{DIFF} -4 to 2 mmHg) had a mean $PbtO_2$ of 25 (9) mmHg; quartile 3 (MAP_{DIFF} 2 to 9 mmHg) had a mean $PbtO_2$ of 23 (10) mmHg; and quartile 4 (MAP_{DIFF} > 9 mmHg) had a mean $PbtO_2$ of 26 (9) mmHg.

Visually, there did not appear to be any relationship between either $PbtO_2$ (eFigure 1) or PRx (eFigure 2) and temperature or $ETCO_2$.

As part of an exploratory analysis, we compared PRx over time in survivors and non-survivors. The mean PRx was 0.31 (SD 0.19) in survivors and 0.16 (SD 0.32) in non-survivors. There were several patterns that emerged when visually inspecting PRx over time. Survivors appeared to either have improving (Figure 3, patients 3 & 5) or preserved (Figure 3, patients 1 & 9) autoregulation. Non-survivors appeared to have dysfunctional (Figure 3, patient 2 & 4) or worsening (Figure 3, patient 4 & 10) autoregulation. In non-survivors, the PRx increased each hour by 0.0052 (95%CI: 0.0032 to 0.0071) whereas in survivors, PRx decreased over each hour by -0.0078 (95%CI: -0.0090 to -0.0065) (p-interaction <0.001).

Discussion

We present the first prospective study using invasive multimodal neuromonitoring to evaluate brain hypoxia and cerebral autoregulation using PRx in patients with HIBI. Overall, there was a significant burden of brain hypoxia demonstrated in our cohort. Although there was a linear relationship between $PbtO_2$ and $SjvO_2$ with MAP, there was marked between-patient variability. We were also able to characterize cerebral autoregulation using PRx and identify MAP_{OPT}, LLA and ULA. Interestingly, the overall mean MAP_{OPT} was 89 mmHg which is markedly higher than recommended by international guidelines (29). Finally, we found an association between perfusion within proximity of PRx derived MAP_{OPT} and $PbtO_2$. $PbtO_2$ improved when the actual MAP approached within 10 mmHg of MAP_{OPT}, suggesting improved CDO_2 within proximity to MAP_{OPT}.

It is increasingly evident that secondary injury leads to adverse neurologic outcome and identification of ongoing brain hypoxia after ROSC is imperative. Human studies have principally focussed on establishing links between decreased rSO_2 as a surrogate marker of brain oxygenation and neurological outcome, but have yielded conflicting results in its predictive utility (30–33). These conflicting results, along with technical limitations of NIRS have hindered its routine use in evaluating brain hypoxia post cardiac arrest. We present the first prospective study evaluating the burden of brain hypoxia using a direct invasive measure of cerebral oxygenation in post cardiac arrest patients with HIBI. Our results demonstrating a significant burden of brain hypoxia in our cohort during the *'no reflow'* period are in keeping with prior physiologic and animal studies confirming the presence of oligemic CBF, brain hypoxia and neuronal ischemia after ROSC (29-31). Eight of ten subjects in our study exhibited an initial $PbtO_2 < 20$mmHg (figure 1) indicating that we may have captured the cerebrovascular

physiologic profile in these subjects during '*no reflow*'. Importantly, the median duration from time of cardiac arrest to data collection was 15 hours in our study, a timeline that is relatively late in the *'no reflow'* period when the resolution of reduced CBF and CDO_2 would be expected. As such, it is possible that the burden of brain hypoxia may be underestimated in our study.

Delineating the significance of brain tissue hypoxia as a modifiable factor, as opposed to an expected epiphenomenon in the natural history of HIBI, is essential. In animal models, MAP augmentation using exogenous vasopressors has demonstrated improved $PbtO_2$ in thalamic and cortical tissue, structures which are exquisitely susceptible to secondary injury (9, 11). We also observed a relationship between MAP and $PbtO_2$ in individual patients over time. Although significant, the variation of this relationship within patients could be explained by numerous factors including simultaneous fluctuations in other physiologic variables such as $ETCO_2$, temperature and hemoglobin. As part of the study protocol, attending physicians were able to manipulate multiple physiologic variables to achieve $PbtO_2$ > 20mmHg and hence, we are unable to imply causality to augmented MAP and increased $PbtO_2$. We also sought to delineate the relationships between MAP and non-invasive measures of CDO_2, namely rSO_2 and $SjvO_2$. We did observe a significant association between increasing MAP and $SjvO_2$, but this relationship was less robust than the relationship between MAP and $PbtO_2$. As opposed to $PbtO_2$, which is principally determined by CBF in the setting of stable PaO_2, $SjvO_2$ is additionally dependent cerebral metabolic rate and arterial oxygen content (35). These were not held constant in our study. We did not find a relationship between MAP and rSO_2, raising doubts as to the validity of rSO_2 by itself to monitor cerebral perfusion in HIBI. NIRS has been advocated as a surrogate measure of CBF and CDO_2 during cardiopulmonary resuscitation and in identifying early ROSC

(36), however, data is lacking in establishing rSO_2 as a reliable estimator of CBF beyond the immediate post ROSC period.

Our results are consistent with epidemiologic data which suggests that post-ROSC hypotension may contribute to worse neurologic outcomes (6). A systematic review of studies examining MAP thresholds in patients following cardiac arrest demonstrated that increased MAP targets were associated with improved neurologic outcomes (12). Although generalized increased MAP targets post cardiac arrest may be a viable therapeutic intervention, the '*one size fits all'* approach fails to account for physiological differences between patients. Furthermore, uniform MAP augmentation using vasopressors carries significant risks, including increased afterload on decompensated left ventricular function, arrhythmias, and mesenteric or limb ischemia. Therefore, an individualized approach to MAP targets in HIBI patients has emerged as an attractive area of research (13).

The mean MAP_{OPT} observed in our study (89 mmHg) is higher than international post cardiac arrest guidelines which recommend MAP > 65 mmHg (29). Importantly, there was considerable between and within-patient MAP_{OPT} variability which further highlights the heterogeneous nature of HIBI. This marked heterogeneity may serve as an opportunity to therapeutically target individual MAP thresholds in patients with HIBI (13), rather than the current uniform approach. In particular, we found that cerebral autoregulation, as assessed by PRx, changes over time. Our data also suggests that the change in PRx over time may differ between survivors and non-survivors, although more data is clearly needed to elucidate this relationship. The relative importance of MAP_{OPT} versus LLA and ULA remain unclear. It may be that LLA is a crucial physiologic parameter to target as thresholds below LLA are associated with cerebral oligemia and brain hypoxia (37). Importantly, the mean LLA (82 mmHg) in our

cohort was also still markedly higher than post cardiac arrest guidelines for MAP > 65 mmHg. The importance of LLA and ULA as perfusion targets in HIBI requires further research.

Our results are also consistent with a prior study using transcranial Doppler to assess cerebral autoregulation in patients following cardiac arrest which demonstrated a right shifted lower limit of autoregulation using transcranial Doppler (38). Furthermore, Ameloot et al. retrospectively calculated COx, a correlation coefficient between MAP and the rSO_2 from NIRS to characterize autoregulation and found the mean MAP_{OPT} in their cohort to be 85 mmHg (39). Using a similar, but prospective COx based assessment of cerebral autoregulation, our research group recently observed a mean MAP_{OPT} to be 76 mmHg in a cohort of post cardiac arrest patients using COx (40).

We attempted to assess the physiologic relationship between MAP_{OPT} and CDO_2, as measured by $PbtO_2$. Despite heterogeneity between patients, there appeared to be a non-linear relationship between MAP_{DIFF} and $PbtO_2$. When the actual MAP was more extreme than -10 mmHg below MAP_{OPT}, there was a linear rise of $PbtO_2$ as MAP_{DIFF} approached -10 mmHg. Between MAP_{DIFF} of -10 to +10 mmHg, there was a less steep rise in $PbtO_2$, with this relationship becoming more attenuated at the top of this range. MAP_{DIFF} above +10 mmHg was not associated with further improvements in $PbtO_2$. This relationship highlights that perfusion within proximity of MAP_{OPT} is associated with improved $PbtO_2$ and its physiologic significance must be further evaluated. Importantly, perfusion beyond the MAP_{OPT} was not associated with increasing $PbtO_2$, thereby suggesting that uniformly increased MAP targets will unreliably lead to improved $PbtO_2$ and could simply expose patients to the harmful effects of unnecessary exogenous vasopressors. Similar findings have been observed in patients with traumatic brain injury where Jaeger et al. demonstrated that $PbtO_2$ increased significantly as actual CPP

approached optimal CPP derived from PRx (41). These findings were further corroborated with a physiologic study revealing that perfusion pressures associated with negative PRx (intact autoregulation) were associated with improved CDO_2, cerebral oxygen metabolic rate and cerebral blood flow (42). In traumatic brain injury, the clinical significance of these observed physiologic benefits are illustrated as deviation of actual CPP from the optimal CPP is associated with worse long term neurological outcomes (21). We found over half of the actual MAP measurements were more than 5 mmHg from MAP_{OPT}, suggesting an opportunity for future interventional research to target adherence to MAP_{OPT}.

Our study is novel and characterizes the cerebrovascular pathophysiological sequelae of HIBI after cardiac arrest. Strengths of our study include the high granularity of data collection (300Hz) with time-stamped neurophysiologic variables to facilitate examining the underlying relationships between various measures of brain oxygenation and CDO_2. We gathered considerable longitudinal data over time with a mean duration of monitoring during the study of 46 hours and were able to evaluate the physiological profile of a key determinant of CDO_2 (MAP) on brain oxygenation in HIBI. Finally, we demonstrated improved $PbtO_2$ within proximity of MAP_{OPT}, raising the possibility of beneficial targeted individualized perfusion targets in HIBI, however, this concept requires significant further physiologic and clinical delineation.

Our study has important limitations. Our small sample size limits our ability to draw firm conclusions on HIBI pathophysiology and indeed suggests that there are likely distinct HIBI phenotypes. This is particularly important when trying to examine for other factors that may confound the relationship between MAP and $PbtO_2$, namely $ETCO_2$ and temperature. This is the first study of its kind and necessarily is exploratory and hypothesis-generating in nature, we are

unable to imply causal associations between MAP and MAP_{OPT} with assessments of brain oxygenation. Instead, the observed associations in our study are intended to provide further justification to delineate their clinical and physiological significance in the future. Secondly, our definition of brain hypoxia ($PbtO_2$ < 20mmHg) is extrapolated from traumatic brain injury literature (24) and may not reflect an important threshold in patients in HIBI. Owing to the reduced cerebral metabolic demand immediately after cardiac arrest, patients with HIBI may tolerate lower levels of $PbtO_2$ (43). Establishing HIBI specific $PbtO_2$ thresholds in humans of brain hypoxia against gold standard assessments of CDO_2 such as positron emission scanning is an essential gap in the current literature. In addition, the observed relationship between MAP and $PbtO_2$ does not reflect the end organ balance of aerobic versus anaerobic metabolism.

We used PRx as a measure of autoregulation, however, we acknowledge that PRx is an indirect estimator of dynamic autoregulation which relies upon repeated longitudinal integration between fluctuations in values of MAP and changes in CBF / cerebrovascular blood volume and downstream ICP fluctuations. Dynamic changes in CBF may occur from alternative physiologic stressors independent from MAP including changes in arterial carbon dioxide tension, cerebral metabolic rate and temperature fluctuations, thereby negating the accuracy of PRx. We attempted to control these variables in our study by mandating strict $PaCO_2$ 35 to 40mmHg, targeted temperature management (36^{o}C) and intravenous sedation using propofol to target burst suppression during the study period. However, it is possible that such goals were uniformly achieved and have affected our results.

Importantly, the patients in our cohort primarily underwent cardiac arrest from pulseless electrical activity secondary to underlying causes that likely resulted in pre-circulatory arrest cerebral ischemia (hemorrhage, hypoxia) as opposed to primary sudden cardiac arrest from

arrythmias. As such, our results must be interpreted under premise that the majority of patients in our cohort likely fall on the severe end of the HIBI pathophysiology spectrum. Therefore, our results should not be extrapolated to patients with sudden cardiac arrest from arrythmias who undergo immediate cardiopulmonary resuscitation and further work is needed to delineate the pathophysiology in this sub-population.

Finally, increased MAP also may not translate into definitively increased CBF as we did not account for changes in cerebrovascular resistance. Future steps of study in this disease should evaluate direct measures of CBF as well as measures of cerebral metabolism using cerebral microdialysis and positron emission scanning.

Conclusion

Episodes of brain hypoxia are prevalent and there appears to be a linear relationship between increased MAP and $PbtO_2$ in adult human HIBI patients. Perfusion within proximity of MAP_{OPT}, as determined by PRx, may be associated with improved $PbtO_2$. Further physiologic research is warranted to delineate the significance of these observations.

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Figure Legends

Figure 1: Scatter plots and locally weighted scatterplot smoothing function of $PbtO_2$ (mmHg, black) and MAP (mmHg, cyan) versus time (hours, x-axis) for each patient. The numbers in each respective box represent the corresponding patient and demographics displayed in table 1.

Figure 2: Brain oxygen variables ($PbtO_2$, rSO_2 and $SjvO_2$) on the y-axis vs. mean arterial pressure (MAP) in mmHg (x axis). The dots are scatterplots between the two variables. Light grey lines are locally weighted scatterplot smoothing function for each individual patient. Black line is the overall regression line. R^2_m is the marginal R^2. R^2_c is the conditional R^2.

Figure 3: Scatter plots of PRx over time for all patients. The solid lines are a locally weighted scatterplot smooth for each patient. Values above the dashed line at a PRx of 0.3 represents a threshold of dysfunctional autoregulation. Patients denoted by the colour cyan were survivors. Patients in black were non-survivors.

Figure 4: Optimal MAP (MAP_{OPT}), Lower Limit of Autoregulation (LLA) and Upper Limit of Autoregulation (ULA) over time for each patient. The solid black line is MAP_{OPT}. The grey dashed lines represent the LLA and ULA.

Figure 5: Scatter plot between $PbtO_2$ and the difference between MAP and MAP_{OPT} (MAP_{DIFF}). The light grey dots are corresponding $PbtO_2$ and MAP_{DIFF}. The light grey solid lines are a locally weighted scatterplot smooth for each patient. The solid black line is a predicted curve generated using a restricted cubic splines model. Fractional polynomial (fp) regression confirmed there was a non-linear relationship between $PbtO_2$ and MAP_{DIFF}. The best parameterization of MAP_{DIFF} was using $X^{0.5}$ (fp 0.5).

eFigure 1: Scatter plots between $PbtO_2$ and temperature (left panel) or ETCO2 (right panel). The light grey dots are corresponding values of $PbtO_2$ and the variable of interest. The light grey solid lines are a locally weighted scatterplot smooth for each patient.

eFigure 2: Scatter plots between PRx and temperature (left panel) or ETCO2 (right panel). The light grey dots are corresponding values of $PbtO_2$ and the variable of interest. The light grey solid lines are a locally weighted scatterplot smooth for each patient. Values above the dashed grey line at a PRx of 0.3 represent dysfunctional autoregulation.