Infection and Other Clinical Correlates of Abnormal Heart Rate Characteristics in Preterm Infants

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Objective To identify clinical conditions associated with a large increase (spike) in the heart rate characteristics index in very low birth weight (VLBW) infants.

Study design Retrospective medical record review within a day of all large heart rate characteristics index spikes (increase of ≥3 from the previous 5-day average) in VLBW infants at a single center enrolled from 2007 to 2010 in a multicenter trial of heart rate characteristics monitoring. In the trial, infants were randomized to having their heart rate characteristics index displayed to clinicians or not displayed.

Results Of 274 eligible infants, 224 large heart rate characteristics spikes occurred in 105 infants. Thirty-three spikes were associated with surgery or procedures requiring anesthetic or anticholinergic medications, and infection-related conditions were the most common clinical association with the other spikes. Of the first spikes in 47 infants randomized to conventional monitoring (heart rate characteristics index not displayed to clinicians), 53% were associated with suspected or proven infection. Respiratory deterioration without suspected infection occurred with 34%, and no association was identified in 13%. Infants randomized to having their heart rate characteristics index displayed were more likely to have antibiotics initiated around the time of a large heart rate characteristics index spike.

Conclusions Sepsis, other infectious or systemic inflammatory conditions, respiratory deterioration, and surgical procedures are the most common clinical associations with a large increase in the heart rate characteristics index in VLBW infants. This information may improve use of heart rate characteristics monitors in patients in the neonatal intensive care unit. *(J Pediatr 2014;164:775-80)*.

Abnormal heart rate characteristics of decreased variability and transient decelerations occur in preterm infants with sepsis, often before any clinical signs are recognized.[1] This observation led to the development of a monitor that displays heart rate characteristics as an index representing the fold-increase in risk of clinical deterioration from sepsis in the next 24 hours.[2,3] A mathematical algorithm uses electrocardiogram signals from standard bedside monitors in the neonatal intensive care unit (NICU) to continuously calculate and display the heart rate characteristics index, which reflects heart rate variability (normal small accelerations and decelerations) and presence of larger-than-normal decelerations occurring during the previous 12 hours.[4-7] The heart rate characteristics index added to laboratory tests[8] and clinical signs[9] for diagnosis of sepsis. Displaying infants' heart rate characteristics index to clinicians reduced mortality in a randomized clinical trial of 3003 very low birth weight (VLBW) infants.[10]

Abnormal heart rate characteristics may occur in sepsis or in other conditions that cause disturbances in autonomic nervous system function.[5,11-14] Heart rate is controlled by sympathetic (norepinephrine) and parasympathetic (acetylcholine) signaling to cardiac pacemaker cells, leading to frequent small accelerations and decelerations in rate, respectively.[15] Sepsis leads to decreased heart rate variability, usually represented as low SD of interheartbeat time intervals, in part through effects of cytokines released during a systemic inflammatory response.[16] Transient decelerations of heart rate also occur in infants with sepsis, sometimes in association with apnea, and sometimes during regular spontaneous breathing or mechanical ventilation. Vagus nerve firing is one cause of these heart rate decelerations.[17] Pathophysiologic conditions other than sepsis may lead to a systemic inflammatory response or altered autonomic nervous system function. In our previous work, we have reported increases in the heart rate characteristics index (reflecting low heart rate variability and/or transient decelerations) in patients in the NICU with urinary tract infection,[5] necrotizing enterocolitis (NEC),[18] respiratory deterioration leading to intubation,[19] and after surgical or other procedures requiring administration of anesthetic or anticholinergic medications.[20,21]

CBC	Complete blood count
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
VLBW	Very low birth weight

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Optimizing the clinical utility of heart rate characteristics monitoring requires that clinicians understand the various clinical conditions associated with abnormal heart rate characteristics. Toward this goal, the aim of the current study was to quantify the occurrence of and clinical conditions associated with all abrupt, large increases (spikes) in the heart rate characteristics index in VLBW infants at the University of Virginia NICU enrolled in the multicenter randomized trial of heart rate characteristics monitoring.

Methods

We performed a retrospective medical record review of clinical events around the time of large heart rate characteristics index spikes in VLBW (<1500 g birth weight) infants. We included all VLBW infants at the University of Virginia NICU during a 3-year period (2007-2010) enrolled in the multicenter clinical trial of heart rate characteristics index monitoring (HeRO study). In the trial, infants were randomized to having their heart rate characteristics index displayed to clinicians or to conventional monitoring only (heart rate characteristics index recorded but not displayed). Clinicians were instructed about how the monitor was developed and were encouraged to evaluate infants whose heart rate characteristics index was increasing, but there were no mandated interventions for a specific score or rate of rise. Results of the clinical trial, in which 3003 VLBW infants in 9 NICUs underwent continuous heart rate characteristics index monitoring, were published in 2011.[10] The Institutional Review Board approved the randomized control trial, which required parental consent, and this retrospective review.

The heart rate characteristics index monitor (HeRO; Medical Predictive Science Corporation, Charlottesville, Virginia) uses existing electrocardiogram or heart rate data from standard bedside monitors to calculate the heart rate characteristics index, which is derived from an externally validated logistic regression calculation that relates decreased heart rate variability and transient heart rate decelerations to the fold increased risk over baseline risk that an infant will be diagnosed with sepsis in the next 24 hours. The monitor displays each infant's current heart rate characteristics index, which is updated every hour and represents heart rate characteristics over the previous 12 hours, and also displays the 5-day heart rate characteristics index trend (**Figure 1**).

We analyzed hourly heart rate characteristics index values and identified all large, abrupt increases in the heart rate characteristics index ("spikes"), defined as an increase in magnitude of at least 3 compared with the previous 5-day average, excluding the 12 hours before the peak (**Figure 1**, B). Spikes were excluded if they occurred within 5 days of a previous large spike or if there were not at least 24 hours of heart rate characteristics index baseline data before the spike.

Medical records were reviewed for birth weight, gestational age, and day of age at the time of the spike. Progress notes were reviewed on the day of the spike and the day before and after for descriptions of clinical status and events. Surgical or other procedures involving anesthetic or anticholinergic administration, including therapy for retinopathy of prematurity, were recorded. Dates of antibiotic administration and results of cultures and complete blood counts (CBCs) and leukocyte differential within 24 hours of the spike were collected. Infants who had antibiotics initiated or changed within a day of the spike were further classified as having septicemia (signs of sepsis, blood culture positive, and at least 5 days of antibiotics), clinical sepsis (signs of sepsis, negative cultures, and at least 5 days of antibiotics), or sepsis ruled out (signs of sepsis, negative cultures, and <5 days of antibiotics). Urinary tract infection was defined as a positive urine culture for which clinicians decided to continue antibiotics at least 5 days. NEC was defined as clinical and radiographic signs consistent with Bell stage II or III NEC. For infants who did not have antibiotics started or changed within a day of the spike, indications of respiratory deterioration were recorded. Respiratory deterioration was defined as a 50% increase in number of documented apnea events, supplemental oxygen, or ventilator support over the infant's previous 24-hour baseline.

Two clinicians independently reviewed medical records and assigned a clinical association to each spike. There was 80% agreement on the aforementioned designations on independent chart review by 2 clinicians and 100% agreement after joint review.

Because it was possible to have more than one clinical event temporally associated with the heart rate characteristics index spike, we established the following hierarchy of associations: (1) surgery or procedure requiring anesthetic or anticholinergic medication; (2) antibiotics initiated or changed for a suspected infection-related condition (further classified based on culture results and antibiotic duration); (3) respiratory deterioration, no antibiotics initiated; and (4) unknown (including infants already on antibiotics with no change in agent within a day of the spike).

Continuous variables were assessed by Student *t* test and categorical variables by Fisher exact test. Mean and SD are given, unless otherwise indicated. Statistical analyses were performed in GraphPad Prism (GraphPad Software, San Diego, California) with 2-tailed significance set at $P < .05$.

Results

Of 274 infants enrolled in the heart rate characteristics monitoring randomized clinical trial at the University of Virginia from 2007 to 2010, 224 large heart rate characteristics index spikes occurred in 105 infants (38%). Gestational age of infants with spikes was 25.8 ± 2.1 weeks (mean, SD) and birth weight 828 ± 228 g. Infants without spikes were of significantly greater gestational age and birth weight (28.9 ± 2.9 weeks, $P < .001$ and 1082 ± 281g, $P < .001$). Fifty-two infants had a single spike, 43 had 2-4 spikes, and 10 had 5 or more spikes. Mortality before discharge from the NICU of infants with and without large heart rate characteristics index spikes was 12% (16/138) and 7% (9/136) ($P = .45$), and mortality within 30 days of a large spike was 9% (5/53) for infants with heart rate characteristics index displayed and 12% (6/52) for nondisplay infants ($P = .76$).