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Post-anoxic quantitative MRI changes may predict emergence from coma and functional outcomes at discharge

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Abstract

Background—Traditional predictors of neurological prognosis after cardiac arrest are unreliable after targeted temperature management. Absence of pupillary reflexes remains a reliable predictor of poor outcome. Diffusion-weighted imaging has emerged as a potential predictor of recovery, and here we compare imaging characteristics to pupillary exam.

Methods—We identified 69 patients who had MRIs within seven days of arrest and used a semi-automated algorithm to perform quantitative volumetric analysis of apparent diffusion coefficient (ADC) sequences at various thresholds. Area under receiver operating characteristic curves (ROC-AUC) were estimated to compare predictive values of quantitative MRI with pupillary exam at days 3, 5 and 7 post-arrest, for persistence of coma and functional outcomes at discharge. Cerebral Performance Category scores of 3–4 were considered poor outcome.

Results—Excluding patients where life support was withdrawn, 2.8% diffusion restriction of the entire brain at an ADC of $650 \times 10^{-6} \text{ m}^2/\text{s}$ was 100% specific and 68% sensitive for failure to wake up from coma before discharge. The ROC-AUC of ADC changes at $450 \times 10^{-6} \text{ mm}^2/\text{s}$ and $650 \times 10^{-6} \text{ mm}^2/\text{s}$ were significantly superior in predicting failure to wake up from coma compared to bilateral absence of pupillary reflexes. Among survivors, >0.01% of diffusion restriction of the entire brain at an ADC $450 \times 10^{-6} \text{ m}^2/\text{s}$ was 100% specific and 46% sensitive for poor functional outcome at discharge. The ROC curve predicting poor functional outcome at ADC $450 \times 10^{-6} \text{ mm}^2/\text{s}$ had an AUC of 0.737 (0.574–0.899, $p = 0.04$).

Conclusion—Post-anoxic diffusion changes using quantitative brain MRI may aid in predicting persistent coma and poor functional outcomes at hospital discharge.

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Appendix A. Supplementary data: Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.resuscitation.2017.06.010>.

Keywords

Quantitative brain MRI; Cardiac arrest; Pupillary exam; Clinical outcomes; Coma

Introduction

Cardiac arrest can be associated with significant neurologic burden due to hypoxic-ischemic encephalopathy [1]. Prior to the ubiquitous use of targeted temperature management (TTM), clinical guidelines to predict functional outcome were widely accepted [2]. However, many predictors have been shown to have significant false positive rates in the post-TTM era. Bilaterally absent pupillary light reflexes remain predictive of poor outcome even after TTM [3–6]. More recently, diffusion-weighted imaging (DWI) sequence on magnetic resonance imaging (MRI) has emerged as a potential novel tool to predict recovery [7–11]. In this study, we investigate the utility of quantifying apparent diffusion coefficient (ADC) injury burden within the first seven days post-resuscitation using a semi-automated algorithm in predicting awakening from coma and functional outcome at discharge, and compare it to pupillary exam for the same time period.

Methods

Subjects

We retrospectively identified 460 adult cardiac arrest patients admitted to an intensive care unit at Columbia University Medical Center between January 2007 and November 2015 who remained comatose and were candidates for TTM. Post-arrest MRIs were obtained in 104 patients (22.6%), and 72 of these (69.2% with MRI) had an MRI within seven days of the arrest. One patient was excluded because of unavailability of ADC sequences, and two because of significant acute structural abnormalities, leaving 69 total scans analysed. None of the 69 patients suffered a second arrest within the seven days after index arrest. The following variables from the Utstein reporting guidelines [12] were recorded: age, sex, race, initial cardiac rhythm, whether arrest was witnessed or bystander cardiopulmonary resuscitation (CPR) administered, time to return of spontaneous circulation (ROSC), and whether TTM was used. Additional data collected included time to first MRI, withdrawal of life-sustaining therapies (WLST), and cerebral performance categories (CPC) [13] prior to arrest and at discharge. Poor functional outcome was defined as CPC of 3–5. WLST was defined as terminal extubation and/or withdrawal of vasopressors, inotropes and any mechanical circulatory assistance. Coma was defined as Glasgow Coma Scale ≤ 8 . Pupillary exams at days 3, 5 and 7 post-arrest were collected. Our TTM protocol appears in supplementary material. The Columbia University institutional review board approved the collection of these data.

MR techniques

In this retrospective study, MRI was obtained for clinical purposes at the discretion of treating attending. All MRIs were de-identified and diffusion restriction was identified on DWI 1000 sequences and volumetric analysis calculated on corresponding ADC sequences at thresholds of $450 \times 10^{-6} \text{ mm}^2/\text{s}$ and $650 \times 10^{-6} \text{ mm}^2/\text{s}$, thresholds shown to be

significant in prior studies on MRI after cardiac arrest [7,11]. Total brain volume was calculated for each subject to standardize injury burden in each patient. Information on the semi-automated algorithm, which is highly correlated with a neuroradiologist's manual technique (Pearson correlation of 0.995) [14], is available in supplementary material.

Statistical analysis

All segmented ADC volumes were expressed as percent of total brain volume [7,11]. As distributions were non-normal, medians were compared using the Mann–Whitney *U* test. Categorical variables were compared using Fisher's exact test or Pearson chi-square, as appropriate. Predictive value of pupillary exam and radiographic parameters were analysed using receiver operator characteristics (ROC) curve analysis and compared using the Hanley and McNeil method [15]. A *p* value of <0.05 was considered significant. SPSS version 23 (Chicago, IL) was used for all analyses.

Results

Patient characteristics

Of the 69 patients included, 85% had a good functional status prior to arrest and 87% successfully completed TTM. WLST occurred in 30%. Compared to 391 patients who remained comatose post-resuscitation but did not undergo MRI within the first week, these patients were younger, more likely to have good functional status prior to arrest and survive to discharge with severe disability or in comatose/persistent vegetative state (Table 1). Among patients that underwent MRI within one week of the arrest, 80% (*n* = 55) were comatose at the time the MRI was obtained and the remaining 20% (*n* = 14) were awake but not yet back to their baseline mental status. MRI was performed a median of four days after arrest (IQR 3, 6 days).

MRI diffusion abnormalities

The supplementary table lists location-specific diffusion changes. Diffusion changes were never found in the brainstem. Notably, diffusion changes in the thalamus were seen in 20% (*n* = 14) patients and were always associated with concomitant cortical and/or subcortical abnormalities. Presence of ADC changes in the thalamus at an ADC threshold of $650 \times 10^{-6} \text{ mm}^2/\text{s}$ had a 100% specificity in predicting poor outcome (CPC 3–5) regardless of WLST. Sensitivity ranged from 18% (*n* = 69) to 21% (excluding patients with WLST; *n* = 22).

Comparing MRI to pupillary exam

Among patients who were comatose at the time of MRI (*n* = 55), the median percent of total brain volume affected at both ADC 450 and $650 \times 10^{-6} \text{ mm}^2/\text{s}$ was significantly different between those who were awake versus comatose or dead at discharge (Table 2). This difference was present even when excluding 22 patients with WLST. The AUC of quantitative ADC changes at a threshold of $450 \times 10^{-6} \text{ mm}^2/\text{s}$ and $650 \times 10^{-6} \text{ mm}^2/\text{s}$ in predicting failure to wake up before discharge were 0.878 (95% CI 0.786–0.970, *p* < 0.001) and 0.884 (95% CI 0.798–0.971, *p* < 0.001), respectively. Both were significantly superior in predicting persistence of coma or death than bilaterally absent pupillary light reflexes on day

3 (0.617, 95% CI 0.420–0.813, $p = 0.316$), day 5 (0.580, 95% CI 0.374–0.786, $p = 0.482$), or day 7 (0.568, 95% CI 0.354–0.782, $p = 0.557$), ($p < 0.03$) (Fig. 1). When excluding patients with WLST, a burden of $\geq 2.8\%$ of diffusion restriction of the entire brain at an ADC of $650 \times 10^{-6} \text{ m}^2/\text{s}$ was 100% specific and 68% sensitive for failure to wake up from coma before discharge.

Among 36 survivors (52% of cohort), only MRI changes at an ADC threshold $450 \times 10^{-6} \text{ mm}^2/\text{s}$ were significantly different between those who were independent on discharge (CPC 1–2) and those who were not (CPC 3–4) (0.00% (IQR 0.000, 0.001) vs 0.01% (IQR < 0.001 , 0.093), $p = 0.04$). Among survivors, a burden of $> 0.01\%$ of diffusion restriction of the entire brain at an ADC of $450 \times 10^{-6} \text{ m}^2/\text{s}$ was 100% specific and 46% sensitive for poor functional outcome at discharge. The ROC curve predicting poor functional outcome (CPC 3–4) at the same threshold had an AUC of 0.737 (95% CI 0.574–0.899, $p = 0.04$), while ROC curves for bilaterally absent pupillary light reflexes at days 3, 5 and 7 were not statistically different from the null hypothesis.

Discussion

In this study, we found that diffusion restriction burden within the entire brain at ADC $650 \times 10^{-6} \text{ mm}^2/\text{s}$ was predictive of failure to wake up from coma. Median diffusion restriction burden at ADC $450 \times 10^{-6} \text{ mm}^2/\text{s}$ was different among survivors with good versus poor functional status. These findings are consistent with previous studies [7,11]. Notably, we used a semi-automated algorithm because of the potential for interrater disagreements [16]. Our findings were confirmed when excluding patients with WLST. Compared with pupillary exam, MRI was superior in predicting persistence of coma. Previous studies show that absence of pupillary reflex is extremely specific but only about 20% sensitive [6], which is consistent with our finding of 16% sensitivity. At 100% specificity, MRI findings had a sensitivity of 68%. It is possible that MRI may identify patients with preserved pupillary reflexes who will not wake up.

Further, we found that thalamic changes were never found in isolation. This is supported by animal studies which show regional differences in cerebral blood flow in the cortex versus thalamus both during hypoperfusion and reperfusion, suggesting the thalamus is more protected from hypoxia than the cortex [17,18]. Consistent with one animal study showing decreased neuronal apoptosis in the thalamus, cerebellum and medulla after cardiac arrest when compared with the cortex and hippocampus [19], we believe that thalamic involvement represents more severe hypoxic-ischemic injury.

There are several limitations of this retrospective study. First, the cardiac arrest literature is plagued by high rates of WLST, resulting in low numbers when analyzing functional outcome in an unbiased group and making it difficult to perform predictive analyses. An additional self-fulfilling prophecy can occur when an MRI shows significant diffusion restriction and physicians use that information to prognosticate for families. We attempted to account for this by repeating analyses while excluding patients with WLST. Second, MRIs were obtained at the discretion of treating physicians. Our data show a bias in ordering early MRIs in younger and more functional patients, perhaps reflecting more aggressive care.

Patients who remained comatose or had focal abnormalities may have been more likely to get an MRI. Additionally, patients with good exams after rewarming may not have MRIs, so the true rates of diffusion abnormalities in those with good outcome may not be accurate. Our cohort likely reflects the current practice of most of the academic centers where MRIs are not ordered routinely. Third, in this study MRIs could have been done any time within the first seven days after arrest. One case series has shown diffusion abnormalities in the post-arrest can temporally and spatially evolve over a 12 day time period [20], and perhaps MRIs done within the first seven days are not comparable to each other. Last, we do not have long-term functional or cognitive outcomes in this cohort.

Conclusion

Quantitative MRI diffusion changes within the first seven days post-arrest may be predictive of remaining in coma or functional outcomes at discharge. Thalamic changes may signify more severe hypoxic-ischemic injury.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Patient Demographics.

Characteristic	Patients with MRI within first 7 days (n = 69)	Patients without MRI in first 7 days (n = 391)	P-value
Median age, years (IQR)	60 (50, 73)	65 (55, 78)	0.03
Female sex	46% (n = 32)	46% (n = 178)	NS
Race			
White, non-Hispanic	39% (n = 27)	36% (n = 142)	NS
Black, non-Hispanic	23% (n = 16)	26% (n = 100)	
Hispanic	32% (n = 22)	32% (n = 126)	
Asian	1% (n = 1)	3% (n = 10)	
Other	0%	0.6% (n = 2)	
Unknown	4% (n = 3)	3% (n = 10)	
Pre-arrest good functional status (CPC 1–2)	85% (n = 59)	74% (n = 290)	0.04
Out-of-hospital arrest	77% (n = 53)	67% (n = 262)	NS
Witnessed arrest	84% (n = 58)	76% (n = 297)	NS
Bystander CPR	58% (n = 40)	63% (n = 248)	NS
Initial rhythm			NS
VT/VF	23% (n = 16)	22% (n = 84)	
PEA	42% (n = 29)	47% (n = 182)	
Asystole	28% (n = 19)	25% (n = 97)	
Unknown	7% (n = 5)	7% (n = 28)	
Median ROSC, min (IQR)	21 (12, 28)	35 (24, 30)	NS
TTM completed	87% (n = 60)	72% (n = 280)	<0.01
WLST	30% (n = 21)	43% (n = 168)	NS
Survival to discharge	52% (n = 36)	29% (n = 112)	<0.01
Good functional status at discharge	13% (n = 9)	15% (n = 59)	NS
CPC at discharge			
1	4% (n = 3)	5% (n = 19)	<0.01
2	9% (n = 6)	10% (n = 40)	
3	22% (n = 15)	9% (n = 35)	
4	17% (n = 12)	5% (n = 18)	
5	48% (n = 33)	71% (n = 279)	

IQR, interquartile range; CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; VT/VF, ventricular tachycardia/ventricular fibrillation; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; TTM, targeted temperature management; WLST, withdrawal of life-sustaining therapy; NS, not significant.

Table 2

Consciousness after coma.*

Characteristic	Conscious at discharge (n = 11)		Including WLST (n = 44)		Excluding WLST (n = 22)	
	Unconscious/dead at discharge	p-value, if significant**	Unconscious/dead at discharge	p-value, if significant**	Unconscious/dead at discharge	p-value, if significant**
Median age, years (IQR)	57 (47, 73)		63 (46, 73)	NS	56 (29, 63)	NS
Female sex	36% (n = 4)		45% (n = 20)	NS	41% (n = 9)	NS
Pre-arrest good functional status	82% (n = 9)		84% (n = 37)	NS	91% (n = 20)	NS
Witnessed arrest	91% (n = 10)		77% (n = 34)	NS	77% (n = 17)	NS
Out-of-hospital arrest	64% (n = 7)		86% (n = 38)	NS	95% (n = 21)	0.03
Bystander CPR	45% (n = 5)		59% (n = 26)	NS	59% (n = 13)	NS
Shockable rhythm	55% (n = 6)		16% (n = 7)	0.01	23% (n = 5)	NS
Median ROSC, min (IQR)	15 (10, 25)		25 (17, 30)	0.05	30 (18, 40)	0.02
TTM completed	82% (n = 9)		93% (n = 41)	NS	91% (n = 20)	NS
Total percent of brain involved at ADC - 450, median (IQR)	0.001% (<0.001%, 0.007%)		0.53% (0.02%, 5.15%)	<0.01	1.3% (0.01%, 17.77%)	<0.01
Total percent of brain involved at ADC - 650, median (IQR)	0.11% (<0.001%, 0.35%)		7.03% (1.68%, 21.44%)	<0.01	7.50% (1.22%, 43.42%)	<0.01

WLST, withdrawal of life-sustaining therapy; IQR, interquartile range; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; TTM, targeted temperature management; NS, not significant.

* Among 55 patients who were comatose at time of MRI.

** Compared to those conscious at discharge.