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Clinical paper

Intracranial pressure and compliance in hypoxic ischemic brain injury patients after cardiac arrest☆

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Abstract

Introduction: In hypoxic ischemic brain injury (HIBI), increased intracranial pressure (ICP) can ensue from cerebral edema stemming from cytotoxic and vasogenic mechanisms. Downstream sequelae of restricted cerebral blood flow lead to neurologic braindeath. There is limited data characterizing the temporal trends and patterns of ICP and compliance in human HIBI patients.

Methods: Patients underwent invasive ICP monitoring with a parenchymal probe (Camino) and were managed with a tier-based management algorithm for elevated ICP. Data pertaining to mean arterial pressure (MAP), ICP, brain tissue oxygenation ($PbtO_2$), end tidal carbon dioxide ($ETCO_2$), core body temperature and RAP (moving correlation coefficient between mean ICP and its mean pulse amplitude) as a measure of intracranial compliance were recorded in the ICM + software. Data pertaining to ICP lowering interventions was also collected.

Results: Ten patients were included with a median age of 47 (range 20–71) and seven were male (7/10). The mean ICP was 14 mmHg (SD 11) and time of ICP > 20 mmHg was 22% (range 0–100). The mean MAP, $ETCO_2$ and temperature were 89 mmHg (SD 13), 31 mmHg (SD 7), 35.7 °C (SD 0.9), respectively. The mean RAP was 0.58 (SD 0.34) and time of RAP > 0.4 was 78% (range 57–97). There were no significant relationships between $ETCO_2$ and temperature with ICP.

Conclusions: In our cohort, HIBI was characterized by normal ICP but with limited intracranial compliance. However, significant in between patient heterogeneity exists with respect to temporal patterns of intracranial pressure — volume relationships in HIBI.

Trial registration: clinicaltrials.gov (NCT03609333).

Keywords: Hypoxic ischemic brain injury, Intracranial pressure, Cardiac arrest, Intracranial compliance

☆ The manuscript reflects positions of the authors own work and not of a third party.

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Introduction

In patients with hypoxic-ischemic brain injury (HIBI) after cardiac arrest, cerebral edema occurs following return of spontaneous circulation (ROSC) from underlying mechanisms attributable partly to vasogenic edema and reperfusion injury from blood brain barrier disruption after ROSC.[1,2] Additionally, cerebral ischemia during circulatory arrest and following ROSC can lead to brain hypoxia with eventual formation of cytotoxic cerebral edema and elevated intracranial pressure (ICP).[3] Elevated ICP itself can further reduce cerebral blood flow leading to a cycle of worsening ischemia and elevated ICP which may culminate in trans-tentorial herniation and neurologic death.[4,5]

Observational studies have demonstrated that the presence of cerebral edema on computed tomography after ROSC is associated with adverse neurologic outcome.[6–7,8] Furthermore, increased ICP – as determined using ultrasound measurement of the optic nerve sheath diameter – is associated with adverse neurological outcome after cardiac arrest.[9,10] However, non-invasive techniques for estimating ICP, such as at the aforementioned optic nerve sheath ultrasonography and computed tomography, only provide intermittent estimates over time. Studies of invasive ICP monitoring using is limited to small case series and have yielded conflicting results with respect to the burden of intracranial hypertension[11,12]. Furthermore, these studies only measured ICP intermittently, thus there is limited granularity of data.[12,11] As such, the precise evaluation of intracranial pressure — volume relationships over time in patients with HIBI is unknown. Furthermore, the associations between ICP and physiologic variables that may affect the intracranial pressure-volume relationships have not been well described in HIBI.

Therefore, we performed a single center interventional study of ICP monitoring in HIBI patients as an a priori analysis. The specific aims of this study were to (a) characterize the burden of intracranial hypertension (ICP $>$ 20 mmHg), (b) evaluate the changes in ICP and intracranial compliance over time; and (c) examine the relationships between core body temperature and carbon dioxide tension with ICP in patients with HIBI after cardiac arrest.

Methods

This current study is an *a priori* planned analysis of a previously published prospective interventional study using invasive multimodal neuromonitoring in patients with HIBI after cardiac arrest.[13] The study was approved by the University of British Columbia Clinical Research Ethics Board (H16-00466). Consent was obtained from the substitute decision maker for all participants prior to enrollment.

Setting

The study was conducted in the intensive care unit (ICU) at Vancouver General Hospital, which is a provincial medical and surgical unit with subspecialty trained intensive care physicians. Our institution conducts invasive ICP monitoring in more than 50 neurocritically ill patients per year using direct intra-parenchymal and intra-ventricular approaches.

Study subjects

The inclusion criteria for the study were: (a) age $>$ than 18 years; (b) greater than 10 min from onset of cardiac arrest to ROSC; (c) Glasgow Coma Score of $<$9 or motor score $<$5; (d) enrollment within 72 h of initial cardiac arrest. Exclusion criteria were: (a) previous or concurrent history of traumatic brain injury, intracranial hemorrhage or ischemic stroke; (b) concurrent or anticipated use of anti-platelet or anticoagulant medications; (c) anticipated cardiac catheterization within the next 7 days; (d) coagulopathy (international normalized ratio $>$1.5, prothrombin time $<$40 s, platelets $<100 \times 10^9$ cells/ml) or e) anticipated withdrawal of life-sustaining therapy within 72 h.

Data collection

In addition to demographic data, the following clinical data were collected: (a) initial rhythm and cardiac arrest cause; (b) witnessed or unwitnessed cardiac arrest; (c) number of defibrillation attempts during resuscitation; (d) epinephrine administration during resuscitation; (e) episodes of post ROSC pre-hospital hypotension (systolic blood pressure $<$90 mmHg) or hypoxia (pulse oximetry oxygen saturation $<$90%); (f) time from initial cardiac arrest to ROSC; (g) time and date of ICU admission and (h) time from initial cardiac arrest to insertion of invasive ICP monitoring. We collected the date and time of ICP monitor insertion and removal as well as any complications related to its use (hemorrhage or infection). In addition to the hourly dose of intravenous propofol (mcg/kg/min), we collected any therapeutic interventions for the management of intracranial hypertension: use and dose of mannitol, hypertonic saline or barbiturates, and the use and temperature target for therapeutic hypothermia. Six-month neurological outcome was collected with the Glasgow Outcome Scale.

HIBI and ICP management

All management decisions were decided by the attending intensivist. Patients with HIBI are managed in our unit with normothermia temperature management (temperature 35–36 °C) for 24–48 h. We use a management algorithm for increased ICP with an aim to maintain ICP $<$ 20–25 mmHg in patients managed with multimodal neuromonitoring[14] incorporating interventions pertaining to: (a) intravenous sedation (propofol – 1st line, narcotic and midazolam – 2nd line); (b) osmotherapy (2–3 ml/kg 5% hypertonic saline or 2–3 ml/kg 20% mannitol intermittent intravenous boluses) and (c) normocapnic ventilation. With refractory increased ICP, we selectively undertake therapeutic hypothermia (temperature 33–34 °C) or intravenous barbiturate administration at the intensivist's discretion. ICP monitoring was placed in the non-dominant frontal lobe via a single burr hole and bolt (Integra Lifesciences, New Jersey, USA). A follow up head computed tomography scan was conducted to ensure adequate placement.

Neurophysiologic monitoring

The following neurophysiologic data were collected: (a) ICP (Camino®, Integra Lifesciences, Plainsboro, New Jersey, USA); (b) invasively monitored mean arterial pressure (MAP); (c) brain tissue oxygenation ($PbtO_2$) (Licox®, Integra Lifesciences, Plainsboro, New Jersey, USA); (d) end tidal carbon dioxide tension ($ETCO_2$) and (e) central core body temperature using an esophageal temperature monitoring. All physiologic data was displayed on our bedside monitors (Carescape®, General Electric, USA) and then subsequently slaved into the ICM + monitoring software (Cambridge Enterprise,

United Kingdom) using a USB to RS232 converter to serial DB9 cable at a frequency of 300 Hz.

RAP and intracranial compliance

Intracranial compliance can be estimated in real time using a correlation coefficient between the mean absolute ICP and mean pulse amplitude pressure of the ICP waveform, termed the compensatory reserve index (RAP).[15] A RAP $>$ 0.4 denotes limited intracranial compensatory reserve and intracranial compliance and has been primarily studied in patients with traumatic brain injury.[16,17] ICM+® software calculates RAP in real-time as a moving Pearson correlation coefficient between 30 consecutive, 10-s averaged values of mean absolute ICP and the mean pulse amplitude from ICP signals.[18]

Statistical analysis

From the ICM+® software, all the neuromonitoring data was exported into Microsoft Excel (Redmond, WA, USA). From Microsoft Excel, data were transferred to RStudio software (version 3.4.1) for statistical analysis. In RStudio, we averaged data for physiologic variables over 10 min.

*Modeling ICP and RAP over time.*We assessed the temporal relationships of ICP and RAP over time visually for all study subjects in the cohort. A mixed-methods linear regression was used to analyze the temporal trends of RAP and ICP over time in each study subject (RStudio package *lme4* (19)). Thereby, we were able to consider the within patient variability of data for ICP and RAP. To examine the change of ICP and RAP over time in survivors vs. non-survivors, we used a mixed effects linear regression model. The final model included an interaction between time (collapsed over 10 min) and favourable neurologic outcome as a dichotomous variable. We present the differences of ICP and RAP in survivors versus non-survivors and we considered $p < 0.05$ to be a significant value.

*Modeling brain oxygenation $PbtO_2$, $ETCO_2$ and temperature*versus*ICP.* We assessed these relationships by plotting $PbtO_2$, $ETCO_2$ and temperature against ICP for the entire cohort. Associations were modeled using a generalized linear model specifying 'patient' as a random-effect (RStusdio package *lme4*[19]). We used fractional polynomial regression (RStudio function *mfp*) to analyze the associations to interrogate the potential non-linear relationship between $PbtO_2$, $ETCO_2$ and temperature versus ICP.

Results

During the study period, 22 potential study subjects were identified with and 10 patients fulfilled inclusion criteria as previously published.[13] Table 1 demonstrates the clinical and demographic data of each individual study subject. Table 2 reveals the ICP management interventions used in the cohort during the course of the study.

Characterization of temporal patterns of ICP

The mean ICP was 14 mmHg (SD 11) across the entire cohort. There were 2419 data points pertaining to ICP values and of these, 279 (11%) had an ICP above 20 mmHg. Patients were exposed to intracranial hypertension (ICP $>$ 20 mmHg) for an average of 22% (range 0–100) of the total time of invasive neuromonitoring. Fig. 1 demonstrates the ICP longitudinally for each study subject in the cohort. Most study subjects exhibited normal ICP over time; however, two demonstrated refractory increased ICP despite maximal medical management (Fig. 1, Patients 7 & 8). The mean ICP was 12 mmHg (SD 5) in survivors and 16 mmHg (SD 15) in non-survivors ($p = 0.27$).

Description of intracranial compliance using RAP

For the entire cohort, the mean RAP was 0.58 (SD 0.34). Considering all RAP data points (1849), 76% were greater than 0.4, indicating a large burden of limited compensatory reserve and intracranial compliance across the entire cohort. There was no difference in mean RAP in survivors [0.58 (SD 0.37)] compared to non-survivors [0.58 (SD 0.32), $p = 0.90$)]. The percentage of time with a RAP of greater than 0.4 was 78% (range 57–97) within individual study subjects thereby demonstrating limited intracranial compliance despite normal absolute ICP in most patients. Fig. 2 demonstrates the RAP longitudinally for each patient. Overall, all patients presented patterns of depleted compensatory reserve when visually inspecting RAP over time (RAP $>$ 0.4). For instance, Patient 7 displayed an inverse relationship between ICP and ICP pulse amplitude (RAP close to −1) after reaching the ICP upper

Table 1 – Patient demographics and clinical outcome of study cohort. (Table adapted from Sekhon et al.[13]).

Study ID	Age	Gender	Arrest etiology	Rhythm	Witnessed	Time to ROSC (mins)	Time to ICP monitoring (h)	Duration of ICP monitoring (h)	6 month GOS
1	20	Male	Hypoxia	PEA	No	12	16	24	4
2	47	Male	Hypoxia	PEA	No	15	6	39	1
3	23	Male	Hemorrhage	PEA	Yes	22	14	51	5
4	71	Female	Hypoxia	PEA	No	14	8	37	1
5	31	Female	VF	VF	Yes	25	43	94	5
6	57	Male	Anaphylaxis	PEA	No	24	7	42	1
7	37	Male	Drowning	PEA	Yes	36	6	18	1
8	67	Female	Hypoxia	PEA	Yes	17	8	8	1
9	48	Male	Opioid overdose	PEA	No	27	10	62	5
10	49	Male	Asthma	PEA	Yes	18	9	47	1

Abbreviations: ID – identification; VF – ventricular fibrillation; ROSC – return of spontaneous circulation; ICP – intracranial pressure; GOS – glasgow outcome scale.

Table 2 – Intracranial pressure guided interventions in all cohort patients.

Study ID	Temperature (°C, mean, SD)	Sedation hours (h)	Propofol dose (ug/kg/min, mean, SD)	2nd line Sedative	ETCO2 (mmHg, mean, SD)	PaCO2 (mmHg, mean, SD)	HTS boluses	Mannitol Boluses
1	36.9 (0.1)	29	31 (7)	No	45 (7)	35 (2)	0	0
2	35.9 (1.9)	41	86 (21)	No	36 (1)	40 (1)	2	2
3	35.2 (0.8)	39	89 (12)	No	31 (3)	35 (3)	1	0
4	36.4 (1.5)	44	37 (27)	No	28 (2)	36 (2)	0	0
5	36.9 (1.6)	108	37 (27)	No	27 (2)	41 (1)	4	4
6	35.3 (1.9)	42	35 (50)	No	26 (10)	38 (8)	1	0
7	35.0 (0.5)	24	100 (0)	No	28 (6)	33 (0)	2	2
8	35.0 (0.1)	8	62 (35)	No	24 (19)	40 (11)	0	0
9	35.2 (0.8)	63	73 (35)	No	30 (6)	49 (1)	1	0
10	35.8 (0.2)	54	79 (14)	Yes	38 (13)	57 (7)	2	1

Abbreviations: HTS – hypertonic saline; $PaCO_2$ – arterial carbon dioxide tension; SD – standard deviation.

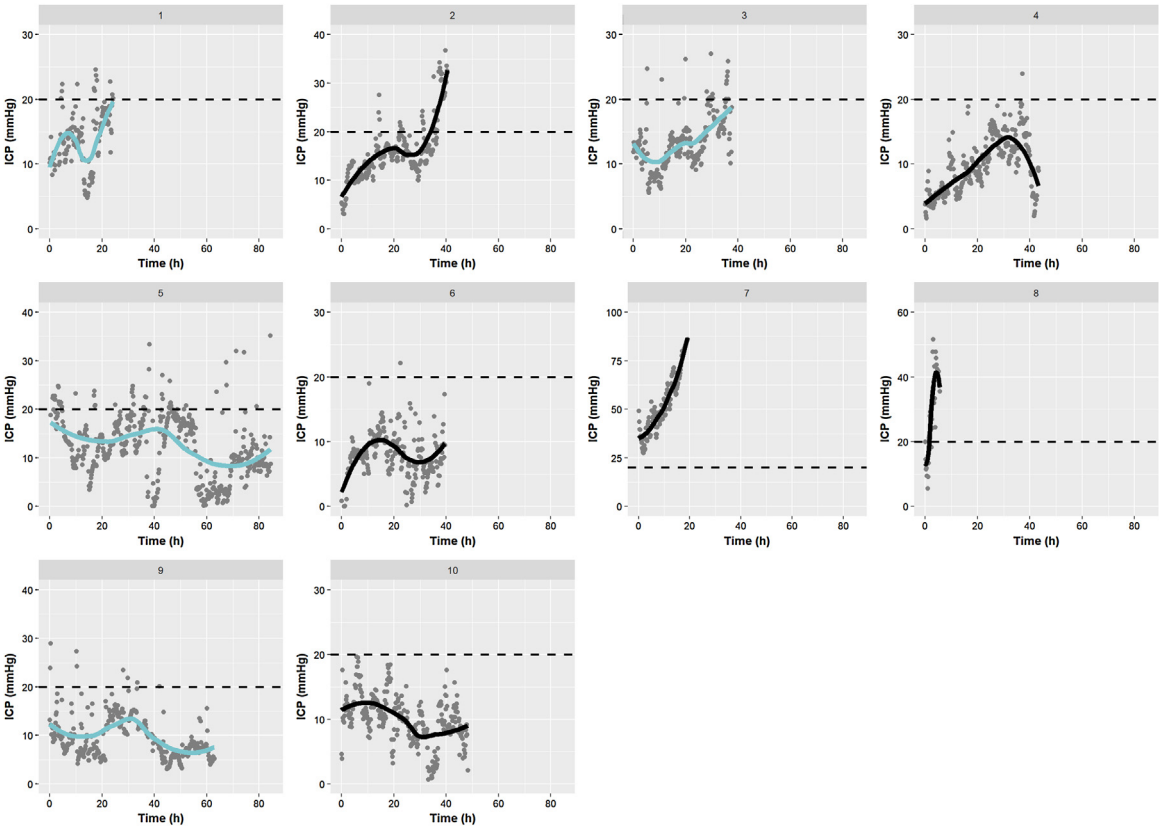

Fig. 1 – Each individual panel represents patients 1–10 in the cohort and plots intracranial pressure (mmHg, y-axis) versus time (hours, x-axis). The dotted line denotes an intracranial pressure >20 mmHg as the threshold for intracranial hypertension. The solid lines displayed in cyan are referent to survivors, and in black to non-survivors.

breakpoint, a pathological state indicative of complete exhaustion of the intracranial compensatory reserve (Fig. 3, panel A).

Relationship of ICP vs. $PbtO_2$, $ETCO_2$ and temperature

Bby plotting the relationship between $PbtO_2$, $ETCO_2$, temperature and ICP, there did not demonstrate any obvious relationship. Relationships between ICP and $PbtO_2$, $ETCO_2$ and temperature during the monitoring period are presented in the Supplementary appendix (Figure S1).

ICP management of study subjects

The mean $ETCO_2$ was 32 mmHg (SD 6), mean arterial carbon dioxide tension was 40 mmHg (SD 7) and mean core body temperature was 35.7 °C (SD 0.8). The median duration of intravenous sedation was

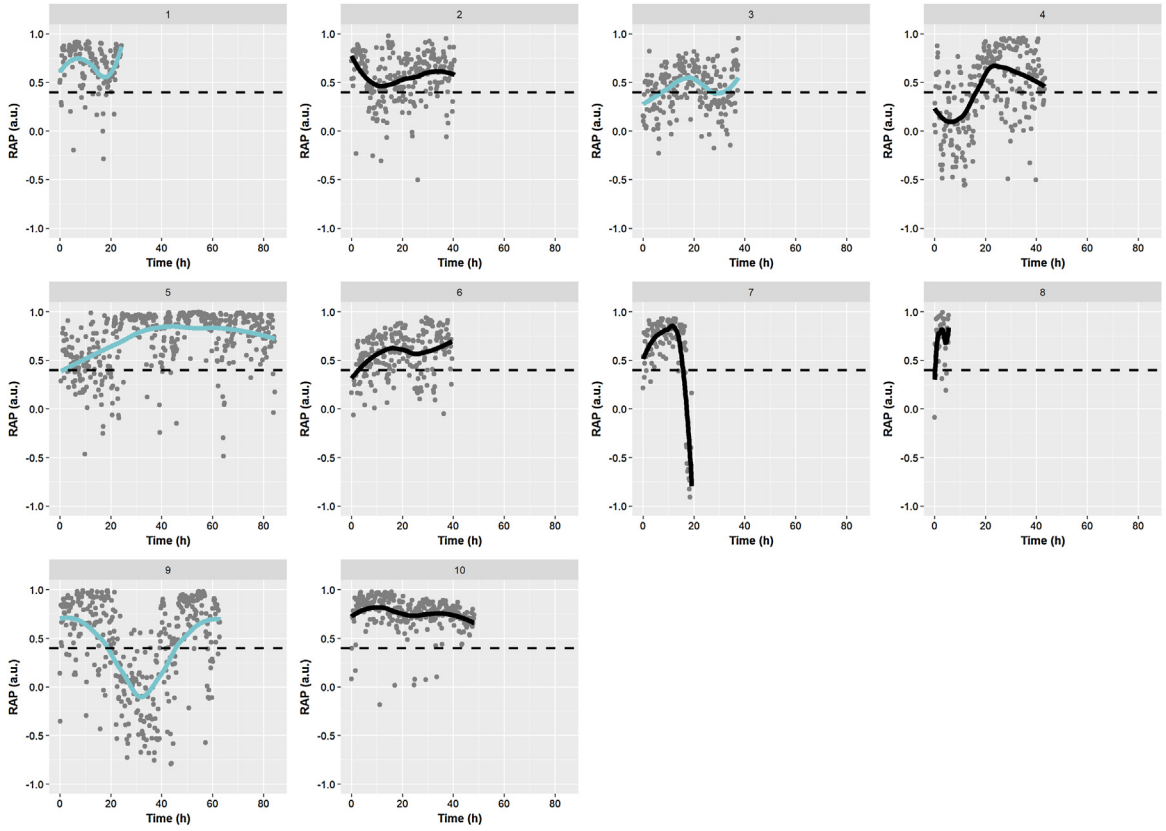

Fig. 2 – Each individual panel represents patients 1–10 in the cohort and plots RAP (y-axis) versus time (hours, x-axis). The dotted line denotes RAP > 0.4 as the threshold for limited intracranial compensatory reserve and brain compliance. The solid lines displayed in cyan are referent to survivors, and in black to non-survivors.

44 h (range (8–106) and the mean dose of propofol was 63 ug/kg/min (SD 24). Six patients (60%) received hypertonic saline boluses and 4 patients (40%) received 20% mannitol boluses.

Discussion

The main findings of our study are that there was a relatively low burden of intracranial hypertension (ICP > 20 mmHg) in the cohort overall but there appeared to be a significant heterogeneous nature of ICP patterns over time between individual patients. Most patients in our cohort demonstrated increased RAP, suggesting a state of limited intracranial compensatory reserve and compliance in HIBI.

In HIBI, cerebral edema can lead to limited intracranial compensatory reserve, compliance, elevated ICP and secondary brain hypoxia induced injury.[1,20,21] In lieu of these pathophysiologic sequelae, authors have attempted to delineate the importance of ICP in HIBI. You et al. demonstrated an association with adverse neurological outcome and increased ICP using cerebral spinal fluid pressure assessment and increased optic nerve sheath diameter (ONSD) via bedside ultrasonography in conducted 83 post-cardiac arrest HIBI.[9] These findings corroborate prior observational studies also demonstrating associations between increased ONSD, using ultrasonography and computed tomography, with adverse neurological outcome in HIBI[7,10] and traumatic brain injury.[22,23,24] Recently, our research group sought to establish the validity of non-invasive estimators of ICP versus invasively monitored ICP in HIBI patients. We found a significant linear relationship between ICP and ONSD ultrasonography in this cohort as part of a sub-study.[25] Although intriguing, non-invasive methods of ICP evaluation are associated with limitations pertaining to inter-observer reliability and evaluation of intracranial pressure — volume dynamics at single time points.

Previous reports using *invasive* ICP monitoring have yielded conflicting results.[11,12] Naito et al. demonstrated, in a cohort of nine cardiac arrest patients, increased ICP during the rewarming period only after therapeutic hypothermia from 6 mmHg [4–9] mmHg to 16 mmHg,[12–26,11] remaining under the accepted threshold of intracranial hypertension (ICP < 20 mmHg).[11] Similarly, Sakabe et al. observed that intracranial hypertension only occurred in one of six HIBI patients after cardiac arrest,[12] thereby suggesting a low burden of intracranial hypertension. Importantly, both studies were limited to intermittent measurements and lacked high resolution data to delineate longitudinal patterns and relationships between associated physiologic variables.

We observed a relatively low burden of intracranial hypertension overall with the percentage of time of ICP > 20 mmHg being 22% (0–100). Two patients in our cohort (patient 7 and 8) developed refractory intracranial hypertension while the remaining patients did not (Fig. 1). Importantly, the interpretation of absolute ICP values must be observed in the context of concomitant therapies aimed at reducing ICP. Given the intensity of active management for ICP control in our cohort (Table 2), it is possible

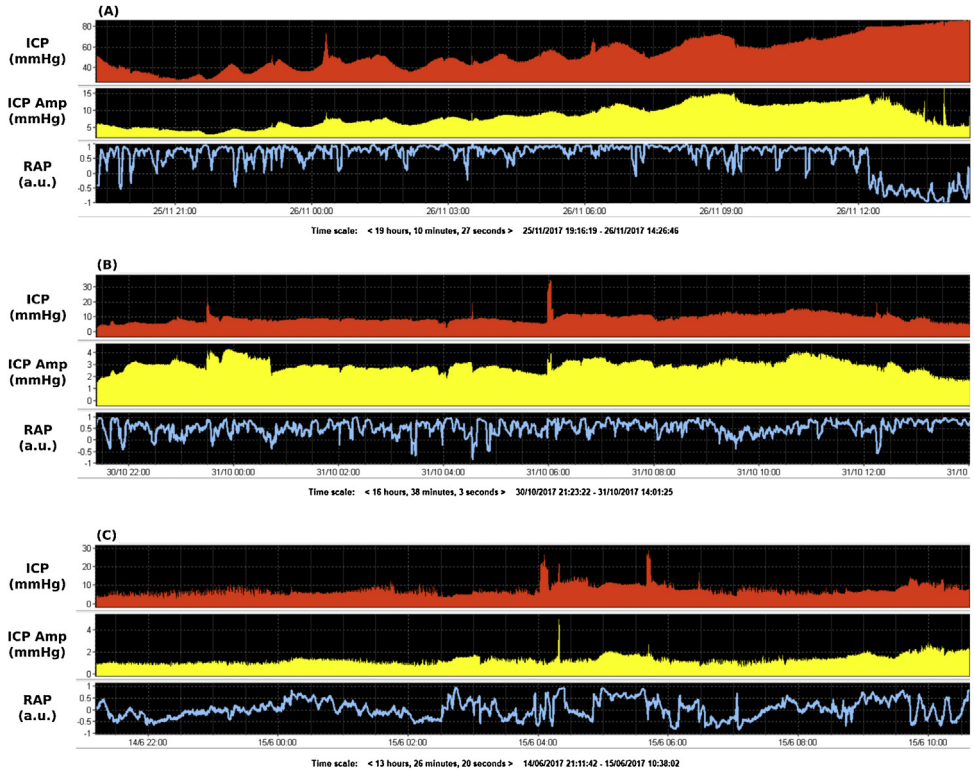

Fig. 3 – Visual description of 3 distinct patterns of ICP and intracranial compliance in HIBI. Panel A demonstrates increased ICP and RAP. On the far right in panel A, refractory intracranial hypertension results in trans-tentorial herniation with resultant decreased in the ICP amplitude and RAP. Panel B shows a patient with low ICP but increased RAP. Finally, panel C demonstrates low ICP and RAP.

the burden of intracranial hypertension may have been far greater if the clinicians were blinded to the ICP monitoring data and may have blunted the natural history of cerebral edema formation and ICP over time. Additionally, we acknowledge that our management trigger for increased ICP is extrapolated from the traumatic brain injury literature.[26] Currently, it is unknown what the specific threshold of intracranial hypertension is in HIBI patients or if management of increased ICP is associated with improved outcome.

Although we did not demonstrate an impressive burden of intracranial hypertension in our study, assessment of the intracranial compensatory reserve and compliance may provide insights into the degree of cerebral edema over time. Previous authors have suggested absolute ICP is a crude measure of the overall bulk of cerebral edema in HIBI.[21] In instances of limited intracranial compliance, ICP only becomes elevated once compensatory mechanisms have been exhausted.[4,5] RAP, a correlation coefficient between the mean and fundamental component of the ICP waveform, varies between −1 and +1.[18,27] Values nearing zero indicate normal intracranial compliance and whereas values approaching +1 suggest limited compensatory reserve.[4] In the setting of exhaustion of compensatory reserve, RAP may approach −1 as the ICP waveform assumes a rounded morphology.[5,28]

RAP was elevated in all study subjects consistently >0.4 during the monitoring period, indicating a state of limited compensatory reserve.[4] This result suggests that although the numerical ICP remained low in most patients in our cohort, elevated RAP indicates that study subjects were at the steep portion of the intracranial pressure — volume relationship. As such, significant perturbations in physiological variables that can alter this relationship dynamically could cause a precipitous shift up the curve towards developing intracranial hypertension and herniation. In particular, overly aggressive rewarming after targeted temperature management, permissive hypercapnia and exacerbation of cerebral edema from hyponatremia could all lead to increased ICP.[11]

On an individual patient level, there appeared to be significant heterogeneity in the patterns of ICP over time after ROSC. Overall, there appeared to be 3 distinct patterns of ICP and compensatory reserve observed. The heterogeneous nature of the ICP and RAP profiles could reflect a spectrum of underlying disease severity and cerebral edema. Furthermore, the pre-morbid volume of cerebral parenchymal bulk likely factors into the heterogeneity of overall pressure – volume dynamics, with older patients exhibiting an increased capacity of compensatory reserve stemming from age related cerebral atrophy. The nature of our study and small cohort preclude us from drawing definitive conclusions or eliciting predictive methods for identifying which patients could be at risk of developing intracranial hypertension.

Our study adds to the existing literature detailing the ICP patterns over time and evaluation of intracranial compliance in HIBI. Strengths of our study include our longitudinal measurements, high resolution of data acquisition and invasive nature of ICP monitoring.

Our study has significant limitations with which the results must be interpreted. The first is that the small sample size and lack of

comparative controls which prohibits causal conclusions to be drawn with respect to the relationships between carbon dioxide tension and temperature with ICP. Other ICP lowering interventions including intravenous sedation and osmotherapy (mannitol and 5% hypertonic saline) were used by clinicians and may have blunted any significant relationships that may be present. Furthermore, we acknowledge our data is not generalizable to the post cardiac arrest HIBI patients who are managed with therapeutic hypothermia (temperature 32–34 °C). Due to potential risks of hypothermia induced coagulopathy and intracranial hemorrhage associated with invasive neuromonitoring, we were unable to characterize the intracranial pressure-volume physiology below normothermia (35–36 °C). It is unclear whether increased ICP is a therapeutically modifiable factor or rather a sign of disease severity in HIBI. Further physiologic and clinical studies are needed to clarify these important questions.

Conclusion

We demonstrate the relatively low burden of intracranial hypertension but abnormal intracranial compliance in HIBI after cardiac arrest. On an individual patient level, there appears to be heterogeneity with ICP and intracranial compliance from cerebral edema in HIBI.

Conflicts of interest

Professor Marek Czosnyka has a financial interest in licensing ICM+ software (Cambridge Enterprise Ltd). The remaining authors have disclosed they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.resuscitation.2019.05.036

REFERENCES

1. Sekhon MS, Ainslie PN, Griesdale DE. Clinical pathophysiology of hypoxic ischemic brain injury after cardiac arrest: a "two-hit" model. Crit Care 2017;21:90.
2. Zeynalov E, Chen C-H, Froehner SC, et al. The perivascular pool of aquaporin-4 mediates the effect of osmotherapy in postischemic cerebral edema. Crit Care Med 2008;36:2634–40.
3. Rungta RL, Choi HB, Tyson JR, et al. The cellular mechanisms of neuronal swelling underlying cytotoxic edema. Cell 2015;161:610–21.
4. Czosnyka M, Pickard JD. Monitoring and interpretation of intracranial pressure. J Neurol Neurosurg Psychiatry 2004;75:813–21.
5. Czosnyka M, Smielewski P, Timofeev I, et al. Intracranial pressure: more than a number. Neurosurg Focus 2007;22:E10.
6. Fugate JE, Wijdicks EFM, Mandrekar J, et al. Predictors of neurologic outcome in hypothermia after cardiac arrest. Ann Neurol 2010;68:907–14.
7. Hwan Kim Y, Ho Lee J, Kun Hong C, et al. Feasibility of Optic Nerve S heath Diameter Measured on Initial Brain Computed Tomography as an Early Neurologic Outcome Predictor After Cardiac Arrest. Mark Courtney D, editor. Acad Emerg Med 2014;21:1121–8.
8. Chae MK, Ko E, Lee JH, et al. Better prognostic value with combined optic nerve sheath diameter and grey-to-white matter ratio on initial brain computed tomography in post-cardiac arrest patients. Resuscitation 2016;104:40–5.
9. You Y, Park J, Min J, et al. Relationship between time related serum albumin concentration, optic nerve sheath diameter, cerebrospinal fluid pressure, and neurological prognosis in cardiac arrest survivors. Resuscitation 2018;131:42–7.
10. Chelly J, Deye N, Guichard J-P, et al. The optic nerve sheath diameter as a useful tool for early prediction of outcome after cardiac arrest: a prospective pilot study. Resuscitation 2016;103:7–13.
11. Naito H, Isotani E, Callaway CW, Hagioka S, Morimoto N. Intracranial pressure increases during rewarming period after mild therapeutic hypothermia in postcardiac arrest patients. Ther Hypothermia Temp Manag 2016;6:189–93.
12. Sakabe T, Tateishi A, Miyauchi Y, et al. Intracranial pressure following cardiopulmonary resuscitation. Intensive Care Med 1987;13:256–9.
13. Sekhon MS, Gooderham P, Menon DK, et al. The burden of brain hypoxia and optimal mean arterial pressure in patients with hypoxic ischemic brain injury after cardiac arrest. Crit Care Med 2019;47(July (7)):960–9.
14. Sekhon MS, Gooderham P, Toyota B, et al. Implementation of neurocritical care is associated with improved outcomes in traumatic brain injury. Can J Neurol Sci 2017;27:1–8.
15. Balestreri M, Czosnyka M, Steiner LA, et al. Intracranial hypertension: what additional information can be derived from ICP waveform after head injury? Acta Neurochir (Wien) 2004;146:131–41.
16. Calviello L, Donnelly J, Cardim D, et al. Compensatory-reserve-weighted intracranial pressure and its association with outcome after traumatic brain injury. Neurocrit Care 2018;28:212–20.
17. Zeiler FA, Kim D-J, Cabeleira M. Impaired cerebral compensatory reserve is associated with admission imaging characteristics of diffuse insult in traumatic brain injury. Acta Neurochir (Wien) 2018;160:2277–87.
18. Kim D, Czosnyka Z, Kasprowicz M, Smieleweski P, Baledent O. Continuous monitoring of the Monro–Kellie doctrine: is it possible? J Neurotrauma 2012;29:1354–63.
19. Bates D, Maechler M, Bolker B, Walker S. Package lme4. J Stat Softw 2015;67:1–91.
20. Nolan JP, Neumar RW, Adrie C, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A Scientific Statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Coun. Resuscitation 2008;79:350–79.
21. Reis C, Akyol O, Araujo C, et al. Pathophysiology and the monitoring methods for cardiac arrest associated brain injury. Int J Mol Sci 2017;18:129.
22. Geeraerts T, Launey Y, Martin L, et al. Ultrasonography of the optic nerve sheath may be useful for detecting raised intracranial pressure after severe brain injury. Intensive Care Med 2007;33:1704–11.
23. Robba C, Cardim D, Tajsic T, et al. Ultrasound non-invasive measurement of intracranial pressure in neurointensive care: a prospective observational study. PLoS Med 201714:.
24. Sekhon MS, Griesdale DE, Robba C, et al. Optic nerve sheath diameter on computed tomography is correlated with simultaneously measured intracranial pressure in patients with severe traumatic brain injury. Intensive Care Med 201440:.
25. Cardim D, Griesdale DE, Ainslie PN, et al. A comparison of non-invasive versus invasive measures of intracranial pressure in hypoxic ischaemic brain injury after cardiac arrest. Resuscitation 2019;137:221–8.

26. Le Roux P, Menon DK, Citerio G, et al. Consensus summary statementof the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care: a statement for healthcare professionals from the Neurocritical Care Society and the European Society of Intensive. Intensive Care Med 2014;40:1189–209.
27. Czosnyka M, Smielewski P, Lavinio A, Czosnyka Z, Pickard JD. A synopsis of brain pressures: which? when? are they all useful?. Neurol Res 2007;29:672–9.
28. Czosnyka M, Pickard J. Monitoring and interpretation of intracranial pressure. J Neurol Neurosurg Psychiatry 2004;75:813–21.