Published in final edited form as:

Clin Perinatol. 2010 September ; 37(3): 581–598. doi:10.1016/j.clp.2010.06.002.

Heart Rate Characteristics: Physiomarkers for Detection of Late-Onset Neonatal Sepsis

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Synopsis

Early detection of late onset neonatal sepsis, prior to obvious and potentially catastrophic clinical signs, is an important goal in neonatal medicine. Sepsis causes a well-known series of physiologic changes including abnormalities of blood pressure, respiration, temperature, and heart rate, and less well-known changes in heart rate variability. While vital signs are frequently or continuously monitored in NICU patients, changes in these parameters are subtle in the early phase of sepsis and difficult to interpret using traditional NICU monitoring tools. A new tool, continuous monitoring of heart rate characteristics, is now available for clinical use. Recent research has established that two abnormalities of heart rate characteristics which have long been used by obstetricians to identify fetal compromise - reduced heart rate variability and transient decelerations - occur early in the course of sepsis in NICU patients, often before clinical signs of illness. Through mathematical modeling of electrocardiogram data from hundreds of NICU patients, a heart rate characteristics (HRC) index was derived that represents the fold increase in risk that a neonate will be diagnosed with clinical or culture-proven sepsis within the next 24 hours. The impact of continuous HRC monitoring on outcomes in preterm very low birthweight infants is the subject of a multicenter randomized clinical trial of 3000 patients which will be complete in 2010. Further research into mechanisms of abnormal HRC and regulation of autonomic nervous system function in sepsis and other disease processes will shed light on additional applications of this exciting new technology.

Toward an earlier diagnosis of late-onset neonatal sepsis in NICU patients

Late onset neonatal sepsis (LONS) kills thousands of preterm infants in the US each year, and many survivors suffer permanent neurologic impairment[1-2]. Typically, after a NICU patient develops signs and symptoms of sepsis, tests are sent and antibiotic therapy and other supportive care is initiated. However, waiting for a baby to deteriorate clinically is suboptimal and results in mortality rates as high as 40%. Earlier detection and treatment of LONS offers the best opportunity to improve outcomes. To date, the approach has been to use biomarker screening or empiric antibiotic therapy for every patient with subtle non-specific symptoms. Neither of these strategies is satisfactory due to insufficient diagnostic accuracy of biomarkers and complications associated with overuse of antibiotics. A new technology, continuous monitoring of neonatal heart rate characteristics, has been developed for earlier diagnosis and treatment of LONS in NICU patients[3-9]. In this chapter we will review the physiology of heart rate variability in healthy and diseased states, with particular focus on the role of the

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autonomic nervous system and inflammation in decreased HRV in sepsis. We will then review research showing that continuous monitoring of heart rate characteristics in NICU patients can detect late onset neonatal sepsis, often in its early stages prior to onset of symptoms. A randomized clinical trial to assess the impact of continuous HRC monitoring in 3000 preterm infants will be complete in 2010, and it is important for clinicians to understand the basis of this new technology.

Heart Rate Variability (HRV) and Heart Rate Characteristics (HRC)

In healthy animals and humans, the interval between heart beats is not constant but rather constantly changing. Beat-to-beat variability is regulated by neural input to the heart, with sympathetic and parasympathetic branches of the autonomic nervous system contributing to accelerations and decelerations of heart rate, respectively[10]. Heart rate and heart rate variability (HRV) are linked to other vital signs, respiration, temperature, and blood pressure, through reflex feedback from the central nervous system to cardiac pacemaker cells. Heart rate characteristics (HRC) in the context of neonatal sepsis detection are comprised of two components: depressed heart rate variability and transient heart rate decelerations. HRC analysis will be described in more detail in the section on clinical applications, while the term HRV will be used in the discussions of physiology of heart rate control in health and disease.

Autonomic Nervous System regulation of HRV

Chronotropic regulation of the heart occurs primarily through autonomic innervation of sinoatrial (SA) node pacemaker cells. The SA node is a small region of specialized impulse-generating cells on the posterolateral wall of the right atrium at the juncture with the superior vena cava. While other cardiomyocytes have pacemaker potential, SA node cells have a faster pacing rate and thus their signals override the intrinsic rate of other atrial and ventricular cells. The SA node is innervated by efferent autonomic nerves which release neurotransmitters and trigger changes in ion flux resulting in heart rate accelerations and decelerations[11].

Sympathetic nervous system

The sympathetic nervous system (SNS) is responsible for the acute stress “fight or flight” response, which includes increase in heart rate and cardiac contractility and inhibition of other visceral functions, mediated in large part by adrenomedullary release of epinephrine. Under basal conditions the SNS also plays a role in maintenance of physiologic homeostasis in many organ systems including the immune system. Sympathetic sensory neurons send afferent signals to paravertebral ganglia anterior to the thoracic segment of the spinal cord. From there, postganglionic sympathetic neurons extend to the brainstem and then to the heart, lungs, and viscera where they regulate functions through release of norepinephrine.

The sympathetic nervous system plays a major role in regulating heart rate, cardiac output, peripheral vascular resistance, and blood pressure. Afferent signals arise from baroreceptors and chemoreceptors in the brainstem (medulla oblongata), carotid arteries, and aortic arch. Baroreceptors sense increases and decreases in blood pressure, and trigger sympathetic and parasympathetic responses in blood pressure and heart rate to restore homeostasis. Chemoreceptors sense changes in the content of carbon dioxide, oxygen, and hydrogen ion in the blood, leading to signals sent via sympathetic nerves to the diaphragm and the heart. These receptors are primarily involved in control of breathing but can also respond to a fall in blood pressure causing decreased oxygen delivery to the receptors. Sympathetic nerve endings in the SA node of the heart release norepinephrine, which binds to beta1-adrenergic receptors leading to adenylyl cyclase activation, increased cAMP, altered ion flux, faster depolarization, and increased heart rate and contractility.

Parasympathetic nervous system

The parasympathetic nervous system (PNS) plays a critical role in regulation of heart rate and numerous other vital functions. The vagus nerve (cranial nerve X) both senses and signals physiologic changes in healthy and diseased states. In the heart, parasympathetic vagal nerve endings release acetylcholine, which binds to muscarinic cholinergic receptors on pacemaker cells, causing opening of potassium channels, hyperpolarization of the membrane potential, and a fall in heart rate.

Vagal immune-brain communications

The vagus nerve, in addition to playing a major role in regulation of heart rate and gastrointestinal and lung function, is also a key modulator of the host defense against infection. A two-way interaction exists between the immune system and the brain, with afferent and efferent signals relayed via vagal fibers. The presence of peripheral infectious or inflammatory insults is relayed to the brain by vagal afferent nerve fibers (Figure 1). For example, animal models have demonstrated that intraperitoneal administration of endotoxin from Gram-negative bacteria, or pro-inflammatory cytokines such as interleukin-1 beta results in rapid signaling via abdominal branches of the vagus nerve to nuclei in the brainstem. Vagal motor efferent neurons then stimulate physiologic changes in the brain including fever and “sickness behaviors” such as anorexia, and apathy [12]. Effects of vagal efferent signaling on the heart in sepsis are not well studied, but could include heart rate decelerations as found in mice immediately after intraperitoneal endotoxin administration[13] and in neonates with sepsis.

The vagus nerve also serves a potent anti-inflammatory function. Tracey and colleagues discovered that vagal efferent signaling significantly dampens production of proinflammatory cytokines. The effect, termed the cholinergic anti-inflammatory response, results from acetylcholine binding to nicotinic acetylcholine receptors on tissue macrophages, resulting in decreased activation of the transcription factor NF-kappa B and decreased release of tumor necrosis factor alpha, interleukin-1beta (IL-1 β), and other cytokines [14-15]. In animal models of sepsis, vagotomy increases cytokine production and mortality, while electrical stimulation of the vagus or pharmacotherapy with nicotine or nicotinic cholinergic receptor agonists reduces cytokine production and mortality [16-17]. Recent research studies indicate that activation of the cholinergic anti-inflammatory pathway could also be beneficial in sepsis-associated acute lung injury[18-19] and neuroinflammation[20].

Humoral and Mechanical Factors contributing to HRV

While direct neurotransmitter release at the SA node is the major mediator of heart rate accelerations and decelerations, there is also evidence of indirect humoral and mechanical (stretch) effects on heart rate and its variability. In denervated hearts, limited variability in beating rate has been observed. Mechanoreceptors in the atrium respond to stretch (such as that which occurs during normal respiration with changes in intrathoracic volume and venous return) and signal changes in heart rate directly without neural input[21]. Systemic release of adrenomedullary catecholamines in response to stress can lead to increased heart rate in absence of sympathetic nerve firing to pacemaker cells. Glucocorticoids have also been found to enhance heart rate variability in both animals and humans. Our group demonstrated that mice treated with dexamethasone experienced a 2-3-fold increase in various measures of heart rate variability even in absence of an inflammatory insult [13]. Fetal heart rate variability is also reported to be increased acutely following maternal administration of dexamethasone or betamethasone[22]. In adults with sepsis, adrenal insufficiency is associated with depressed HRV while glucocorticoid treatment leads to normalization of HRV[23]. Effects of glucocorticoids on HRV may be dose specific, as a study in healthy adults showed that

continuous infusion of low-dose hydrocortisone did not alter baseline heart rate variability or HRV changes in response to endotoxin administration[24].

Relationship between heart rate, HRV, and other vital signs

The centuries-old observation that heart rate increases during inhalation and decreases during exhalation is termed respiratory sinus arrhythmia (RSA). This normal physiologic phenomenon involves an increase in intrathoracic volume during inspiration resulting in an increase in sympathetic and decrease in parasympathetic tone, leading to increased heart rate. Respiratory sinus arrhythmia may play a role in maintaining ventilation-perfusion matching through the two phases of respiration. RSA is reflected in high-frequency heart rate variability, with accelerations occurring at 0.15-0.4 Hz, or 9-24 cycles per minute, the normal respiratory rate in adults. High frequency HRV is widely accepted as a measure of vagal tone in adults, whereas low frequency HRV is thought to reflect both sympathetic and parasympathetic input to the heart. Since neonates typically breathe about three times faster than adults, the frequency range for respiratory sinus arrhythmia (high-frequency HRV) is higher.

Breathing also contributes to heart rate variability through the chemoreceptor reflex and the sympathetic arm of the autonomic nervous system. Central chemoreceptors in the brainstem and peripheral chemoreceptors in the carotid sinus and aortic arch detect blood levels of carbon dioxide, oxygen, and hydrogen ions and trigger action potentials which travel along afferent nerves to sympathetic ganglia. Postganglionic sympathetic nerve fibers then extend to an effector organ such as the diaphragm (triggering inspiration) or the heart (triggering norepinephrine release and increased beating rate).

Body temperature appears to play a relatively minor role in heart rate variability. It is well known that hypothermia is associated with sinus bradycardia and fever with tachycardia, but the contribution of baseline heart rate to heart rate variability appears to be small. Fluctuations in body temperature may be reflected in changes in heart rate variability in the very low and ultralow frequency ranges.

Blood pressure impacts heart rate through the baroreceptor reflex. In response to high blood pressure, stretch-sensitive receptors in the carotid sinus and aortic arch send action potentials via the vagus and glossopharyngeal nerves to the solitary tract nucleus (NTS) of the brainstem. The NTS in turn triggers the ventrolateral medulla to send inhibitory signals to the sympathetic nervous system and triggers the nucleus ambiguus to activate the parasympathetic nervous system. The net result is decreased heart rate and decreased blood pressure. In response to hypotension, the baroreceptor reflex works in reverse, increasing sympathetic and decreasing vagal tone to raise blood pressure and heart rate.

Measurement of HRV

HRV analysis is generally performed using linear time-domain or frequency-domain methods, but can also be accomplished with non-linear methods as reviewed elsewhere[25].

Time-domain analysis of heart rate variability primarily involves calculation of the standard deviation of "normal" R-R intervals in the electrocardiogram, (SDNN). Aberrant beats and artifact are removed prior to analysis. Multiple other time-domain measures are also used for clinical research[26]. Frequency-domain or power spectral analysis may be used to determine the relative contribution of parasympathetic neural input to HRV. Electrocardiogram time-series data are transformed to quantitate variability (power) within different frequency ranges. The two major spectra in adult humans are high-frequency, 0.15-0.4 Hz or 9-24 cycles per minute, and low frequency, 0.04-0.15 Hz. High frequency fluctuations in heart rate reflect rapid

vagal responses to breathing, while the sympathetic nervous system response to physiologic changes is slower and is reflected in low frequency HRV.

Research into optimum methods for analyzing HRV in neonates revealed that power spectral analysis did not add additional information to time-domain analysis for detecting sepsis [27-28]. The three time-based measures used for calculation of the heart rate characteristics (HRC) index in neonates, standard deviation of RR intervals, sample asymmetry, and sample entropy, are discussed later in this review.

Pathologic states associated with abnormal HRV

Obstetricians have long known that loss of fetal heart rate variability and repetitive heart rate decelerations are ominous signs associated with asphyxia[29] or chorioamnionitis[30-31]. In adults, a number of cardiovascular diseases are associated with depressed HRV including coronary artery disease, myocardial infarction, and congestive heart failure[10]. Acute brain injury has also been linked to decreased HRV in adults, children, neonates, and fetuses [32-36]. Chronic endocrine, metabolic, and renal conditions including diabetes, hyperglycemia, hyperlipidemia, obesity, and kidney failure, may lead to autonomic dysregulation and low HRV [37]. HRV is impacted by psychiatric disorders as well, notably major depression[38]. In some of these conditions abnormal HRV appears to be linked to overactivation of the sympathetic nervous system and hypothalamic-pituitary-adrenal axis [39].

Sepsis has a strong association with decreased HRV in animal models and in humans of all ages. In a mouse model of sepsis-like illness, administration of endotoxin from Gram negative bacteria caused a dose-dependent decrease in heart rate variability [40]. Human volunteers administered intravenous endotoxin also exhibit a significant decrease in HRV concurrent with other symptoms of illness such as fever, tachypnea, tachycardia, and hypotension [41]. In adults, children, and neonates, sepsis is associated with decrease in multiple measures of HRV and lower HRV generally correlates with higher illness severity scores and higher mortality [4,42-43].

Mechanisms of decreased HRV in sepsis

Dampening of heart rate variability during sepsis likely reflects impairment of normal autonomic homeostatic functions. The precise mechanisms of this phenomenon are not well understood, but there is evidence of abnormalities of both sympathetic and parasympathetic tone during sepsis. Increasing evidence points to an important role of the systemic inflammatory response (notably inflammatory cytokines) in decreased HRV in sepsis and other disease processes.

Autonomic dysfunction in sepsis

Sepsis-associated sympathetic dysfunction, both overactivation and down-regulation, have been described. Activation of the adrenergic system in sepsis, while critical for initiating a physiologic response to pathogens, can become detrimental if excessive, as overproduction of catecholamines leads to tachycardia, diastolic dysfunction, and myocardial ischemia. Non-cardiac adverse effects of sympathetic overstimulation in sepsis have also been reported, including elevated pulmonary vascular resistance and pulmonary edema, hypercoagulability, intestinal ischemia, bone marrow suppression, hyperglycemia and hyperlipidemia, and stimulation of bacterial growth[44]. There is also evidence that sepsis can lead to impaired sympathetic cardiovascular responsiveness. For example, a study of adults with sepsis found that those patients with shock had higher circulating norepinephrine yet they also demonstrated decreased low frequency heart rate variability [45]. A small study of pediatric patients with

septic shock also showed decreased low-frequency HRV in the acute phase of illness [43]. Adrenergic responsiveness has been shown to be down-regulated at the cellular level in sepsis [46-47], which may contribute to depressed HRV.

Altered vagal tone may also play a role in decreased HRV in sepsis. In an experimental sepsis model in adults, sympathetic activation by infusion of epinephrine prior to administration of endotoxin reduced high-frequency HRV suggesting vagal hyporesponsiveness [48]. It is plausible that severe sepsis could induce a state of generally decreased vagal efferent firing or responsiveness, leading to fewer normal small decelerations in heart rate. On the other hand, activation of a cholinergic anti-inflammatory response in sepsis, as previously discussed, involves vagal efferent signaling that would theoretically decrease the heart rate and increase heart rate variability. These two effects could explain the findings in neonates with sepsis of both reduced HRV and intermittent transient HR decelerations, as discussed later in this review.

Cytokine link to decreased HRV in sepsis and other diseases

Increasing evidence in both animal and human studies points to an inverse correlation between heart rate variability and proinflammatory cytokine production in sepsis and other disease processes. We showed that in mice, administration of *E. coli* endotoxin induced a dose-dependent decrease in heart rate variability, which was temporally correlated with increased serum levels of multiple cytokines. Suppression of cytokine production with dexamethasone resulted in resolution of abnormal HRV, while administration of a single cytokine, tumor necrosis factor alpha, was sufficient to depress HRV[40]. In a study of healthy middle-aged adults, baseline vagal tone (high-frequency HRV) was found to be inversely correlated with endotoxin-stimulated production of proinflammatory cytokines[49]. A number of studies in septic adults have found an association between low HRV and high levels of cytokines [50-51] The association between cytokines (e.g., IL-6) and decreased HRV has also been made in chronic disease processes including cardiovascular and kidney disease[48] [38].[52], and in healthy adults[53] It remains to be determined whether cytokines directly impact SA node firing or indirectly influence HRV via effects on sympathovagal function. At the *in vitro* level, cytokines and endotoxin have been shown to affect cardiomyocyte adrenergic receptor and ion channel functions[54].

To summarize, experimental data from animals and observational studies in adult humans indicate that abnormal HRV is a physiomaer for processes triggered by sepsis. We now will discuss how this physiomaer might be used as an early signal for impending sepsis in neonates.

Clinical research and applications of HRC monitoring in neonates

Abnormal heart rate characteristics prior to sepsis

Initial studies in the neonatal intensive care unit tested the hypothesis that the early stages of neonatal sepsis lead to decreased heart rate variability. These studies revealed that there was not only decreased HRV but also transient, repetitive heart rate decelerations coinciding with or preceding clinical signs of sepsis. Figure 2 depicts both of these findings at onset of sepsis in a preterm neonate. Such abnormalities have been observed during fetal distress and severe neonatal illness[55-56]. Heart rate decelerations have not been reported in older patients with sepsis, and their etiology is not well understood at present. While some of these events could reflect breathing pauses, other mechanisms appear to be involved since the decelerations occur in patients on mechanical ventilation without a fall in oxygen saturation. One possible explanation is intermittent vagal firing in the setting of a systemic inflammatory response.

From a practical standpoint, to detect the abnormal heart rate characteristics discussed here, no additional monitoring leads are required; the information is derived from the analog electrocardiogram voltage signal from bedside monitors. This signal is digitized, filtered, and QRS complexes identified, and heart rate characteristics are derived from each 4096 beat epoch of RR intervals (~20 to 30 minutes of electrocardiogram recording).

In an initial test of the hypothesis that sepsis is associated with both decreased heart rate variability and decelerations, continuous monitoring was performed in 89 neonates hospitalized in the neonatal intensive care unit at the University of Virginia[9]. Forty had one or more episodes of culture-positive sepsis (a total of 46 episodes), 23 had a total of 27 episodes of culture negative sepsis-like illness, and 29 had neither. As compared to infants who had neither sepsis nor sepsis-like illness, infants with sepsis had reduced baseline variability and more frequent transient decelerations. These differences were found for infants with a positive blood culture as well as those with culture-negative sepsis-like illness. A quantitative measure of the frequency of decelerations (i.e., skewness; discussed below), began to increase as much as 24 hours prior to an abrupt clinical deterioration. This measure, which indirectly reports on decelerations as a tail in the histogram of RR intervals, added to the predictive value of a validated indicator of illness severity, the Score for Neonatal Acute Physiology[57].

Heart rate characteristics index

Based on the initial clinical observations in infants with sepsis, statistical descriptors were sought to detect these abnormalities using RR interval time series. One descriptor is the standard deviation, a conventional measure of variability. A novel measure, called sample asymmetry, detects decelerations, as indicated by asymmetry of the frequency histograms of heart rate[58] (Fig.3). A symmetric histogram has a value of 1, whereas the sample asymmetry is greater than one for a frequency histogram with a tail to the right of the median (accelerations), and less than 1 for a frequency histogram with a tail to the left of the median (decelerations). Thus it is a more flexible and informative measure than the skewness alone.

The third mathematical measure used to detect the heart rate alterations preceding neonatal sepsis is a novel measure, prompted by the observation that approximate entropy, a measure of regularity in time series data, is decreased in fetuses with acidosis[56]. A similar measure that was designed to have more accuracy in short records, sample entropy, decreases prior to clinical deterioration due to sepsis, [59].

From these three descriptors of the RR interval time series a heart rate characteristics index (HRCi) was developed (Figure 4). HRCi is derived from the output of a logistic regression model that uses standard deviation, sample asymmetry, and sample entropy data to predict the occurrence of an acute clinical deterioration in the next 24 hours. When an individual infant's risk is divided by the average probability of a clinical deterioration (averaged over all infants and all epochs), the result is the fold-increase in risk for that infant. This quantitative number is referred to as the heart rate characteristics index (HRCi), and is interpreted as the fold-increase in risk of a clinical deterioration (clinical or culture-proven sepsis) in the next 24 hours [8]. Regression coefficients for each heart rate characteristic were derived using data on 316 infants hospitalized in the years 1999-2001 at the University of Virginia neonatal intensive care unit. The resulting logistic regression model was then applied to heart rate characteristics data collected on 317 infants hospitalized in the years 1999-2001 at Wake Forest University NICU. The predictive value of the model, expressed as the area under the receiver-operator characteristics (ROC) curve, was as high at Wake Forest University NICU (the test sample) as at the University of Virginia NICU (the training sample)[7].

It is noteworthy that, some NICU patients have multiple, self-resolved increases in HRCi prior to clinical deterioration. As shown in figure 5, acute "spikes" in HRCi score from the normal

range (≤ 1) to >2 -fold increase in risk of sepsis may occur, followed by spontaneous return to normal. In some cases these self-resolved spikes are followed by acute clinical deterioration consistent with sepsis. The mechanisms and significance of this phenomenon are not precisely known. One possibility is that it represents host defenses keeping an infection or inflammatory response under control for a time but finally breaking down, leading to clinical deterioration.

HRCi and prediction of sepsis

To determine the clinical utility of HRCi, data were analyzed on 678 infants admitted to the University of Virginia NICU in 1999-2003, and 344 infants admitted to Wake Forest University NICU in 1999-2001. Figure 6A illustrates the observed rates of an adverse event (sepsis, urinary tract infection, or death) in the next 24 hours as a function of the patient having HRCi in the high risk range (defined as $>90^{\text{th}}$ percentile or score >3). HRCi in the high risk zone was more strongly associated with sepsis than individual laboratory tests or clinical symptoms (Fig. 6B) [5].

To compare the predictive value of HRCi and clinical signs of sepsis, a clinical score was developed that assigned 2 points for feeding intolerance, severe apnea, and an abnormal ratio of immature to total neutrophils (> 0.2), and 1 point for increase in ventilator support, lethargy or hypotonia, temperature instability, hyperglycemia, or a white blood cell count above 25,000 or below 5,000[5]. The mean of this score over the entire hospital course was highly correlated with the mean HRCi and both the clinical score and HRCi were predictive of sepsis in the next 24 hours, with receiver-operator characteristics (ROC) curve areas of 0.62 and 0.67, respectively. The ROC curve area was 0.70 for a model containing both HRCi and clinical score, and the HRCi added significantly to the clinical score (Figure 6).

Cumulative heart rate characteristics index

Further validation of the significance of the HRCi was obtained from two studies of an index referred to as the cumulative HRCi (cHRC). cHRC was calculated as the sum, across all 6-hour epochs during an infants' NICU hospitalization, of the difference between the HRCi and the expected risk of sepsis or sepsis-like illness in the next 24 hours, based on gestational age, birth weight, and postnatal age. This cumulative difference would be zero for days when an infant's heart rate characteristics led to a predicted risk identical to the risk predicted on the basis of gestational age, birth weight, and postnatal age. Summing this difference across all hospital days provides information as to whether the infant had a more-than-expected burden of illness (as reflected in abnormal heart rate characteristics and high cHRC) or a less-than-expected burden of illness (low cHRC). Cumulative HRC was near 0 for survivors, validating the hypothesis, and was significantly higher in infants who died, suggesting that this value was indicative of the overall burden of disease[60]. Furthermore, among surviving very low birth weight infants, those with cerebral palsy or developmental delays (Bayley Scales of Infant Development mental or motor scale scores more than 2 standard deviations below the mean) had significantly higher cHRC than infants without these developmental problems[61].

Potential clinical utility of heart rate characteristics monitoring

One advantage of heart rate characteristics monitoring is that it can be performed continuously and non-invasively, regardless of whether an infant is showing signs of sepsis. For the NICU patients whose ECG data were used to develop and validate the HRCi, heart rate characteristics data were available 92% of the time.[5] In comparison, laboratory tests used to evaluate infants for sepsis were only available a small fraction of the time. HRCi added information about the risk of sepsis over and above that provided by laboratory tests or clinical findings. An additional advantage is that HRCi often rises hours before the clinical deterioration that prompts laboratory measurements.

The research findings described above were based on experience with HRCi in two neonatal intensive care units, and it remains to be determined how broadly representative these findings are. Furthermore, it is unknown whether patient outcomes are improved by heart rate characteristics monitoring. This issue is being addressed by an ongoing randomized controlled trial (ClinicalTrials.gov Identifier: NCT00307333). In this study, 3000 VLBW infants are being randomized to display or no-display of the HRCi, with the primary outcome being number of days alive and not on a ventilator in the 120 days after randomization. Enrollment for this trial is expected to be complete in May, 2010.

The optimal strategy for using HRCi would incorporate information from both a clinical risk assessment and HRCi, an example of which is depicted in Table 1. Infants with a high clinical risk score are at high risk for sepsis irrespective of their HRCi, and those with a high risk HRCi (>2-fold increase in risk) are at increased risk for sepsis irrespective of their clinical risk score. For infants with a clinical risk score or HRCi in the low risk or intermediate risk zones, the risk of sepsis can be best predicted based on knowledge of both scores[8].

Other factors that might alter HRCi

Gestational and chronologic ages are associated with changes in heart rate characteristics. Among very premature infants, as compared to more mature infants, variability, as indexed by the standard deviation and sample entropy, is lower, and sample asymmetry and HRCi are higher. With increasing postmenstrual age, sample entropy and sample asymmetry increase and HRCi decreases[7]. Our observations of over 300 infants at the University of Virginia and Wake Forest University NICUs suggest that surgery, initiation of mechanical ventilation, and treatment with pancuronium or fentanyl are associated with an acute increase in HRCi, whereas dexamethasone treatment is associated with an acute decrease. Initiation of dobutamine or dopamine is also associated with an acute increase in HRCi, which might be explained by the underlying condition for which a vasopressor is prescribed.

Conclusions and Future Directions

Sepsis occurs frequently in hospitalized infants and increases mortality risk, hospital costs, and the risk of long-term developmental impairments. Each of these outcomes might be improved by earlier identification and treatment of infants with sepsis. Continuous monitoring of heart rate characteristics, such as standard deviation, sample asymmetry, and sample entropy, can be used to identify infants with sepsis prior to the development of clinical signs. An ongoing clinical trial might provide an answer to the question of whether continuous heart rate characteristics monitoring can improve the outcome of hospitalized infants.

There is some evidence to suggest that the heart rate characteristics accompanying sepsis, i.e., transient heart rate decelerations and decreased variability, are associated with a systemic inflammatory response. Thus continuous heart rate characteristics monitoring might provide a research tool for investigating the putative link between systemic inflammation and neurodevelopmental impairments and interventions to prevent inflammation-related brain damage in neonates.

Acknowledgments

Funding sources:

NIH HD048562 (JR Moorman, PI); NIH HD051609 (KDF); Coulter Foundation Translational Research Award; University of Virginia Children's Hospital Grants

Appendix 1

Illustrative clinical case #1: Increased HRCi associated with sepsis

HRCi (red line) and clinical course (shaded boxes) of an infant born at 26 weeks' gestation. (Note: these HRCi data were recorded but not displayed to clinicians) On day 27 the patient had apnea and leucocytosis. A blood culture that day showed no growth but a repeat blood culture on day 29 yielded coagulase negative staphylococcus. On day 30 the patient required endotracheal intubation and mechanical ventilation and antibiotics were started. Note that over the 12 hours prior to the episode of apnea and the first blood culture on day 27, the HRCi rose from a level of about 0.5, signifying a lower than average risk of sepsis, to a nearly 4-fold risk of sepsis. It rose in the next several days but fell after initiation of antibiotics. The shaded boxes indicate symptoms, laboratory tests, and interventions (WBC = white blood cell count; T =temperature). (Figure 7)

Appendix 2

Illustrative clinical case #2: Increased HRCi associated with surgical procedure

HRCi findings and clinical course of an infant born at 26 weeks gestation. On day 74, the patient had laser retinal photocoagulation under general anesthesia. HRC monitoring resumed after the procedure. Blood culture was not sent and no antibiotics were given. A large, transient increase in HRCi is a typical finding following surgical procedures (T = temperature). (Figure 8)

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Figure 1. Immune-Nervous System-Heart interactions

Pathogens or cytokines send impulses to the brainstem via afferent nerves. Afferent autonomic signals are also triggered by baroreceptors in response to changes in blood pressure.

Sympathetic and parasympathetic (vagus) nerves then send efferent signals to the SA node leading to compensatory heart rate (HR) accelerations and decelerations, respectively. In sepsis, there is decreased heart rate variability (HRV), with fewer small accelerations and decelerations, likely reflecting dysregulation of autonomic responses. Neonates with sepsis may have both decreased HRV and occasional large decelerations. The autonomic nervous system, in addition to regulating HRV, also plays an important role in host defense by sending adrenergic and cholinergic signals to the periphery modulating release of inflammatory mediators such as cytokines. (Copyright 2010, Anita Impagliazzo, MA, CMI, with permission)

Figure 2. Heart rate tracings from a neonate

A) Normal heart rate variability **B)** Decreased heart rate variability with one deceleration, **C)** Decreased variability with multiple superimposed transient decelerations.

Figure 3. Normal and abnormal heart rate histograms

A) Heart rate tracing (beats per minute) from a healthy neonate showing many small HR accelerations and decelerations resulting in a symmetric histogram. **B)** Heart rate tracing from a septic neonate showing few accelerations and many large decelerations, resulting in an asymmetric histogram skewed to the left.

Figure 4. Heart rate characteristics in a representative neonate around the time of sepsis

A) HRC index (HRCi, fold increase in risk of sepsis) was calculated from seven days before until 3 days after a positive blood culture on day 0. a, b, and c show 30 minute heart rate tracings (beats per minute) in the periods indicated on the top graph before, during, and after diagnosis of sepsis. Note normal variability in periods a and c (low HRCi) and few accelerations and many decelerations in period b (high HRCi) at the time of positive blood culture. Also note that baseline heart rate is similar in all three periods. **B)** Three components of HRCi in 12h tracing from period “b” prior to positive blood culture. Top: Standard deviation of RR intervals. Middle: Sample asymmetry. Bottom: Sample entropy. The heart rate characteristics monitor calculates HRCi every 60 minutes using amathematical algorithm incorporating these three components over the previous 12h.

Figure 5. Multiple spikes in HRCi prior to clinical deterioration with sepsis

Fold increase in odds for sepsis (HRCi) from four to seven weeks of age in a preterm infant. Note that the HRCi increased to ~2-3 on postnatal days 30, 36, and 39, then spontaneously returned to normal (<1). On day 41, the infant had an acute clinical deterioration associated with a positive blood culture. Antibiotics were started, clinical status improved, and the HRCi returned to normal.

Figure 6.

HRC index percentiles correlate with risk for sepsis. **A)** Patients were classified in three risk categories. Low risk was defined as HRCi <75th percentile (score <1). Medium risk (light grey boxes) includes infants with HRCi in the 75th-90th percentile (score 1-2). The high risk HRC group (dark grey box) has HRCi >90th percentile (score >3). **B)** Performance of heart rate characteristics index monitoring, laboratory tests, and clinical signs for prediction of sepsis in the next 24 hours.

Figure 7.
Increased HRCi associated with sepsis

Figure 8.
Increased HRCi associated with surgical procedure

Table 1
Clinical factors and HRCi incorporated into a sepsis risk score

A clinical score was developed that assigns 2 points for severe apnea or feeding intolerance or an elevated ratio of immature to total neutrophils (> 0.2), and 1 point for increase in ventilator support, lethargy or hypotonia, temperature instability, hyperglycemia, or white blood cell count above 25,000 or below 5,000. HRC are classified as low- intermediate- or high risk for sepsis as defined in Fig.6. Odds of sepsis is highest (darker gray cells) when both clinical score and HRCi are high and lowest (white cells) when both are low. Combining HRCi monitoring with clinical risk assessment gives the best predictive accuracy for sepsis diagnosis[8]. (Data from Pediatric Research 2007; 61: 222-227)

		Heart rate characteristics			
		Not measured	Low	Intermediate	High
Clinical score	Not measured	1.0	< 1	1-2	≥ 2
	0	0.7	0.5	1	2.5
	1	2	1	2	4
	≥ 2	3	3	3	4