Early Heart Rate Characteristics Predict Death and Morbidities in Preterm Infants

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Objectives To determine whether an early heart rate characteristics (HRC) index (HeRO score), measured in the first day and week after birth predicts death and morbidities compared with established illness severity scores.

Study design For all very low birth weight infants in a single neonatal intensive care unit from 2004-2014, the average first day HRC index was calculated within 24 hours of birth (aHRC-24h) and the average first week HRC index within 7 days of birth (aHRC-7d). The Score for Neonatal Acute Physiology (SNAP-II) and Clinical Risk Indicator for Babies (CRIB-II) were calculated when data were available. The aHRC was compared with the SNAP-II and CRIB-II for predicting death, late-onset septicemia, necrotizing enterocolitis, bronchopulmonary dysplasia, severe intraventricular hemorrhage, or severe retinopathy of prematurity.

Results All 4 scores were associated with death and severe intraventricular hemorrhage ($P < .01$). The OR and 95% CI for every 1-point increase in aHRC for predicting mortality, adjusted for gestational age, was 1.59 (1.25-2.00) for aHRC-24h and 2.61 (1.58-4.33) for aHRC-7d. High aHRC-7d, SNAP-II, and CRIB-II were associated with bronchopulmonary dysplasia ($P < .001$). High aHRC-7d was associated with late-onset septicemia ($P < .05$). None of the scores predicted necrotizing enterocolitis or severe retinopathy of prematurity.

Conclusions HRC assessed in the first day or first week after birth compares favorably to established risk scores to predict death and morbidities in very low birth weight infants. *(J Pediatr 2016;174:57-62)*.

Risk prediction scores based on illness severity are important for interinstitutional quality assessment and for clinical research. In the neonatal intensive care unit (NICU), gestational age (GA) alone is a strong predictor of adverse events and outcomes. Adding physiological and laboratory data can improve the accuracy of predictive models and could help identify infants who might benefit from heightened surveillance or preventative measures. Two established risk scores, the Score for Neonatal Acute Physiology (SNAP) and Clinical Risk Indicator for Babies (CRIB) and their updated versions (SNAP-II and CRIB-II), rely on clinical and blood gas data to calculate. A relatively new physiologic measure, the heart rate characteristics (HRC) index, was designed to assess risk of imminent sepsis in very low birth weight (VLBW) infants and is calculated continuously from the bedside monitor electrocardiogram (ECG) signal. Because depressed heart rate variability may occur in both acute and chronic pathologic conditions, we reasoned that a high HRC index shortly after birth might indicate high risk of death or morbidities in VLBW infants in the NICU.

Depressed heart rate variability reflects dysregulation of autonomic nervous system function and occurs in acute conditions such as sepsis or asphyxia.[1,2] In fetuses, abnormal HRC of transient decelerations on a background of depressed variability are a well-known sign of distress and are associated with adverse outcomes. In neonates, the most common cause of these abnormal HRC is sepsis.[3,4] A HRC monitor (HeRO Monitor, Medical Predictive Science Corporation, Charlottesville, Virginia) was developed as an early warning system for sepsis in VLBW infants in the NICU, and display of the HRC index (HeRO score) reduces all-cause mortality by 22%[5] and sepsis-associated mortality by 40%.[6] Abnormal HRC are not specific for sepsis, and acute or chronic elevations in the HRC index have been reported in a number of other pathologic conditions, including necrotizing enterocolitis (NEC), respiratory failure, and brain hemorrhage.[7-9]

Although not specifically designed for mortality prediction, a high HRC index throughout the NICU stay was associated with high risk for death.[10] SNAP-II and CRIB-II, which were designed to predict mortality, incorporate a limited number of vital

aHRC-7d	Average first week HRC index	LOS	Late-onset septicemia
aHRC-24h	Average first day HRC index	NEC	Necrotizing enterocolitis
AUC	Area under the ROC curve	NICU	Neonatal intensive care unit
BPD	Bronchopulmonary dysplasia	NRI	Net reclassification improvement
CRIB-II	Clinical Risk Indicator for Babies II	ROC	Receiver operator characteristic
		ROP	Retinopathy of prematurity
ECG	Electrocardiogram	SNAP-II	Score for Neonatal Acute Physiology II
GA	Gestational age		
HRC	Heart rate characteristics	UVA	University of Virginia
IVH	Intraventricular hemorrhage	VLBW	Very low birth weight

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sign metrics and laboratory values from the first 12 hours after birth.[11,12] Limited studies suggest that high SNAP or CRIB scores are associated with increased risk for other adverse outcomes, including intraventricular hemorrhage (IVH) and bronchopulmonary dysplasia (BPD).[13-15]

Prior studies have examined the association of abnormal HRC (a high HRC index) throughout the NICU stay with acute and chronic conditions. In the current study, we determined whether early measurement of the HRC index, in the first day and first week after birth, predicts later adverse events and conditions in VLBW infants, as compared with SNAP-II and CRIB-II.

Methods

The University of Virginia (UVA) Institutional Review Board approved this study. We reviewed HRC monitoring data for all VLBW infants (<1500 g at birth) admitted to the UVA NICU between May 2004 and May 2014. Medical records were reviewed for occurrence of death before NICU discharge, severe IVH (grades III-IV), late-onset septicemia (LOS), NEC, BPD (supplemental oxygen at 36 weeks' postmenstrual age), and severe retinopathy of prematurity (ROP requiring laser or bevacizumab treatment). LOS was defined as clinical signs of sepsis after 3 days of age with a positive blood culture, and antibiotics given for ≥5 days. NEC included cases of medical or surgical NEC or intestinal perforation.

HRC Index Monitoring

A commercially available monitor (HeRO, Medical Predictive Science Corporation) calculates the HRC index for all infants throughout their stay in the UVA NICU. The monitor analyzes the ECG signal from bedside monitors using an algorithm designed to detect imminent sepsis, incorporating measures of heart rate variability and decelerations. The 3 measures included in the algorithm are the SD of R-R intervals, sample asymmetry (increased decelerations and few accelerations), and sample entropy.[1,2] The HRC index is calculated every hour from the previous 12 hours of ECG signal and represents the fold increase in risk that the infant will be diagnosed with sepsis in the ensuing 24 hours compared with the average risk of sepsis for all VLBW infants at all times during the NICU stay.[16] The HRC index was externally validated for sepsis detection[2] and was tested in a large, multicenter randomized clinical trial.[5]

Calculation of Average First Day HRC Index, Average First Week HRC Index, SNAP-II, and CRIB-II

Average first day HRC index (aHRC-24h) was calculated when ≥6 hours of HRC index data were available in the first 24 hours after birth. Average first week HRC index was calculated when ≥5 days (120 hours) of HRC index data were available in the first 7 days (average first week HRC index [aHRC-7d]). For infants with either first day or first week HRC index calculated, medical records were reviewed for clinical and laboratory measurements in the first 12 hours after birth to calculate SNAP-II and CRIB-II Scores. The following components are included in SNAP-II: lowest temperature and blood pressure, lowest PaO_2/FiO_2 ratio, lowest pH, urine output, and seizures. A normal value was assumed for PaO_2/FiO_2 ratio if an arterial blood gas was not obtained. This has been suggested by the authors who developed SNAP and SNAP-II as an acceptable method of calculation when data are unavailable.[11,17] The following components are included in CRIB-II: GA, birth weight, sex, admission temperature, and highest base deficit.[12]

Statistical Analyses

Differences in scores for infants with and without each adverse outcome were assessed by *t* tests with and without logistic regression to adjust for GA. The additive value of each score compared with GA alone for risk prediction was quantified by the change of the area under receiver operator characteristic (ROC) curve as well as by the net reclassification improvement (NRI). NRI is a measure of the sum of proportions of patients reclassified into the correct risk group by a new risk marker compared with an established risk marker.[17] For example, an NRI of 0.2 with respect to death would indicate that a high HRC index correctly identified survival in 20% more infants compared with the established risk marker of GA. As an additional measure of risk assessment, we calculated the OR and 95% CI for every 1-point increase in aHRC-24h and aHRC-7d over zero for predicting mortality. Statistical analyses were performed in MATLAB (MathWorks, Inc, Natick, Massachusetts) and all *P* values are 2-tailed.

Results

In the years of the study, 566 VLBW infants had ≥6 hours of HRC index data within 24 hours of birth for aHRC-24h analysis and data available for calculation of SNAP-II and CRIB-II, and 480 had >120 hours (5 days) of HRC monitoring data available in the first week for calculation of aHRC-7d. Mean GA was similar for infants in the aHRC-24h and aHRC-7d groups (28.6 ± 2.9 and 28.9 ± 2.8 weeks, respectively). Of the 566 infants, 52% were male and 32% were <1000 g. During the same time period, approximately 1300 VLBW infants were admitted to the UVA NICU (mean GA, 27.5 ± 3.0 weeks; 51% male). Infants without early HRC data available for analysis were either born at another institution or did not have ECG leads placed in the first days after birth owing to poor skin integrity. The incidences of death, severe IVH, LOS, NEC, BPD, and severe ROP of the 566 infants included in the analysis are shown in **Table I**.

Predictive Performance of aHRC-24h, aHRC-7d, SNAP-II, and CRIB-II

Higher aHRC-24h and aHRC-7d were associated with death and severe IVH, with the difference remaining significant after accounting for GA ($P \leq .01$; **Figure 1**, A). The OR and 95% CI