HeRO monitoring in the NICU: sepsis detection and beyond

Heart rate observation (HeRO) monitoring was developed for detection of sepsis in preterm infants. In a randomised clinical trial of 3,003 very low birthweight infants, displaying the HeRO score to clinicians significantly reduced mortality. The HeRO monitor is now in use in many NICUs in the USA and was approved in 2012 for use in Europe.

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Glossary
HRV = heart rate variability
HRC = heart rate characteristics (HRV + decelerations)
HeRO monitor = heart rate observation monitor
HRC index = HeRO score

Keywords

neonatal sepsis; heart rate variability; heart rate characteristics; very low birth weight; prematurity

Key points

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1. Use of the HeRO monitor reduces sepsis-associated mortality in preterm infants.
2. Combining HRC with other predictive monitoring strategies (eg biomarker screening and respiratory analysis) may lead to further improvement in patient outcomes.

Heart rate patterns offer a 'window' into autonomic nervous system function: when they become abnormal they signal an underlying pathology[1]. Preterm infants in the neonatal intensive care unit (NICU) are extremely vulnerable to sepsis, which is often associated with decreased heart rate variability (HRV) and transient heart rate decelerations[2]. A monitor was developed – the HeRO monitor – to analyse these abnormal heart rate characteristics (HRC) and display to clinicians a score, which indicates the risk of an infant deteriorating from sepsis in the next day[3-5]. Display of this HeRO score resulted in a 22% relative reduction in mortality in a large randomised clinical trial (RCT) of very low birthweight (VLBW) NICU patients[6]. New research has elucidated various pathological conditions that can cause worsening of HRC and a rise in the HeRO score. To assist clinicians in appropriate use of the HeRO monitor for the benefit of NICU patients, this article will review:

- The physiological basis of abnormal HRC in sepsis
- Development and validation of the HeRO algorithm
- Results of the RCT of HeRO monitoring
- Answers to frequently asked questions about the monitor
- Clinical conditions associated with a high HeRO score
- Current research aimed at developing even more sophisticated and effective predictive monitoring algorithms to improve outcomes of patients in the NICU and elsewhere in the hospital.

Neonatal sepsis: past and present

The following section describes two actual cases. The first case demonstrates conventional NICU care and the second, NICU care that includes predictive monitoring for sepsis using the HeRO monitor.

Case 1, 2003

Baby boy D is a four-week-old, former 28-week infant on nasal cannula oxygen and full enteral feeds. He normally has one or two self-resolved apnoea events per day but develops increased apnoea requiring stimulation. He looks well and a caffeine bolus is given. Within a day, he requires intubation and mechanical ventilation and is lethargic with poor perfusion. A sepsis evaluation is performed and antibiotics are initiated. In spite of aggressive treatment, he develops septic shock and dies two days later. His blood culture yields *Serratia marcescens*.

Case 2, 2013

Baby girl W is a two-week-old, former 30-week infant on nasal CPAP. She is building up her feeds but develops temperature instability. She looks well but her HeRO score has risen from one to 2.5 in the past six hours, so cultures are obtained and antibiotics initiated. Blood and urine cultures yield *Klebsiella pneumoniae*. Antibiotics are continued for 14 days and she recovers uneventfully.

The physiology of abnormal HRV and HRC

In the healthy state there are frequent small accelerations and decelerations in heart rate in response to sympathetic and parasympathetic signals to cardiac pacemaker cells. Pathological processes leading to disturbances in autonomic

nervous system function may be associated with depressed HRV. In some cases the decreased HRV may be accompanied by transient heart rate decelerations. A well-known example is the asphyxiated fetus with poor beat-to-beat variability and superimposed decelerations. These abnormal HRC, of decreased HRV and decelerations, also occur in neonates with sepsis[3]. Other physiological perturbations and several medications can also lead to abnormal HRC, as discussed later.

Subtle changes in HRC often occur in the early stages of sepsis before an infant develops any clinical signs. This finding raised the possibility of developing a monitoring system to predict that an infant would, in the near future, experience a clinical deterioration from sepsis, allowing earlier interventions leading to improved outcomes.

Development and testing of the HeRO monitor

Abnormal HRC cannot be discerned simply by observing the electrocardiogram (ECG) signal or the absolute values of heart rate as they quickly pass by on standard NICU cardiorespiratory monitors. Researchers at the University of Virginia developed a monitor that analyses ECG and heart rate signals from the bedside monitor, for patterns that predict impending sepsis. The monitor presents a score to aid in the clinical decision-making process. Using data from over 300 VLBW infants with over 100 sepsis events, a mathematical algorithm was derived that includes three components[4-5,7-8]:

1. Standard deviation of inter-heartbeat (RR) intervals
2. Sample asymmetry
3. Sample entropy.

The standard deviation of RR intervals is a classic and commonly used time-series measure of HRV. Further work showed that analysis of high and low-frequency HRV, which are thought to represent parasympathetic and sympathetic tone, respectively, does not improve on time-series analysis for detection of neonatal sepsis[9]. Simple measurement of HRV would be ineffective for predicting early stages of neonatal sepsis due to the occurrence of transient decelerations, which may be pathological yet would lead to normalisation of HRV. Consequently two other measures were incorporated into the HeRO score algorithm.

Sample asymmetry measures skewing of heart rate toward frequent large decelerations and few accelerations. Sample entropy relates to the normal irregularity of heart rate[7-8,10]. Low HRV, high sample asymmetry (skewed toward decelerations) and low sample entropy increase the HeRO score, which is a multivariable logistic regression expression that represents the fold increase in risk that an infant will have a clinical deterioration from sepsis within 24 hours[3,5,11-13]. After being developed on data from infants in one NICU, the HeRO score was externally validated for sepsis detection in VLBW infants in a second NICU[3,5].

The HeRO monitor (Medical Predictive Science Corporation, Charlottesville, Virginia, USA) was approved by the US Food and Drug Administration in 2003 for measurement of HRC in infants and children (510k clearance), and received CE marking for use in Europe in 2012. The HeRO score is continuously calculated from the previous 12 hours of ECG and heart rate recordings and is updated hourly. The monitor provides individual patient display (**FIGURE 1**) that shows the infant's current HeRO score, the trend in the score over the previous five days and the heart rate over the previous 30 minutes. Clinicians can also select multi-patient views that display current HeRO scores and the prior five-day trends in clusters of patients (**FIGURE 2**) or in all patients in the NICU (**FIGURE 3**).

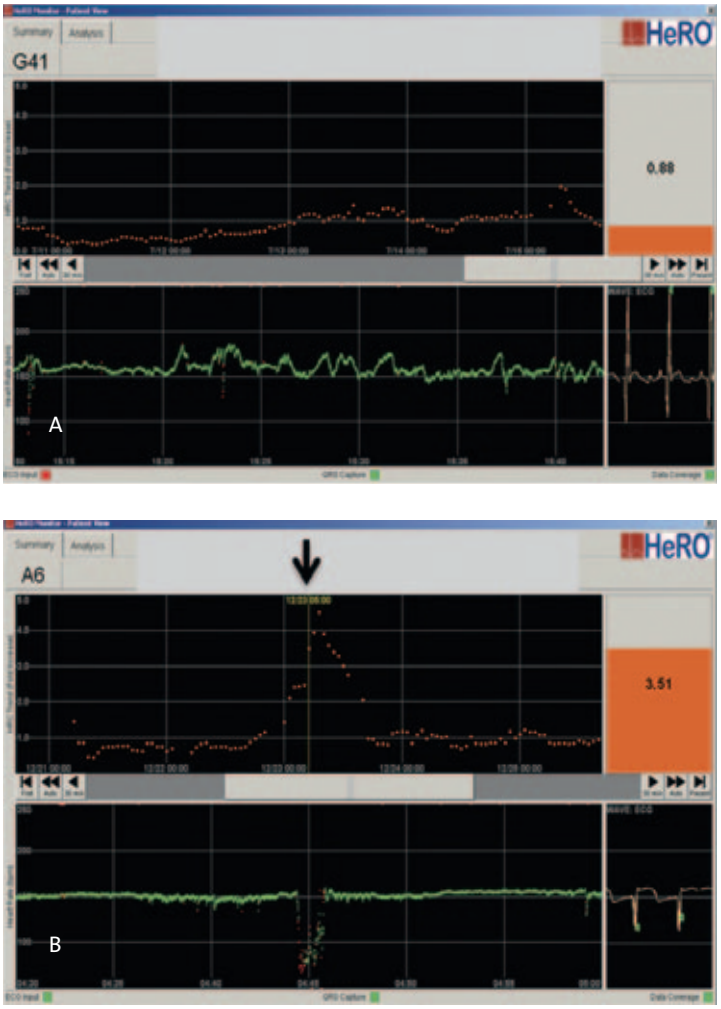

FIGURE 1 Display screens from the HeRO monitor showing an individual patient's normal and abnormal HRC. The monitor displays the last five days of the HeRO score (top, orange) and the last 30 minutes of heart rate (bottom, green, beats per minute). (A) Screen shot from an infant with normal HRC and a low HeRO score (0.88, shown in top right panel). (B) Screen shot showing a large transient 'spike' in the HeRO score (arrow) with decreased HRV and decelerations.

The HeRO trial

To test the utility of the HeRO monitor for improving outcomes of VLBW infants, a RCT was conducted from 2004 to 2010[6]. In the HeRO trial, which was sponsored by the National Institutes of Health (NIH), VLBW infants in nine NICUs in the US underwent continuous HeRO monitoring and were randomised (with parental consent) to having their HeRO score displayed or not displayed to clinicians. Clinicians were educated on how the HeRO score was developed and encouraged to evaluate infants whose score was rising, but there were no mandated interventions for a particular score or rate of rise. The primary outcome was days alive and not on mechanical ventilation in

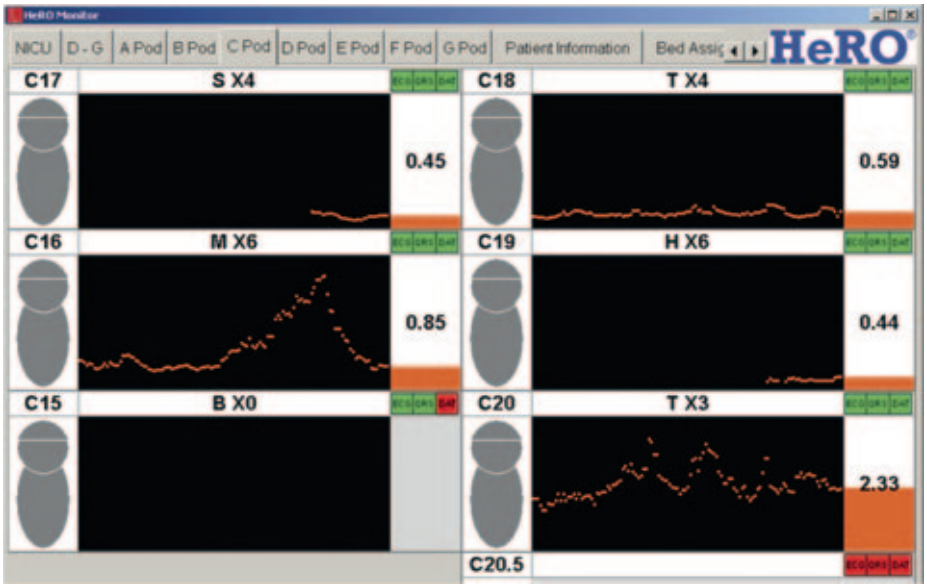

FIGURE 2 A 'pod view' from the HeRO monitor showing HeRO scores on multiple patients. In this view, five-day trends for five patients are shown by orange dotted lines and current HeRO scores are indicated in the right hand panels.

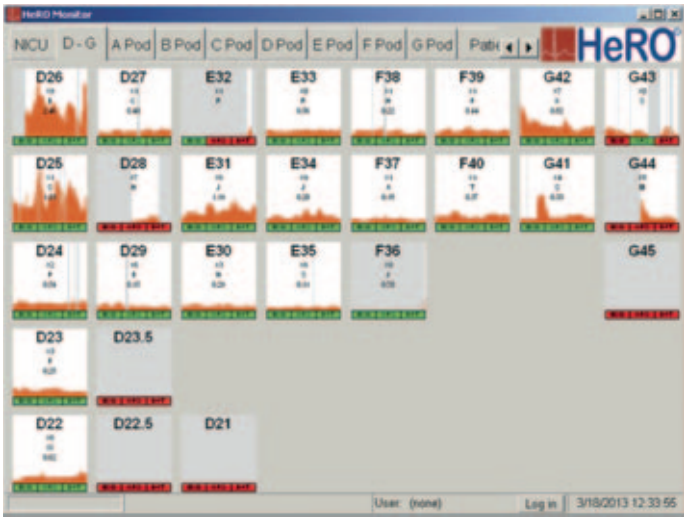

FIGURE 3 A 'unit view' from the HeRO monitor showing HeRO scores from all patients in the NICU. HeRO scores may be displayed in the patient care areas and visualised remotely in real time.

the 120 days after randomisation. Mortality was a secondary outcome. With 3,003 infants enrolled, this was the largest RCT published to date in VLBW infants. The statistically significant and clinically important outcome was a 22% relative reduction in mortality (from 10.2% to 8.1%, p=0.04) for infants whose HeRO score was displayed, which translated to one extra survivor for every 48 VLBW or 23 ELBW infants monitored.

A subsequent analysis focusing on the 974 cases of septicaemia among 700 infants in the HeRO trial, revealed that mortality within 30 days of septicaemia was reduced by 40% (from 19.6% to 11.8%, p<0.01) when the HeRO score was displayed[14]. In that analysis, another interesting finding was that large, transient increases in the HeRO score ('spikes') often occurred several days prior to diagnosis of septicaemia and were more common in infants whose HeRO score was not displayed. The exact time that bacteria enter the bloodstream of an infant is of course not known, but it can be speculated that some infants experience a sepsis prodrome as their immune system works to contain pathogens. The stuttering increases in the HeRO score prior to clinical deterioration could reflect 'waxing and waning' of host responses or of bacterial burden in the bloodstream and display of these pre-clinical HeRO spikes to clinicians could represent opportunities for earlier treatment and improved outcomes.

HeRO frequently asked questions

Are there drawbacks to HeRO monitoring?

Continuously displaying a number indicating risk for sepsis could result in infants undergoing more medical examinations and receiving more antibiotics. In the RCT, infants in the HeRO display group had 10% more blood cultures obtained (1.8 compared with 1.6 blood cultures per month, p=0.05) and 5% more days on antibiotics (15.7 compared with 15.0 days, p=0.31). In the subsequent analysis of septicaemia cases in the clinical trial, the infants who never experienced septicaemia had no difference in antibiotic days, whereas the 700 infants who had one or more episodes of septicaemia had a 10% increase in total antibiotic days during their NICU stay if their HeRO score was displayed (32 versus 29 days)[14]. While this illustrates a trade-off for reduced mortality, the rather small increase in antibiotic days suggests that clinicians may have used the HeRO score not only in decisions to start antibiotics, but also in decisions (when infants had mild or non-specific symptoms and the score was low) to either withhold or shorten duration of antibiotics.

Another concern regarding HeRO monitoring is that abnormal HRC are not specific to sepsis and occur in other pathological conditions in sick NICU patients. This presents a challenge to clinicians and the HeRO score should not be the sole factor in decision making, but should be considered in the context of other clinical information. An understanding of the various conditions that can affect HRC and increase the HeRO score is important for appropriate use of the HeRO monitor.

What conditions cause an increased HeRO score?

Sepsis (and other infection-related conditions) is the leading cause of significant increases in the HeRO score in VLBW infants. In a subset of infants in the clinical trial (those randomised to clinicians blinded to their HeRO score at one centre), over half of large increases in the score (an increase of three points over the prior baseline) were temporally associated with a suspected or proven infection-related condition, including urinary tract infection or necrotising enterocolitis (NEC). In some of these cases, sepsis was initially suspected due to symptoms and/or abnormal laboratory findings and subsequently ruled out with negative cultures. A systemic inflammatory response or other physiological perturbation without infection may be responsible for increases in the HeRO score in some cases.

NEC, like sepsis, may lead to cardiorespiratory instability and abnormal HRC. In a study of 97 cases of NEC in infants enrolled in the HeRO RCT at three centres, the HeRO score increased significantly 16 hours before clinicians diagnosed surgical NEC and six hours before diagnosis of medical NEC, irrespective of whether septicaemia was also present[15]. In contrast to sepsis, in which the HeRO score tends to decline once antibiotics are started, in NEC the score often continues to rise for up to 24 hours after treatment is initiated. This is likely to reflect ongoing systemic and bowel inflammation.

Respiratory deterioration without infection can also lead to an increase in the HeRO score, possibly due to apnoea, hypoxia, acidosis or lung inflammation. In a study of multiple cardiorespiratory measurements in VLBW NICU patients, an elevated HeRO score was highly predictive of the need for non-elective intubation[16]. Further studies are needed to determine whether predictive monitoring for respiratory failure would improve outcomes of ICU patients, by alerting clinicians to a patient's worsening respiratory status leading to interventions to avoid the need for mechanical ventilation.

Surgery and procedures requiring anaesthetic or anticholinergic medications, including treatment for retinopathy of prematurity, tend to cause decreased HRV and an acute rise in the HeRO score. In uncomplicated cases, the score rises quickly and returns to baseline within 12 to 18 hours.

Medications known to affect the HeRO score include atropine, paralytics and dexamethasone. Premedication is increasingly used for intubation in NICU patients and atropine and paralytics depress HRV and raise the HeRO score. Dexamethasone administration tends to lower the HeRO score, possibly in part by reducing cytokine production and systemic inflammation[17]. Other medications commonly used in the NICU have not been observed to affect the HeRO score.

Cardiac arrhythmias can impact the HeRO score. The most common arrhythmia in NICU patients, supraventricular tachycardia, leads to a dramatic decrease in HRV and, if persistent, a large increase in the HeRO score. The impact of other cardiac conditions on the HeRO score is less established.

Brain injury may be associated with decreased HRV in ICU patients[18-20]. Preterm infants with severe intraventricular haemorrhage may have chronic intermittent increases in their HeRO score, not attributable to infection in the first few weeks after birth, possibly reflecting neurological dysfunction or a chronic systemic inflammatory response to the haemorrhage. Since a high HeRO score can reflect both acute intracranial pathology and occurrence of adverse events, such as sepsis and NEC, that can adversely impact neurodevelopmental outcomes, the average or cumulative HeRO score during part or all of the NICU stay could serve as a prognostic marker for long-term neurological outcomes. In a study of 65 VLBW infants enrolled in the HeRO trial, an association between a high cumulative HeRO score during the NICU stay and cerebral palsy or cognitive impairment at one year of age was reported[21].

What should clinicians do when an infant's HeRO score is rising?

1. Look at the infant. Are there any indications of infection on physical examination or in recent vital sign trends?
2. Talk to the bedside caregivers. Has the nurse or the mother noted any change in the infant's condition? Is the infant having increased apnoea, feeding intolerance, temperature instability, lethargy or other signs of illness?
3. Review the HeRO score trends. What is the height of the HeRO score and the trend over the past week? Is this a chronically ill infant with a history of score increases not related to infection (perhaps associated with severe lung disease or intraventricular haemorrhage)?
4. Decide, based on the above considerations, whether to:
    a. Wait and watch the infant closely
    b. Obtain laboratory or radiographic studies to evaluate for infection or NEC
    c. Start antibiotics.
5. There is no 'threshold' HeRO score that should prompt initiation of antibiotics in every patient. A rise of 1-2 points over the prior baseline should at least lead to very close observation and consideration of whether antibiotics are indicated, bearing in mind that the goal is to initiate therapy *before* the infant experiences obvious clinical deterioration.

Can the HeRO score be used to predict early onset neonatal sepsis?

The HeRO score was developed and validated for prediction of late onset sepsis (LOS) at three days of age and beyond. Culture-positive early onset sepsis is uncommon, occurring in only approximately 2% of VLBW infants compared to up to 20% LOS[22-23]. HRC may be abnormal in early onset sepsis, but there are many other pathophysiological conditions occurring in the perinatal and early neonatal period that could impact on the HeRO score. The predictive value of the HeRO score for sepsis or other conditions in the first few days after birth remains to be studied.

How should we use the HeRO score for a chronically ill infant whose score is frequently high?

These very sick infants present a challenge, since they are at high risk for infection but may have abnormal HRC due to respiratory, neurological or other pathological conditions. In these infants it is especially important to carefully consider all clinical variables in conjunction with the HeRO score trends to make judicious decisions about starting and stopping antibiotics. Laboratory tests such as leukocyte differential, acute phase reactant levels (eg C-reactive protein) or cytokine measurements may be useful in some cases.

The future of predictive monitoring

The HeRO monitor is the first example of predictive monitoring being taken from bench to bedside, with a randomised trial showing lower mortality in preterm infants when clinicians could see the HeRO score[6]. Research is underway to add analysis of other vital signs to algorithms for predicting sepsis, NEC, and other pathological conditions for which early detection and intervention would be expected to lead to better patient outcomes.

Respiratory analysis

Apnoea is one of the most common signs of late onset sepsis in preterm infants[24]. It is difficult to measure since chest impedance analysis of respiratory rate can be inaccurate leading to false positive and false negative monitor alarms and since manual documentation of apnoea events in the medical record is inefficient and inaccurate[25]. The researchers who

developed the HeRO monitor recently developed a computerised apnoea detection system[25-26] that is being used to develop combined cardiorespiratory algorithms for early detection of sepsis and NEC. Sepsis-associated apnoea may be, not only quantitatively but also qualitatively, different to physiological apnoea of prematurity and preliminary evidence suggests that exaggerated periodic breathing may also be a harbinger of sepsis or NEC in some preterm infants.

Adding laboratory tests to cardiorespiratory monitoring algorithms

Combining targeted biomarker testing with continuous physiomarker screening is likely to have a much greater impact on improving patient outcomes than either strategy alone. Biomarker testing is typically performed once a patient is suspected to have a condition such as sepsis, and by this time (when signs and symptoms have become obvious to clinicians) the condition may be in advanced stages and the outcome may be poor. Cardiorespiratory predictive monitoring may detect subtle physiological changes in the early, pre-clinical stage of life-threatening illness, but the positive predictive accuracy and specificity of existing algorithms leave room for improvement. Addition of laboratory tests or biomarker screens at the time that a predictive monitoring score is becoming abnormal could assist in decisions about whether to initiate therapy. In the case of sepsis, for example, testing of cytokines or acute phase reactants (such as C-reactive protein) at the time that the HeRO score is rising, could provide further evidence of infection or reassurance about absence of infection. Of course, for the patient in whom there is significant clinical suspicion of sepsis based on signs, symptoms or abnormal laboratory tests, treatment should be initiated expeditiously regardless of the HeRO score, biomarkers or any other risk predictor.

Conclusion

Predictive monitoring for early detection of potentially catastrophic illness is the wave of the future in ICU medicine. The HeRO monitor has been shown to reduce sepsis-associated mortality in preterm infants. New algorithms incorporating other vital signs and laboratory tests may enhance the diagnostic utility of this new technology and lead to further improvement in patient outcomes.

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