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Heart rate variability analysis is more sensitive at identifying neonatal sepsis than conventional vital signs

Fredrick J. Bohanon, M.D.[a], Amy A. Mrazek, M.D.[a], Mohamed T. Shabana, B.S.[a], Sarah Mims, R.N., F.N.P.[a], Geetha L. Radhakrishnan, M.D.[b], George C. Kramer, Ph.D.[c], Ravi S. Radhakrishnan, M.D., M.B.A.[a,b,*]

Departments of [a]Surgery, [b]Pediatrics, and [c]Anesthesiology, University of Texas Medical Branch, 301 University Boulevard, Galveston, TX, 77555, USA

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Abstract

BACKGROUND: Sepsis remains the largest preventable source of neonatal mortality in the world. Heart rate variability (HRV) analysis and noninvasive cardiac output have been shown to be useful adjuncts to sepsis detection in many patient groups.

METHODS: With Institutional Review Board approval, 4 septic and 6 nonseptic extremely low birth weight patients were enrolled. Data from septic and healthy patients were collected for 5 hours. Electrocardiogram waveform and traditional vital signs were collected and the RR intervals were calculated; then HRV analysis was performed in both the time and frequency domain.

RESULTS: HRV measurements in time domain, heart rate, and pulse oximetry (SpO2) were significantly different in septic patients vs nonseptic controls.

CONCLUSIONS: These results indicate that nonconventional vital signs such as HRV are more sensitive than traditionally used vital signs, such as cardiac output and mean arterial pressure, in the confirmation of sepsis in extremely low birth weight neonates. HRV may allow for earlier identification of septic physiology.

With the implementation of the Millennium Development Goals, there has been a reduction in live born children deaths, before the age of 5, from 9.9 million in 2000 to 6.3 million in 2013.[1] Despite advances in neonatal critical care, there were 2.76 million (44%) deaths in the neonatal period (0 to 27 days) with sepsis accounting for 421,000 deaths.[1] Prematurity and low birth weight exacerbate the risk for sepsis with 20% to 40% of premature infants having at least one episode of sepsis during their hospitalization, with higher incidences in the extremely low birth weight patients (ELBW, 401 to 1,000 g).[2,3] In addition, sepsis leading to cardiovascular collapse results in significantly increased mortality rates, reaching 20%,

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* Corresponding author. Tel.: +1-409-772-5666; fax: +1-409-772-4253.
E-mail address: rsradhak@utmb.edu

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as well as increased hospital stay.[3] In the patients who survive the episode of sepsis, the morbidity is significant, with 17% developing cerebral palsy and 15% with vision impairment.[4,5] Early recognition and appropriate goal-directed therapy remain the foundations for successful sepsis therapy.

Blood culture is the gold standard for the diagnosis of sepsis; however, it can take up to 48 hours for diagnosis and is associated with false positive and negative results.[6,7] The length of time needed for positive culture limits the ability to initiate and treat neonatal sepsis appropriately. Currently, blood pressure, heart rate (HR), and pulse oximetry are objective measures of shock, while capillary refill is a subjective tool. However, these metrics provide limited information as to the severity of shock, need for blood transfusion, and as a means to assess resuscitation with fluids and drugs.[8] A variety of "new vital signs" are emerging in medicine.[9–11] We define new vital sign to be a physiologic variable that, until recently, has not been available for clinical care. Examples of these new vital signs are tissue oxygenation and heart rate variability (HRV).[12–17] Additional new vital signs are clinical variables that could only be intermittently or invasively measured with traditional technology, but now can be measured continuously and noninvasively, such as cardiac output (CO).[18,19] HRV has been shown, prospectively, to have a high negative predictive value with a low positive predictive value (~15%) in identifying neonatal patients at high risk for sepsis and death. This positive predictive value improves with the incorporation of laboratory values.[20,21] Studies evaluating cardiac diseases (heart failure, hypertension, and myocardial infarction) have shown HRV analysis to be a widespread tool to study the interaction between the sympathetic and parasympathetic effects on HR. There are 2 main ways to evaluate HRV: time and frequency domain analysis. Time domain indices are derived from statistical methods from the time between QRS complexes (RR interval). These indices include standard deviation of the RR interval (SDRR), percentage of absolute difference between consecutive RR intervals that are greater than 50 ms (pNN50), 2 standard descriptors to evaluate short- and long-term variability (SD1 and SD2, respectively), and assessment of autonomic input via cardiac sympathetic and vagal index (CSI and CVI), respectively.[22,23] Frequency domains are a series of indices that evaluate the power spectral density of the contribution of the autonomic nervous system. These frequencies are divided into very low frequency (VLF), low frequency (LF), and high frequency (HF) power, with studies suggesting that HF is associated with parasympathetic activity and LF is associated with sympathetic activity.[24] This is the first study to evaluate the time and frequency domain assessment of HRV along with noninvasive CO monitoring in septic neonates.

Methods

Patients

Data were obtained from a cohort of ELBW (<1,000 g) neonates hospitalized at the Infant Special Care Unit at the University of Texas Medical Branch, Galveston, TX, from August 2012 to May 2013. Inclusion criteria included ELBW and less than 1 month of age. Exclusion criteria included any major chromosomal abnormalities, cardiac defects, or weight more than 1,000 gm. This study consisted of 2 cohorts of patients: healthy patients who met the inclusion criteria and a set of septic patients who had been diagnosed with sepsis within the preceding 12 hours before data collection. This study was approved by the Institutional Review Board of University of Texas Medical Branch. Parents were informed and consent was obtained.

Data collection

The definition of sepsis was based on the sepsis continuum definition proposed by the International Pediatric Sepsis Consensus Conference in 2002 with the modification proposed by Wynn et al to include preterm infants.[25,26] This sepsis continuum definition includes definitions for systemic inflammatory response syndrome, infection, sepsis, severe sepsis, and septic shock. The organ system dysfunction definitions to differentiate sepsis from severe sepsis or septic shock will be taken from the same consensus conference.

Traditional vital signs were collected using Philip IntelliVue (model) monitor (Philips Healthcare, Andover, MA) and Cardiotronic Aesculon monitor (Osypka Medical, Inc, La Jolla, CA). Electrocardiogram data were acquired by PowerLab and analyzed via LabChart software (ADInstruments, Inc, Colorado Springs, CO). Time and frequency domain HRV analyses were performed using Nevrokard aHRV software (Nevrokard Kiauta, d.o.o, Izola, Slovenia).

All patients enrolled in this study had 5 hours of continuous vital signs and electrocardiogram data collection. Vital signs were recorded per standard of care. Healthy patients had the 1st 5 hours after placement of electrodes and monitors collected, while the septic patients had the 1st 5 hours after confirmation of diagnosis.

Statistical analysis

Five hours of continuous data were collected and the median value for each parameter studied was used for each patient. Parameters studied were HR, CO, mean arterial pressure (MAP), pulse oximetry, index of contractility (ICON), SDRR, pNN50, SD1, SD2, CSI, CVI, VLF, LF, HF, and LF/HF ratio. The median values were pooled into the 2 study groups and analyzed using an unpaired Student *t* test (GraphPad Prism 5.0; GraphPad Software, Inc, La Jolla, CA). Statistical significance was achieved if P less than .05.

Results

Study population

Table 1 shows the demographic characteristics of the neonates studied. There were (n = 11) culture positive episodes

Table 1 Demographics

	Nonseptic (n = 6)	Septic (n = 4)	*P* value
Gestational age at birth (weeks)	27.33 ± .67	26.75 ± 1.37	.68
Sex: female (%)	4 (67)	3 (75)	.80
Birth weight (g)	643.00 ± 101.1	697.8 ± 113.8	.73
Length of stay (days)	110.00 ± 17.65	92.00 ± 37.12	.64
Mortality (%)	0 (0)	2 (50)	
Sources of sepsis		Necrotizing enterocolitis, spontaneous intestinal perforation, Group B Streptococcus septicemia	
Bacteria isolated		*Escherichia coli*, coagulase negative Staphylococcus spp., *Staphylococcus epidermidis*, Group B Streptococcus spp., *Enterobacter cloacae*	

Data for age, weight at birth, and length of stay are expressed as mean ± standard error of the mean.

in 4 patients. There were 6 healthy nonseptic neonates as a control population. There was no statistical difference in age between healthy controls and septic patients (27.33 ± .67 vs 26.75 ± 1.37 weeks, $P = .68$). Sixty-seven percent of healthy controls and 75% of septic patients were female ($P = .80$). Birth weight was 643.00 ± 101.1 g in healthy controls vs 697.8 ± 113.8 g in septic patients ($P = .73$). There was no statistical difference in length of stay between healthy

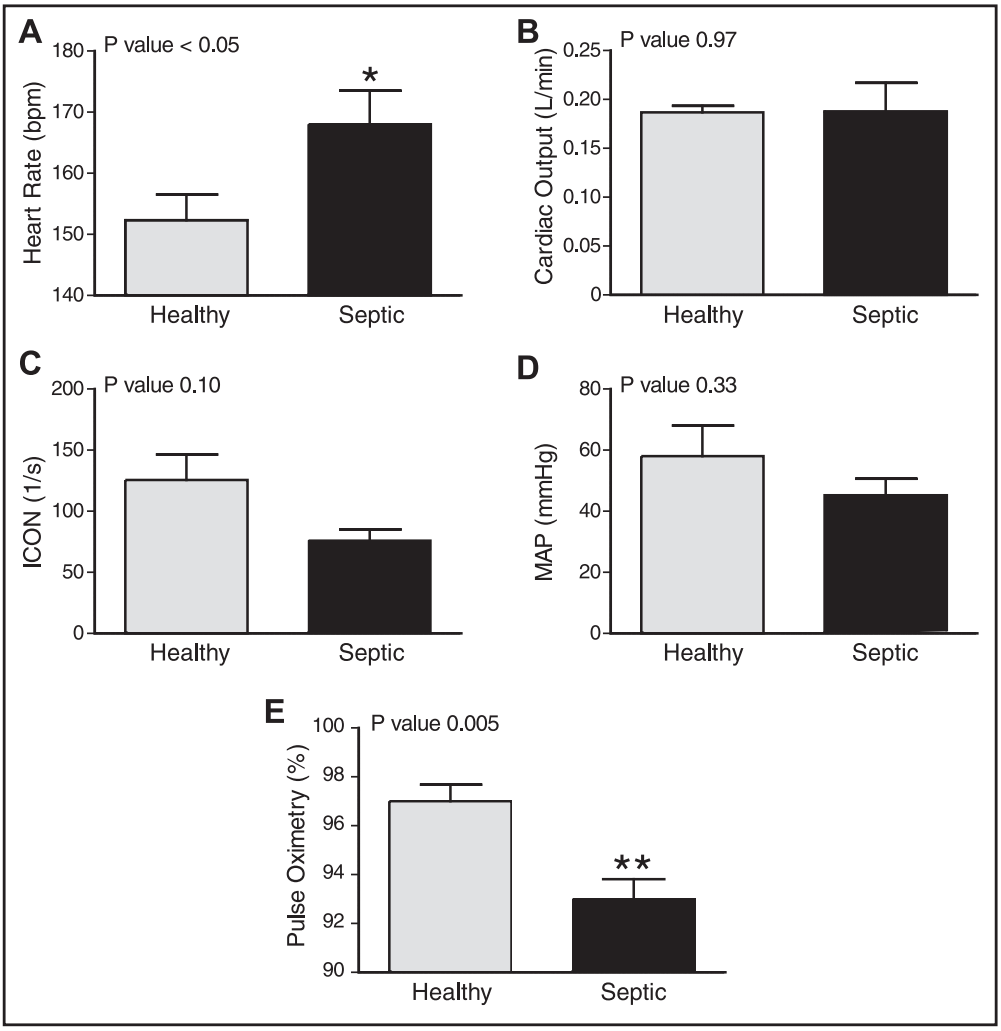

Figure 1 Sepsis effects on traditional vital signs in ELBW neonates: 5 hours of continuous vital signs were collected in septic and healthy neonates. Median values for HR (A), CO (B), ICON (C), MAP (D), and pulse oximetry (E) are represented in the bar graphs. Error bars represent SEM. Sepsis significantly decreased HR and pulse oximetry. *$P < .05$, **$P < .01$. SEM = standard error of the mean.

controls and septic patients (110.00 ± 17.65 vs 92.00 ± 37.12 days, $P = .64$, respectively). No patients died in the control group, while 2 (50%) died in the septic group.

Traditional vital sign analysis

HR analysis revealed a significant increase in HR in septic neonates when compared with healthy controls (168.0 ± 5.5 vs 152.3 ± 4.2 bpm, $P < .05$; Fig. 1A). There was no difference in CO (.188 ± .006 vs .187 ± .006 L/minutes, $P = .97$; Fig. 1B), ICON (76.25 ± 8.75 vs 125.5 ± 20.89 l/seconds, $P = .10$; Fig. 1C), or MAP (45.25 ± 5.39 vs 58.00 ± 10.04 mm Hg, $P = .33$; Fig. 1D) between the septic and healthy groups. SpO2 of septic neonates was significantly reduced to 93.00 ± .82% compared with 97.00 ± .68% in healthy controls ($P = .005$; Fig. 1E).

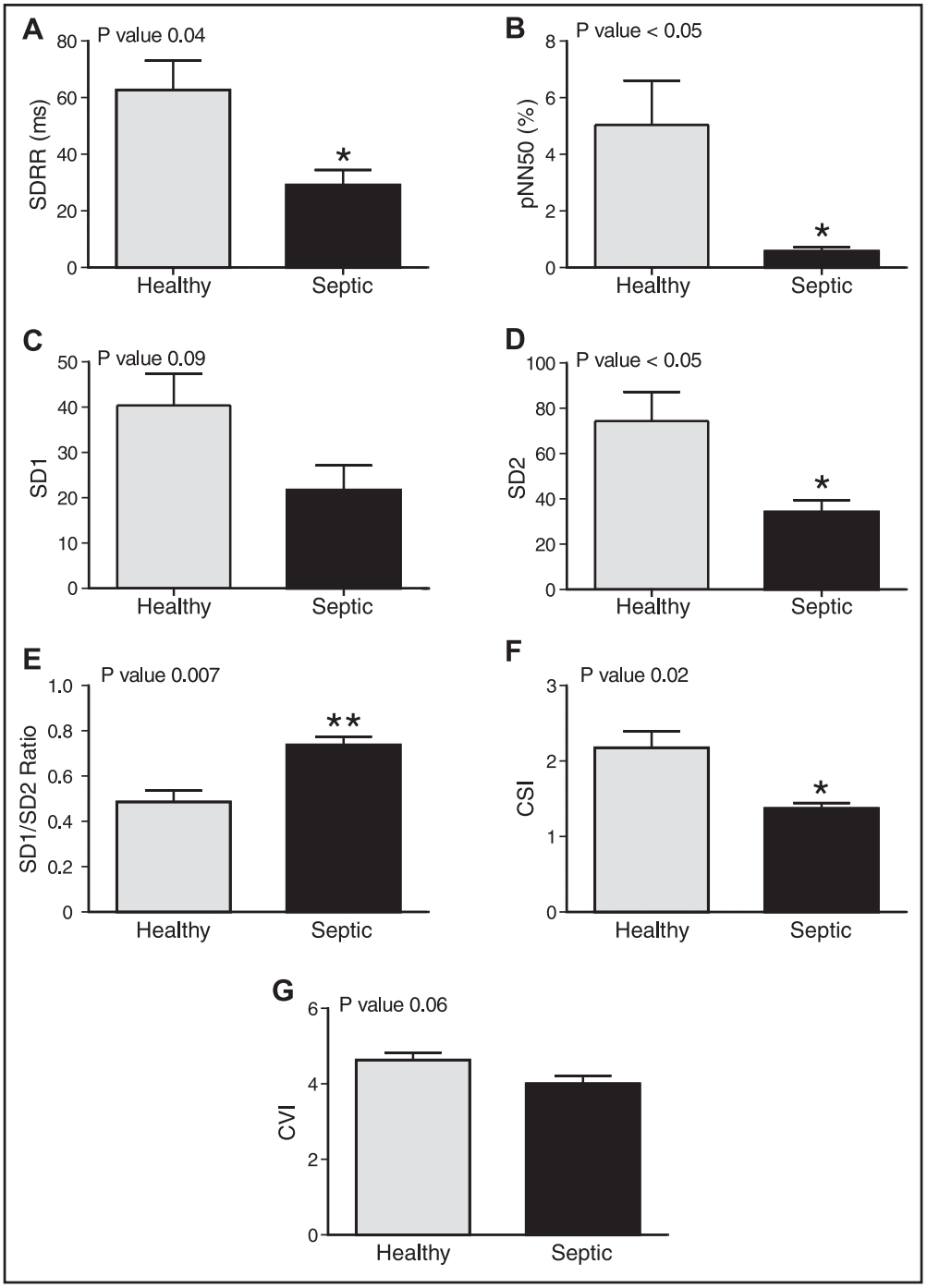

Figure 2 Sepsis significantly affects time domain heart rate variability analysis: 5 hours of continuous heart rates were analyzed in septic and healthy neonates. Median values are shown, error bars represent SEM. Sepsis significantly decreased SDRR (A), pNN50 (B), SD2 (D), SD1/SD2 (E), and CSI (F). Sepsis did not have a statistically significant effect on SD1 (C) and CVI (G). *$P < .05$, **$P < .01$. SEM = standard error of the mean.

New vital signs analysis

Sepsis greatly influenced time domain indices of HRV analysis. SDRR was significantly reduced in the setting of sepsis compared with healthy neonates (29 ± 5.3 vs 63 ± 10 ms; P = .04; Fig. 2A). Fig. 2B illustrates that sepsis decreased the percent of RR intervals greater than 50 ms (pNN50) compared with healthy controls (.57 ± .15% vs 5.04 ± 1.56%, $P < .05$). Short-term variability (SD1) was not changed in the presence of sepsis (21.71 ± 5.34 vs 40.41 ± 7.00, $P = .09$; Fig. 2C). Sepsis reduced long-term variability (SD2) significantly (34.17 ± 5.30) compared with controls (74.35 ± 12.85, $P < .05$; Fig. 2D). The ratio of SD1/SD2, therefore, was significantly increased in septic patients compared with healthy patients (.74 ± .04 vs .48 ± .05, $P = .007$; Fig. 2E). Sepsis greatly reduced CSI (1.37 ± .07) as compared with controls (2.18 ± .22, $P = .02$; Fig. 2F), but sepsis did not influence CVI (Fig. 2G).

VLF remained unchanged in the septic patients compared with controls (11.99 ± 9.00 vs 42.83 ± 12.96 ms^2, $P = .11$; Fig. 3A). Fig. 3B demonstrates a downward, although not significant, reduction in LF in septic (7.77 ± 3.77 ms^2) vs healthy (63.41 ± 22.43 ms^2, $P = .08$) patients. Similarly, HF was reduced but not significantly in sepsis (13.75 ± 5.77 ms^2) vs healthy (104.5 ± 46.18, P =.15; Fig. 3C) patients. LF/HF ratio was unchanged in the setting of sepsis (Fig. 3D).

Comments

Sepsis in ELBW neonates significantly increased HR and decreased SpO2, but had no significant effect on CO, ICON, or MAP. Furthermore, septic neonates had altered HRV analysis characterized with significant changes in the time domain; while there was marked reduction in frequency domain, it was not statistically significant.

Sepsis is a major cause of mortality in ELBW neonates and has an estimated cost, in the United States, of $700 million, and the treatment and long-term outcomes have not changed in decades.[27,28] The need for accurate and timelier diagnosis of sepsis is needed. In this study, we compare traditional vital signs and new vital signs, which include noninvasive monitoring of CO and ICON plus high-resolution HRV analysis between culture positive septic ELBW neonates and healthy ELBW neonates. Sepsis and cardiovascular function in ELBW neonates are understudied in the literature. Of the limited studies on septic ELBW infants, the cardiovascular function is mainly assessed by echocardiography.[29] Noninvasive cardiac monitoring is an emerging technique that has been studied and validated in adults and infants.[19,30–34] To our knowledge, this is the first study examining noninvasive cardiac monitoring in septic ELBW neonates. Our novel findings suggest that in the first few hours of sepsis the neonate maintains an adequate perfusion pressure mainly through increased HR and not through an increase in contractility (increased stroke volume). This adaption, although not great enough to set off alarms on the bedside monitor, is able to maintain an adequate MAP as compared with the control patients. Additionally, we compared high-resolution HRV between septic and healthy ELBW neonates and found that the time domain was more sensitive than frequency domain analysis in identifying sepsis.

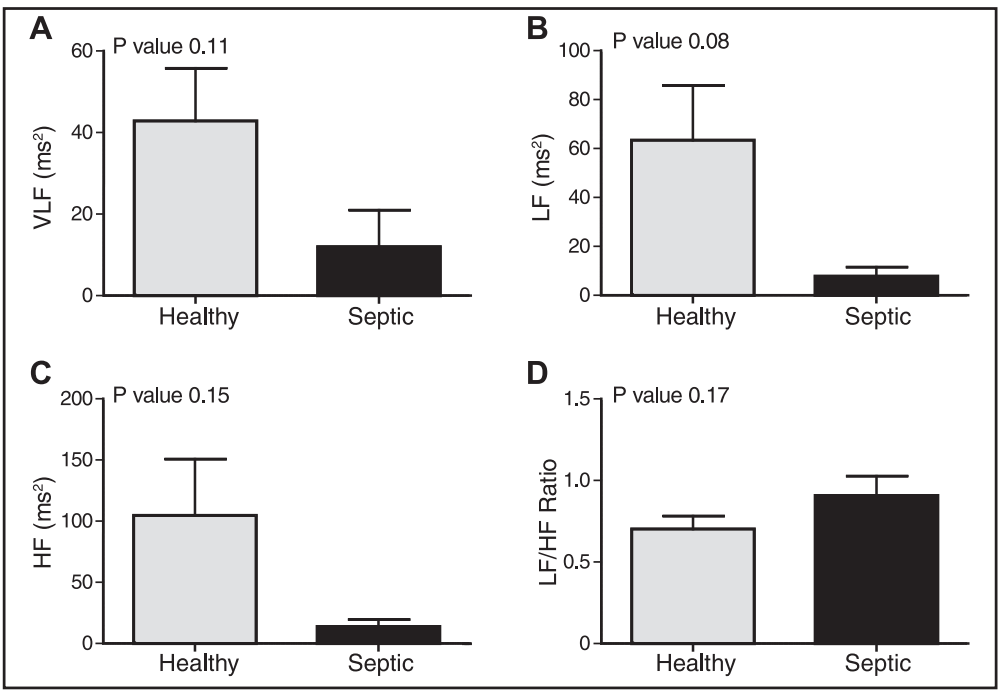

Figure 3 Sepsis affects frequency domain heart rate variability analysis: 5 hours of continuous heart rates were analyzed in septic and healthy neonates. Median values are shown, error bars represent SEM. Sepsis had a nonstatistically significant effect on VLF (A), LF (B), HF (C), and LF/HF ratio (D). SEM = standard error of the mean.

Time domain indices are the simplest to calculate and use similar methods for calculation, making them comparable between different researchers. Time domain indices consist of statistical measures of the inter-beat interval (IBI). SDRR is the standard deviation of the IBI and accounts for all factors that contribute to HRV, and is associated with lower frequency power.[35] pNN50 is the percentage of neighboring IBI that differ from each other by greater than 50 ms and is associated with HF power.[36] In this study, septic neonates had significantly decreased SDRR and pNN50 that in age-adjusted studies predict morbidity and mortality.[35] Poincare analysis (SD1, SD2) is derived from nonlinear dynamics and illustrates the RR interval fluctuations.[36] SD1 is related to the short-term beat-to-beat HRV (associated with HF), while SD2 describes long-term HRV (associated with LF) and the ratio delineates the relationship between the two. ELBW septic neonates demonstrated a greater SD2 than SD1 as compared with healthy neonates, and this correlated with the SDRR, in that sepsis has a greater influence on LF. These findings are similar to an animal study examining HRV after injection of endotoxin.[37] CSI (SD2/SD1) and CVI [log (SD1 × SD2)] are additional values calculated from the Poincare plot.[38] Septic neonates' HRV may be more dependent on the changes in sympathetic output than parasympathetic output.

Frequency domain analysis is a much more powerful tool to examine the autonomic contribution to HRV. HF band represents parasympathetic input. The LF band is less understood and is thought to have input from both sympathetic and parasympathetic inputs, and VLF has been associated with all-cause mortality.[35,36] In this limited study, there was no detectable difference in the frequency domain between septic and healthy neonates, and therefore frequency domain analysis may be less sensitive than time domain analysis in sepsis.

Sepsis in ELBW neonates is a poorly studied disease and demands more rigorous study. In this study, we demonstrate that high-resolution HRV analysis and noninvasive monitoring of new vital signs are sensitive tools to detect the minimal physiological changes in these patients, although it should be stated that, in this study, we are unable to determine if these parameters are useful for the early diagnosis of sepsis. This study only evaluated HRV after a clinical diagnosis of sepsis was made and demonstrated that there are significant physiologic changes in the first hours of sepsis. Further studies of the hours before the patient becoming septic are needed and these results may allow for an earlier diagnosis and treatment, which may lead to decreased morbidity and mortality.

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