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Early Heart Rate Variability and Electroencephalographic Abnormalities in Acutely Brain-Injured Children Who Progress to Brain Death

Juan A. Piantino, MD¹, Amber Lin, MS², Daniel Crowder, MD¹, Cydni N. Williams, MD³, Erick Perez-Alday, PhD⁴, Larisa G. Tereshchenko, MD, PhD⁴, Craig D. Newgard, MD, MPH²

¹Department of Pediatrics, Division of Child Neurology, Doernbecher Children's Hospital, Oregon Health and Science University, Portland, OR.

²Center for Policy and Research in Emergency Medicine, Department of Emergency Medicine, Oregon Health and Science University, Portland, OR.

³Department of Pediatrics, Division of Pediatric Critical Care, Doernbecher Children's Hospital, Oregon Health and Science University, Portland, OR.

⁴Department of Medicine, Knight Cardiovascular Institute, Oregon Health and Science University, Portland, OR.

Abstract

Objectives: Heart rate variability is controlled by the autonomic nervous system. After brain death, this autonomic control stops, and heart rate variability is significantly decreased. However, it is unknown if early changes in heart rate variability are predictive of progression to brain death. We hypothesized that in brain-injured children, lower heart rate variability is an early indicator of autonomic system failure, and it predicts progression to brain death. We additionally explored the association between heart rate variability and markers of brain dysfunction such as electroencephalogram and neurologic examination between brain-injured children who progressed to brain death and those who survived.

Design: Retrospective case-control study.

Setting: PICU, single institution.

Patients: Children up to 18 years with a Glasgow Coma Scale score of less than 8 admitted between August of 2016 and December of 2017, who had electrocardiographic data available for heart rate variability analysis, were included. Exclusion criteria: patients who died of causes other than brain death. Twenty-three patients met inclusion criteria: six progressed to brain death (cases), and 17 survived (controls). Five-minute electrocardiogram segments were used to estimate heart rate variability in the time domain (sd of normal-normal intervals, root mean square successive differences), frequency domain (low frequency, high frequency, low frequency/

Interventions: None.

Measurements and Main Results: Patients who progressed to brain death exhibited significantly lower heart rate variability in the time domain, frequency domain, and Poincaré plots ($p < 0.01$). The odds of death increased with decreasing low frequency (odds ratio, 4.0; 95% CI, 1.2–13.6) and high frequency (odds ratio, 2.5; 95% CI, 1.2–5.4) heart rate variability power ($p < 0.03$). Heart rate variability was significantly lower in those with discontinuous or attenuated/featureless electroencephalogram versus those with slow/disorganized background ($p < 0.03$).

Conclusions: These results support the concept of autonomic system failure as an early indicator of impending brain death in brain-injured children. Furthermore, decreased heart rate variability is associated with markers of CNS dysfunction such as electroencephalogram abnormalities.

Keywords

brain death; children; electroencephalogram; heart rate variability

Introduction

Critical neurologic disease, including infectious/inflammatory disease, traumatic brain injury (TBI), stroke, hypoxic-ischemic injury, and seizure, affects thousands of children annually and accounts for 20% of PICU admissions (1). Early prognostication in this population is difficult, but mortality is substantially higher than other PICU populations and is often secondary to brain death.

In healthy individuals, heart rate variability (HRV) reflects the autonomic nervous system's control of the heart rate (2–4). The balance between the sympathetic and parasympathetic systems is the main determinant of HRV (3, 5, 6). Decreased HRV has been documented in various critical illnesses, both in children and adults, including sepsis (7–10), infant respiratory distress syndrome (11), and neonatal hypoxic-ischemic encephalopathy (12). Acute intracranial lesions cause significant decrease of HRV, likely due to dysfunction of the cerebral influence on cardiac activity mediated by the vagus nerve (13–15). Significant reduction in HRV has been documented in adults and children following brain death (15–18). Despite the findings, whether early HRV could be used to potentially predict children who progress to brain death (prognostication) remains to be determined.

Our first goal was to assess whether HRV measures obtained early in the clinical course predict progression to brain death in children with acute brain injury, accounting for use of typical critical care medications (sedation, cardioactive medications) and presence or absence of brainstem reflexes. Our second goal was to compare HRV with electroencephalogram (EEG) markers of CNS dysfunction. We hypothesized that early measures of HRV are associated with brain death and may provide early prognostication.

MATERIALS AND METHODS

Study Design

This investigation was a retrospective case-control study. The Institutional Review Board approved this protocol and waived the requirement for informed consent.

Study Setting

This study was conducted at Doernbecher Children's Hospital in Portland, Oregon. Doernbecher is an accredited level I pediatric trauma center with 145 beds, including a 25-bed PICU, over 65,000 inpatient admissions, and 130 PICU admissions due to TBI per year.

Patient Population

We included patients 0–18 years old admitted to the PICU at Doernbecher Children's Hospital between August 1, 2016 (date of initiation of the Pediatric Neurocritical Care Outcomes Program electronic database), and December 31, 2017 (last date available on the database), who had a Glasgow Coma Scale (GCS) score less than 8 from all causes and had either 1) continuous EEG plus electrocardiogram (ECG) monitoring recorded and available for analysis or 2) continuous ECG monitoring recorded and available for analysis. The Pediatric Neurocritical Care Outcomes Program was created as a collaboration between PICU, Child Neurology, and Neuropsychology. Patients with acute brain injury are identified in the PICU and enrolled in the program. They receive a neuropsychologic assessment during their hospitalization, and they are followed up at a multidisciplinary clinic after discharge. Data about injury severity, etiology, and hospital length of stay are collected in a database. In addition, outcome measures such as the Pediatric Quality of Life, Glasgow Outcome Scale score, and Patient-Reported Outcomes Measurement Information System measures are obtained at follow-up.

The primary aim of this study was to compare patients who progressed to brain death versus those who survived. For that reason, patients who received EEG monitoring but died due to cardiac arrest were excluded from the primary analysis. There were five of those patients, four died of cardiac arrest after withdrawal of support, and one died of sudden cardiac arrest. Patients with poor quality/uninterpretable ECG tracings ($n = 1$) were also excluded from analysis. Patients who met inclusion criteria were divided into those who died due to brain death (cases, $n = 6$) and those who were discharged alive from the PICU (controls, $n = 17$). Of note, all the patients who were discharged alive from the PICU were alive at hospital discharge.

Variables

HRV Analysis.—The ECG signal was obtained while patients were lying supine in the ICU bed. Data were collected at the time of the worst GCS during the PICU stay, as documented in the Electronic Medical Record. ECG was measured using the XLTECH apparatus (XLTECH, Pleasanton, CA), with a sampling frequency of 250 Hz. In the two patients who did not undergo EEG, ECG was directly recorded from the bedside monitor (Phillips Intellivue MX800; Phillips, Bothell, WA), using Medicollector Bedside (Medicollector, Boston, MA), and also recorded at 250 Hz sampling frequency. A chest lead with good quality and strong R-wave amplitude was chosen for the HRV analysis. In patients with multiday studies, segments were chosen based on the patient's worst GCS score. If several hours of HRV data were available, three 5-minute segments 1 hour apart were saved for analysis. The ECG data were analyzed using Kubios software (Biosignal Medical Group, Kuopio, Finland) (19, 20).

The techniques and methods used to analyze HRV, in accordance with published guidelines, are briefly described below (21). A more detailed description can be found elsewhere (19). The R-wave peaks and R-to-R intervals (noted as RR) were first detected using an automated QRS detection algorithm. These data were manually inspected for potential ectopic beats. The resulting intervals are known as “the normal-to-normal (NN) intervals”. Once the NN intervals were obtained, linear HRV variables in the time and frequency domain, as well as nonlinear indexes including Poincaré plots and approximate entropy (ApEn), were performed (Table 1). Time domain variables included the mean value of the NN intervals, the sd of the NN intervals (SDNN), and the root mean square of successive NN interval differences (rMSSD). Frequency domain analysis was performed using fast Fourier transformation. The resulting heart rate spectra were quantified under two components: low frequency (LF: 0.04–0.15 Hz) and high frequency (HF: 0.15–0.4 Hz) power, as well as LF/ HF ratio. Values with skewed distribution were log-transformed.

EEG Monitoring and Scoring of EEG Background Abnormalities.—EEG monitoring was performed using continuous closed-circuit television/EEG recording using a digital recording apparatus (XLTECH). EEG electrodes were placed using the 10–20 international system conventions. Electrode impedance was maintained below 5K Ohms. Electrodes and scalp integrity were checked on a daily basis at a minimum. All the EEG recordings were interpreted by a pediatric neurophysiologist using remote real-time access for EEG review. EEGs were reviewed immediately after the initiation of the study, at 30–60 minutes, and intermittently every 2–3 hours thereafter. EEGs were analyzed using the American Clinical Neurophysiology Society standardized Critical Care EEG terminology (22). The overall EEG background was scored by categories as follows: 1) normal (including sedated sleep), 2) slow disorganized, 3) discontinuous or burst suppression, and 4) featureless. Previous publications of EEG monitoring in critically ill children have validated this categorical system (23–26).

Demographic and Clinical Data.—Electronic medical records were used to retrieve demographic and clinical data, which included age, gender, primary diagnosis, GCS, imaging data (including head CT or brain MRI), date and time of death (when applicable). Medications were recorded and divided into neurologic medications (i.e., sedatives such as fentanyl, midazolam, and pentobarbital), nonsedating anticonvulsants, and cardiac medications, (e.g., dopamine, epinephrine, nor-epinephrine, phenylephrine, and milrinone).

Outcomes

The primary outcome for this study was brain death, as determined according to published criteria, that is, two examinations and apnea testing, separated by a period of at least 12 hours (27). EEG monitoring was discontinued before this declaration and was not used to determine brain death. Only data preceding the first brain death examination were used to estimate HRV. The period between the first and second brain death examination does not necessarily represent progression and therefore was not used in the analysis. Ultimate outcome (i.e., outcome on PICU discharge) was also documented.

Statistical Analysis

We performed bivariate analyses of all data by case-control status, including HRV and EEG measures using *t* tests for continuous data, Wilcoxon two-sample test for ordinal data, and Fisher exact correction for chi-square tests for categorical data. We also examined HRV values by EEG category (slow disorganized vs discontinuous/attenuated featureless). We performed univariate logistic regression of HRV measurements to determine odds of progression to brain death for each HRV measurement. Data are reported as odds ratios (ORs) with 95% CIs. Because the range of GCS values for cases was restricted to GCS score equals to 3, we performed a sensitivity analysis in which we only included patients with a GCS score of 3 with and without brain death.

RESULTS

Twenty-three patients met inclusion criteria (six cases and 17 controls). The characteristics of the cohort are presented in Table 2. All controls were alive at the time of PICU discharge. Average time from PICU admission to capture of first EEG and ECG (for HRV analysis) was 1 day in cases (range, 0–3 d) and 1.6 days in the controls (range 0–6 d; *p* for comparison = 0.29).

Traumatic and anoxic brain injury were the predominant etiologies among both groups. There was no difference in median GCS between the two groups (median GCS for the brain death group was 3 [range 3–3]; median GCS for the no brain death group was 3 [range 3–7]; *p* = 0.08). There was a higher percentage of controls receiving sedation with fentanyl (0% cases vs 82.4% controls; *p* < 0.01) and midazolam (33.3% cases vs 82.4% controls; *p* = 0.05). More cases were on epinephrine than controls (66.7% cases, 5.9% controls; *p* < 0.01). There were no significant differences in age, gender, etiology, imaging results. Clinical characteristics, including neurologic examination, EEG, and HRV data, are presented in Table 3. Additionally, the timing of worst GCS, loss of brainstem reflexes, first and second brain death examinations, and physiologic data (EEG and HRV) for each individual patient are presented in Supplementary Figure 1.

Four of six children in the brain death group and all in the nonbrain death group had brainstem reflexes present at admission. At the start of the HRV analysis, brainstem reflexes were absent in all but one child in the brain death group (brain death group, patient 23 [Supplementary Fig. 1, Supplemental Digital Content 1, <http://links.lww.com/PCC/A788>]). This child had sluggish pupils, which became unreactive after the last HRV measurement, and preceding the brain death examination. In all but one case of brain death, GCS score of 3 was documented 12–24 hours preceding the lowest documented HRV. The first brain death examination was performed within 24 hours of the lowest documented HRV in all cases.

Patients who died of causes other than brain death (*n* = 5, four with cardiac arrest in the setting of withdrawal of support, and one with an unexpected cardiac arrest) were excluded from the primary analysis. Clinical characteristics, EEG, and HRV data of these patients are presented in Supplementary Figure 2 and Supplementary Table 1

HRV Analysis

Cases had a significantly higher heart rate (cases: 142 beats/min; controls: 102 beats/min; $p < 0.01$). Measures of HRV in the time domain (rMSSD and SDNN), frequency domain (LF power [log], HF power [log], LF/HF ratio), and Poincaré analysis (sd1 and sd2) showed more than a 10-fold decrease in HRV in cases compared with controls ($p < 0.01$) (Table 3). These differences remained significant even when only controls with GCS score of 3 were included ($n = 10$; $p < 0.03$; data not shown). Analysis of ApEn showed no significant differences between the two groups.

Logistic regression results indicated that there was a significant increase in odds of death related to a decrease in LF and HF power (Table 4). For every one point decrease in LF power, the odds of death increased by 4 (OR of death, 4.0; 95% CI, 1.2–13.6; $p = 0.03$). For every one point decrease in HF power, the odds of death increased by 2.5 (OR of death, 2.5; 95% CI, 1.2–5.4; $p = 0.02$). When only controls with GCS score of 3 were included in the analysis, HF power remained statistically significant ($p = 0.03$) (Supplementary Table 2, Supplemental Digital Content 4, <http://links.lww.com/PCC/A791>). We were not able to perform multivariable logistic regression to control for patient characteristics due to small sample size.

Examples of Poincaré plots obtained from a child who progressed to brain death, and another one who survived are shown in Figure 1. The three plots in each row represent 5-minute samples, obtained over a 3-hour period of worst documented GCS. Figure 1D shows HRV data obtained at 7 am, the patient was declared brain dead the following day at 2 am. As the patient GCS decreases, and the EEG gradually progresses to an attenuated featureless pattern, ECG variability decreases, with points gradually approximating the center of the plot. In Figure 1F, HRV falls below the sampling frequency of the ECG acquisition software (250 Hz), creating a linear artifact (box). Of note, no patient with this linear pattern shown persistently throughout the monitoring period survived. This pattern is not seen in any of the segments analyzed in the nonbrain death group. The timing of appearance of this linear pattern is noted in Supplementary Figure 1.

EEG Analysis

EEG was obtained in 21 patients (four cases and 17 controls). Cases were more likely to have discontinuous or attenuated featureless EEG background than controls (Table 3; and Supplementary Fig. 1). A temporal analysis of HRV and EEG (Supplementary Fig. 1) shows that in all but one brain death case, the EEG remains attenuated/featureless, whereas HRV shows increasingly lower values. Table 5 shows different HRV measures in patients with severe encephalopathy (discontinuous or attenuated featureless EEG background) versus those with mild-moderate encephalopathy (slow disorganized EEG background). Time domain HRV measures (SDNN, rMSSD), frequency-domain (LF power, HF power) and Poincaré plots (sd1, sd2) are all significantly lower in the patients with discontinuous or attenuated featureless EEG background. Median RR interval, ApEn, and LF/HF ratio are not significantly different among the two groups.

DISCUSSION

In this single-center, retrospective case-control study, we demonstrate that HRV is significantly decreased early in critically ill children who progressed to brain death, compared with a control group of comatose children who survived. In addition, we showed that certain patterns of HRV seen using Poincaré plots, such as a linear clustering artifact due to HRV falling below the sampling frequency of the bedside ECG monitor, are highly associated with progression to brain death.

Modulation of the HRV is achieved mainly through the sympathetic and the parasympathetic systems (2). Assessment of HRV, including linear (time and frequency domain) and non-linear (Poincaré plots and ApEn) analysis, provide information about the balance between these two opposing systems (12, 15, 28). Frequency-domain analysis uses fast Fourier transform to assess the power across the frequency spectrum (21). Very LF power is modulated by neuroendocrine activity. Vagal activity is the major modulator of the HF power, whereas LF power is influenced by both sympathetic and parasympathetic tone (21). In adults, time domain HRV analysis has revealed significant differences in autonomic function between comatose and brain dead patients (16, 29, 30). In brain dead patients, only residual HRV was detected at the respiratory frequency. This residual activity, not modulated by the autonomic system, was thought to be the result of phasic changes in the sinus pressure caused by the ventilator (16).

These earlier studies of HRV in brain death are limited by the lack of documentation of sedation status, presence or absence of brainstem reflexes, and the lack of use of more sophisticated nonlinear HRV analysis. One of these more novel, nonlinear HRV analysis, that is, the Poincaré plot, provides a visual representation of the interaction between the sympathetic and the parasympathetic activity (28, 31, 32). As both sympathetic and parasympathetic autonomic activities decrease, the points in the plot tend to converge around the center. Although Poincaré plots have been used to assess HRV in anesthetized patients (28), to our knowledge, they have not been used to study critically ill children.

Our findings are in agreement with the previous literature and expand our understanding of decreased HRV as a predictor of brain death in children by including sedation status, use of cardiac medications, neurologic examination, and assessment of CNS function through EEG. In healthy individuals, both branches of the autonomic system are balanced. In our study, as patients approach brain death, there is progressive autonomic nervous system failure. During this process, HRV variables mostly determined by vagal tone such as the HF power and sd1 decrease significantly. The extent of sympathetic dysfunction is harder to assess, as there are no HRV variables purely modulated by sympathetic activity. A possibility is that, as patients approach brain death, brainstem-mediated parasympathetic tone decreases. The balance is therefore tilted toward a predominantly spinal cord-mediated sympathetic tone. Another possibility is that both branches of the autonomic system become impaired, and as patients progress to brain death, the cardiac activity starts resembling that of a denervated heart. In a study by Goldstein et al (15), the authors found significantly decreased levels of catecholamines in brain dead children, which supports the denervated heart hypothesis.

It is now well known that benzodiazepines, thiopental, and propofol significantly decrease HRV (18). In our series, controls, not cases, were more likely to be sedated with fentanyl and midazolam. This reflects an effort to minimize sedation in patients with acute brain injury, thus avoiding any confounding in their neurologic examination. Therefore, our findings argue against the observed HRV differences being a result of sedation status. In our series, more cases were on epinephrine than controls. There was, however, no difference in any other cardiovascular medication among groups. The expected effect would be a decrease in the parasympathetic tone, in favor of a sympathetic drive. Our observations indicate a decrease in both sympathetic and parasympathetic tone in patients who progressed to brain death. This, again, makes medication effects less likely. Poincaré plots were significantly different among the two groups, indicating that nonlinear analysis may be a useful tool to assess HRV in this population. Furthermore, the plots offered an easy-to-interpret visual estimation of HRV, which could be used in real-time HRV analysis. The appearance of a linear clustering artifact on Poincaré plots was only seen in the brain death group. Of note, our analysis is limited to the times patients were monitored on EEG. It is possible that, in survivors, this pattern appeared at other times. These findings warrant further investigation. Interestingly, of all the HRV variables analyzed, ApEn was not different between groups. This could be due to small sample size or it could suggest that ApEn is a less sensitive marker of autonomic dysfunction than the more commonly used HRV variables.

The presence of low HRV preceded the first brain death examination for up to 12 hours. These findings suggest that autonomic failure may be viewed as an early physiologic marker of impending brain death. The diagnosis of pediatric brain death requires two examinations and two apnea tests separated by an observation period of 12 hours for children greater than 30 days old (33). In addition, the brain death examination is often delayed to allow parents to cope with this devastating diagnosis. In this situation, analysis of HRV may be used as an early physiologic marker, allowing physicians and family members time to prepare for an imminent poor outcome.

Our study shows a strong association between low HRV and a featureless, discontinuous EEG background. Although sensitive at detecting abnormal cerebral electrical activity, the EEG background changes in the presence of sedatives. Our data show how, in patients who progress to brain death, there is a temporal progression of HRV, even in the background of a seemingly unchanging, featureless EEG. HRV and EEG provide dynamic information about the integrity of two different components of the nervous system, namely the cortex and the autonomic system. Combining HRV with EEG findings may inform the treating physician in real time about changes in both systems, particularly in regards to progression of brain death. Currently, EEG devices provide real-time EEG spectral analysis available at the bedside. Most conventional EEG devices are equipped to perform ECG telemetry. Therefore, it would be feasible to incorporate HRV spectral analysis to the bedside EEG monitors currently used in most ICUs.

This study has several limitations. First, the low number of cases did not allow for a more in-depth investigation of the different cofactors affecting low HRV, such as etiology, location of structural brain abnormalities, and others. Second, although sedation was represented in a dichotomous way, the influence of different doses of sedatives on HRV was not explored.

Third, all pediatric patients were grouped regardless of their age. A subject's age is a known HRV modifier, and the effect of age on low HRV in this population remains to be determined (34). It is also unknown whether earlier EEG and HRV findings (i.e., done in the emergency department shortly after arrival) might show similar findings. Despite these limitations, the differences between patients who progressed to brain death and those who survived remain strongly significant. This warrants further investigation in a larger cohort to validate these findings.

CONCLUSIONS

Our study shows that in children with acute brain injury, decreased HRV obtained at the bedside may serve as an early indicator of imminent progression to brain death.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Comparison of Poincaré plots over a 3-hr period on a comatose child who survived PICU admission (**A**, **B**, **C**), and one who progressed to brain death (**D**, **E**, **F**). Poincaré plots: each RR interval (RR_n) is plotted against its previous one (RR_{n-1}). $sd1$ (red), $sd2$ (green) are indicators of parasympathetic and sympathetic activity, respectively. Box in (**F**) shows a linear artifact on Poincaré plot when the heart rate variability falls below the monitor's sampling frequency.

TABLE 1.

Summary of Heart Rate Variability Variables

Variable Name (unit)	Description	Main Modulator
Linear analysis		
Time domain		
measures Mean RR (ms) SDNN (ms)	Mean RR interval sd of the normal-to-normal RR intervals	Sympathetic and vagal activity Vagal activity
rMSSD (ms)	Root mean square of successive RR interval differences	Sympathetic and vagal activity
Frequency-domain measures		
VLF power (m ²) ^b	band Absolute power of the low-frequency	Sympathetic and vagal activity
LF power (ms ²)	band Absolute power of the high-frequency	Vagal activity
HF power (ms ²)	band Low frequency to high frequency power ratio	Sympathovagal balance
LF/HF		
Nonlinear analysis		
sd1 (ms)	sd along the short axis of the plot	Vagal activity
sd2 (ms)	sd along the long axis of the plot	
	Sympathetic and vagal activity	
ApEn	Sample approximate entropy ^a	

RR = R-to-R interval.

^aThe contribution of vagal and sympathetic tone to these variables is not completely understood.^bNot reported in this study.

TABLE 2.

Patient Demographics, Clinical Characteristics, and Outcomes by Case-Control Status

Characteristics	All Patients (<i>n</i> = 23, 100%)	Brain Death (Cases) (<i>n</i> = 6, 26.1%)	No Brain Death (Controls) (<i>n</i> = 17, 73.9%)	<i>p</i> ^a
Patient demographics, <i>n</i> (%)				
Male gender	10 (43.5)	3 (50.0)	7 (41.2)	1.00
Age (yr)	5.83 (6.05)	2.83 (5.04)	6.88 (6.15)	0.16
Clinical characteristics				
Glasgow Coma Scale score, median (minimum–maximum)	3 (3–7)	3 (3)	3 (3–7)	0.08
Etiology, <i>n</i> (%)				
Anoxia/ischemia	9 (39.1)	5 (83.3)	4 (23.5)	0.13
Traumatic brain injury	9 (39.1)	1 (16.7)	8 (47.1)	
Intracranial hemorrhage	2 (8.7)	0 (0.0)	2 (11.8)	
Infection	3 (13.0)	0 (0.0)	3 (17.6)	
Intubated, <i>n</i> (%)	23 (100.0)	6 (100.0)	17 (100.0)	
Medications				
Fentanyl	14 (60.9)	0 (0.0)	14 (82.4)	< 0.01
Midazolam	16 (69.6)	2 (33.3)	14 (82.4)	0.05
Nonsedating anticonvulsants	13 (56.5)	2 (33.3)	11 (64.7)	0.34
Propofol	2 (8.7)	0 (0.0)	2 (11.8)	1.00
Phenobarbital	2 (8.7)	1 (16.7)	1 (5.9)	0.46
Dopamine	5 (21.7)	3 (50.0)	2 (11.8)	0.09
Epinephrine	5 (21.7)	4 (66.7)	1 (5.9)	< 0.01
Norepinephrine	4 (17.4)	1 (16.7)	3 (17.6)	1.00
Phenylephrine	1 (4.3)	0 (0.0)	1 (5.9)	1.00
Milrinone	2 (8.7)	1 (16.7)	1 (5.9)	0.46
Image modality, <i>n</i> (%)				
None	2 (8.7)	1 (16.7)	1 (5.9)	< 0.01
CT	8 (34.8)	5 (83.3)	3 (17.6)	
MRI	9 (39.1)	0 (0.0)	9 (52.9)	
CT and MRI	4 (17.4)	0 (0.0)	4 (23.5)	
Imaging result, <i>n</i> (%)				
Ischemia	11 (47.8)	4 (66.7)	7 (41.2)	0.37
Edema	10 (43.5)	3 (50.0)	7 (41.2)	1.00
Ischemia or edema	14 (60.9)	4 (66.7)	10 (58.8)	1.00
Intracranial bleed	9 (39.1)	1 (16.7)	8 (47.1)	0.34
Other	7 (30.4)	0 (0.0)	7 (41.2)	0.12

^a*p* values were generated using *t* tests (pooled or Satterthwaite variance used where appropriate) for continuous data, Wilcoxon two-sample test for ordinal data, and Fisher exact tests for categorical data.

Boldface values are significant, *p* < 0.05.

TABLE 3.

Patient Electroencephalogram, Neurologic Examination, and Heart Rate Variability by Case-Control Status

Physiologic Variables and Neurologic Examination	All Patients (<i>n</i> = 23, 100%)	Brain Death (Cases) (<i>n</i> = 6, 26.1%)	No Brain Death (Controls) (<i>n</i> = 17, 73.9%)	<i>p</i> ^a
EEG report, <i>n</i> (%)				
Not reported	2 (8.7)	2 (33.3)	0 (0.0)	< 0.01
Normal	0 (0.0)	0 (0.0)	0 (0.0)	
Slow disorganized	16 (69.6)	0 (0.0)	16 (94.1)	
Discontinuous	2 (8.7)	1 (16.7)	1 (5.9)	
Attenuated featureless	3 (13.0)	3 (50.0)	0 (0.0)	
EEG report, <i>n</i> (%)				
Not reported	2 (8.7)	2 (33.3)	0 (0.0)	< 0.01
Slow disorganized	16 (69.6)	0 (0.0)	16 (94.1)	
Discontinuous or attenuated featureless	5 (21.7)	4 (66.7)	1 (5.9)	
Brainstem reflexes or posturing present at admission, <i>n</i> (%)	21 (91.3)	4 (66.7)	17 (100.0)	0.06
Heart rate variability, mean (sd)				
Heart rate (beats/min)	113 (29.6)	142 (15.7)	102 (26.3)	< 0.01
sd of normal-normal intervals (ms)	10.4 (9.89)	0.98 (0.64)	13.73 (9.45)	< 0.01
Root mean square successive difference (ms)	9.99 (9.87)	0.98 (0.43)	13.17 (9.63)	< 0.01
LF power FFT (log)	1.89 (3.16)	-2.29 (1.94)	3.36 (1.93)	< 0.01
HF power FFT (log)	1.47 (2.87)	-1.79 (1.51)	2.62 (2.28)	< 0.01
sd1 (ms)	7.07 (6.99)	0.7 (0.3)	9.32 (6.82)	< 0.01
sd2 (ms)	12.64 (12.32)	1.18 (0.87)	16.68 (11.91)	< 0.01
Mean R-to-R interval (ms)	536.4 (146.39)	421.32 (45.46)	577.01 (148.67)	< 0.01
Approximate entropy	1.25 (0.12)	1.27 (0.11)	1.25 (0.12)	0.74
LF/HF ratio	3.44 (3.58)	1.02 (0.87)	4.29 (3.8)	< 0.01

EEG = electroencephalogram, FFT = fast Fourier transform, HF = high frequency, LF = low frequency.

^a*p* values were generated using *t* tests (pooled or Satterthwaite variance used where appropriate). Boldface values are significant, *p* < 0.05.

TABLE 4.

Odds of Death and Measures of Heart Rate Variability

Heart Rate Variability	OR (95% CI) ^a	<i>p</i> ^b
sd of normal-normal intervals (ms)	11.4 (0.6–207.0)	0.10
Root mean square successive difference (ms)	<i>c</i>	
LF power FFT (log)	4.0 (1.2–13.6)	0.03
HF power FFT (log)	2.5 (1.2–5.4)	0.02
sd1 (ms)	<i>c</i>	
sd2 (ms)	5.6 (0.8–40.2)	0.09
Mean R-to-R interval (ms)	1.0 (1.0–1.0)	0.06
Approximate entropy	<i>c</i>	
LF/HF ratio	2.3 (0.9–5.8)	0.08

FFT = fast Fourier transform, HF = high-frequency, LF = low-frequency, OR = odds ratio.

^aOdds of death for every one point increase in heart rate variability (HRV).

^b*p* generated using logistic regression. Each HRV measurement was modeled separately.

^cORs and corresponding *p* values were not able to be calculated. Boldface values are significant, *p* < 0.05.

TABLE 5.**Heart Rate Variability by Electroencephalogram Results**

Heart Rate Variability	All Patients (<i>n</i> = 21, 100%)	Discontinuous or Attenuated Featureless (<i>n</i> = 5, 23.8%)	Slow Disorganized (<i>n</i> = 16, 76.2%)	<i>p</i>^a
sd of normal-normal intervals (ms), mean (sd)	11.31 (9.87)	2.5 (3.32)	14.07 (9.65)	0.02
Root mean square successive difference (ms), mean (sd)	10.86 (9.91)	2.43 (3.16)	13.49 (9.85)	< 0.01
LF power FFT (log), mean (sd)	2.26 (3.04)	−1.32 (3.2)	3.38 (2)	< 0.01
HF power FFT (log), mean (sd)	1.72 (2.87)	−1.37 (2.24)	2.68 (2.33)	< 0.01
sd 1 (ms), mean (sd)	7.68 (7.01)	1.72 (2.24)	9.55 (6.98)	< 0.01
sd2 (ms), mean (sd)	13.75 (12.34)	3.05 (4.1)	17.09 (12.18)	<0.01
Mean R-to-R interval (ms), mean (sd)	547.42 (148.37)	436.42 (56.57)	582.1 (152.01)	0.05
Approximate entropy, mean (sd)	1.24 (0.12)	1.24 (0.11)	1.25 (0.13)	0.88
LF/HF ratio, mean (sd)	3.73 (3.62)	3.51 (4.94)	3.79 (3.31)	0.88

FFT = fast Fourier transform, HF = high-frequency, LF = low-frequency.

^a*p* values were generated using *t* tests (pooled or Satterthwaite variance used where appropriate) for continuous data and Fisher exact tests for categorical data. Boldface values are significant, *p* < 0.05.