



Published in final edited form as:

J Perinatol. 2013 November ; 33(11): 847–850. doi:10.1038/jp.2013.63.

Abnormal Heart Rate Characteristics Prior to Clinical Diagnosis of Necrotizing Enterocolitis

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Abstract

Objective—Earlier diagnosis and treatment of necrotizing enterocolitis (NEC) in preterm infants, prior to clinical deterioration, might improve outcomes. A monitor that measures abnormal heart rate characteristics (HRC) of decreased variability and repetitive decelerations was developed as an early warning system for sepsis. Since NEC shares pathophysiologic features with sepsis, we tested the hypothesis that abnormal HRC occur prior to clinical diagnosis of NEC.

Study Design—Retrospective review of Bells stage II to III NEC cases among infants <34 weeks gestation enrolled in a prospective randomized clinical trial of HRC monitoring at 3 neonatal intensive care units.

Results—Of 97 infants with NEC and HRC data, 33 underwent surgical intervention within one week of diagnosis. The baseline HRC index from 1 to 3 days before diagnosis was higher in patients who developed surgical versus medical NEC (2.06 ± 1.98 vs. 1.22 ± 1.10 , $p=0.009$). The HRC index increased significantly 16 hours prior to the clinical diagnosis of surgical NEC and 6 hours prior to medical NEC. At the time of clinical diagnosis, the HRC index was higher in patients with surgical versus medical NEC (3.3 ± 2.2 vs 1.9 ± 1.7 , $p<0.001$).

Conclusions—Abnormal HRC occur before clinical diagnosis of NEC, suggesting that continuous HRC monitoring may facilitate earlier detection and treatment.

Keywords

neonatal intensive care unit; preterm infant; heart rate variability; predictive monitoring

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Introduction

Necrotizing enterocolitis (NEC) is the most common acquired intestinal disease of preterm infants, and despite advances in neonatal intensive care unit (NICU) care, mortality may be as high as 30%.^{1, 2, 3} Survivors of NEC have longer hospital stay and are at risk for long-term nutritional and neurologic problems.^{4, 5, 6} A major challenge toward improving outcomes is identifying and treating infants in the early stages of NEC, when clinical signs may be subtle and nonspecific. Once more definitive signs appear, adverse outcomes such as extensive bowel necrosis leading to death or short bowel syndrome are more likely.⁷ Discovering markers of NEC that appear prior to overt clinical signs would facilitate earlier goal-directed therapies which could improve outcomes.

Abnormal heart rate characteristics (HRC) have been established as a biomarker for late-onset neonatal sepsis and mortality in NICU patients.⁸ Our group has shown that reduced heart rate variability and repetitive transient decelerations often occur in the preclinical phase of sepsis.⁹ This finding inspired the development of a monitor that calculates an HRC index, a mathematical representation of decreased beat-to-beat variability and decelerations which is the fold-increase in probability of sepsis being diagnosed in the next 24 hours.^{10, 11} In a recent randomized clinical trial of 3003 infants, HRC monitoring reduced mortality in VLBW infants from 10.2% to 8.1%, a statistically significant and clinically meaningful result.¹²

Necrotizing enterocolitis and sepsis share pathophysiologic features, including a systemic inflammatory response,¹³ hemodynamic compromise, and organ hypoperfusion.¹⁴ We and others have shown that elevated circulating levels of proinflammatory cytokines contribute to decreased heart rate variability^{15, 16, 17, 18} In NEC, serum cytokines are elevated, particularly when there is significant intestinal necrosis or associated bacteremia.¹⁹ Intestinal hypomotility, ileus, and bowel distension have also been associated with increased vagal tone and altered heart rate characteristics in adults.^{20, 21} Our studies in preclinical models indicate that peritoneal administration of bacteria or fungi activates vagus nerve pathways leading to transient heart rate decelerations similar to those seen in neonates with sepsis.²² Heart rate characteristics changes may thus reflect activation of the cholinergic anti-inflammatory pathway which plays a critical role in host defense.²³

Abnormal heart rate characteristics have not previously been studied in infants with NEC, and we therefore undertook a retrospective review of cases of NEC in VLBW infants during a prospective randomized clinical trial of HRC monitoring. Our goal was to determine whether the HRC index could identify patients in the early, preclinical phase of disease when aggressive treatment may improve outcomes.

Methods

Study population

We retrospectively identified all cases of NEC Bell's stage II to III²⁴ in very low birth weight (VLBW <1500 grams) infants admitted from January 2005 to April 2010 to 3 centers

participating in a prospective randomized clinical trial (RCT) of HRC monitoring. In the HRC (HeRO) RCT, 3003 VLBW infants in 9 NICUs had HRC continuously monitored and were randomized to having their HRC index displayed to clinicians, or not displayed, then followed for 120 days or until death or NICU discharge. Results of this study were published in 2011.¹² Institutional Review Boards of each institution approved the RCT, which required parental consent, and approved retrospective review of deidentified patient data for the current analysis. The three centers participating in the current analysis were the University of Virginia, Wake Forest University (Brenner Children's Hospital and Forsyth Medical Center), and Vanderbilt University. At the University of Virginia, the principle site for the RCT, VLBW infants not enrolled in the HRC trial had HRC monitored but not displayed to clinicians. At the other units, infants not enrolled in the RCT did not have HRC monitored.

NEC diagnosis and clinical features

Through database review, we identified all cases of NEC in the three centers in the date range indicated above, and then identified cases meeting the following criteria: less than 34 weeks gestational age, clinical and radiographic evidence of Bell's stage II to III NEC, at least 7 days of age at diagnosis, and at least 7 days of treatment with bowel rest and antibiotics. Clinical signs included abdominal distention, ileus, and hematochezia. Radiographic signs included fixed dilated loops, pneumatosis intestinalis, portal venous gas, and pneumoperitoneum. We excluded patients in whom a diagnosis of spontaneous intestinal perforation was made at the time of laparotomy, as well as repeat episodes of NEC in the same patient.

Medical records were reviewed for demographic and clinical variables. The time of NEC diagnosis was defined as the time of the initial abdominal radiograph that led to the diagnosis of NEC. Cases were classified as medical or surgical, the latter defined as peritoneal drain placement or laparotomy within 7 days of NEC diagnosis. Mortality was considered within 14 days of NEC diagnosis.

Heart rate characteristics index monitoring

The heart rate characteristics (HeRO) monitor (Medical Predictive Science Corporation, Charlottesville, VA) uses the electrocardiogram from standard NICU bedside monitors to continuously calculate an HRC index. The mathematical algorithm from which the HRC index is derived incorporates decreased variability and transient decelerations and, using logistic regression, is the fold increase in probability of sepsis being diagnosed in the next 24 hours. The monitor continuously displays the HRC index which is updated hourly and represents HRC over the previous 12 hours. In the randomized trial, clinicians were educated about the HRC index but no course of action was mandated for patients with a rising score.

Statistical analysis

Comparisons of hourly HRC index between the two groups (medical and surgical NEC) were made by t-test for continuous variables and Fisher's exact test for categorical variables. Paired signed rank test was used to analyze the rise in the HRC index before NEC diagnosis.

Average HRC index \pm standard deviation is given, unless otherwise noted. Statistical analyses were performed in MatLab (MathWorks, Natick, MA) with a two-tailed level of significance of 0.05.

Results

Patient demographics and clinical course

We identified 97 episodes of NEC Bell's stage II to III in VLBW infants <34 weeks gestation with heart rate characteristics data available at the time of diagnosis. 33 of these patients underwent either laparotomy or peritoneal drain placement within 7 days of diagnosis and were classified as surgical NEC for this analysis. Clinical characteristics and outcomes are shown in Table 1. Patients that had surgical intervention (laparotomy or peritoneal drain placement) within one week of NEC diagnosis were of lower gestational age, were more likely to have a positive blood culture, and were more likely to die within 14 days of NEC diagnosis.

Figure 1 shows screen shots from the HRC monitor, with representative examples of normal HRC and abnormal HRC occurring prior to clinical presentation of NEC.

HRC index in infants with medical and surgical NEC

The baseline HRC index from 1 to 3 days before NEC diagnosis was higher in patients who developed surgical versus medical NEC (2.06 ± 1.98 vs. 1.22 ± 1.10 , $p=0.009$), and this difference persisted after adjustment for gestational age and birth weight. In the hours leading up to the clinical diagnosis of NEC, there was a significant rise in the HRC index over patients' prior 24 hour baseline (Figure 2). This occurred 16 hours before clinical diagnosis of surgical NEC and 6 hours prior to diagnosis of medical NEC.

At the time of diagnosis, patients with surgical NEC had a higher average HRC index compared to those with medical NEC (3.3 ± 2.2 vs 1.9 ± 1.7 , $p<0.001$), and patients who died had a higher HRC index compared with survivors (4.0 ± 1.9 vs. 2.5 ± 1.7 , $p=0.004$) (Table 1). Blood culture within 24 hours of NEC diagnosis was positive in 22 cases, negative in 74, and not obtained in 1. The HRC index in patients with a positive blood culture was 3.0 ± 1.5 and in those with a negative blood culture was 2.6 ± 1.9 , ($p=0.44$). Considering only patients with a negative blood culture at the time of NEC diagnosis, there was a significantly higher HRC index in those with surgical compared to those with medical NEC (3.8 ± 2.0 vs. 2.2 ± 1.7 , $p=0.007$).

After NEC diagnosis, the HRC index increased in both groups, peaking 15 hours after clinical diagnosis (Figure 2). Of note, general anesthesia and surgery lead to abnormal heart rate characteristics, and the figure therefore displays the HRC index only prior to surgical intervention.

HRC index display versus non-display

Of the 97 patients with NEC, 88 had been enrolled, with parental consent, in a randomized clinical trial in which the HRC index was either displayed to clinicians or not displayed (47 randomized to HRC display and 41 to non-display). The remaining 9 patients were at the

University of Virginia and were not enrolled in the RCT but had HRC monitored and not displayed to clinicians, per unit protocol. Thus, there were 47 patients with HRC displayed and 50 non-displayed. Figure 3 shows the HRC index around the time of NEC diagnosis in patients in the non-display group compared to the HRC display group..

Discussion

Identification of biomarkers for prediction or early detection of NEC has been the subject of intense investigation, which is appropriate given the high incidence and potentially devastating consequences of the disease. In the current analysis of VLBW infants admitted to 3 centers during a randomized clinical trial of heart rate characteristics monitoring, we found that abnormal HRC similar to those seen in sepsis also occur in preterm infants prior to clinical presentation of NEC. If clinicians are alerted to this physiologic change they may be prompted to closely evaluate the patient and consider further testing and treatment, potentially leading to improved outcomes through early intervention.

Prior studies of NEC biomarkers have not yet yielded clinically useful tests. Daily calculation of the Score for Neonatal Acute Physiology-II (SNAP-II), which includes measures of hypotension, hypothermia, acidosis, and oxygenation, was shown not to predict or detect NEC.²⁵ Genetic susceptibility testing, breath hydrogen sampling, and testing for inflammatory markers in blood or stool have all been shown to have limited diagnostic value.²⁶ Measurements of altered mesenteric blood flow^{27, 28} and changes in intestinal microbiota²⁹ show promise for predicting or detecting NEC but are in early stages of investigation. Our study indicates that a commercially available monitor that is FDA-cleared for reporting on abnormal heart rate characteristics in neonates can detect biological changes associated with NEC up to a day before clinicians recognize that a patient is ill.

Abnormal heart rate characteristics of decreased variability and decelerations were discovered by our group to be strongly associated with late-onset sepsis in preterm infants.^{9, 30, 31, 32} Since NEC shares pathophysiologic features with sepsis it is not surprising that HRC are abnormal in infants at the time of diagnosis of NEC. The systemic inflammatory response, intestinal distension, and tissue necrosis may all contribute indirectly (via autonomic nervous system activation and dysfunction) or directly (via effects on sinoatrial node pacemaker cells) to abnormal heart rate characteristics. In the current analysis we found that the HRC index continued to rise after diagnosis and the start of treatment of NEC, in contrast to sepsis where we previously have shown that peak HRC occurs near the time of diagnosis and declines after antibiotics and other therapies are started. The continued worsening of HRC in patients with NEC parallels the clinical course in these infants in whom a dramatic systemic inflammatory response and, in some cases, significant bowel necrosis, often lead to progressive clinical deterioration even after initiation of therapy. The clinical relevance of this finding is that, in NICU patients started on antibiotics for suspected infection, a continued rise in the HRC index could be a sign of an ongoing inflammatory process and should lead to careful clinical assessment and consideration of additional studies or therapies.

Most patients in the current analysis were participating in a randomized clinical trial of 3003 VLBW infants in which the HRC index was monitored in all infants but displayed to clinicians in only half. In this large clinical trial, mortality was significantly reduced in patients who had their HRC index continuously displayed. In the current analysis, we did not find a statistically significant difference in the average HRC index prior to NEC diagnosis in infants in the HRC display and non-display groups. A limitation of the current analysis is that the number of infants was small, and in the randomized clinical trial there was no mandated intervention for infants with an acute rise in their HRC index. A larger number of infants with NEC would be required to determine whether display of the HRC index leads to earlier treatment or improved outcomes

Conclusion

Earlier diagnosis of NEC and institution of therapies to decrease the metabolic demand (bowel rest), reduce intestinal distension (gastric decompression), treat infection (broad-spectrum antibiotics), and optimize tissue oxygen delivery (fluid resuscitation and blood pressure support) may improve outcomes. Newer therapies for NEC such as anti-inflammatory agents³³ may also be more effective if patients can be identified in the early phases of illness. Continuous monitoring of heart rate characteristics provides clinicians with information about subtle physiologic changes associated with the systemic inflammatory response that proceed clinical deterioration associated with NEC, raising the possibility of improving patient outcomes through earlier intervention.

Acknowledgments

Funding: National Institutes of Health (grant R01-HD48562 to J.R.M.)

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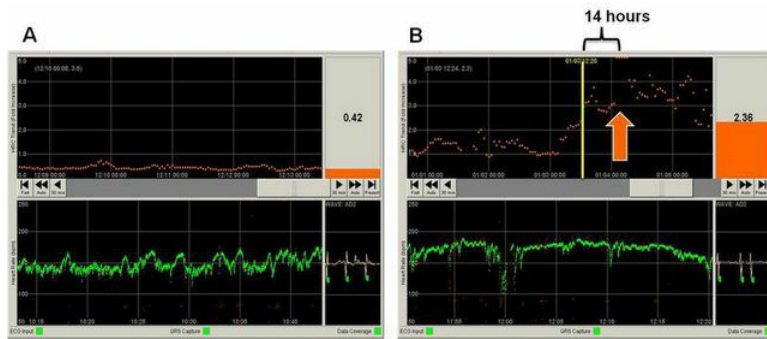


Figure 1. Heart rate characteristics monitor screen shots showing normal HRC and abnormal HRC in a patient with NEC

A) HRC monitor screen for an individual patient with normal heart rate characteristics. The bottom panel shows the last 30 minutes of heart rate (green) with a baseline HR of 150 beats per minute and normal frequent small accelerations and decelerations. The top panel shows the 5-day trend in the HRC index, which is derived from measures of heart rate variability and repetitive decelerations and is the probability the patient will be diagnosed with sepsis in the next 24 hours. In this patient, the HRC index has been low (<1) for 5 days indicating normal HRC and low probability of sepsis. The current HRC index is displayed in the upper right corner (0.42). **B)** HRC monitor screen for a patient with necrotizing enterocolitis and E. coli bacteremia. The time of clinical diagnosis of NEC is indicated by the orange arrow, at which time the HRC index was >5. Fourteen hours before NEC diagnosis (yellow vertical line) the HRC index had risen to 2.36 reflecting decreased accelerations and transient decelerations as seen in the corresponding HR tracing (green, bottom).

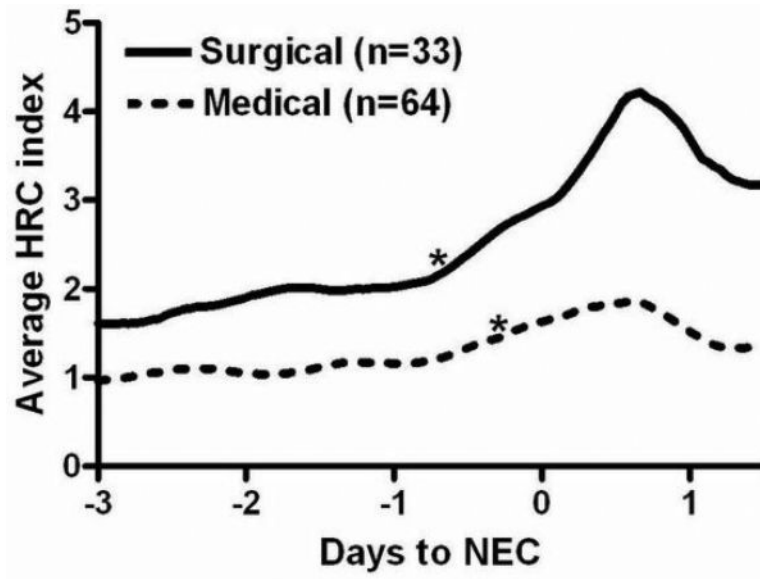


Figure 2. Heart rate characteristics index in very low birth weight infants with medical or surgical necrotizing enterocolitis
97 VLBW infants with Bell's stage II or III NEC at 3 centers had HRC index monitoring data available around the time of NEC diagnosis (day 0). *indicates significant increase in average HRC index compared to the previous 24 hour average ($p < 0.01$).

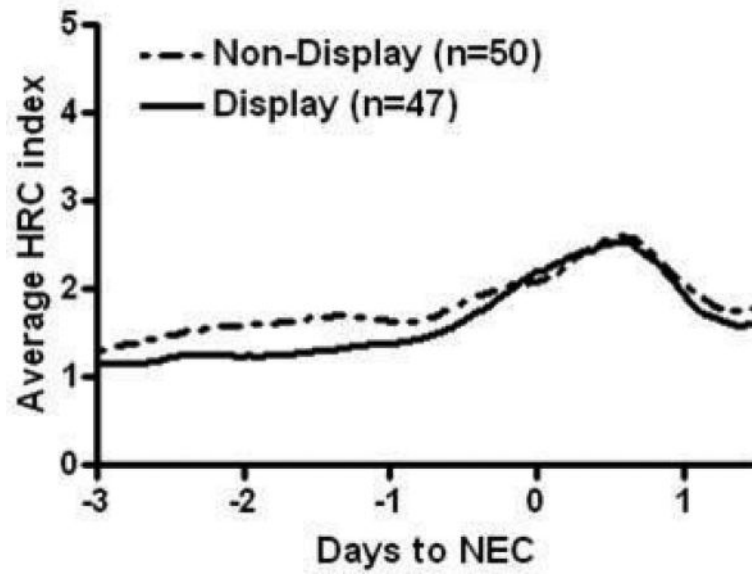


Figure 3. HRC index in infants with NEC with HRC index displayed or not displayed to clinicians

Of 97 infants with NEC, 88 were enrolled in a clinical trial of HRC monitoring in which infants were randomized to having their HRC index displayed to clinicians, and 9 had HRC monitored but not displayed outside the clinical trial. Average HRC index is shown before and after NEC diagnosis at day 0 for infants with HRC displayed, (solid line, n=47) or not displayed (dashed line, n=50).

Table 1

Clinical characteristics and outcomes of patients with medical and surgical NEC

	Medical NEC (n = 64)	Surgical NEC (n = 33)	p =
Gestational age (weeks)	27.0 ± 2.7	25.8 ± 2.3	0.03
Birth weight (grams)	914 ± 236	827 ± 231	0.09
Female gender (n,%)	28 (44%)	13 (39%)	0.83
Age at NEC (days)	30 ± 17	31 ± 22	0.95
HRC at diagnosis	1.9 ± 1.7	3.3 ± 2.2	0.002
Positive blood culture	11 (17%)	11 (33%)	0.08
Mortality (n,%)	4 (6%)	15 (46%)	<0.001

Mean ± SD or n (%), where indicated

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