Available online at www.sciencedirect.com

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical paper

Duration and clinical features of cardiac arrest predict early severe cerebral edema

C. Jayson Esdaille[a], *Patrick J. Coppler*[b], *John W. Faro*[c], *Zachary M. Weisner*[d], *Joseph P. Condle*[b], *Jonathan Elmer*[b], *Clifton W. Callaway*[b,*], *Pittsburgh Post Cardiac Arrest Service*

[a] *Howard University College of Medicine, Washington, DC, United States*
[b] *Pittsburgh Post Cardiac Arrest Service, Department of Emergency Medicine, University of Pittsburgh, Pittsburgh, PA, United States*
[c] *University of Cincinnati, Cincinnati, OH, United States*
[d] *Lake Erie College of Osteopathic Medicine, Erie, PA, United States*

Abstract

Background: Severe brain edema appears early after cardiopulmonary resuscitation (CPR) in a subset of patients and portends a poor prognosis. We tested whether clinical features of patients or resuscitation during out-of-hospital cardiac arrest (OHCA) are associated with early, severe cerebral edema.

Method/research design: We reviewed pre-hospital and hospital records for comatose patients surviving to hospital admission after OHCA who had computed tomography (CT) of brain at the time of hospital admission available for inspection. We measured the gray-white ratio (GWR) of X-ray attenuation between the caudate nucleus and posterior limb of the internal capsule, defining severe cerebral edema as GWR < 1.20. We calculated associations between severe cerebral edema and patient or resuscitation variables.

Results: Between 2010 and 2019, 1340 subjects were admitted of whom 296 (22%) showed severe cerebral edema on initial CT. Subjects with severe edema had lower survival (5/296, 2% vs. 377/1044, 36%). Severe edema was independently associated with total CPR duration, total dose of epinephrine, younger age, non-shockable arrest rhythms, fewer total number of rescue shocks, rearrest after initial return of pulses, and non-cardiac arrest etiology. Prevalence of severe cerebral edema increased from 2% among subjects with 0−10 min of CPR to 31% among subjects with >40 min of CPR.

Conclusion: CPR duration along with easily measurable clinical and resuscitation characteristics predict early severe cerebral edema after OHCA. Future interventional trials should consider targeting or preventing cerebral edema after prolonged hypoxic-ischemic brain injury especially in patients with high risk clinical features.

Keywords: Cerebral edema, Imaging, Prognostication

Introduction

Cardiac arrest is the sudden loss of heart function, resulting in circulatory collapse, loss of consciousness and death if untreated. Each year, out-of-hospital cardiac arrest (OHCA) affects more than 360,000 persons in the United States.[1] Rapid cardiopulmonary resuscitation (CPR) can result in restoration of spontaneous circulation (ROSC), but the majority of patients with ROSC have some neurological injury.[2] The pathophysiology of brain damage after cardiac arrest is multifactorial, involving molecular and neurovascular responses to global ischemia and reperfusion.[3] Neurological deficits range from mild cognitive impairment to persistent coma to brain death. Many patients who survive hospitalization still have neurological impairments that interfere with return to normal function.[4]

* Corresponding author at: Department of Emergency Medicine, 400A Iroquois, 3600 Forbes Avenue, Pittsburgh, PA 15260, United States.
E-mail address: callawaycw@upmc.edu (C.W. Callaway).

https://doi.org/10.1016/j.resuscitation.2020.05.049
Received 9 February 2020; Received in revised form 22 May 2020; Accepted 31 May 2020
0300-9572/

Some patients develop severe cerebral edema early after ROSC, which appears in radiographs as decreased X-ray attenuation by gray matter, sulcal effacement, and compression of the ventricles and basal cisterns.[5–10] Post-CPR cerebral edema involves translocation of vascular water into cells, but it is unclear if this precedes or follows cell death.[5,11,12] Cerebral edema within the closed skull can increase intracranial pressure, compromise cerebral blood flow, and contribute to secondary brain injury.[11] Patients with severe cerebral edema early after CPR have lower survival and worse neurological outcomes.[5]

What clinical factors increase risk of cerebral edema after cardiac arrest is unknown. Prevention of edema or initiating treatment as soon as possible would offer the best chances for improving outcomes for these patients. However, imaging or invasive monitoring to detect cerebral edema is often delayed for hours after ROSC. Therefore, we set out to identify whether any clinical features could identify patients at risk of post-ROSC cerebral edema in a cohort of OHCA patients. We hypothesized that clinical features of the patient or variables related to the resuscitation are associated with early severe cerebral edema.

Methods

We reviewed clinical data from patients who were admitted to a single hospital in Southwestern Pennsylvania after OHCA using a prospectively curated quality improvement database. The University of Pittsburgh Human Research Subjects Protection Office approved retrospective analysis of our database with a waiver of informed consent.

Subjects

We included OHCA patients admitted to the hospital who had a computed tomography (CT) scan of the brain within 24 h of hospital admission which could be inspected for cerebral edema. We chose to include subjects with cardiac arrest in the emergency department (ED) because they were outpatients at the time of arrest and their records of resuscitation were complete and comparable to EMS records. These cases include patients recognized to be pulseless upon EMS arrival at the ED. Usual care of OHCA patients after ROSC in our facility includes obtaining non-contrast CT scans of patients who are comatose after ROSC prior to transfer from the ED to the cardiac catheterization laboratory or intensive care unit.

Resuscitation data

We reviewed original emergency medical service (EMS) patient care reports, ED records, and interfacility transport reports to obtain details of resuscitation.

We recorded initial arrest rhythm as the first rhythm when EMS connected a cardiac monitor to the patient. For patients who had multiple rhythms during arrest, we recorded only the first rhythm. Ventricular tachycardia or fibrillation (VT/VF) included persons where an AED shocked the patient prior to placement of a monitor. When no recording of an initial rhythm was documented, we coded the rhythm as "unknown."

We recorded number of rescue shocks including AED shocks for each patient. When patients had multiple arrests, we included all shocks by EMS or in the ED.

In cases where the patient arrested in the presence of family members, bystanders or any individual in the general public, we recorded collapse as "layperson witnessed". If the arrest occurred in the presence of EMS, nurses or any other health care providers, we recorded collapse as "EMS witnessed". When the patient was found unconscious but collapse was not observed, then we coded collapse as "not witnessed."

If a family member, layperson, or police officer, who was not a healthcare professional performed CPR prior to EMS, then we coded as "layperson-initiated CPR." If a nurse, firefighter, EMS provider, or any other health care worker initiated CPR, we documented "professional CPR." If both a layperson and a professional performed CPR prior to EMS, we coded "professional CPR" to reflect the training highest level of rescuer. When EMS was the first to initiate CPR, we recorded that the patient did not receive any layperson CPR.

We recorded the date and time of cardiac arrest, using EMS dispatch time if arrest time was not documented. We recorded EMS CPR duration in minutes as the documented duration of CPR that the patient received from the EMS service or ED personnel. We excluded layperson CPR from EMS CPR duration. We recorded total CPR duration as EMS CPR duration plus layperson CPR duration if any. If records did not provide estimates for CPR duration with at least 5-min precision, we recorded CPR duration as missing.

We recorded most advanced airway successfully placed during CPR. Unless notes specifically stated that the airway was inserted after ROSC, we assumed that providers placed advanced airways during CPR. We coded King-laryngeal tube and laryngeal mask as a "supraglottic airway," and endotracheal tubes as "endotracheal tube". If no respiratory support was provided before ROSC, we recorded no new airway as "none." If the patient had no advanced airway placed but received positive pressure ventilation from a bag valve mask, then we recorded "bag-valve-mask". We coded all other airways, such as ventilation via a pre-existing tracheostomy, as "other". For analysis, we combined no new airway, bag-valve-mask and other into a single category ("none or other") to focus on the qualitative difference compared to procedural airways (endotracheal tube and supraglottic). Results did not differ when we considered any procedural advanced airway (endotracheal tube or supraglottic) versus "none or other," and we therefore presented airway using the three levels of "none or other", supraglottic airway, or endotracheal tube.

We recorded total doses of epinephrine (1 mg) and sodium bicarbonate (50 mEq. bolus doses, consistent with practice in our region. We did not include medications administered after ROSC in these totals.

We recorded number of rearrests as the number of times that a patient lost pulses again, requiring providers to resume CPR, after any period of having pulses.

Cerebral edema

We calculated gray-white ratio (GWR) from CT images at the level of the genu of the corpus callosum by measuring Hounsfeld Units (HU) for 1 cm^2 regions of interest in the deep gray matter (caudate) and deep white matter (posterior limb of internal capsule). GWR = HU (deep gray)/HU (deep white). Based on values for non-injured patients and previous studies,[6] we defined severe cerebral edema as GWR < 1.20.

Patient treatment and outcomes

Our facility provides a comprehensive plan of care for patients after cardiac arrest, which we described previously.[13] Key features of treatment for comatose patients include CT imaging of brain, targeted

temperature management (33 °C prior to 2014 or 36 °C, based on provider preference from 2014 onward), continuous electroencephalographic monitoring, multimodal prognostic evaluation, mean arterial pressure goals of >80 mmHg, ventilator $PaCO_2$ goals of 40–50 mmHg, and PaO2 goals of ~100 mmHg. Treatment of suspected acute coronary syndrome, regardless of coma, includes early coronary angiography when indicated.

We recorded cardiac arrest etiology adjudicated by independent abstractors using all available data for each patient, including testing performed in the hospital as described previously.[14] We noted vital status at hospital discharge (live/dead). For subjects who died in the hospital, we determined the date of death, and classified the mechanism of death as (1) rearrest, multiple organ failure, or cardiovascular collapse, (2) brain death, (3) withdrawal of life sustaining treatments (WLST) because of poor neurological prognosis, or (4) WLST for non-neurological reasons (e.g. advanced directives). Among survivors, an independent abstractor rated functional outcome at hospital discharge using modified Rankin Scale (mRS) as described previously.[15]

Data analysis

We described continuous data about the population, resuscitation variables, and outcomes using mean and standard deviation (SD) for normally distributed variables, median and interquartile range (IQR) for non-normal distributions, and percentages for categorical variables. We compared variables between groups using mean differences for continuous variables or odds ratios for categorical variables.

We tested for univariable associations of severe cerebral edema (GWR < 1.20) with patient or resuscitation variables using odds-ratios with confidence intervals. Variables that had strong associations ($p < 0.05$) with severe cerebral edema were entered into a multivariable model to determine variables with independent associations with edema. We tested for multicollinearity among variables using variance inflation factor (VIF), considering VIF > 10 as significant collinearity. We included only one of highly collinear variables in the final model: AED shocks was perfectly collinear with initial arrest rhythm; number of shocks contained more information than received shocks; total CPR duration was more complete than EMS CPR duration; bicarbonate dose varied little, favoring use of bicarbonate given; epinephrine dose contained more information than epinephrine given. For multivariable models, we dichotomized cardiac arrest etiology into cardiac and non-cardiac for simplicity. Because a neurological etiology of cardiac arrest might cause cerebral edema for reasons unrelated to global ischemia, we repeated the regression analyses excluding cases with neurological causes of cardiac arrest.

There were missing data for many variables primarily because of incomplete documentation. Thus, we conducted the multivariable regression first on cases with complete data. We then confirmed that data were not missing completely at random using Little's test. We then repeated the multivariable regression on 10 data sets in which missing values were imputed. We used chained equations for multiple imputation. We present results from both complete and imputed data.

We used Stata 16.0 (College Park, Tx) for all analyses.

Results

Among 2622 cardiac arrest patients from January 2010 to August 2019, 621 were in-hospital cardiac arrests. Of 2001 OHCA patients, 152 did not have EMS or ED records of the arrest and 456 did not have an initial CT scan of the brain for inspection (201 were awake and others had imaging outside of our system or expired prior to imaging), and 19 had CT scan artifact, contrast, or anatomy that prevented calculation of GWR. In detailed records we could not confirm that an additional 34 cases were pulseless (e.g. CPR was performed only by

Table 1 – Clinical and resuscitation features of cohort (*n* = 1340).

Variables (*n* of complete data if some data missing)	*n*	% or mean (SD)
Mean age in years (SD)		59 (17)
Female	550	41%
Witnessed collapse (*n* = 1172)		
Layperson Witnessed	583	50%
EMS Witnessed	240	20%
Unwitnessed	349	30%
Initial arrest rhythm (*n* = 1220)		
VF/VT or AED Shock Delivered	393	32%
Asystole	400	35%
PEA	427	33%
Received rescue shock ever	601	45%
AED shocks prior to ALS arrival	103	9%
Mean number of rescue shocks delivered (SD)		1.1 (1.8)
Layperson CPR (Excluding EMS witnessed) (*n* = 932)	379	41%
Total CPR duration (*n* = 1149)	1149	23 (17)
EMS CPR duration (*n* = 1136)	1136	20 (14)
Epinephrine given (*n* = 1285)	1133	88%
Mean dose in mg (SD)		3.3(2.5)
Sodium bicarbonate given (*n* = 1253)	337	30%
Mean number of 50 mEq doses (SD)		0.5 (1.0)
Most advanced airway placed during CPR (*n* = 1260)		
Endotracheal tube	726	58%
Supraglottic airway	234	19%
None or other	300	24%
Pre-hospital ROSC (*n* = 1172)	875	75%
Rearrests (*n* = 1249)	234	19%
Etiology of arrest (*n* = 1320)		
Cardiac	339	26%
Toxicological	165	13%
Respiratory	211	16%
Neurological event	44	3%
Bleeding	62	5%
Distributive/metabolic	82	6%
Multiple etiologies	417	32%
Severe cerebral edema (GWR < 1.2)	296	22%
Survived to hospital discharge	382	29%

AED – automated external defibrillator; ALS – advanced life support; CPR – cardiopulmonary resuscitation; GWR – gray white ratio; PEA – pulseless electrical activity; ROSC – return of spontaneous circulation; VF – ventricular fibrillation; VT – ventricular tachycardia;

laypersons). Thus, we included 1340 subjects whose characteristics are in Table 1. For 180 subjects, cardiac arrest occurred after arrival at the ED. The majority of subjects (916, 68%) were transferred to our facility from another hospital. CT scans were obtained a median 4.1 h (IQR 2.6–5.6 h) after cardiac arrest.

A total of 296 subjects (22%) had early severe cerebral edema on CT scan. Timing of CT scans was later among subjects with cerebral edema compared to subjects without cerebral edema (median 4.6 vs. 3.9 h, mean difference 0.5 h, 95% CI 0.1–0.9 h). GWR was negatively correlated with interval from collapse to CT scan (slope (95%CI) = −0.005 (−0.008 to −0.002)/h; $r = 0.10$) (Fig. 1).

Compared to subjects with no cerebral edema, subjects with early severe cerebral edema were younger, more often presenting with non-shockable rhythms, were less often shocked by an AED, and received fewer rescue shocks (Table 2). Subjects with cerebral edema had longer total CPR durations, more often received an advanced airway, received more epinephrine, and more often received sodium bicarbonate. Prevalence of severe edema increased from 2% among subjects with 0–10 min of CPR to 31% among subjects with >40 min of CPR (Fig. 2). There was a similar increase in prevalence of cerebral edema with cumulative dose of epinephrine (Fig. 2). Subjects with cerebral edema more often had rearrest after initial ROSC and were less likely to have ROSC prior to arrival at the hospital. The final etiology of cardiac arrest was less likely to be a cardiac cause in patients with cerebral edema.

In multivariable analysis of cases with complete data, severe cerebral edema was independently associated with younger age, non-shockable arrest rhythms, total CPR duration, total dose of epinephrine, fewer total number of rescue shocks, rearrest after initial ROSC, and non-cardiac etiology (Table 3). When all cases were included with imputed values for missing data, PEA was no longer associated with severe cerebral edema, and receiving sodium bicarbonate was associated with lower odds of severe cerebral edema. Other relationships were similar. We observed the same relationships, when we excluded cases with neurological etiologies of arrest (Supplemental table).

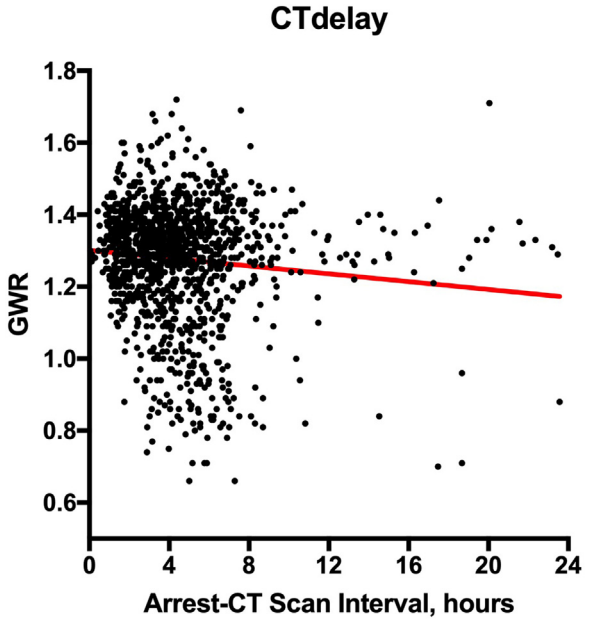

Fig. 1 – Association between time interval from cardiac arrest to CT scan and GWR. Each point represents a single subject, and the regression line is least-squares regression between the variables. GWR decreases with increasing delay until CT scan (slope (95%CI) = −0.005 (−0.008 to −0.002)/h, $r = 0.10$).

Subjects with severe cerebral edema, compared to subjects without cerebral edema, had lower survival to hospital discharge (5/296, 2% vs. 377/1044, 36%; OR 0.03, 95% CI 0.01–0.09). Subjects with cerebral edema who died in the hospital did so sooner after arrest than subjects without cerebral edema (median 1 day, IQR 1–2, vs. 3 days, IQR 1–5; $p = 0.0001$), primarily because of WLST for neurological reasons (median 1.5 days, IQR 1–3 vs. 3 days, IQR 2–6; $p = 0.0001$). Among nonsurvivors for whom circumstances of death could be adjudicated, cerebral edema was associated with higher odds of brain death (86/286, 30%, vs. 50/652, 8%; OR 4.04, 95% CI 2.46–6.63) and lower odds of WLST for non-neurological reasons (15/286, 5%, vs. 98/652, 15%; OR 0.36, 95% CI 0.19–0.68). Rearrest (57/286, 20%, vs. 134/652, 21%) and WLST for neurological reasons (128/286, 45%, vs. 370/652, 57%) were similar.

While there were too few survivors in the cerebral edema group to permit meaningful statistical comparisons, functional status at hospital discharge appeared worse among survivors with cerebral edema relative to survivors without edema: mRS 0–3 (0/5, 0%, vs.153/377, 41%), mRS 4 (2/5, 40%, vs. 136/377, 36%), mRS 5 (3/5, 60% vs. 88/377, 23%).

Discussion

CT signs of cerebral edema increase with duration of CPR and with markers of more prolonged total ischemia, which suggests that brain edema is a predictable consequence either of ischemia or of ischemia-reperfusion. We identified several other clinical features of OHCA patients that are associated with early severe cerebral edema. While it is unknown if specific treatments or modifications of resuscitation practices can reduce or prevent cerebral edema after CPR, these data help identify patients who are at higher risk for brain edema. The clinical implication is that providers should expect acute severe brain swelling in patients who require prolonged CPR.

The association of longer durations of CPR with early edema has mechanistic implications. Depolarization of neurons occurs quickly with anoxia, ischemia or substrate depletion, leading to swelling when water follows ion redistribution, particularly sodium and chloride, into the intracellular space.[11,12] Swelling of neurons, glial and perivascular cells is termed cytotoxic edema, and may be reversible if substrate is restored in less than 30 min.[16] However, these changes become irreversible with longer durations, committing cells to death.[17] Changes in extracellular ionic concentrations and disruption of vascular integrity can subsequently lead to shifts of intravascular water into the tissue in a process of ionic or vasogenic edema respectively.[18] Our data do not directly address to what extent cytotoxic, ionic, or vasogenic edema contribute to cerebral edema, but the rapid onset of cerebral edema after cardiac arrest may favor cytotoxic edema.

Cerebral edema is constrained within the intracranial space. Swelling becomes malignant when intracranial compliance is exhausted, resulting in increased intracranial pressure or herniation. This physiology accounts for our observation of a high incidence of progression to brain death among patients with early severe cerebral edema. Association of cerebral edema with younger age may reflect differences in cerebrovascular physiology or changes in water content

Table 2 – Univariable Association with Early Severe Cerebral Edema (GWR < 1.20).

Variable	No cerebral edema		Cerebral edema		Odds ratio	(95% CI)
N	1044		296			
Mean age in years (SD)	60 (16) *n* = 1044		56 (17) *n* = 296		0.99	(0.98–0.99)
Female	415/1044	40%	135/296	46%	1.27	(0.97–1.65)
Witnessed collapse	662/887	63%	161/285	54%	0.44	(0.33–0.59)
Initial arrest rhythm						
VF/VT or AED shock delivered	360/951	34%	33/269	11%	Reference	
PEA	340/951	33%	87/269	30%	2.79	(1.81–4.31)
Asystole	251/951	24%	149/269	50%	6.48	(4.18–10.0)
Layperson CPR (excludes EMS witnessed)	273/687	32%	106/245	41%	1.15	(0.86–1.55)
Shocked by AED	92/884	9%	11/284	4%	0.35	(0.18–0.66)
Mean total CPR duration in minutes (SD)	20 (14) *n* = 894		35 (19) *n* = 255		1.76	(1.60–1.95)
Mean EMS CPR duration in minutes (SD)	17 (12) *n* = 859		27 (15) *n* = 277		1.71	(1.54–1.90)
Airway management						
None or other	267/973	26%	33/287	11%	Reference	
Endotracheal tube	549/973	53%	177/287	60%	2.61	(1.74–3.91)
Supraglottic airway	157/973	15%	77/287	26%	3.97	(2.48–6.35)
Epinephrine given	847/995	81%	286/290	97%	12.5	(4.50–34.6)
Mean dose in mg (SD)	2.9 (2.3) *n* = 995		4.8 (2.6) *n* = 290		1.35	(1.28–1.43)
Sodium bicarbonate given	270/970	26%	107/283	36%	1.57	(1.19–2.08)
Mean number of 50 mEq doses (SD)	0.6 (1.0) *n* = 970		0.8 (1.2) *n* = 283		1.27	(1.13–1.43)
Rescue shocks given	476/1004	45%	78/289	26%	0.41	(0.31–0.55)
Mean number of shocks (SD)	1.2 (1.8) *n* = 1004		0.7 (1.8) *n* = 289		0.78	(0.71–0.86)
Prehospital ROSC	704/887	67%	171/285	58%	0.39	(0.29–0.52)
Rearrest	157/969	15%	77/280	26%	1.96	(1.43–2.69)
Etiology of arrest						
Cardiac	309/1029	30%	30/291	10%	Reference	
Toxicological	106/1029	10%	59/291	20%	5.73	(3.40–9.66)
Respiratory	164/1029	16%	47/291	16%	2.95	(1.78–4.89)
Neurological	25/1029	2%	19/291	6%	7.82	(3.71–16.5)
Bleeding	43/1029	4%	19/291	6%	4.55	(2.31–8.97)
Distributive/metabolic	71/1029	7%	11/291	4%	1.60	(0.76–3.34)
Multiple possible etiologies	311/1029	30%	106/291	35%	3.51	(2.48–5.48)
Cardiac etiology	309/1029	30%	30/291	10%	0.27	(0.18–0.40)

AED – automated external defibrillator; ALS – advanced life support; CPR – cardiopulmonary resuscitation; GWR – gray white ratio; PEA – pulseless electrical activity; ROSC – return of spontaneous circulation; VF – ventricular fibrillation; VT – ventricular tachycardia.

with cerebral atrophy. Alternatively, the effect of age may be related to a higher prevalence of non-cardiac etiologies among younger patients that could not be completely accounted for in statistical models.

Imaging evidence of brain edema evolves over time after ischemia.[5] It is possible that many patients without severe edema on initial CT scan developed edema later. We do not believe the mean difference of 0.5 h in time to CT scans is large enough to account for the presence or absence of early edema on the CT scans in this cohort. The association between arrest-to-CT scan interval and GWR is weak in our data, and the regression line would only explain a decrease of GWR by 0.0025 over 0.5 h (Fig. 1). It is more likely that visible edema on CT scans obtained during the first few hours after ROSC represents rapid appearance of edema among a subgroup of patients with more severe brain injury rather than the gradually increasing edema associated with post-ischemic changes in the majority of patients. We speculate that repeating CT scans at a later time point would show an even higher prevalence of cerebral edema,[5] but this would best be tested in a study of serial CT imaging within individual patients. In support of this hypothesis, a recent study found sensitivity of low GWR for predicting poor outcome did not increase in CT scans obtained 0–6 h or 6–24 h after cardiac arrest, but did increase in repeat CT scans obtained 24 h – 7 days after cardiac arrest.[19]

Whether therapeutic interventions can mitigate the effects of cerebral edema in patients is unknown. Hypertonic fluid administration to patient with OHCA is associated with improved short-term outcomes,[20] and a small, randomized controlled trial found hypertonic therapy was associated with more patients having favorable functional status at hospital discharge.[21] However, these studies did not explicitly examine signs of cerebral edema nor target patients with prolonged cardiac arrest duration. In our data, sodium bicarbonate administration, which represents a hypertonic fluid bolus, was associated with lower odds of cerebral edema in multivariate analyses, which account for the fact that this drug is usually only given late during resuscitation. Because use of sodium bicarbonate may also reflect different resuscitation practices, we cannot be sure that this is not just a chance association. Other specific interventions to prevent or treat cerebral edema have not yet been tested in humans after cardiac arrest.[11]

Our data are limited in their ability to confirm the association of early CT scan evidence of severe edema with poor outcome. These data are confounded by the fact that treating teams were aware of all

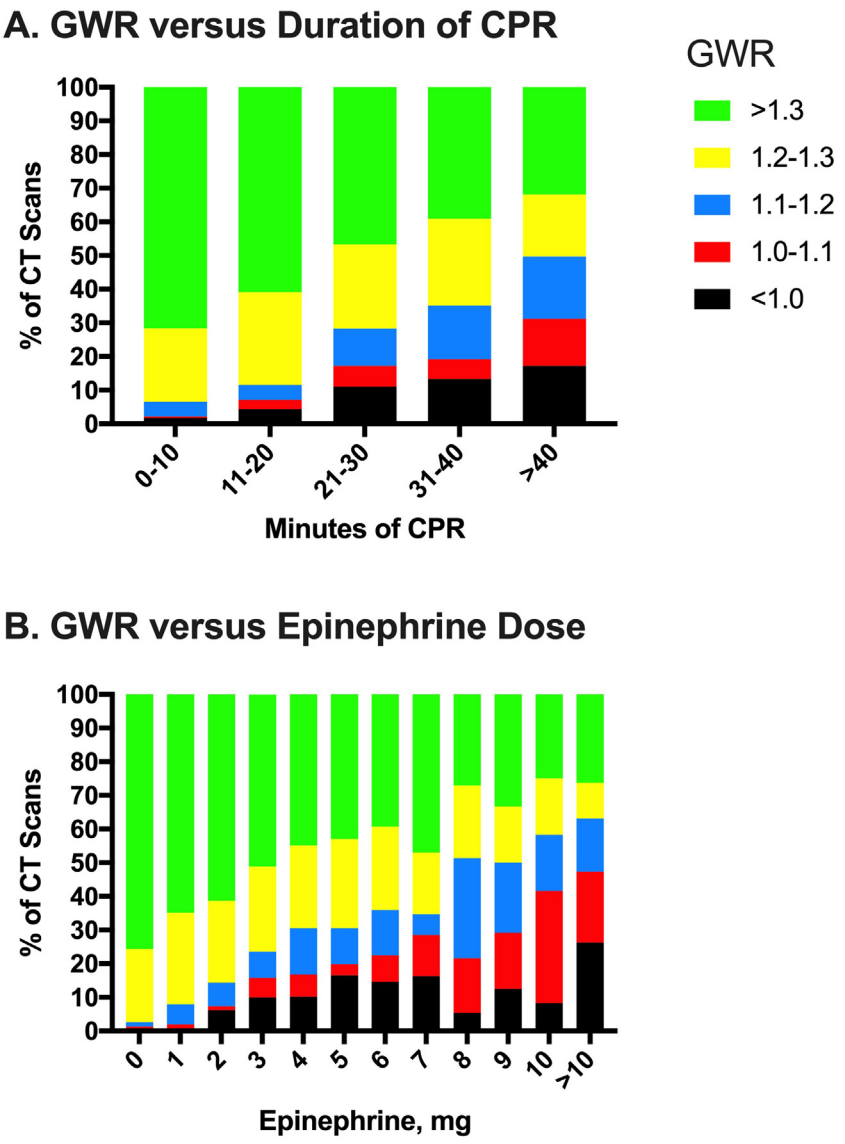

Fig. 2 – (A) GWR decreases with increasing duration of CPR. Proportion of CT scans for subjects with each GWR is depicted for 10-min bins of CPR duration. Number of subjects for each bin: 0–10 min: 186; 11–20 min: 220; 21–30 min: 181; 31–40 min: 106; >40 min: 119. (B) GWR decreases with increasing total number of epinephrine doses. Number of subjects for each dose: 0 mg: 136; 1 mg: 136, 2 mg: 216; 3 mg: 191; 4 mg: 146; 5 mg: 103; 6 mg: 77; 7 mg: 45; 8 mg: 32: 9 mg: 22; 10 mg: 8; >10 mg: 18.

CT scans, and may have altered duration of life support based on this imaging. This hypothesis is supported by the marked difference in survival time for patients who died in the hospital (median of 1 day for patients with severe cerebral edema versus 3 days for patients without severe cerebral edema). Furthermore. while all of these patients had a poor functional outcome at hospital discharge, neurological recovery continues for months after hospital discharge. Thus, true long-term outcomes are uncertain. Any potential bias due to lack of blinding probably did not influence the higher incidence of brain death among patients with early severe edema. Age, non-cardiac etiology, and prolonged CPR also are associated with risk of brain death in other cohorts.[22] Blinding also could not affect the observed associations between clinical variables and early cerebral edema.

Despite the limitations posed by lack of blinding and potential influence of scans on subsequent care, our data support the idea that severely abnormal CT scans provides some prognostic or injury-severity information about cardiac arrest patients that may be useful to clinicians. Prior studies report different thresholds for cerebral edema that represent very low chance of recovery.[5,19,23,24] These studies generally report that presence of cerebral edema or low GWR is very specific for poor neurological outcome even if not very sensitive.[19,24] In two prospective series of patients from Korea and Italy, in whom WLST was not practiced, mean GWR was lower for patients with poor outcomes than for patients with good outcomes at 6 months.[23,24] However, the Korean series did not find GWR to be an independent predictor of outcome in multivariable analysis.[23] In our series, 2% of patients with GWR < 1.2 survived, and only one patient with GWR < 1.1 survived. None of the surviving patients had good functional recovery by the end of hospitalization. Lack of perfect prediction is not surprising, given that a single measurement of GWR

Table 3 – Multivariable association with early severe cerebral edema (GWR < 1.20).

Variables		Complete case analysis (n = 894)		Include imputed data (n = 1340)	
		Odds Ratio	(95% CI)	Odds Ratio	(95% CI)
Age		0.99	(0.97–1.00)	0.99	(0.98–1.00)
Witnessed collapse		0.60	(0.41–0.88)	0.59	(0.42–0.82)
Initial rhythm	VF/VT or AED Shock Delivered	Reference		Reference	
	PEA	2.14	(1.08–4.26)	1.43	(0.82–2.51)
	Asystole	2.87	(1.47–5.60)	2.47	(1.41–4.32)
Number of rescue shocks		0.82	(0.69–0.95)	0.82	(0.71–0.93)
Total CPR duration		1.56	(1.33–1.84)	1.55	(1.34–1.70)
Airway management	None or other	Reference		Reference	
	Endotracheal tube	0.98	(0.54–1.76)	1.06	(0.65–1.70)
	Supraglottic airway	1.29	(0.67–2.49)	1.58	(0.92–2.71)
Epinephrine dose		1.16	(1.05–1.28)	1.16	(1.07–1.27)
Sodium bicarbonate given		0.84	(0.55–1.29)	0.67	(0.47–0.97)
Prehospital ROSC		0.87	(0.55–1.37)	0.78	(0.54–1.11)
Rearrest after ROSC		1.79	(1.14–2.82)	1.50	(1.02–2.22)
Cardiac etiology		0.54	(0.30–0.96)	0.46	(0.28–0.75)

AED – automated external defibrillator; CPR – cardiopulmonary resuscitation; GWR – gray white ratio; PEA – pulseless electrical activity; ROSC – return of spontaneous circulation; VF – ventricular fibrillation; VT – ventricular tachycardia.

does not take into account anatomical variation in edema and injury across the entire brain.

Conclusion

Severe brain edema on initial CT scan is associated with longer durations of CPR, younger age, non-shockable rhythms, non-cardiac etiology, and markers of more prolonged resuscitation such as epinephrine dose and rearrest. Future interventional trials should consider targeting or preventing cerebral edema after prolonged hypoxic-ischemic brain injury especially in patients with high risk clinical features.

Author contribution

C. Jayson Esdaille: investigation, writing-original draft; writing-review & editing, methodology. Patrick J. Coppler: validation, data curation, writing-review & editing. John W. Faro: investigation, methodology, validation, data curation. Zachary M. Weisner: investigation, validation. Joseph P. Condle: investigation, validation, data curation. Jonathan Elmer: methodology, formal analysis, supervision, writing-review & editing. Clifton W. Callaway: conceptualization, methodology, formal analysis, supervision, writing-review & editing, funding acquisition.

Conflicts of interest

CJE and ZW received support from NHLBI as part of an institutional training grant to the University of Pittsburgh (T32 HL134615).

JE received salary support from an NINDS career development award (K23 NS097629).

CWC has research support from NINDS to study and to conduct clinical trials in emergency care. He receives support from NCATS to support clinical and translational research at the University of Pittsburgh. He has prior patents related to defibrillation that are not currently licensed to any commercial entity.

PJC has research support from the Zoll Foundation to study cerebral perfusion after cardiac arrest.

Acknowledgements

CJE and ZMW received support from NHLBI as part of an institutional training grant to the University of Pittsburgh (T32 HL134615). JE received support from an NINDS career development award (K23 NS097629).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.resuscitation.2020.05.049.

REFERENCES

1. Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistics-2020 update: a report from the American Heart Association. Circulation 2020 Jan 29, doi:http://dx.doi.org/10.1161/CIR.0000000000000757 CIR0000000000000757.
2. Elmer J, Callaway CW. The brain after cardiac arrest. Semin Neurol 2017;37:19–24.
3. 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 Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; the Council on Stroke. Resuscitation 2008;79:350–79.
4. Cronberg T, Lilja G, Horn J, et al. Neurologic function and health-related quality of life in patients following targeted temperature management at 33 °C vs 36 °C after out-of-hospital cardiac arrest: a randomized clinical trial. JAMA Neurol 2015;72:634–41.
5. Keijzer HM, Hoedemaekers CWE, Meijer FJA, Tonino BAR, Klijn CJM, Hofmeijer J. Brain imaging in comatose survivors of cardiac arrest:

Pathophysiological correlates and prognostic properties. Resuscitation 2018;133:124–36.
6. Metter RB, Rittenberger JC, Guyette F, Callaway CW. Association between quantitative CT scan measures of brain edema and outcome after cardiac arrest. Resuscitation 2011;82:180–1185.
7. Cristia C, Ho ML, Levy S, et al. The association between a quantitative computed tomography (CT) measurement of cerebral edema and outcomes in post-cardiac arrest – a validation study. Resuscitation 2014;85:1348–53.
8. Choi SP, Park HK, Park KN, et al. The density ratio of grey to white matter on computed tomography as an early predictor of vegetative state or death after cardiac arrest. Emerg Med J 2008;25:666–9.
9. Torbey MT, Selim M, Knorr J, Bigelow C, Recht L. Quantitative analysis of the loss of distinction between gray and white matter in comatose patients after cardiac arrest. Stroke 2000;31:2163–7.
10. Lee BK, Kim WY, Shin J, et al. Prognostic value of gray matter to white matter ratio in hypoxic and non-hypoxic cardiac arrest with non-cardiac etiology. Am J Emerg Med 2016;34:1583–8.
11. Hayman EG, Patel AP, Kimberly WT, Sheth KN, Simard JM. Cerebral edema after cardiopulmonary resuscitation: a therapeutic target following cardiac arrest? Neurocrit Care 2018;28:276–87.
12. Simard JM, Kent TA, Chen M, Tarasov KV, Gerzanich V. Brain oedema in focal ischaemia: molecular pathophysiology and theoretical implications. Lancet Neurol 2007;6:258–68.
13. Rittenberger JC, Guyette FX, Callaway CW, et al. Outcomes of hospital-wide plan to improve care of comatose survivors in cardiac arrest. Resuscitation 2008;79:198–204.
14. Chen N, Callaway CW, Guyette FX, et al. Arrest etiology among patients resuscitated from cardiac arrest. Resuscitation 2018;130: 33–40.
15. Rittenberger JC, Raina K, Holm MB, Kim YJ, Callaway CW. Association between cerebral performance category, modified Rankin scale, and discharge disposition after cardiac arrest. Resuscitation 2011;82:1036–40.
16. Rumpel H, Buchli R, Gehrmann J, Aguzzi A, Illi O, Martin E. Magnetic resonance imaging of brain edema in the neonatal rat: a comparison of short and long term hypoxia-ischemia. Pediatr Res 1995;38:113–8.
17. Liang D, Bhatta S, Gerzanich V, Simard JM. Cytotoxic edema: mechanisms of pathological cell swelling. Neurosurg Focus 2007; 22:E2.
18. Hall CN, Reynell C, Gesslein B, et al. Capillary pericytes regulate cerebral blood flow in health and disease. Nature 2014;508:55–60.
19. Streitberger KJ, Endisch C, Ploner CJ, et al. Timing of brain computed tomography and accuracy of outcome prediction after cardiac arrest. Resuscitation 2019;145:8–14.
20. Hahn C, Breil M, Schewe J, et al. Hypertonic saline infusion during resuscitation from out-of-hospital cardiac arrest: a matched-pair study from the German Resuscitation Registry. Resuscitation 2014;85: 628–36.
21. Breil M, Krep H, Heister U, et al. Randomised study of hypertonic saline infusion during resuscitation from out-of-hospital cardiac arrest. Resuscitation 2012;83:347–52.
22. Cour M, Turc J, Madelaine T, Argaud L. Risk factors for progression toward brain death after out-of-hospital cardiac arrest. Ann Intensive Care 2019;9:45.
23. Hong JY, Lee DH, Oh JH, et al. Korean Hypothermia Network Investigators, Grey-white matter ratio measured using early unenhanced brain computed tomography shows no correlation with neurological outcomes in patients undergoing targeted temperature management after cardiac arrest. Resuscitation 2019;140:161–9.
24. Scarpino M, Lolli F, Lanzo G, et al. Neurophysiology and neuroimaging accurately predict poor neurological outcome within 24 hours after cardiac arrest: the ProNeCA prospective multicentre prognostication study. Resuscitation 2019;143:115–23.