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Heart Rate Change as a Potential Digital Biomarker of Brain Death in Critically Ill Children With Acute Catastrophic Brain Injury

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IMPORTANCE: Bedside measurement of heart rate (HR) change (HRC) may provide an objective physiologic marker for when brain death (BD) may have occurred, and BD testing is indicated in children.

OBJECTIVES: To determine whether HRC, calculated using numeric HR measurements sampled every 5 seconds, can identify patients with BD among patients with catastrophic brain injury (CBI).

DESIGN, SETTING, AND PARTICIPANTS: Single-center, retrospective study (2008–2020) of critically ill children with acute CBI. Patients with CBI had a neurocritical care consultation, were admitted to an ICU, had acute neurologic injury on presentation or during hospitalization based on clinical and/or imaging findings, and died or survived with Glasgow Coma Scale (GCS) less than 13 at hospital discharge. Patients meeting BD criteria (BD group) were compared with those with cardiopulmonary death (CD group) or those who survived to discharge.

MAIN OUTCOMES AND MEASURES: HRC was calculated as the interquartile range of HR divided by median HR using 5-minute windows with 50% overlap for up to 5 days before death or end of recording. HRC was compared among the BD, CD, and survivor groups.

RESULTS: Of 96 patients with CBI (69% male, median age 4 years), 28 died (8 BD, 20 CD) and 20 survived (median GCS 9 at discharge). Within 24 hours before death, HRC was lower in BD compared with CD patients or survivors (0.01 vs 0.03 vs 0.04, $p = 0.001$). In BD patients, HRC decreased at least 1 day before death. HRC discriminated BD from CD patients and survivors with 90% sensitivity, 70% specificity, 44% positive predictive value, 96% negative predictive value (area under the receiver operating characteristic curve 0.88, 95% CI, 0.80–0.93).

CONCLUSIONS AND RELEVANCE: HRC is a novel digital biomarker that, with further validation, may be useful as a classifier for BD in the overall course of patients with CBI.

KEY WORDS: brain injuries; critical illness; heart rate variability; intensive care units; pediatric

Brain death (BD) in children is an uncommon event, occurring in children admitted to critical care units on average 5–10 times per year (1). BD is a clinical diagnosis determined by the absence of cortical and brainstem functions, including loss of the ability to breathe independently (2, 3). Timely testing of BD in children is important for goals of care discussions and communication with families about potential for recovery. A digital biomarker of BD that is easy to measure and available at the bedside may guide optimal timing for when to perform formal BD testing.

Heart rate (HR) variability (HRV) is a parameter obtained from electrocardiogram (ECG) waveforms that represents normal spontaneous beat-to-beat

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KEY POINTS

- **Question:** We aimed to determine whether heart rate change (HRC), calculated using numeric HR measurements sampled every 5 seconds (0.2 Hz) could distinguish patients with brain death (BD) from non-BD patients among children with acute catastrophic brain injury (CBI).
- **Findings:** In this pilot study, HRC had 44% positive predictive value and 96% negative predictive value (area under the receiver operating characteristic curve 0.88) for discriminating BD from CD patients and survivors. Reduced HRC in BD was evident at least 1 day before death.
- **Meaning:** With further validation, HRC may be useful as a classifier for brain death in the overall course of patients with CBI.

variation in HR modulated by the efferent limbs of the autonomic nervous system (4). The brain is an important regulator of autonomic efferents to the heart through interconnected brain structures that include the cortex and brainstem (5). In BD patients with complete cessation of brain to heart autonomic control, HRV is reduced, with values close to zero, and is associated with progression to BD (6–8). HRV calculation requires HR measurement with high sampling frequency (> 250 Hz) (9), which limits its applicability in many ICUs. In contrast, systems for archiving HR with lower sampling frequency from discrete, numeric HR recordings are more common. Among children with acute catastrophic brain injury (CBI), we hypothesized that heart rate change (HRC), calculated using these discrete HR recordings, will be reduced in BD patients compared with patients with cardiopulmonary death (CD) and survivors with prolonged disorder of consciousness (DOC).

METHODS

Study procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975. The Institutional Review Board (IRB) at Boston Children's Hospital reviewed the study protocol titled "Curing Coma in Children: Defining Catastrophic Brain Injury, Prevalence and Outcomes," and determined that it qualified as exempt from the requirements of 45 Code of Federal Regulations (CFR) 46 (Protocol Number IRB-P00034673, Approval date: March 6, 2020). The above-referenced protocol was determined to be exempt because it was limited to research activities in which the only involvement of human subjects was in secondary research for which consent is not required as described in 45 CFR 46.104 (d).

Study Design and Population

For this retrospective study, we analyzed data from patients admitted to the PICU or cardiac ICU (CICU) at Boston Children's Hospital from December 23, 2008, to March 5, 2020 with acute CBI. Selection criteria for patients with acute CBI were previously published (10). Patients with CBI in this study had a neurocritical care consultation, were admitted to a PICU or CICU, and had acute neurologic injury on presentation or during hospitalization based on clinical and/or imaging findings (e.g., traumatic brain injury, stroke, brain mass, hydrocephalus, cardiac arrest, CNS infection/demyelination, status epilepticus), and died or survived with a prolonged DOC (defined as Glasgow Coma Scale [GCS] < 13 at hospital discharge, though median GCS at discharge among survivors was markedly lower) (10). Patients with CBI were included if they had any HR recordings within 5 days before time of death or end of the recording for survivors. Although sinus rhythm was not required for inclusion, we confirmed by chart review that patients included in this study were not frequently in arrhythmia. We excluded patients who were using a pacemaker or who were on extracorporeal membrane oxygenation (ECMO) at the time of death based on prior literature suggesting that patients being treated with ECMO have reduced HRV (11, 12).

At our institution, we have a written protocol for BD determination that includes a structured, digitized checklist for documentation of requisite findings and detailed instructions for performing each component of the clinical examination to ensure consistency among examiners. Patients were classified into three groups: 1) BD if the mechanism of death indicated in the official death note entered into the medical record

was determination of death by neurologic criteria; 2) CD if the patient died from cardiopulmonary arrest and not BD; or 3) survival to hospital discharge. In an additional, secondary analysis, HRC was analyzed for patients who had bilateral unreactive pupils but did not undergo formal BD testing. This group of patients, who died by CD but may have potentially met or progressed to meet BD criteria if they had been tested (CD-BD group), was a priori analyzed separately because we were unable to ascertain their true cause of death grouping. Therefore, we did not assign CD-BD patients to either the CD or BD groups to avoid potential mislabeling. Clinical data extracted from the electronic health records included age, sex, etiology of CBI, chronic illness (defined as ≥ 1 comorbidity), intensive care therapies, pediatric severe organ failure assessment (pSOFA) score, and GCS. Vasoactive pSOFA subscores were collected for all patients at admission and at the time of discharge using the maximum continuous vasoactive infusion administered for at least 1 hour at each timepoint (13).

Measurement of Heart Rate Change

HR measurements were obtained from the local Etiometry Platform database (Etiometry, Boston, MA). The Etiometry system collects discrete HR measurements from bedside monitors at a sampling frequency of 0.2 Hz (every 5 seconds). We excluded all values for HR greater than 250 beats per minute (bpm) or equal to zero after confirming through chart review that these values represented erroneous data and not patient events. Using a window size of 5 minutes and overlap of 50% between windows, HRC was calculated as the ratio of the interquartile range (IQR) of HR to the median HR in each window (14). HRC values were then subsequently averaged over 6-hour windows leading up to the time of death.

Statistical Analyses

HRC data were summarized as mean and 95% CI. A Kruskal-Wallis test was used to test whether HRC distributions differed among outcome groups over the 24-hour period after admission and before death or end of the recording. Dunn-Sidak multiple comparisons (post hoc) tests were performed to assess for pairwise differences between outcome groups. We assessed discrimination within 24 hours of death or end of recording using the area under the receiver operating characteristic (AUROC) comparing two groups (BD vs CD and survivors) with optimal HRC threshold determined by Youden Index (15). Since BD is a rare outcome and the data were imbalanced with a larger number of survivors and CD patients, a precision-recall curve analysis was performed to assess the tradeoff between precision (positive predictive value; PPV) and recall (sensitivity), where the area under the precision-recall curve (AUPRC) reflects this tradeoff across the range of potential cutpoints at which BD may be classified (16). We reported variations in performance of AUROC and AUPRC using 10,000 bootstrap replications of the dataset. To visualize changes in HRC over time, we aligned survivors to the end of their HR recording, BD patients to the time of their second BD examination (time of death), and CD patients to the time of death. Analyses were conducted using Stata 16.1 (StataCorp, College Station, TX) and MATLAB Version 9.7.0 (MathWorks, Natick, MA).

RESULTS

Patient and Data Characteristics

Of 96 patients (69% male, median age 4 years) with acute CBI, 21 were excluded because they were paced (n = 4) or on ECMO at the time of death (n = 17, including 1 who was paced), **Figure 1**. Of the 75 remaining patients, an additional 12 patients were excluded due to lack of HR data that could be matched to patients' medical record numbers within 5 days before death (4 BD patients, 6 CD patients, 2 CD-BD patients). Of 63 patients included in the final analysis, 8 met BD criteria, 20 died by CD with reactive pupils, 15 died by CD with unreactive pupils, and 20 survived hospital discharge (Fig. 1). The cause of death in the CD group was withdrawal of life-sustaining therapies in 18 patients and failed cardiopulmonary resuscitation in two patients. Compared with CD patients and survivors, patients with BD were older (median age 13.9 years in BD vs 1.1 years in CD vs 5.5 years in survivors), and more commonly treated with catecholaminergic agents (pSOFA score ≥ 2) at time of death (6 of 8 [75%] in BD vs 8 of 20 [40%] in CD), but less likely to be admitted to the CICU (1 of 8 [13%] in BD vs 8 of 20 [40%] in CD vs 6 of 20 [30%] in survivors) (**Table 1**).

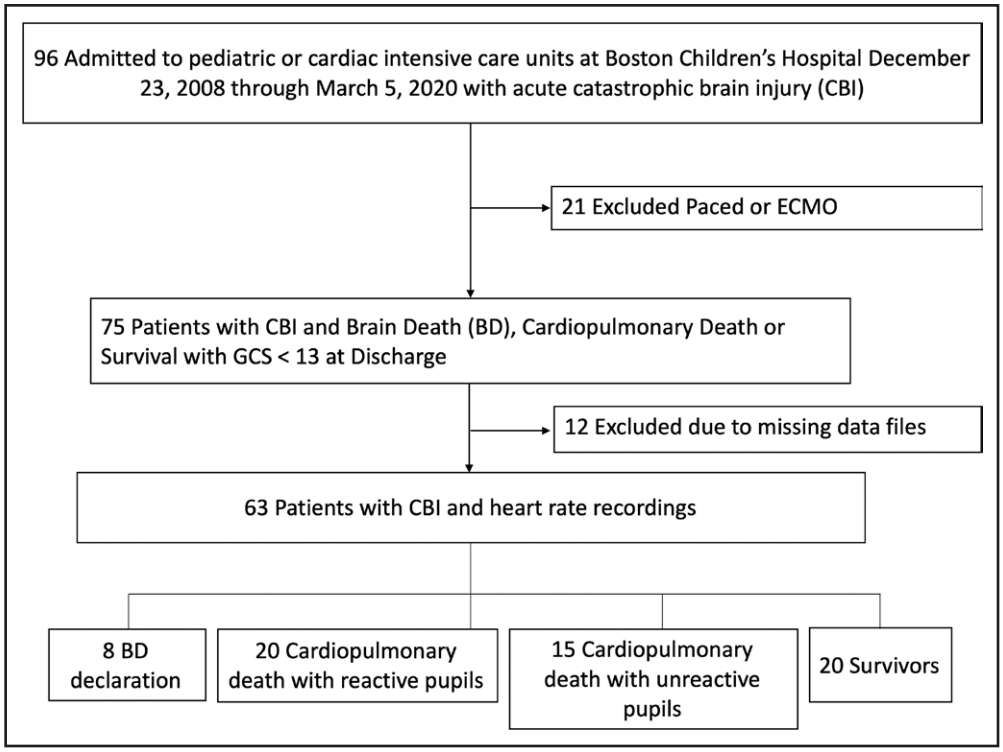

Figure 1. Eligibility flowchart of 96 children admitted to pediatric and cardiac intensive care units with acute catastrophic brain injury, from December 23, 2008 to March 5, 2020. ECMO = extracorporeal membrane oxygenation, GCS = Glasgow Coma Scale.

Summary of HRC Measurements

We removed a total of 0.07% of data points (mean 17.2 ± 81.4 minutes of recording per patient) with HR = 0 or > 250 bpm. Within the first 24 hours of admission, we failed to find a difference in HRC between the outcome groups (BD 0.03 [95% CI, 0.01–0.05]; CD 0.04 [95% CI, 0.03–0.06]; CD-BD 0.05 [95% CI, 0.04–0.07]; and survivors 0.03 [95% CI, 0.02–0.04]; H(2) = 5.8, p = 0.12). However, within 24 hours of declaration of death or end of the recording, mean HRC was significantly reduced in BD patients (0.01 [95% CI, 0.005–0.01]) when compared with CD patients (0.03 [95% CI, 0.02–0.05]), CD-BD patients (0.03 [95% CI, 0.01–0.05]), and survivors (0.04 [95% CI, 0.03–0.05]); H(3) = 14.1, p = 0.003). Post hoc tests of pairwise comparisons showed significant differences in HRC between BD and CD and BD and survivors on discharge (p = 0.04 and p = 0.001, respectively). No significant differences in HRC between CD and survivors were observed at admission or discharge (**Table 2**). At least 1 day before death, HRC decreased in BD patients whereas it remained relatively constant in CBI survivors and those with CD (**Fig. 2**). **Supplemental Figure 1** (http://links.lww.com/CCX/B186) shows plots for HRC in three individual patients representative of the trend in the overall cohort. HRC had AUROC 0.88 (95% CI, 0.80–0.93; **Fig. 3*A***) and AUPRC 0.57 (95% CI, 0.39–0.74; **Fig. 3*B***) for discriminating BD from CD and survivors. At a threshold of 0.016, HRC had a sensitivity 90%, specificity 70%, PPV 44%, and negative predictive value 96%. CD-BD patients' HRC were more similar to CD patients and survivors than to BD patients (**Supplemental Tables 1** and **2**, http://links.lww.com/CCX/B186).

DISCUSSION

In this study, we propose a novel digital biomarker, which we term HRC, for detecting physiologic changes that are present in patients who met clinical diagnostic criteria for BD. HRC is calculable using low-frequency HR data and thus may be more generally applicable than HRV, which has also been proposed in limited studies to correlate with a diagnosis of BD. We demonstrate that HRC may discriminate BD from CD (with and without reactive pupils) and survivors with prolonged DOC at discharge at least 1 day before death. If validated, HRC may provide objective support of potential BD physiology that could add guidance on top of current prerequisites about the correct timeframe for when to perform the formal BD examination with apnea test. HRC may also be used to evaluate when patients progress to BD in future retrospective cohort studies of subjects who underwent formal BD testing.

We found that HRC measures were reduced in BD patients. To put our HRC results into clinically understandable terms, we found that in the 24 hours before the end of the recording for survivors or before death, the IQR of HR in each 5-minute window was 1% of the median HR for BD patients, whereas for the CD patients and survivors the IQR was 3% and 4% of the median HR, respectively. Focusing on distinguishing

TABLE 1.
Characteristics of 48 Children With Catastrophic Brain Injury

Variable	All Patients (*n* = 48)	Survivors (*n* = 20)	Brain Death (*n* = 8)	Cardiopulmonary Death (*n* = 20)
Age (yr), median (IQR)	4.0 (0.6, 13.8)	5.5 (1.3, 13.8)	13.9 (2.2, 15.8)	1.1 (0.2, 10.2)
Male sex, *n* (%)	33 (69)	15 (75)	4 (50)	14 (70)
Coma scales, median (IQR)				
Total GCS, at admission	4 (3, 10)	5 (3, 9)	3 (3, 7)	5 (3, 10)
GCS motor score, at admission	1 (1, 4)	1 (1, 4)	1 (1, 5)	1 (1, 4)
Total GCS, on discharge	5 (3, 10)	9 (8, 10)	3 (3, 3)	3 (3, 5)
GCS motor score, on discharge	1 (1, 4)	4 (3, 5)	1 (1, 1)	1 (1, 2)
Total functional status scale[a], median (IQR)				
At admission	27 (22, 27)	27 (25, 27)	27 (27, 27)	26 (14, 27)
At discharge	27 (19, 27)	19 (15, 26)	27 (27, 27)	27 (27, 27)
Disease etiology, *n* (%)				
Traumatic brain injury	5 (10)	4 (20)	1 (13)	0
Stroke	8 (17)	6 (30)	1 (13)	1 (5)
Brain mass	6 (13)	1 (5)	2 (25)	3 (15)
Cardiac arrest	21 (44)	7 (35)	4 (50)	10 (50)
Other[b]	8 (17)	2 (10)	0	6 (30)
Cardiac intensive care unit, *n* (%)	15 (31)	6 (30)	1 (13)	8 (40)
Chronic illness (≥ 1 chronic disorder), *n* (%)	32 (7)	11 (55)	2 (25)	19 (95)
Total pSOFA scores, mean ± SD				
Admission	7.8 ± 3.3	7. 5 ± 3.7	8.5 ± 3.5	7.9 ± 3.0
Discharge	6.5 ± 4.2	3.0 ± 1.2	9.6 ± 1.8	8.8 ± 4.3
Vasoactive pSOFA score[c] at admission, *n* (%)				
2	3 (6)	0	0	3 (15)
3	8 (17)	4 (20)	2 (25)	2 (10)
4	12 (25)	3 (15)	3 (38)	6 (30)
Vasoactive pSOFA score[c] at discharge, *n* (%)				
2	0	0	0	0
3	5 (10)	0	2 (25)	3 (15)
4	9 (19)	0	4 (50)	5 (25)
ICU therapies, *n* (%)				
Mechanical ventilation	47 (98)	19 (95)	8 (100)	20 (100)
Sedative infusions	38 (79)	18 (90)	4 (50)	16 (80)
Dialysis	4 (8)	1 (5)	0	3 (15)

(*Continued*)

TABLE 1. (*Continued*)
Characteristics of 48 Children With Catastrophic Brain Injury

Variable	All Patients (*n* = 48)	Survivors (*n* = 20)	Brain Death (*n* = 8)	Cardiopulmonary Death (*n* = 20)
ICU length of stay, d, *n* (%), median (IQR)	18 (7, 39)	35 (19, 49)	5 (4, 12)	12 (6, 32)

GCS = Glasgow Coma Scale, IQR = interquartile range (25th percentile–75th percentile), pSOFA = pediatric severe organ failure assessment.

[a]Lower functional status scale scores indicate better functional status.

[b]Other = hydrocephalus, acute CNS infection/demyelination, status epilepticus.

[c]Vasoactive pSOFA scores (2–4), measured in micrograms per kilogram per minute (19): Score 2 = dopamine hydrochloride ≤ 5 or dobutamine hydrochloride (any), Score 3 = dopamine hydrochloride >5 or epinephrine ≤ 0.1 or norepinephrine bitartrate ≤ 0.1, Score 4 = dopamine hydrochloride >15 or epinephrine > 0.1 or norepinephrine bitartrate > 0.1. Patients not receiving one of these vasoactives had scores < 2 (0 or 1) and were not included.

TABLE 2.
Post hoc Tests of Pairwise Group Comparisons

Groups Compared	Pairwise Z-test Statistic	95% CI	*p*
At admission			
CD-BD	4.0	−6.95 to 14.95	0.78
CD-survivors	1.67	−7.11 to 10.44	0.96
BD-survivors	−2.33	−13.66 to 9.00	0.95
On death or end of recording			
CD-BD	11.63	0.69 to 22.58	0.04
CD-survivors	−5.45	−14.23 to 3.33	0.38
BD-survivors	−17.08	−28.41 to −5.75	0.001

BD = brain death, CD = cardiopulmonary death.

dying patients, if the median HR in BD and CD patients were 120 bpm, then the 25th–75th percentiles of HRs for the BD group would range from 120 to 120 bpm (with rounding), whereas for the CD group they would range from 118–122 bpm. Although this difference appears small, it is measurable, and furthermore, we can use this difference to help discriminate the mechanism of death in patients with CBI. Larger studies are needed to externally validate HRC and investigate prospectively how HRC may be applied as a digital biomarker in BD determination. Future studies should examine whether low HRC can be used to identify patients for formal BD testing.

HRC computations are scalable. We measured HRC from 5 second averaged HR recordings over 5 minutes. Such simple computations over small data blocks may have the possibility of real-time operation to assist clinical decision-making at the bedside. HRV is a well-recognized digital measure of autonomic dysregulation (17) that has been shown to be reduced in children with BD in prior studies that are similar in size to ours. Kero et al (6) showed reduced HRV in 12 children diagnosed with BD (based on clinical experience and two sequential "flat" electroencephalograms) when compared with normal infants and children and infants with respiratory distress syndrome. In a study of 105 adults and children with traumatic brain injury, Schwarz et al (7) demonstrated that HRV was less than 2.3% in all 24 adults and children (average age 22 years ± 13 years) with a suspected clinical diagnosis of BD and none of the 44 healthy adult volunteers. Of note, these studies compared patients with BD to healthy controls, which likely magnifies differences in HRV as compared with the difference between BD patients and non-BD patients with severe neurologic injury. In a recent retrospective study by Piantino et al (8), of 23 children less than 18 years old with acute brain injury and GCS less than 8, HRV was reduced by 10-fold in 6 children with BD when compared with 17 comatose survivors. Our study builds on this work by differentiating BD patients from survivors and CD patients (most of whom died from withdrawal of life-sustaining therapies), all of whom had CBI and poor neurologic prognosis (18). HRV methodologies require monitoring systems capable of high sampling frequency, manual review of raw ECG waveforms for artifact rejection, and powerful computing to analyze the waveform data (6), which cannot be accomplished in most settings,

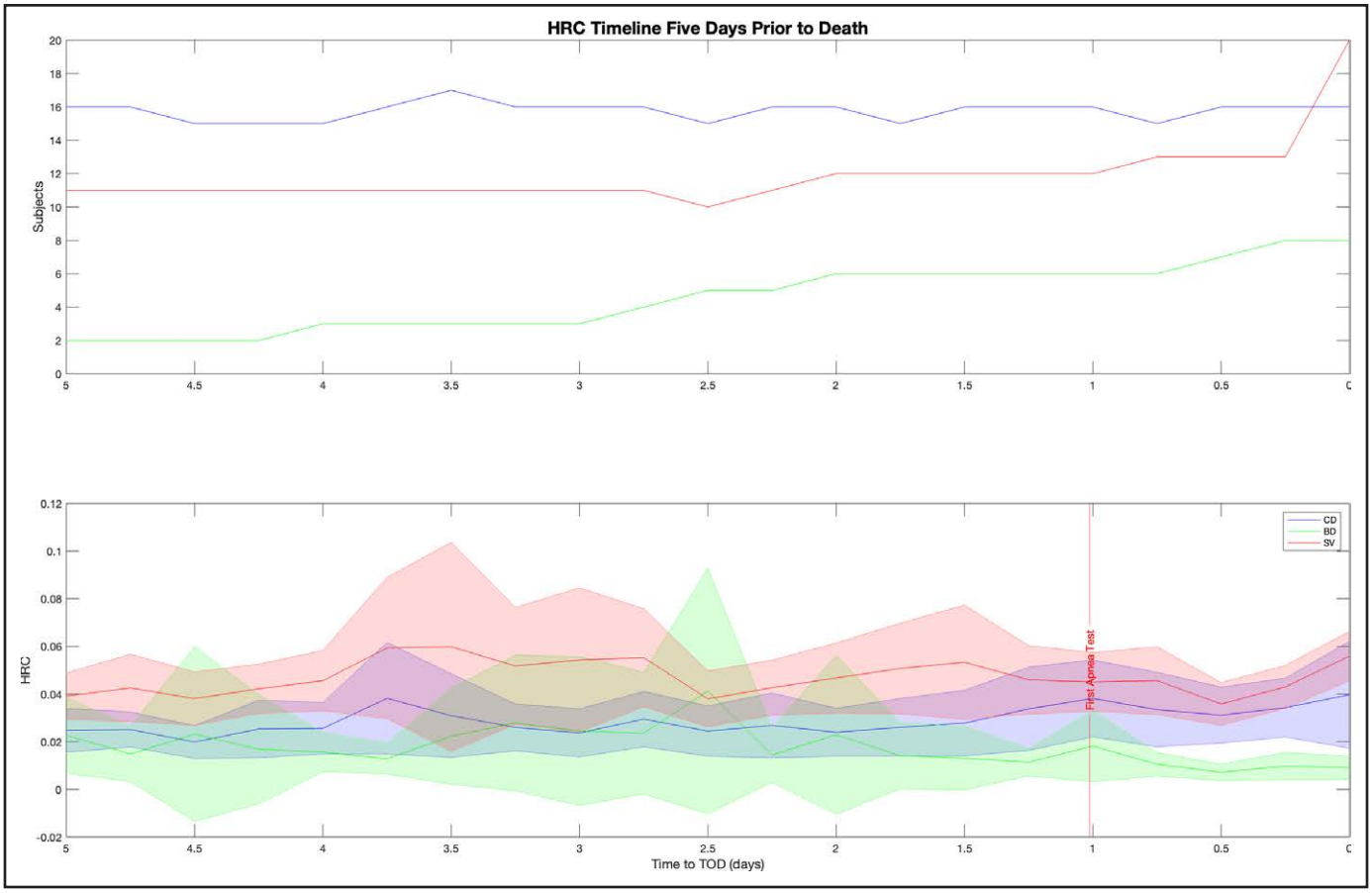

Figure 2. Heart rate change (HRC) timeline five days before time of death or end of heart rate recording. *Top panel* shows number of subjects at each timepoint with heart rate data recordings five days before death or end of recording. *Bottom panel* shows HRC over time (days) before death or end of recording. *Shaded bands* represent 95% CIs around mean values. The median time of the first brain death examination in relation to the second brain death examination at time zero (time of death) is shown for the patients who were declared brain dead (1.01 days [IQR 0.86-1.07]). CD = cardiopulmonary death, BD = brain death, SV = survivors, TOD = time of death.

especially in near-real time. Furthermore, HRV measurements are not standardized and reporting and interpretation standards for HRV are lacking for the critically ill (9). Our use of discrete data sampled at a lower frequency is simpler and may be more generalizable. Further studies are needed to determine the feasibility of the HRC approach at other sites with similar patient monitoring systems.

We detected a decrease in HRC at least 1 day before the second BD examination. Our findings are similar to those of Piantino et al (8) who found that the lowest HRV in 6 children with BD was at least 12 hours before the first BD examination. The earliest timepoint at which any patient may meet BD criteria is unknown since we only know whether a patient may meet BD criteria when formal BD testing is performed. Detection of the initial onset of BD would require serial, unconfounded, standardized neurologic examinations from admission to death that assess for the presence of coma and absence of brainstem function, including spontaneous respirations. In this retrospective study, whether we could have identified patients earlier is unknown. If the goal is to use HRC to guide when to start BD evaluations, future prospective studies should examine serial changes in HRC over time from time of injury (or ICU admission) to time of death. This may help identify other potentially important physiologic changes preceding BD as well as age-related changes in HRC. Nonetheless, even if HRC would not have allowed "early" identification of BD in our center, HRC may be useful for standardizing selection of patients for formal BD testing and for providing insight into how often and how soon after a drop in HRC different centers perform BD testing.

This study has certain limitations. The small sample size cannot statistically justify generalization, subgroup analyses, or adjustment for important confounders. In particular, we found that patients

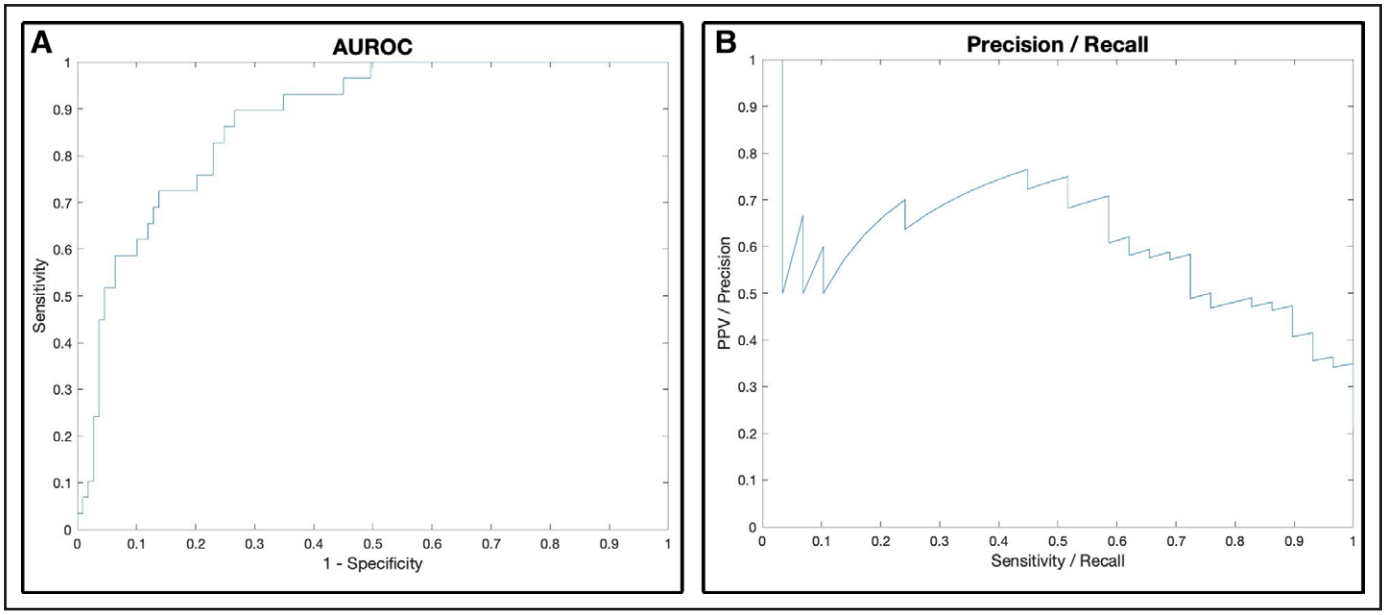

Figure 3. Discrimination of heart rate change (HRC) for brain death within 24 hours of death or end of recording using area under receiver operating characteristic curve (AUROC 0.88 [95% CI, 0.80–0.93] (**A**) and area under the precision recall curve (0.57 [95% CI, 0.39–0.74] (**B**).

in the BD group were older than those in the other two groups, and older children are known to have decreased HRV (6). Since younger patients tend to have higher HRV (6, 19), we tried to mitigate this effect by normalizing HRC to a patient's median HR, which is expected to be higher in younger patients. Future larger, prospective studies should match for age or use multivariable regression analyses to adjust for age and other potential confounders (e.g., sedatives, vasoactive medications, mechanical ventilation, cardiac dysfunction) (20, 21). Finally, due to the retrospective nature of this study, we were not able to assess the ability of HRC to predict BD, which would require HR measurements collected and BD testing performed prospectively.

CONCLUSIONS

Among children with CBI, HRC is a novel digital biomarker that may be reduced at least 1 day before BD declaration. Larger, prospective studies are needed to validate HRC and evaluate its applicability as a classifier for BD in the overall course of patients with CBI.

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