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Clinical paper

Unsupervised learning of early post-arrest brain injury phenotypes

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Abstract

Introduction: Trials may be neutral when they do not appropriately target the experimental intervention. We speculated multimodality assessment of early hypoxic-ischemic brain injury would identify phenotypes likely to benefit from therapeutic interventions.

Methods: We performed a retrospective study including comatose patients resuscitated from out-of-hospital cardiac arrest (OHCA) by one of 126 emergency medical services or in-hospital arrest at one of 26 hospitals from 2011 to 2019. All patients were ultimately transported to a single tertiary center for care including standardized initial neurological examination, brain imaging and electroencephalography; targeted temperature management (TTM); hemodynamic optimization targeting mean arterial pressure (MAP) >80 mmHg; and, coronary angiography for clinical suspicion for acute coronary syndrome. We used unsupervised learning to identify brain injury phenotypes defined by admission neurodiagnostics. We tested for interactions between phenotype and TTM, hemodynamic management and cardiac catheterization in models predicting recovery.

Results: We included 1086 patients with mean (SD) age 58 (17) years of whom 955 (88%) were resuscitated from OHCA. Survival to hospital discharge was 27%, and 248 (23%) were discharged with Cerebral Performance Category (CPC) 1–3. We identified 5 clusters defining distinct brain injury phenotypes, each comprising 14% to 30% of the cohort with discharge CPC 1–3 in 59% to <1%. We found significant interactions between cluster and TTM strategy ($P = 0.01$), MAP ($P < 0.001$) and coronary angiography ($P = 0.04$) in models predicting outcomes.

Conclusions: We identified patterns of early hypoxic-ischemic injury based on multiple diagnostic modalities that predict responsiveness to several therapeutic interventions recently tested in neutral clinical trials.

Keywords: Cardiac arrest, Precision medicine, Unsupervised learning, Clustering, Phenotype, Outcomes

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Introduction

A dearth of positive trials in critical care medicine, including those testing interventions intended to improve recovery after resuscitation from cardiac arrest, reflects in part a failure to appropriately target or titrate the experimental intervention.[1] At best, failure to personalize care based on individual need leads to enrollment of subjects likely to die or recover regardless of treatment allocation. This limits the proportion of subjects able to benefit from interventions, reduces statistical power and obscures true treatment effects. At worst, untargeted interventions may harm some subjects, resulting in a neutral or negative study result despite the intervention's potential for benefit when targeted to the correct subgroup.[2,3]

Principle goals of post-arrest care are minimization of secondary brain injury and correction of treatable inciting causes of arrest. Targeted temperature management (TTM) is a cornerstone of post-arrest neuroprotection.[4–6] However, multiple investigations comparing hypothermia depths, durations and induction strategies have been neutral.[7–9] Optimizing cerebral perfusion is another principle of post-arrest care, but a recent trial comparing two blood pressure targets to optimize cerebral perfusion pressure found no outcome differences across arms.[10] Correcting underlying cardiovascular causes of cardiac arrest is also associated with improved functional outcome, but another trial comparing timing of cardiac catheterization for patients with shockable initial arrest rhythms and absent ST-segment elevation was also neutral.[11]

All of these studies relied on historical characteristics associated with illness severity to identify subgroups predicted to benefit – for example excluding patients with unwitnessed asystolic out-of-hospital cardiac arrest (OHCA) as likely to have brain injury too severe to allow detection of a treatment effect. Furthermore, these trials defined "comatose patients" as those unable to follow verbal commands, a definition that includes a huge range of neurological conditions and severities. We speculate that a more rigorous characterization of acute brain dysfunction might reveal patterns of anoxic injury likely to benefit from neuroprotection or other therapeutic interventions. We used unsupervised learning to identify distinct phenotypes of post-arrest brain injury defined by multimodality baseline testing of neurological structure and function on hospital arrival. We then tested the hypothesis that the associations of TTM, hemodynamic management and cardiac catheterization with outcome differ between phenotypic clusters.

Methods

Patients and setting

The University of Pittsburgh Office of Human Research Protection approved all aspects of this study. We identified patients from a prospective registry of consecutive patients resuscitated from in-hospital (IHCA) or OHCA treated from August 2011 to August 2019. We excluded patients who awakened within 6 h of hospital arrival, defined as following verbal commands or exhibiting purposeful spontaneous motor activity; patients who arrested due to trauma or a primary neurological event; and, patients with a delay of >24 h from arrest to arrival at our facility. Finally, we excluded patients with fewer than two of the following three modalities assessed within 6 h of hospital arrival: neurological examination in the absence of neuromuscular blockade, brain computerized tomography (CT) imaging, and electroencephalography (EEG). We did not consider assessments of brain injury not acquired on presentation (e.g. magnetic resonance imaging and somatosensory evoked potentials, both acquired after 3–5 days in the subset of patients with prognostic uncertainty). All included patients received initial care by a member of the University of Pittsburgh Post-Cardiac Arrest Service (PCAS). We previously described the details of this service line in detail.[12]

As part of initial resuscitation and evaluation, patients undergo a baseline post-arrest neurological examination by the PCAS attending physician before induction of TTM. It is our standard practice to obtain brain CT imaging prior to intensive care unit (ICU) admission (for OHCA) or as soon as feasible after initial stabilization (for IHCA). Imaging may be deferred in cases where it may delay a time-sensitive intervention (for example, coronary angiography for ST-elevation myocardial infarction) or a patient is deemed too unstable to travel to CT scan. We monitor all comatose post-arrest patients with continuous EEG which is available at all times and is typically initiated upon ICU arrival. We have previously described the details of our EEG monitoring protocol,[13,14] which uses 20–22 gold-plated electrodes placed in standard 10–20 international system of electrode placement positions and includes protocolized simulation for reactivity assessment at monitoring initiation and daily thereafter. We do not routinely monitor EEG in cases where initial imaging confirms diffuse cerebral edema and herniation, there is anticipation of a rapid transition toward comfort-oriented care based on pre-existing advanced directives, or rearrest occurs prior to EEG initiation.[14]

We provide TTM to 33 °C or 36 °C for 24 h to comatose post-arrest patients using endovascular or gel-adhesive pad surface cooling. Thereafter, we rewarm patients at 0.25 °C per hour to normothermia, which we actively maintain until 72 h post-arrest or awakening. Choice of target temperature is at the discretion of the treating PCAS physician, and in the exception of cases of hemorrhage where providers consistently favor 36 °C, we have observed considerable between- and within-provider variability in selection of target temperature. We typically provide sedation with propofol or dexmedetomidine, analgesia with fentanyl, and titrate these infusions to patient comfort and suppression of shivering while avoiding deep sedation when possible. We use invasive hemodynamic monitoring and target a mean arterial pressure ≥80 mmHg for at least the first 24 h and achieve this target via infusion of isotonic crystalloids in preload responsive patients and use of vasoactive infusions for persistent hypotension after volume resuscitation. It is our standard practice to perform multimodality neuroprognostic testing, which generally follows recent consensus guidelines,[15,16] except in cases where families are comfortable making decisions based on patient values and preferences despite some uncertainty in overall prognosis.

Clinical covariates and outcomes

We abstracted patient demographics, arrest characteristics, TTM strategy, initial brain injury assessments and functional outcome from our prospective registry. Neurological exam findings included: assessment of pupillary light reflex (both reactive, one reactive or both nonreactive); eye opening (eyelids open spontaneously but not tracking, eyes open to loud voice, eyes open to pain or eyes remain closed to pain); respiratory drive (not intubated, intubated and over-breathing the set ventilator rate, intubated and not over-breathing the ventilator); corneal reflex (both present, one side present or neither present); presence or absence of gag reflex; presence or absence of

cough reflex; and motor response to pain (localizing to pain, flexion or withdrawal to pain, extension to pain, no response or myoclonus).[17]

We considered three initial brain CT characteristics: ratio of gray- to white matter density in Hounsfield unit (GWR), measured at the level of the basal ganglia[18]; presence or absence of sulcal effacement; and presence or absence of effacement of the basal cisterns.

We categorized three domains of EEG features present during the first 60 minutes of monitoring, using definitions consistent with American Clinical Neurophysiology Society standard definitions:[19] background continuity (continuous background activity; suppression-burst; or generalized suppression); presence or absence of super-imposed epileptiform activity; and presence or absence of reactivity. We reviewed all EEG records for research purposes rather than relying on clinical interpretation, as we have previously described.[20] Our primary outcome of interest was non-vegetative survival to hospital discharge, defined as discharge with a Cerebral Performance Category (CPC) of 1–3.

We obtained an automated data extraction from our electronic medical record to obtain all vital signs and laboratory test results for each patient. For the present analysis, we summarized initial markers of end organ injury or dysfunction including presenting lactate, creatinine, alanine transaminase (ALT), aspartate transaminase (AST), pH and partial pressure of arterial oxygen (PaO_2). Finally, we considered presenting systolic and diastolic blood pressures, and the time-weighted average mean arterial pressure over the first 24 h after ICU admission.

Clustering and statistical analysis

We used k-prototypes to define clusters of post-arrest brain injury phenotypes based on results of neurological examination, EEG and brain CT imaging. K-prototypes is a methodological extension of k-means that allows partitional clustering of mixed data types (i.e. continuous and categorical features) with robust handling of missing data.[21] Similar to k-means, k-prototypes first initializes its algorithm by randomly identifying cluster centers (i.e. prototypical individual cases). The algorithm then iteratively calculates the distance from each case to the nearest prototype, assigns individual observations to a cluster defined by the nearest prototype, then updates cluster prototypes to the new centermost cases.[22] The overall distance metric used is a weighted combination of Euclidean distances between continuous variables and the count of mismatches for categorical variables. Approaches to optimize the weight used to calculate this distance metric have been described in detail.[22] In this framework, different modalities of categorical data are weighted equally as an overall mismatch count, as are continuous data by overall Euclidean distance. We calculated C-indices and Dunn indices to validate clustering and select the optimal number of clusters.[23] We summarized baseline patient clinical characteristics and outcomes of the overall cohort and within-cluster using descriptive statistics of patient and arrest-specific variables. We used Firth's penalized logistic regression to build models predicting patient outcome given treatment (TTM strategy, cardiac catheterization and average mean arterial blood pressure) and cluster membership, with and without an interaction between the two. We used likelihood ratio tests comparing full and reduced models to test the global significance of the interaction between treatment and cluster. We then calculated cluster-specific associations between treatment and outcome. We used R (R Foundation for Statistical Computing, Vienna, Austria) for clustering and statistical analysis, completing clustering using the kproto function of the clustMixType package.[22]

Results

There were 2019 patients in our registry during the study period, of whom 55 were deemed not to have had a cardiac arrest after full evaluation, 36 arrested due to a primary neurological event, 55 arrested due to trauma, 160 arrived to our facility >24 h after their initial arrest and 339 were awake. Of the remaining 1374 another 288 did not undergo multiple modalities of brain injury assessment within 6 h of arrival leaving 1086 patients included in the final analysis. Cases of OHCA by one of 126 emergency medical services and cases of IHCA occurred at one of 26 hospitals. Mean (SD) age of the included cohort was 58 (17) years, 437 (40%) were female, and 955 (88%) were resuscitated from OHCA (Table 1). Overall survival to hospital

Table 1 – Overall patient characteristics and outcomes.

Characteristic	Overall cohort ($n = 1086$)
Age, years	58 ± 17
Female sex	437 (40)
Arrested out-of-hospital	955 (88)
Interfacility transfer	720 (66)
Initial arrest rhythm	
VT/VF	306 (28)
PEA	364 (34)
Asystole	337 (31)
Unknown	79 (7)
Witnessed arrest	
Layperson witnessed	427 (43)
EMS-witnessed	154 (15)
Bystander CPR	
Layperson	262 (26)
Professional	348 (35)
Arrest duration, min	20 [11–31]
Epinephrine doses	3 [2–5]
Arrest to initial assessment, hours	2.6 [1.0–3.6]
Target temperature	
33 °C	438 (40)
36 °C	470 (43)
Other target temperature	63 (6)
No TTM	115 (11)
Cardiac catheterization	205 (19)
Awakened from coma	283 (26)
Survived to discharge	289 (27)
Discharge CPC	
1–3	264 (24)
4 or 5	838 (77)
Proximate cause of death	
Rearrest or intractable shock	205 (19)
Brain death	90 (8)
Withdrawal for prior advanced directives	94 (9)
Neurological withdrawal	408 (38)
Hospital length of stay, days	
Survived to discharge	16 [10–24]
Died in-hospital (all-cause)	3 [1–5]
Died after neurological withdrawal	3 [2–5]

Data are presented as number with corresponding percentage, mean ± standard deviation or median [interquartile range]. *Abbreviations*: VT/VF, ventricular tachycardia or fibrillation; CPR, cardiopulmonary resuscitation; CPC, Cerebral Performance Category.

discharge was 27%, and 248 (23%) were discharged with CPC 1–3 (Table 1). Initial neurological assessment occurred a median of 2.6 [IQR 1.0–3.6] hours after initial collapse, while brain CT occurred 4.2 [IQR 2.8–5.8] hours and EEG was acquired a median of 9.3 [IQR 7.3–11] hours after collapse.

We identified 5 clusters summarizing distinct early post-arrest brain injury phenotypes based on brain imaging, EEG and neurological examination acquired on patient presentation. Each cluster comprised between 14% and 30% of the overall cohort. Clinical characteristics of clusters prototypes and outcomes of clusters are summarized in Table 2. Rates of survival with CPC 1–3 varied from 59% to <1% across clusters (Table 2) while proximate cause of death also varied among non-survivors (Table 3). For example, progression to brain death ranged from 1% to 37% across clusters. In addition to brain injury characteristics (Supplemental Table 1), baseline laboratory results that reflect systemic hypoxic-ischemic injury (e.g. serum lactate, pH and liver function tests) varied across groups, but initial hemodynamic profiles did not (Table 3).

Table 2 – Clustering based on neurological assessment, initial brain imaging and initial electroencephalographic findings yields 5 distinct clusters. Reported outcome is for discharge Cerebral Performance Category 1–3. Italics denote abnormal findings observed in each cluster. K-prototypes identifies a single prototypical patient for each cluster; this prototype is akin to the center of clusters identified using other unsupervised approaches.

Cluster–Size (n (%))	Prototype characteristics and # (%) with discharge CPC 1-3 in cluster	Detailed description of cluster prototype patient	
1–330 (30)	Light brain injury; exam, CT and EEG all acceptable 193 (59)	Exam – *Eyes closed to pain* – Flexing or localizing to pain – Intact pupillary light reflex – Intact corneal reflex – Intact gag – Intact cough – Over-breathing the ventilator	Electroencephalography –Continuous background –Nothing epileptiform –Reactive CT imaging –Gray white ratio 1.37 –Sulci preserved –Basal cisterns patent
2–181 (17)	Poor exam, acceptable CT/EEG 35 (19)	Exam –*Eyes closed to pain* –*No motor to pain* –Intact pupillary light reflex –*Absent corneal reflex* –*No motor to pain* –*Absent gag* –*Absent cough* –Over-breathing the ventilator	Electroencephalography –Continuous to SB background –Nothing epileptiform –*Not reactive* CT imaging –Gray white ratio 1.31 –Sulci preserved –Basal cisterns patent
3–216 (20)	Very poor exam and EEG, CT acceptable 13 (6)	Exam –*Eyes closed to pain* –*No motor to pain* –*Absent pupillary light reflex* –*Absent corneal reflex* –*Absent gag* –*Absent cough* –*Not over-breathing the ventilator*	Electroencephalography –*Suppressed background* –Nothing epileptiform –*Not reactive* CT imaging –Gray white ratio 1.28 –Sulci preserved –Basal cisterns patent
4–209 (19)	Myoclonus and/or identical bursts 6 (3)	Exam –*Eyes closed to pain* –*Myoclonus to pain* –Intact pupillary light reflex –*Absent corneal reflex* –*Absent gag* –*Absent cough* –Over-breathing the ventilator	Electroencephalography –*SB background* –*Ictal bursts* –*Not reactive* CT imaging –Gray white ratio 1.35 –Sulci preserved –Basal cisterns patent
5–150 (14)	Cerebral edema 1 (1)	Exam –*Eyes closed to pain* –*No motor to pain* –*Absent pupillary light reflex* –*Absent corneal reflex* –*Absent gag* –*Absent cough* –*Not over-breathing the ventilator*	Electroencephalography –*Suppressed background* –Nothing epileptiform –*Not reactive* CT imaging –*Gray white ratio 1.00* –*Sulci effaced* –*Basal cisterns effaced*

Abbreviations: EEG, electroencephalography; CT, computerized tomographic; SB, suppression burst. Numeric data are reported as raw number with corresponding percentages.

Table 3 – Non-neurological clinical characteristics stratified by cluster.

Characteristic	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5
Age, years	59 ± 16	59 ± 14	60 ± 17	59 ± 17	51 ± 17
Female sex	22 (37)	64 (36)	91 (42)	78 (55)	82 (37)
Arrested out-of-hospital	272 (82)	155 (86)	191 (88)	189 (90)	148 (99)
Interfacility transfer	187 (57)	118 (65)	113 (62)	151 (72)	131 (87)
Initial arrest rhythm					
VT/VF	156 (47)	43 (24)	40 (19)	55 (26)	12 (8)
PEA	104 (32)	77 (43)	82 (38)	66 (32)	35 (23)
Asystole	50 (15)	47 (26)	77 (36)	72 (34)	91 (61)
Unknown	20 (6)	14 (8)	17 (9)	16 (8)	12 (8)
Witnessed arrest					
Layperson witnessed	131 (40)	56 (31)	75 (35)	115 (55)	50 (33)
EMS-witnessed	48 (15)	31 (17)	38 (18)	21 (11)	14 (9)
Bystander CPR					
Layperson	78 (24)	35 (19)	53 (25)	50 (24)	46 (31)
Professional	94 (28)	49 (27)	74 (34)	68 (33)	62 (42)
Arrest duration, min	13 [7–22]	17 [10–29]	25 [15–36]	21 [14–28]	32 [23–48]
Epinephrine doses	2 [1–3]	3 [2–4]	4 [2–6]	3 [2–5]	5 [3–7]
Target temperature					
33 °C	113 (34)	96 (53)	99 (46)	105 (50)	57 (38)
36 °C	174 (53)	61 (34)	80 (37)	81 (39)	42 (28)
Other target temperature	17 (5)	7 (4)	24 (11)	12 (6)	37 (25)
No TTM	26 (8)	17 (9)	11 (5)	11 (5)	12 (9)
Cardiac catheterization	114 (35)	30 (17)	27 (13)	27 (13)	7 (5)
Awakened from coma	216 (65)	42 (23)	18 (8)	6 (3)	1 (1)
Survived to discharge	214 (65)	43 (24)	18 (8)	13 (6)	1 (1)
Discharge CPC					
1–3	205 (62)	39 (22)	14 (6)	5 (2)	1 (1)
4 or 5	125 (38)	142 (78)	202 (94)	204 (98)	149 (99)
Proximate cause of death					
Rearrest or intractable shock	45 (14)	33 (18)	58 (27)	30 (14)	39 (26)
Brain death	3 (1)	7 (4)	22 (10)	3 (1)	55 (37)
Prior advanced directives	25 (8)	19 (11)	28 (13)	17 (8)	5 (3)
Neurological withdrawal	43 (13)	79 (44)	90 (42)	146 (70)	50 (33)
Hospital length of stay, days					
Survived to discharge	15 [9–23]	17 [12–26]	19 [11–32]	19 [15–27]	23 [23–23]
Died in-hospital (all-cause)	4 [2–9]	3 [1–5]	2 [1–4]	3 [2–5]	1 [1–2]
Died after neurological withdrawal	5 [3–9]	4 [2–6]	3 [1–5]	3 [2–5]	1 [1–2]
Clinical details on presentation					
Initial systolic blood pressure, mmHg	127 [106–147]	126 [104–150]	118 [93–142]	126 [108–144]	118 [92–141]
Initial diastolic blood pressure, mmHg	75 [60–91]	74 [57–93]	72 [53–94]	79 [64–91]	72 [51–90]
Mean MAP over 24 h, mmHg	85 [80–93]	85 [77–91]	82 [73–89]	86 [79–91]	82 [74–91]
Lactate, mmol/dL	2.7 [1.4–5.6]	4.9 [2.8–8.3]	6.7 [3.2–12]	3.5 [2.1–6.0]	7.9 [4.7–11]
Creatinine, mg/dL	1.3 [1.0–1.8]	1.5 [1.2–2.3]	1.6 [1.2–2.4]	1.3 [1.0–1.8]	1.4 [1.2–2.0]
Alanine transaminase, U/L	86 [38–171]	77 [36–189]	113 [54–258]	75 [38–144]	251 [113–573]
Aspartate transaminase, U/L	127 [54–231]	128 [57–320]	199 [86–458]	109 [62–236]	387 [198–927]
pH	7.29 [7.12–7.30]	7.23 [7.12–7.30]	7.21 [7.09–7.30]	7.27 [7.21–7.35]	7.16 [7.07–7.24]
PaO_2, mmHg	156 [104–252]	134 [89–261]	160 [93–276]	163 [95–289]	124 [93–291]

Overall, 438 (40%) patients received TTM with goal temperature 36 °C and 470 (43%) received TTM with goal temperature 33 °C (Table 1). Across clusters, 35–53% received TTM to 33 °C, 28–53% received TTM to 36 °C and there was no consistent association between cluster-level outcomes and distribution of TTM target. We found a significant interaction between cluster membership and TTM strategy in a model predicting survival with CPC 1–3 ($P = 0.01$). For cluster 3 patients, TTM to 36 °C was associated with a 3.66-fold increase in the odds of non-vegetative survival at hospital discharge (95% confidence interval (CI) 1.04–13.0, $P = 0.04$). Patient characteristics in this cluster, stratified by target temperature, were well balanced (Supplemental Table 2). Controlling for year of presentation did not significantly affect results, but recovery in this cluster was sufficiently rare to preclude full multivariable adjustment.

Time-weighted average MAP was 85 [IQR 78–91] mmHg over the first 24 h after admission and did not substantially differ across clusters. We found a significant interaction between cluster membership and mean MAP in a model predicting survival with CPC 1–3 ($P < 0.001$). For Cluster 1 patients, higher mean MAP was positively associated with outcome (OR 1.35 (95% CI 1.11–1.65, $P = 0.002$)) but mean MAP did not predict outcome in other clusters (Table 4).

Proportion receiving cardiac catheterization differed significantly across clusters (35–5%). We found a significant interaction between cluster membership and cardiac catheterization in a model predicting survival with CPC 1–3 ($P = 0.04$). Cardiac catheterization was positively associated with non-vegetative survival to discharge in all groups, but the strength of this association varied (Table 4).

Table 4 – Cluster-specific association (odds ratio) of post-arrest therapeutic interventions with outcome.

Cluster	TTM (36C vs 33C)	Cardiac catheterization	Mean MAP (per 10 mmHg)
1: Light brain injury	1.22 (0.76–1.97)	2.40 (1.48–3.90)	1.35 (1.11–1.65)
2: Poor exam, acceptable CT/EEG	0.81 (0.35–1.86)	3.07 (1.32–7.16)	1.02 (0.75–1.38)
3: Ominous exam and EEG, CT acceptable	3.66 (1.04–13.0)	5.22 (1.64–16.6)	1.04 (0.71–1.52)
4: Myoclonus and/or identical burst	3.11 (0.45–21.5)	13.8 (2.78–66.8)	0.92 (0.40–2.13)
5: Cerebral edema	0.44 (0.08–11.1)	66.2 (2.45–1788)	1.27 (0.85–1.90)

Discussion

We used unsupervised learning to define patterns of early post-arrest brain injury assessed using multiple diagnostic modalities of structure and function. Brain injury severity is the dominant determinant of outcome among patients resuscitated from cardiac arrest[24] and ongoing multimodality assessment is at the core of neurological prognostication.[25] Despite this, multimodality characterization of baseline post-arrest brain injury has not been previously described. We demonstrate that there are distinct patterns of post-arrest brain injury quantifiable on patient presentation that reflect clinically important between-patient heterogeneity not captured by a simple diagnosis of "coma." Outcomes widely vary across clusters, but we do not suggest that these data be used to support early limitations of life-sustaining therapy. Rather, the important finding in this proof-of-concept work is that initial patterns of neurological injury may be useful to personalize early resuscitative strategies such as TTM choice or hemodynamic targets.

Our agnostic approach identified clusters with characteristics that prior literature has reported as important for clinical practice: cerebral edema, highly malignant EEG, myoclonus, light coma. Estimates of the incidence of significant early post-arrest cerebral edema are variable, ranging from 10% to 50%.[26] Because early cerebral edema reflects severe primary hypoxic-ischemic injury, it expected that other modalities would also reflect devastating injury. Burst suppression with identical bursts or other highly malignant discontinuous EEG patterns are found in approximately 20–25% of post-arrest patients.[27–30] Prior studies have not well described the exam or imaging features of this subgroup, but limited data parallel our result here. Myoclonus associated with identical bursts is common.[28] A recent autopsy series suggested the midbrain and pons in these patients are often spared severe injury, making preservation of these reflexive functions on exam unsurprising.[31] Patterns of lighter injury (e.g. intact structure and function) are better described in the literature, as is the potential of patients who exhibit little function as assessed by neurological examinations or EEG to improve over time.[13,32–34]

That the association of various post-arrest interventions with outcomes (target temperature, post-arrest blood pressure, and cardiac catheterization) differed across clusters provides additional face validity. Outcomes of patients with devastating anoxic injury are unlikely to be improved with coronary revascularization (which may improve cardiovascular failure but is unlikely to meaningfully affect anoxic-ischemic encephalopathy),[35] and strategies that aim to minimize secondary brain injury are irrelevant when primary injury is irrecoverable.[36] Cerebrovascular autoregulation is often right-shifted in patients with anoxic brain injury, making hemodynamic optimization a potentially intervention to reduce secondary brain injury.[37,38] After more severe primary injury, increasing blood pressure to preserve cerebral perfusion may be insufficient to appreciably alter outcomes, or autoregulation may be absent altogether.[38] Why we observed a differential association of target temperature with outcome among patients with moderate brain injury (Cluster 3) is less clear. The association does not appear to result from measurable between-patient differences, though might reflect unmeasured confounding. Drug metabolism is reduced at 33 °C,[39] for example, delaying signs of recovery[40] and thus might increase mortality from withdrawal of life-sustaining therapies based on perceived poor neurological prognosis.

Our study has important limitations. The single center design limits broad generalizability of our results with regards to the specific incidence of each brain injury phenotype in the population at large. Because withdrawal of life-sustaining therapy for perceived poor neurological prognosis was common and was likely influenced by prognostic factors that contributed to clustering, subgroup-specific outcomes may be confounded by self-fulfilling prophecies. Likewise, the selection of diagnostic and evaluative tests in our center may bias toward identification of phenotypes defined by the worst findings from those particular tests: for example, cerebral edema and highly malignant EEG. Therapies may have been offered based on some findings that defined clusters. For example, cardiac catheterization in some cases may have been prompted by signs of neurological recovery, thereby confounding the observed association of this intervention with outcome. While this analysis focused on neurological phenotypes as proof in principle, post-arrest patients also have many non-neurological physiological derangements that might improve specification of clusters. Neurological examination and EEG findings may also be affected by sedation administration. Robust medication data were not available for analysis, so we cannot differentiate the role of medications from underlying anoxic brain injury in defining phenotypic characteristics. Finally, although we decided *a priori* which associations of treatment with outcomes to test across clusters, this aspect of our work is exploratory and should not immediately affect clinical care.

In conclusion, we identified subgroups of patients resuscitated from cardiac arrest with distinct patterns of early anoxic brain injury based on multiple diagnostic modalities. More importantly, we demonstrate the association of early injury patterns with a response to promising therapeutic interventions recently tested in neutral clinical trials. As a scientific community, we must be mindful to measure and account for between patient heterogeneity using the most rigorous approaches available. Even the best treatments are effective only when targeted to patients likely to benefit.

Declaration of interest

Dr. Elmer's research time is supported by the NIH through grant 5K23NS097629. The authors report no conflicts of interest and have no other relevant declarations.

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.2020.05.051.

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