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Post-arrest Therapeutic Hypothermia in Pediatric Patients with Congenital Heart Disease

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Abstract

Background—While therapeutic hypothermia (TH) is an effective neuroprotective therapy for neonatal hypoxic-ischemic encephalopathy, TH has not been demonstrated to improve outcome in other pediatric populations. Patients with acquired or congenital heart disease (CHD) are at high risk of both cardiac arrest and neurodevelopmental impairments, and therapies are needed to improve neurologic outcome. The primary goal of our study was to compare safety/efficacy outcomes in post-arrest CHD patients treated with TH versus controls not treated with TH.

Methods—Patients with CHD treated during the first 18 months after initiation of a post-arrest TH protocol (temperature goal: 33.5°C) were compared to historical and contemporary post-arrest controls not treated with TH. Post-arrest data, including temperature, safety measures (e.g. arrhythmia, bleeding), neurodiagnostic data (EEG, neuroimaging), and survival were compared.

Results—Thirty arrest episodes treated with TH and 51 control arrest episodes were included. The groups did not differ in age, duration of arrest, post-arrest lactate, or use of ECMO-CPR. The TH group's post-arrest temperature was significantly lower than control's (33.6±0.2°C vs 34.7±0.5°C, $p<0.001$). There was no difference between the groups in safety/efficacy measures, including arrhythmia, infections, chest-tube output, or neuroimaging abnormalities, nor in hospital survival (TH 61.5% vs control 59.1%, $p=NS$). Significantly more controls had seizures than TH patients (26.1% vs. 4.0%, $p=0.04$). Almost all seizures were subclinical and occurred more than 24 hours post-arrest.

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Conflicts of Interests
None

Conclusion—Our data show that pediatric CHD patients who suffer cardiac arrest can be treated effectively and safely with TH, which may decrease the incidence of seizures.

Keywords

Pediatric Cardiology; Cardiac Arrest; Therapeutic Hypothermia; Congenital Heart Disease; Seizures; Intensive Care

Introduction

Therapeutic hypothermia (TH) has been studied as a neuroprotective therapy to minimize brain injury and improve neurologic outcome after hypoxic-ischemic encephalopathy (HIE) in several patient groups. The use of TH is well established for neonatal HIE, where it has been shown to improve both survival and neurodevelopmental outcome.[1–5] In other patient populations, TH has been utilized safely but without evidence of improved outcome. [6–9]

Given the risk of hemodynamic instability and cardiac arrest in patients with acquired or congenital heart disease (CHD), neuroprotective therapies such as TH are needed to improve neurologic outcome. However, TH in CHD patients may involve greater risk, given that adverse events such as arrhythmia and bleeding may occur more frequently in CHD patients, particularly in the post-operative period.

The primary goal of our study was to compare safety and efficacy outcomes in patients with CHD treated under a TH protocol versus a group of historical and contemporary controls not treated with TH.

Methods

A clinical TH protocol was established in August 2013 for CHD patients who sustained a cardiac arrest within the cardiovascular program at our institution. Patients were considered for inclusion in the TH protocol if they had CHD and: 1. underwent cardiopulmonary resuscitation (CPR) for greater than 5 minutes, or 2. suffered cardiac arrest that was treated with extracorporeal membrane oxygenation cardiopulmonary resuscitation (ECMO-CPR). Inclusion in the TH protocol was at the discretion of the clinical team.

Patients

After obtaining approval for this retrospective study from the institutional review board, the Cardiovascular Program cardiac arrest database was searched to identify patients for this study. Patients were included if they were treated under the TH protocol in the first 18 months of its initiation (8/2013–1/2015, TH patients). Patients were considered as treated under the TH protocol if TH orders were placed in the medical record and/or the TH protocol was included in the daily notes. A comparison control group consisted of 2 sets of patients: 1. historical control patients who met criteria for TH (CPR >5 minutes or ECMO-CPR) in the 18 months prior to initiation of the TH protocol (2/2012–7/2013), and 2. contemporary control patients who met criteria for the TH protocol in the first 18 months of

its initiation (8/2013–1/2015) but were not treated under the TH protocol, based on the management decisions of the clinical team.

Therapeutic Hypothermia Protocol

Under the TH protocol, patient temperature was targeted to be 33.5°C for either 72 hours (<1 year of age) or 48 hours (≥1 year of age). Patients <1 year of age were cooled for 72 hours based on published neonatal trials, while patients ≥1 year of age were cooled 48 hours based on the THAPCA trial.[3, 4, 8] Cooling was managed via the ECMO circuit or via cooling blanket for those not on ECMO. An esophageal temperature probe was placed for temperature monitoring. Patients were excluded from the protocol for known significant intracranial hemorrhage (large epidural, subdural, or parenchymal hemorrhage, or Grade III or IV intraventricular hemorrhage), pregnancy, or postmenstrual age <36 weeks. Sedation and paralytic medications were not specified in the TH protocol, but were administered at the discretion of the clinical team. Monitoring during cooling included a minimum of 24 hours of continuous video-electroencephalogram monitoring (cvEEG) and head ultrasound (HUS, every other day if fontanel open), and/or other brain imaging as clinically indicated. Other clinical and safety monitoring included daily electrolytes/hematologic profile, continuous telemetry, and measurement of chest tube losses (if applicable) and urine output.

Per protocol, patients were rewarmed at a rate of 0.5°C every 2 hours to a goal temperature of 36.5°C, although goal temperature was set by the medical care team.

Clinical Data

For TH patients, temperature and monitoring data were collected from time of arrest and through the rewarming period. For control patients, data were collected over a “therapeutic window” time period which paralleled the data collection time period for TH patients. The “therapeutic window” consisted of either 72 hours (<1 year of age) or 48 hours (≥1 year of age) to represent the TH time period post-arrest, plus 12 hours to represent rewarming. Thus, control patients had temperature and monitoring data collected for 84 hours post-arrest if <1 year of age and 60 hours if ≥1 year of age.

Retrospective chart reviews were completed to collect demographic, cardiac, neurologic and other clinical data at the time of cardiac arrest and through the cooling and rewarming period or “therapeutic window” in controls. Data collected included location/duration of arrest, use of ECMO-CPR, and initial lactate measured after arrest. During cooling/rewarming in TH patients and the “therapeutic window” in control patients, temperatures, urine/chest tube output, arrhythmias, cultures (blood, sputum, urine, wound), and labs were recorded. Arrhythmias during the post-arrest period were examined to determine whether they occurred prior to arrest or had new onset post-arrest, and whether they required intervention (e.g. antiarrhythmic medications, direct current cardioversion, temporary pacing).

Any temperature >38°C was considered a fever, and any temperature <32°C was considered severe hypothermia. All head imaging performed was reviewed by a single pediatric neuroradiologist (AD). All cvEEGs were performed as part of the TH protocol or for other clinical indications, and were interpreted daily for clinical management. For this study, all cvEEGs were analyzed again by a single pediatric neurophysiologist (AJS) for presence of

seizures, background features and state changes, per American Clinical Neurophysiology Society terminology.[10] The time to first seizure post-arrest was determined by the first clinical or subclinical seizure.

Statistical Analysis

Continuous measures are presented as medians and interquartile measures (P25, P75) or mean and standard deviation, as appropriate. The t-test or the non-parametric Wilcoxon rank sum test was used to test for patient-level differences between groups, as appropriate. Categorical measures are presented as counts with percentages. The Fisher's exact test was used to test for patient-level differences between groups for categorical measures. Because some patients had more than one arrest, for arrest-level comparisons, repeated measures analysis was performed with generalized estimating equations. A p-value < 0.05 was considered statistically significant. SAS software (version 9.4, SAS Institute, Cary, NC) was used for all statistical analyses.

Results

A total of 75 patients sustained 81 cardiac arrests and were included in the analysis, with 30 arrest episodes treated with TH, and 51 arrest episodes not treated with TH (35 historical, 16 contemporary).

Demographic, cardiac, and arrest data are shown in Table 1. The groups did not differ with regards to sex, age, duration of arrest, post-arrest lactate, or use of ECMO-CPR. There was no significant difference between groups in the proportion of neonates (< 28 days old) or their median gestational age at birth. The TH group had fewer patients with single ventricle than the control group (p<0.01).

Protocol Institution

Post-arrest monitoring data are shown in Table 2. Median time from end of arrest to target temperature was 1.4 hours (IQR 0.7, 3.6). During the TH window, the TH group had a mean temperature of 33.6°C (SD 0.2), which was significantly lower than the control group (34.7°C, SD 0.5; p<0.001). Patients <1 year of age were cooled for a median duration of 63.1 hours (IQR 41.3, 73.8), and patients ≥ 1 year of age were cooled for a median duration of 45.9 hours (IQR 41.0, 51.5). Figure 1 shows mean temperature for each 6-hour post-arrest period comparing TH and control episodes, separated by age < or ≥ 1 year.

Fourteen TH patients were rewarmed early or deviated from the TH protocol for the following indications: improper protocol adherence (7 patients, 4 within first 3 months of protocol), patient taken for surgery or cardiac catheterization (3), patient death (2), sinus bradycardia (1, patient remained bradycardic after rewarming), bleeding (1, patient arrested secondary to post-operative bleeding, with chest tube output similar during and after TH).

No TH patients had fevers in the post-arrest period while 2 control patients had fever (p=NS). There was no difference in severe hypothermia (<32°C) between the groups.

Safety Monitoring

There was no difference between the groups in post-arrest monitoring labs, including potassium and glucose levels (Table 2). The two groups had similar chest tube output, but TH patients had higher urine output compared to control patients ($p=0.03$).

New arrhythmias occurred during 9 TH episodes (30%) and 14 control episodes (27%, NS). The most common new arrhythmia in both TH and control patients was sinus bradycardia (Table 3).

Almost all patients were treated with antibiotics during TH time periods, and there was a higher rate of cultures collected in TH than control arrest episodes (culture rate: 87% vs 61%, $p=0.03$). There was no difference between groups in either new or any culture proven infections, with 7 TH (23%) and 5 control (10%) episodes having new culture proven infections ($p=NS$).

Neurodiagnostic Data

Pre-arrest neuroimaging was available for 19 TH (63%) and 23 control episodes (45%, NS, Table 4), with similar incidence of abnormalities between groups ($p=NS$). Twenty-eight TH (93%) and 42 control episodes (82%) underwent neuroimaging in the post-arrest period ($p=NS$, Table 4). The median time from arrest to first neuroimaging study was 0 days (IQR 0, 1) for both groups. There was a similar incidence of new post-arrest neuroimaging abnormalities in the two groups (50% vs. 55%, NS); the most frequent new imaging abnormalities were subdural hemorrhages, stroke, volume loss/encephalomalacia, and ventriculomegaly. There was no difference in the incidence of new post-arrest neuroimaging abnormalities comparing single with biventricular patients, and a borderline significance comparing those with postoperative arrest (30%) versus non-post-operative arrest (56%, $p=0.05$).

Post-arrest cvEEG monitoring was performed for 24 TH episodes (80%) and 24 control episodes (47%, $p<0.01$). (Table 5) There was a higher percentage of subjects with single ventricle in the control (52.4%) vs. TH (9.1%) groups with cvEEG monitoring ($p<0.01$), but no difference in age at arrest, arrest duration, post-arrest lactate, post-arrest pH, and use of ECMO-CPR between groups ($p=NS$). Significantly more control patients had seizures than TH patients (26.1% vs. 4.0%, $p=0.04$), all confirmed by cvEEG. There was no difference in seizure incidence between historical and contemporary controls (NS). One control patient (but no TH patients) had pre-arrest seizures treated with phenobarbital. The total dose of opioids and benzodiazepines (weight adjusted) received by both groups were similar ($p=NS$). Seizures were first noted at a median time of 56 hours (IQR 36, 78) after arrest in control patients, and during the rewarming period (73 hours after arrest) in the one 3-month old TH patient. Almost all seizures were subclinical, and 4 of 7 patients had only subclinical seizures. EEG background measures, including state changes, burst suppression, excess discontinuity and/or focal slowing, were not statistically different between the two groups, including initial cvEEG background pattern.[11, 12] All surviving patients were discharged home on anti-epileptic drugs (AEDs), with no difference between groups (Table 6).

Survival

There was no difference between TH and control patients with regard to hospital survival or post-arrest hospital length of stay for survivors (Table 2). At a median follow-up time of 26.5 months (IQR 20.5, 32.0), 15 TH patients (57.7%) remained alive, compared to 23 control patients (46.9%) at a median follow-up of 33 months (IQR 14.5, 45.5; $p=NS$).

Discussion

We have reported our experience using TH for 26 patients with CHD after 30 cardiac arrests, compared with a control group of concurrent and recent CHD patients, showing the safety and possible efficacy of TH, with reduced seizure incidence with TH. We demonstrated a significant change in temperature management and post-arrest monitoring within our post-arrest population with implementation of our TH protocol. Despite possibly increased susceptibility of CHD patients to the adverse effects of TH (especially post-operative), we did not find a significant difference between TH and control groups in potential adverse effects associated with TH such as arrhythmias, infections, electrolyte abnormalities, or bleeding. While there was no difference between groups in hospital survival or length of stay, there was a significantly lower incidence of acute post-arrest seizures in TH patients compared to controls.

We found a lower incidence of post-arrest seizures in patients treated with TH despite more frequent cvEEG monitoring in TH than control patients. These results may indicate a previously unreported benefit of TH in patients with CHD, particularly since TH trials have not employed cvEEG monitoring for all subjects, and most seizures in our study were subclinical. In the trials of TH for neonatal HIE, there was no difference in seizure occurrence (40–50%) in TH versus controls, but cvEEG monitoring was not routinely employed.[3, 4] However, studies using cvEEG monitoring showed a reduced seizure burden with TH, particularly for moderate neonatal HIE.[13, 14] The in-hospital Therapeutic Hypothermia After Pediatric Cardiac Arrest (THAPCA) trial showed no difference in seizures (~20%) between TH and control patients (many etiologies, 16% with CHD, no neonates), but again, cvEEG was not used in all subjects.[9] Two related studies from a large pediatric hospital reported cvEEG monitoring and seizures following cardiac arrest.[15, 16] In the first report of pediatric patients treated with 24 hours of TH post-arrest (no neonates, 3 with CHD), 47% of just 19 patients had seizures.[15] Interestingly, 5 patients had seizure onset at ~12–24 hours post-arrest, while 4 had onset at >24 hours, during rewarming, and all patients with seizures had burst-suppression or discontinuous background.[15] In contrast, their subsequent study of 128 post-arrest patients *not* treated with TH reported a lower incidence of seizures of just 13% for in-hospital and 20% for out-of-hospital arrest (no neonates, unclear number of CHD patients).[16] Our data showed some important differences from these two studies, in that the incidence of seizures was lower in those treated with TH than controls, seizures did not occur invariably in those with a burst-suppression or discontinuous background, and seizures had onset >36 hours post cardiac arrest. This suggests that ACNS guidelines recommending a minimum of 24 hours of cvEEG monitoring in all high risk patients is not long enough to detect seizures in patients with CHD after cardiac arrest.[10] Since such a wide range of seizure incidence in pediatric

post-arrest patients has been reported, larger studies of prolonged cvEEG monitoring in post-arrest patients are needed to determine the true seizure incidence and burden, both with and without TH treatment.

It would be particularly important to determine if TH reduced seizure burden in patients with CHD, since they are already at high risk for seizures from complications of their underlying CHD and its treatment, including intracranial hemorrhage and ischemic brain injury from decreased perfusion or thromboembolic disease. Children with CHD often have right to left shunting and undergo repeated procedures utilizing catheters and cardiopulmonary bypass that put them at risk for brain injury. The large number of risk factors for seizures in CHD patients, when added to hypoxia-ischemia from cardiac arrest, may exacerbate brain injury. [17] In addition, both presence and increased burden of seizures have been shown to worsen outcome in critically ill pediatric and CHD patients.[18, 19] Hence, it would be important to determine if seizures may be ameliorated by TH. Prospective studies employing prolonged cvEEG monitoring together with long-term neurodevelopmental outcome are needed to evaluate the possible benefit of TH on seizure burden and its relationship to neurologic outcome in patients with CHD.

The effect of TH on overall neurologic outcome has been studied in many patient populations, with varying results. While use of TH in adult cardiac arrest patients showed benefit in both survival and neurologic outcome in early studies, more recent data has shown no difference in outcome for targeted temperature control (TTC) at 36°C compared with TH at 33°C.[20–22] In contrast, trials of TH for newborns with perinatal asphyxia have consistently shown improved survival and neurodevelopmental outcome.[3–5, 23] Studies of pediatric patients (non-newborns) with cardiac arrest have not demonstrated efficacy of TH. Most notably, the THAPCA group tested TH (33°C) versus targeted normothermia (36.8°C) after both out-of-hospital and in-hospital arrests in pediatric patients.[8, 9] In both cases, there was no difference in survival or good functional outcome between the groups, although patients selected for these trials were severely ill, as eligibility criteria required dependence on mechanical ventilation with Glasgow Coma Scale <5 prior to randomization, up to 6 hours after arrest.[8, 9] Of note, 22% of patients in the in-hospital arrest trial had CHD, and subgroup analysis also showed no difference in efficacy outcomes for these patients. There was also no difference in safety outcomes between the groups with regards to infection, serious arrhythmias, use of blood products, or 28-day mortality, similar to the results from our study.

Our work has several limitations. Our data represents experience from a single institution and may not be generalizable to other populations. Our analyses are limited by small sample size and few long-term data, hence difficult to ascertain whether or not TH affects incidence of later epilepsy or neurodevelopmental outcome. Patients were not randomized and given the differences between our TH and control patients, we are unable to draw definitive conclusions about the efficacy of TH. If the control episodes had been normothermic (36±0.5°C), it's possible some adverse events would have been significantly different between groups, or added benefits of TH could have become evident. Nevertheless, the high rate of cvEEG monitoring and frequent neuroimaging studies, and detailed clinical and

laboratory data available for analysis in our cardiac arrest patients provides compelling results that deserve study in larger populations.

Conclusions

In summary, our new finding of reduced seizure incidence in CHD patients treated with TH adds new findings to the mixed results from studies of TH to improve neurologic outcome after cardiac arrest. The different apparent efficacy of TH among patients of differing ages, severity and etiologies of hypoxia-ischemia leaves open important questions regarding the use of this relatively safe neuroprotective therapy. It would be important to address whether TH reduces seizure incidence/burden and improves neurologic outcome in patients with cardiac arrest, particularly for children with more moderate than severe encephalopathy, as appears to be the case for asphyxiated newborns.

In conclusion, our data show that pediatric patients with CHD who suffer cardiac arrest can be treated effectively and safely with a TH protocol that may decrease the incidence of seizures.

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Figure 1.

Post-arrest temperatures for TH and control episodes <1yo (A) and ≥1yo (B) * $p < 0.05$ for mean temperature between TH and control episodes for specific time period TH, therapeutic hypothermia; yo, years of age

Table 1

Demographic and Medical Characteristics

	Therapeutic Hypothermia	Control	p-value
Demographics			
Number of patients	26	49	
Male (% of patients)	12 (46.2%)	33 (67.3%)	0.08
Number of arrests	30	51	
Age at arrest (mo)	6.0 (0.9, 27.4)	2.5 (0.5, 13.2)	NS
Neonates (<28days at arrest)	7 (23%)	17 (33%)	NS
Gestational age at birth [*] (w)	39.0 (37.1, 39.4, n=7)	38.4 (36.1, 39.3, n=17)	NS
Single Ventricle Circulation	4 (13.3%)	21 (41.2%)	0.01
Pre-operative/Unpalliated	0	1 (4.8%)	NS
Stage 1	1 (25%)	10 (47.6%)	
Systemic to pulmonary Shunt	1 (25%)	6 (28.6%)	
Bidirectional Glenn	0	0	
Fontan	1 (25%)	3 (14%)	
Other	1 (25%)	1 (5%)	
Two Ventricle Circulation	26 (86.7%)	30 (58.8%)	0.01
Tetralogy of Fallot	4 (15%)	5 (17%)	NS
Heart transplant	4 (15%)	0	
Cardiomyopathy	3 (12%)	2 (7%)	
Complex heterotaxy	2 (8%)	7 (23%)	
Aortic arch obstruction	1 (4%)	5 (17%)	
Other ^{**}	12 (46%)	11 (37%)	
Arrest Details			
Number of patients	26	49	
Male (% of patients)	12 (46.2%)	33 (67.3%)	0.08
Number of arrests	30	51	
Arrest duration (min)	22.0 (14.0, 40.0)	21.0 (13.0, 33.0)	NS
Post-arrest pH	7.18 (7.06, 7.30) (n=30)	7.23 (7.09, 7.35) (n=51)	NS
Post-arrest lactate	11.7 (7.1, 17.0) (n=28)	11.6 (9.2, 15.0) (n=49)	NS
Post-operative arrest ^{***}	14 (46.7%)	33 (64.7%)	NS
ECMO-CPR	18 (60.0%)	37 (72.5%)	NS
Location of Arrest			
Cardiac ICU	22 (73.3%)	43 (84.3%)	NS
Cardiac floor	2 (6.7%)	1 (2.0%)	
Catheterization lab	3 (10.0%)	2 (3.9%)	
Cardiac OR	0	3 (5.9%)	
General OR	1 (3.3%)	2 (3.9%)	

	Therapeutic Hypothermia	Control	p-value
Other	2 (6.7%)	0	

Number (%) or Median (IQR), % of arrests unless otherwise noted

* Data only for neonates

** No diagnosis with more than 2 patients

*** <30d from surgery

ECMO, Extracorporeal Membrane Oxygenation

Table 2

Temperature and Post-Arrest Monitoring

	Therapeutic Hypothermia (n=30)	Control (n=51)	p-value
Temperature Management			
Post-arrest mean temperature *			
All subjects	33.6°C (0.2)	34.7°C (0.8)	<0.001
Age at arrest <1yo	33.5°C (0.2) n=20	34.7°C (0.7) n=36	<0.001
Age at arrest ≥1yo	33.7°C (0.3) n=10	34.6°C (1.1) n=15	0.009
Patients with fever (>38°C)	0	2 (4%)	NS
Severe hypothermia (<32°C)	4 (13%)	12 (24%)	NS
Duration of TH (h)			
Age at Arrest <1yo	63.1 (41.3, 73.8) n=20	NA	
≥1yo	45.9 (41.0, 51.5) n=10		
Time from end of Arrest to TH (h)	1.4 (0.7, 3.6)	NA	
Rewarming duration (h)	7.3 (5.0, 10.0)	NA	
Temperature at rewarming end	35.6°C (35.5, 36.0)	NA	
Post-arrest Monitoring			
Potassium	3.16 (0.29)	3.37 (0.51)	0.09
Platelet count	162.03 (82.75)	135.43 (43.61)	NS
Prothrombin time	15.39 (3.33)	16.47 (4.14)	NS
Partial thromboplastin time	67.61 (35.49)	79.12 (36.70)	NS
INR	1.43 (0.28)	1.56 (0.44)	NS
Glucose	178.90 (75.19)	157.76 (65.24)	NS
Urine output (ml/kg/h)	3.6 (2.4, 5.4)	2.9 (1.3, 4.2)	0.03
Chest tube output (ml/kg/h)	1.4 (0.6, 5.3) n=17	1.8 (1.0, 2.7) n=33	NS
ECMO duration (h)	117.8 (63.3, 216.8) (n=18)	92.5 (63.2, 152.9) (n=37)	NS
Post-arrest length of hospitalization (d, for survivors)	51.5 (34.5, 78.5) (n=16)	38.0 (21.0, 57.0) (n=29)	NS
Hospital survival (% of patients)	16 (61.5%)	29 (59.1%)	NS

Number (%) or Median (IQR) or Mean (SD), % of arrests unless otherwise noted

* During cooling period for TH patients and during equivalent therapeutic window for Control patients

TH, Therapeutic Hypothermia; ECMO, Extracorporeal Membrane Oxygenation

Table 3**Arrhythmia**

	Therapeutic Hypothermia (n=30)	Control (n=51)	p-value
Episodes with any arrhythmia	10 (33%)	27 (53%)	NS
Episodes with new arrhythmia *	9 (30%)	14 (27%)	NS
Episodes with new arrhythmias requiring intervention	3 (10%)	6 (12%)	NS
New arrhythmias			NS
Sinus bradycardia	5	7	NS
Junctional escape	2	2	
1 st degree heart block	0	2	
2 nd degree heart block	0	1	
AV nodal reentrant tachycardia	1	0	
Ventricular tachycardia	1 **	0	
Junctional ectopic tachycardia	0	2	
Ectopic atrial tachycardia	0	2	
Interventions for New Arrhythmias			
Temporary pacing	2	3	NS
Antiarrhythmic medication	0	3	
Early rewarming	1 ***	0	

Number (%), % of arrests unless otherwise noted

* 2 controls episodes with 2 new arrhythmias each

** At time of redirection of care secondary to brain herniation

*** Patient rewarmed for sinus bradycardia which persisted after rewarming

Table 4**Neuroimaging**

	Therapeutic Hypothermia (n=30)	Control (n=51)	p-value *
Episodes with pre-arrest neuroimaging	19 (63%)	23 (45%)	NS
HUS	16 (84%)	18 (78%)	NS
CT	1 (5%)	4 (17%)	
MRI	2 (11%)	1 (5%)	
Time from previous neuroimaging to arrest (d)	13 (6, 157)	15 (3, 53)	NS
Episodes with previous neuroimaging abnormality (% of pre-arrest neuroimaging)	6 (32%)	9 (39%)	NS
Pre-arrest Neuroimaging Abnormalities (% of pre-arrest neuroimaging)			NS
Germinal matrix hemorrhage	0	3 (13%)	
Grade 2 GMH/TVH	0	0	
Grade 3 GMH/TVH	0	0	
Parenchymal hemorrhage	0	2 (9%)	
Subdural hemorrhage	1 (5%)	0	
Focal stroke	1 (5%)	2 (9%)	
Diffuse cerebral edema	0	0	
Diffuse hypoxic-ischemic injury	0	0	
Volume loss/ Encephalomalacia	1 (5%)	3 (13%)	
Ventriculomegaly	2 (11%)	0	
Other	1 (5%)	2 (9%)	
Episodes with post-arrest neuroimaging	28 (93%)	42 (82%)	NS
Time from arrest to neuroimaging (d)	0 (0,1)	0 (0,1)	NS
Number of neuroimaging studies per episode	1.5 (1,2)	2 (1, 3)	0.02
Head ultrasounds per episode	1 (0,2)	2 (1,2)	0.02
CT scans per episode	0 (0,1)	0 (0,1)	NS
Episodes with new imaging abnormality (% of post-arrest neuroimaging)	8 (29%)	20 (48%)	NS
New Imaging Abnormalities (% of post-arrest neuroimaging)			NS
Germinal matrix hemorrhage	1 (4%)	1 (2%)	
Grade 2 GMH/TVH	0	2 (5%)	
Grade 3 GMH/TVH	0	2 (5%)	
Parenchymal hemorrhage	2 (7%)	2 (5%)	
Subdural hemorrhage	4 (14%)	6 (14%)	
Focal stroke	4 (14%)	3 (7%)	
Diffuse cerebral edema	2 (7%)	0	
Diffuse hypoxic-ischemic injury	1 (3%)	0	
Volume loss/ Encephalomalacia	0	6 (14%)	
Ventriculomegaly	0	5 (12%)	
Other	0	3 (7%)	

Number (%) or Median (IQR), % of arrests unless otherwise noted

* based on repeated measures analysis with generalized estimating equations

GMH, germinal matrix hemorrhage; IVH, intraventricular hemorrhage

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Table 5

cvEEG Monitoring

	Therapeutic Hypothermia (n=30)	Control (n=51)	p-value
Episodes with cvEEG monitoring (% of total episodes)	25 (83%)	23 (45%)	<0.01
Pre-arrest seizures	0	1 (4%)	NS
Cardiac arrest to cvEEG start (h)	13.7 (6.1, 25.1)	28.9 (12.2, 43.2)	NS
Duration of cvEEG monitoring (h)	42.7 (33.7, 66.8)	35.0 (16.7, 80.7)	NS
Initial cvEEG Background Pattern			
Neonates * (n=5 TH, 9 control, % of neonates)			NS
Excessive discontinuity	4 (80%)	6 (67%)	
Normal	1 (20%)	3 (33%)	
Pediatric * (n=20 TH, 14 control, % of pediatric)			NS
Slow/Disorganized	17 (85%)	9 (64%)	
Discontinuous	2 (10%)	4 (29%)	
Attenuated/Featureless	1 (5%)	0	
Normal	0	1 (7%)	
Patients with excess discontinuity	9 (36%)	9 (39%)	NS
Maximum interburst interval (n=9)	8 (8,15)	20 (13,20)	NS
Typical interburst interval (n=9)	8 (8,8)	8 (8,8)	NS
Burst suppression	3 (12%)	3 (13%)	NS
No state changes	16 (64%)	17 (74%)	NS
Episodes with electrographic Seizures	1/25 (4%)	6/23 (26.1%)	0.04
Episodes with status epilepticus	1/25 (4%)	1/23(14.3%)	NS
Subjects with cvEEG Seizures	n=1 (4%)	n=6 (26%)	
Time from Cardiac Arrest to 1 st Seizure (h)	73	56 (36, 78)	NA
Age at Arrest (mo)	2.8	12.5 (0.2, 16.6)	NA
Days of electrographic Seizures	4	1 (1, 1)	NA
Electrographic seizures per day	77.0 (41.0, 130.5)	45.0 (10.0, 101.0)	NA
Total number of electrographic seizures per patient	343	55.0 (16.0, 101.0)	NA

* Neonates: <28 days old at time of arrest, Pediatric: >=28 days old at time of arrest

Median (IQR) or Number (%), % of arrest episodes with cvEEG monitoring unless otherwise noted

cvEEG, continuous video-electroencephalograms

Total dose of opioids and benzodiazepines (weight adjusted) received by both groups were similar (p=NS)

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Table 6**Treatment and Follow-up of Seizures**

Cohort	Acute AEDs*	Hospital Survival?	AEDs at Discharge	Current Status	Meds at last f/u	f/u time (mo)
TH	phenobarbital levetiracetam topiramate	yes	phenobarbital levetiracetam topiramate	Alive, focal motor onset clonic seizure disorder	levetirac etam	37
Control	levetiracetam	yes	levetiracetam	Alive, generalized non motor onset seizure disorder	levetirac etam	32
Control	phenobarbital	yes	phenobarbital	alive	none	58
Control	phenobarbital	yes	phenobarbital	deceased	phenobar bital	8
Control	phenobarbital	yes	phenobarbital	deceased	none	11
Control	phenobarbital levetiracetam fosphenytoin midazolam**	no	NA	deceased	NA	NA
Control	levetiracetam fosphenytoin	no	NA	deceased	NA	NA

* AEDs listed in order of their treatment initiation

** Patient continued to seize on 3 AEDs and midazolam increased to aid with seizure control

AED, anti-epileptic drug; TH, therapeutic hypothermia; f/u, follow-up