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Global and Regional Derangements of Cerebral Blood Flow and Diffusion MRI after Pediatric Cardiac Arrest

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Abstract

Objective—To quantify and examine the relationship between global and regional cerebral blood flow (CBF) and water diffusion on brain MRI in children after cardiac arrest.

Study design—Children admitted to a tertiary care children's hospital from 7/11-4/13 who received a brain MRI within 2 weeks post-cardiac arrest that included arterial spin-labeling and apparent diffusion coefficient (ADC) sequences were studied. CBF and ADC values were calculated globally and in 19 regions of interest (ROIs). Outcome variables included survival and favorable neurologic outcome, which was defined as Pediatric Cerebral Performance Category 3 at 6 months. We examined global and regional relationships between CBF and ADC, and their association with outcome.

Results—This sample included 14 pediatric patients (mean time to MRI 6 ± 4 days), 9 of whom survived and 6 who survived with favorable outcome. Global ADC was significantly decreased in patients with unfavorable outcome ($p=0.02$). Increased CBF and decreased ADC were often co-localized in the same region, especially in children who had unfavorable outcomes.

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Conclusions—In this exploratory study, global restricted water diffusion on ADC after pediatric cardiac arrest was associated with unfavorable outcome. MRI assessments of perfusion and diffusion may have prognostic value after pediatric cardiac arrest.

Keywords

Arterial spin labeling; ADC

Cardiac arrest in children, which is typically due to either asphyxia or shock, results in mortality rates ranging from 40–85% (1, 2). Neurologic dysfunction is a leading cause of death and disability in children with cardiac arrest (3). Clinical care for children following cardiac arrest is largely supportive as there are no targeted neuroprotective therapies shown to improve outcome.

Conventional modalities of brain magnetic resonance imaging (MRI) can be used in assisting with neurological prognostication, although further research into a radiologic biomarker could greatly enhance their prognostic ability (4, 5).

A study in newborns with birth asphyxia discovered that decreased apparent diffusion coefficient (ADC) values frequently occurred in regions with concurrent hyperperfusion (6). ADC is used to assess cerebral water diffusion, with low levels depicting cytotoxic cellular edema (7). Theories regarding this association between cytotoxic edema and hyperperfusion include loss of cerebral autoregulation, metabolic derangements, mitochondrial injury, and hyperglycolysis (8–11). Cerebral blood flow (CBF) is modifiable after brain injury but it is not yet known whether a specific intervention will affect outcome, particularly given that it was hyperperfusion rather than ischemia that was associated with cytotoxic edema (12, 13). Although alterations in CBF and water diffusion have individually been studied after cardiac arrest, there are no data examining the relationship between them in children after cardiac arrest (14–16).

Our objective was to perform an exploratory study on a sample of children following cardiac arrest in order to quantify global and regional CBF and water diffusion changes on brain MRI. We hypothesized that brain regions known to be vulnerable to hypoxia-ischemia and reperfusion injury would demonstrate the most noticeable derangements in CBF and water diffusion.

Methods

This was an observational study with prospective brain MRI analysis conducted at a single tertiary care pediatric hospital. The study was approved by the local institutional review board and conducted in compliance with the Health Insurance Portability and Accountability Act regulations.

We studied children ages 1 week–18 years admitted to the pediatric intensive care unit (PICU) from July 2011 to April 2013 with a diagnosis of cardiac arrest. All subjects had brain MRI including arterial spin labeling (ASL) and ADC sequences within two weeks of

resuscitation. Patients with a history of prior or simultaneous (ie, concurrent trauma) neurological injury were excluded.

Clinical Care

Patients received standard post-cardiac arrest care. Clinical goals included maintaining normotension, normoxia, normocarbica, and treatment and prevention of fever. Analgesics, sedatives, and neuromuscular blocking agents were used at the discretion of the attending PICU physician. Patients received a brain MRI when requested by the treating team as part of standard of care. Patients did not receive a brain MRI until the clinical team was comfortable with the patient's physiologic stability (ie, temperature, blood pressure, or oxygenation) and seizure-free prior to intra-facility transport.

Data Collection

Medical record review was used to collect patient demographics; disease characteristics; patient outcomes including PICU and hospital lengths of stay (LOS); arterial blood gas (ABG) within 4 hours of the MRI; and mean arterial pressure (MAP) during the scan. A pediatric cerebral performance category (PCPC) score was assigned based on chart information regarding the patients neurological functioning on the day of hospital discharge. A PCPC score of 1–3 was classified as a favorable outcome, a PCPC of 4–6 was classified as an unfavorable outcome (17).

MRI Sequences

All patients were examined with brain MRI at 3T (Signa platform; GE Healthcare, Milwaukee, Wisconsin), by use of an 8-channel head coil. Whole brain DWI was performed at $b=1000 \text{ s/mm}^2$ with 6 directions. In-plane resolution was $1.1 \times 1.1 \times 6.0 \text{ mm}^3$ with no gap. Scan time was $TE/TR=87.4/10000 \text{ ms}$. The matrix size was $256 \text{ pixels} \times 256 \text{ pixels} \times 27 \text{ slices}$. The technique used to perform perfusion ASL MR imaging has been described in detail elsewhere (18). Our vendor-supplied ASL was performed by use of a pseudocontinuous labeling period of 1500 ms, followed by a 1500-ms postlabel delay. Whole-brain images were acquired with a 3D background-suppressed FSE stack-of-spirals method, with a TR of approximately 5 seconds. Multi-arm spiral imaging was used, with 8 arms and 512 points acquired on each arm (bandwidth, 62.5 kHz), yielding in-plane and through-plane spatial resolution of 3 and 4 mm, respectively. A high level of background suppression was achieved by the use of 4 separate inversion pulses spaced around the pseudocontinuous labeling pulse. The sequence required 5 minutes to acquire, which included proton attenuation images required for CBF quantification. The sagittal image following the 3-plane localizer was used for alignment. Postprocessing was performed by use of the microsphere methodology described by Buxton et al (19). Other ASL MR imaging parameters were TR/TE, 4632/10.5; FOV, $24 \times 24 \text{ cm}$; matrix, 512×8 ; and NEX of 3.

Image Processing

DICOM images were converted to NII files using the MRI convert program; all further image processing used the MIPAV software package (NIH, Bethesda MD). ASL and ADC

scans were co-registered with a B_0 image due to its similar resolution to the ADC and ASL scans. Nineteen regions of interest (ROIs) were hand drawn onto the B_0 image and included cortical gray and white matter in each lobe (frontal, insula, parietal, temporal, and occipital), corpus callosum (genu and splenium), deep gray matter (caudate, putamen, thalamus, hippocampus, substantia nigra), cerebellar cortex, middle cerebellar peduncles, and pons (Figure 1; available at www.jpeds.com). All ROI placements were verified by an experienced board certified pediatric neuroradiologist (AP).

CBF and ADC values were quantified at each ROI. Cardiac arrest results in a global hypoxic-ischemic injury and no subjects were found to have unilateral lesions; therefore, the ROI values were averaged between hemispheres. A global average was also calculated for ADC and ASL.

Data Analyses

Data were normally distributed; hence parametric tests were used. Univariate regression analyses tested for effect on CBF and ADC results by using the following covariates: patient age, time between cardiac arrest and MRI, mean arterial pressure (MAP) during scan, and arterial blood gas (ABG) values. Pearson correlations were used to examine the relationship between CBF and ADC globally and regionally. We used the student t test to compare global CBF and ADC between outcome groups. Sample size did not allow for regional statistical analyses; however, raw data are reported. All p values were two-sided. Data analysis was performed using Stata version 11.

Results

Fourteen children (mean age 5.8 ± 6.5 years), 9 of whom survived and 6 who survived with favorable outcome were studied (Table I). All cardiac arrest events were a result of asphyxia, and 11 of the events occurred outside the hospital with subjects having 28.1 ± 13.6 minutes of cardiopulmonary resuscitation prior to return of circulation. Brain MRI was performed 6 ± 4 days after cardiac arrest. There was no relationship between age, days between cardiac arrest and MRI scan, MAP, PaO_2 , or $PaCO_2$ on global CBF or ADC values. A post hoc analysis focusing on ROIs that are most commonly injured after cardiac arrest (putamen, caudate, thalamus, and occipital white and gray matter) did find associations between days from cardiac arrest to MRI scan and with increasing ADC in occipital gray matter ($p=0.016$), decreasing CBF in occipital gray matter ($p=0.029$) and white matter ($p=0.035$), and decreasing CBF:ADC in occipital white matter ($p=0.040$) with longer times between cardiac arrest and scan.

Global Cerebral Blood Flow

Global CBF averaged 85.2 mL/100g/min, with a trend toward higher values in gray matter than in white matter. The highest CBF values were in the occipital cortex (162.7 mL/100g/min) following pediatric cardiac arrest. The gray matter region with the lowest CBF was the frontal cortex at 68.1 mL/100g/min. Global CBF values were not significantly different between outcome groups (76.8 ± 32.5 mL/100g/min favorable vs. 91.6 ± 38.9 mL/100g/min unfavorable, $p=0.47$).

Global Apparent Diffusion Coefficient

Global ADC averaged 1.12 mm²/s, with higher values found in white matter than in gray matter. The highest ADC values were in the frontal cortex (1.11 mm²/s). The lowest ADC values were in the occipito-parietal cortex, thalamus, and putamen regions (0.77 to 0.79 mm²/s). Children with unfavorable outcome had decreased ADC values globally as compared with children with a favorable outcome (0.98 ± 0.22 mm²/s vs. 1.31 ± 0.23 mm²/s, $p = 0.02$).

Relationships between CBF and ADC

Global and regional correlations of CBF and ADC are described in Table II. Globally, there was a correlation of -0.43 . Eight of the ROIs showed moderate to strong negative correlations ($r > 0.6$) between CBF and ADC, specifically in the genu, caudate, putamen, occipital gray matter, substantia nigra, and middle cerebellar peduncles. Correlations appeared to be more pronounced in children with unfavorable outcomes (Figure 3).

Discussion

We report global and regional alterations in CBF using ASL and water diffusion following pediatric cardiac arrest in a pilot ($n=14$) sample of children after cardiac arrest. Children with unfavorable outcomes after cardiac arrest show significantly decreased ADC values compared with those with favorable outcomes. There was no significant difference in global CBF between outcome groups.

Furthermore, brain regions with diffusion abnormalities consistent with cytotoxic edema frequently had concomitant increased CBF, especially in children with unfavorable outcomes. Further research in this area could uncover a pivotal biomarker for prognosis after pediatric cardiac arrest.

Brain water diffusion alterations after hypoxia-ischemia have been previously characterized. Decreased ADC (signifying cytotoxic edema) in the basal ganglia and cortical lesions on conventional MRI has been associated with unfavorable outcomes in children after cardiac arrest (14, 16). Globally decreased ADC is associated with poor outcome in adults after cardiac arrest, and was best assessed 49 and 108 hours after return of spontaneous circulation (20). We found decreased ADC in gray and white matter regions in children with unfavorable outcome, signifying cytotoxic edema. Histopathologic findings in regions with decreased water diffusion after severe hypoxia-ischemia frequently show cellular necrosis and apoptosis (21). Lesser insults may still demonstrate ADC changes, however, which may be reversible, potentially representing a therapeutic window for optimizing the cellular environment with supportive care and/or novel neuroprotective therapies.

CBF patterns after cardiac arrest have been explored. Using serial Xenon-133 brain CT, global CBF increased over 24–48 hours in adults who died following cardiac arrest. In contrast, adults who regained consciousness had relatively normal CBF for the entire duration (23). Xenon is not currently approved for diagnostic use in CT-CBF studies in children in the United States, but CBF can currently be measured using MRI with intravenous contrast agents or ASL techniques, which do not require contrast injection or

radiation exposure. In a case series that included both children (n=2) and adults (n=14) with anoxic or hypoxic-ischemic insult, global gray matter hyperperfusion measured via ASL was common at 4.6 days after insult as compared with age- matched controls, hypothesizing that the hyperperfusion was due to loss of autoregulation (14).

In an experimental model of asphyxial cardiac arrest, subcortical hyperemia appeared by 5 min post-return of spontaneous circulation using MRI ASL, with return to baseline at milder asphyxia durations by 10 min. With longer duration of asphyxia, hyperperfusion was absent, hypoperfusion was marked in the cortex, and outcomes were uniformly poor (12). In an adult rat model, CBF patterns differed by etiology. Following 8 min arrhythmia-induced or asphyxia cardiac arrest, CBF assessed with ASL displayed early hyperperfusion and delayed hypoperfusion patterns.

However, in asphyxiated animals, hyperperfusion occurred in the thalamus and cortex, and in the group with arrhythmia, this only occurred in the cortex (22). These studies thus demonstrate a propensity for cerebral hyperperfusion in the setting of asphyxial cardiac arrest. Although the duration on hyperperfusion appeared to last for a relatively short duration (on the order of minutes), there may be important differences between these experimental models and children in our study, including the severity of injury, ongoing physiological instability, and range of ages and developmental stages included for study.

Evaluating the relationship between diffusion and perfusion, Pienaar et al found strong negative correlations between CBF and diffusion abnormalities following global ischemic (n=7) or focal ischemic (n=2) events in neonates with birth asphyxia (6). We similarly found regions of increased CBF with concurrent restricted diffusion, especially in those with poor neurological outcome and in regions known to be selectively vulnerable to hypoxia-ischemia-reperfusion injury (24). Children with cardiac arrest differ from neonates with birth asphyxia in that they uniformly experience global hypoxia-ischemia and reperfusion, and the timing of reperfusion is typically identifiable. Timing is important if a clinician is employing imaging to establish evidence of a therapeutic window and for testing efficacy of interventions with repeat scanning. Given that post-cardiac arrest derangements in ADC and CBF are known to change over time, further research with prospective study design and serial imaging is needed to validate these preliminary findings.

The mechanism(s) responsible for and implications of the finding of concurrent water restriction and increased perfusion are unclear but several possibilities exist. 1) CBF is thought to be linked with the cerebral metabolic rate (CMR) in the healthy brain through neurovascular coupling (8). Therefore, children with increased CBF post-cardiac arrest may have increased CMR due to ongoing neuronal excitation, with subsequent arteriolar and/or pericyte vasodilation mediated by molecules such as adenosine, nitric oxide, or vasodilatory prostanoids (25–27). Coupled with increased glutamate uptake by astrocytes and obligate water uptake, this leads to cellular swelling. CMR, however, was not assessed in this study (28); 2) Mitochondrial injury following resuscitation results in a commensurate increase in cerebral anaerobic metabolism to support tissue demand (9) Thus, CBF could be increased in a coupled manner –driven by lactate/pH and other vasodilatory substances to meet these metabolic needs. This is evidenced by increased cerebral lactate levels seen on brain MR

spectroscopy, often lasting days to weeks in children with poor outcome after cardiac arrest (29). ADC will be decreased in regions where there is lactic acidosis as this leads to astrocyte swelling via an aquaporin-4 mechanism (30, 31); 3) Increased CBF can also occur in response to hyperglycolysis, in which increased glucose is necessary for the creation of nicotinamide adenine dinucleotide phosphate (NADPH) to counter oxidative stress as studied in traumatic brain injury (10); 4) Alternatively, CBF in injured brain regions with decreased ADC may become uncoupled to brain metabolism due to a loss of autoregulation. This could result in pathologic vasodilatation due to release of mediators such as nitric oxide from microglia and neurons (11); 5) A combination of these mechanisms may also be occurring.

Even though CBF can be modified by multiple techniques after cardiac arrest, it is unknown whether manipulation of CBF after cardiac arrest would improve outcome as it is not known whether hyperperfusion itself is harmful. CBF has been altered in experimental models as a potential therapeutic target. In one model, treatment with polynitroxyl albumin, an anti-oxidant, normalized the hyperemia which occurred 5 minutes after resuscitation. Epinephrine infusion in the same model, provided to animals with profoundly low cortical CBF caused pressure-passive global hyperemia (12, 13). Commonly prescribed ICU medications such as neuromuscular blockade and sedation agents and hyperosmolar therapy may decrease CBF (32). Other interventions that decrease CBF include mild hyperventilation ($\text{PaCO}_2 < 35 \text{ mmHg}$), which causes a reactive vasoconstriction, and hypothermia ($< 35^\circ\text{C}$), which reduces metabolic demand in the brain (33). There are no data regarding the benefit of hyperventilation or metabolic alterations in improving outcomes for pediatric cardiac arrest (5).

Our study is not without limitations. We lack ADC and CBF data from healthy control subjects. Study subjects were heterogeneous in terms of age, days to brain MRI, and outcome. Normal brain CBF and ADC values vary over development, which was not compensated for in this study. ASL data were variable within each ROI (range $> 100 \text{ mL}/100\text{g}/\text{min}$ and $\text{SD} > 50 \text{ mL}/100\text{g}/\text{min}$ in many ROIs), which could not be overcome with the small sample size, thus precluding any regional statistical analyses. PCPC score was determined by a non-blinded rater via retrospective chart review.

Despite these limitations, in this exploratory study, global restricted water diffusion on ADC after pediatric cardiac arrest was associated with unfavorable outcome. MRI assessments of perfusion and diffusion may have prognostic value after pediatric cardiac arrest.

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List of Abbreviations

CBF	cerebral blood flow
ADC	apparent diffusion coefficient

ASL	arterial spin labeling
MRI	magnetic resonance imaging
ROI	region of interest

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Figure 1.

Brain regions of interest used to quantify ADC and CBF values.

Top, First slice of B0 image showing example cortical and deep white and gray matter ROIs.

Middle, Lower slice of B0 image showing example of temporal, hippocampus, and midbrain ROIs.

C, Bottom, Lowest slice of B0 image showing example of brainstem and cerebellar ROIs.

Figure 2.

Top, Average cerebral blood flow in each examined brain region for favorable and unfavorable outcome groups. Bottom, Average ADC values in each examined brain region for favorable and unfavorable outcome groups. Error bars represent standard deviation. gm: gray matter, wm: white matter

Figure 3.

To aid in interpretation, on ADC images areas of dark gray signify restricted diffusion (cytotoxic edema), and bright regions (limited to ventricles and sulci in these cases) represent increased diffusion. On the colored ASL images, the bright orange/yellow regions demonstrate higher CBF than the blue/black regions. Top, 4-year-old child with a favorable outcome. ADC map was without focal lesions and CBF was highest in posterior gray matter, similar to published results in healthy children (34, 35) Middle, 16-year-old child with an unfavorable outcome. ADC showed decreased signal in bilateral basal ganglia and occipital lobes with concurrent hyperperfusion in these regions on the ASL map. Bottom, 3-year-old child who later died after care was withdrawn due to poor prognosis. There was restricted

diffusion throughout occipital, temporal, and parietal lobes and thalamus with corresponding increased CBF in the same regions.

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Table 1

Patient and Clinical Variables

Data presented as n (%) or mean $\pm$ SD	All subjects (n=14)	Unfavorable outcome (n=8)	Favorable outcome (n=6)	P-value
Age, yr	5.8 $\pm$ 6.5	8.7 $\pm$ 7.4	1.8 $\pm$ 1.4	0.05
Sex, male/female (%male)	7/7 (50)	5/3 (63)	2/4 (33)	0.32
CA to MRI, d	6 $\pm$ 4	6 $\pm$ 4	7 $\pm$ 4	0.63
Location of CA				0.02
IH	3 (21)	0 (0)	3 (50)	
OOH	11 (79)	8 (100)	3 (50)	
CPR to ROSC, min	28.1 $\pm$ 13.6	35.1 $\pm$ 11.9	18.8 $\pm$ 10.0	0.02
PICU LOS, d	19 $\pm$ 14	16 $\pm$ 9	23 $\pm$ 19	0.37
Hospital LOS, d	22 $\pm$ 15	18 $\pm$ 12	27 $\pm$ 19	0.28
Survival to HD	9 (64)	3 (37.5)	6 (100)	0.01
Pre-CA PCPC				0.70
1	10 (71)	6 (75)	4 (66)	
2	2 (14)	0 (0)	2 (33)	
3	2 (14)	2 (25)	0 (0)	
PCPC at HD				
1	1 (7)	0 (0)	1 (17)	
2	2 (14)	0 (0)	2 (33)	
3	3 (21)	0 (0)	3 (50)	
4	0 (0)	0 (0)	0 (0)	
5	3 (21)	3 (38)	0 (0)	
6	5 (36)	5 (63)	0 (0)	

SD: standard deviation, IH: in hospital, OOH: out of hospital, ROSC: return of spontaneous circulation, PICU: pediatric intensive care unit, LOS: length of stay, HD: hospital discharge, PCPC: pediatric cerebral performance category; CPR, cardiopulmonary resuscitation.

Table 2

Correlations between CBF and ADC for whole brain and brain regions by favorable and unfavorable outcome.

ROI	All (n=14)	Unfavorable Outcome (n=8)	Favorable Outcome (n=6)
Whole Brain	-0.43	-0.65	0.03
Genu	-0.88	-0.87	-0.89
Splenium	-0.02	-0.004	0.21
Caudate	-0.77	-0.87	-0.20
Putamen	-0.73	-0.88	0.05
Thalamus	-0.53	-0.69	0.39
Hippocampus	-0.52	-0.54	0.12
Frontal GM	-0.50	-0.45	-0.80
Frontal WM	-0.12	-0.79	0.23
Insular Cortex	-0.40	-0.39	-0.17
Temporal GM	-0.16	-0.05	-0.21
Temporal WM	-0.20	-0.12	-0.38
Parietal GM	-0.28	-0.51	-0.59
Parietal WM	-0.45	-0.63	-0.14
Occipital GM	-0.60	-0.64	-0.39
Occipital WM	-0.26	-0.47	0.74
Substantia Nigra	-0.68	-0.69	-0.27
Pons	-0.25	-0.30	-0.45
Cerebellum	-0.48	-0.27	-0.49
Middle Cerebellar Peduncles	-0.70	-0.76	-0.10

ROI: region of interest, CA: cardiac arrest, GM: gray matter, WM: white matter.