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Egyptian Pediatric Association Gazette (2024) 72:37
https://doi.org/10.1186/s43054-024-00278-y

Egyptian Pediatric Association Gazette

REVIEW

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Advancements in understanding the association of sepsis with heart rate variability in premature infants

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Abstract

Background With the rapid development of perinatal medicine and neonatal resuscitation technology, neonatal mortality gradually reduces, but sepsis is still a neonatal critical illness and an important cause of death. The onset of sepsis in premature infants is insidious, and the clinical symptoms lack of specificity. The available laboratory tests exhibit limited sensitivity and specificity for diagnosis, and there is a certain degree of time lag. Therefore, it is particularly important to find a method for early detection of severe infection in premature infants.

Main body Sepsis is the third leading cause of death with poor prognosis in infants. Early and accurate identification of sepsis are particularly important. Heart rate variability may present before clinical symptoms of sepsis. The study is to summarize the available data on the relationship between heart rate variability and development of sepsis in early infants.

We searched six database, PubMed, Web of Science, Embase, Cochrane Library, Wanfang, and CNKI, using the following terms for our search strategy (Infants, Newborn) OR (Newborn Infant) OR (Newborn Infants) OR (Newborns) OR (Newborn) OR (Neonate) OR (Neonates) AND (Sepsis) OR (Bloodstream Infection) OR (Bloodstream Infections) OR (Pyemia) OR (Pyemias) OR (Pyohemia) OR (Pyohemias) OR (Pyaemia) OR (Pyaemias) OR (Septicemia) OR (Septicemias) OR (Blood Poisoning) OR (Blood Poisonings) OR (Severe Sepsis) OR (Sepsis, Severe) AND (Heart Rate Variability). Premature infants would experience the reduction in heart rate variability before clinical symptoms of sepsis present.

Conclusion The application of heart rate variability, a noninvasive monitoring method, to the identification and diagnosis of sepsis in premature infants can enable clinicians to identify, diagnose, and treat children with sepsis early, thereby reducing the mortality of premature infants and neurological damage.

Keywords Neonatal sepsis, Heart rate variability monitoring, Prediction of sepsis, Early diagnosis of sepsis

Background

Neonatal sepsis refers to the diseases that occur in the neonatal period and are caused by various pathogenic bacteria and are accompanied by systemic inflammatory response syndrome. Among them, neonatal septicemia is caused by bacterial or fungal through hematogenous spread to the whole body [1]. In recent years, with the rapid development of perinatal medicine and neonatal resuscitation technology, neonatal mortality gradually reduces, but sepsis is still a neonatal critical illness and an important cause of death. Therefore, early clinical diagnosis of sepsis and effective comprehensive treatment are very important, which can significantly reduce mortality and serious complications. The onset of sepsis in premature infants is insidious, and the clinical symptoms lack of specificity, the sensitivity, and specificity of

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the existing laboratory tests are not high, and there is a certain time lag. Therefore, it is particularly important to find a method for early detection of severe infection in premature infants. Heart rate variability (HRV) is a noninvasive monitoring method, and studies have shown that HRV presents changes at early stage of infection. HRV has become a new research hotspot of sepsis in premature infants and provides a basis for early diagnosis of sepsis in premature infants. This article reviews the relationship between HRV and sepsis in premature infants and its application in early diagnosis.

Searching strategies

This study searched all literature in six databases published prior to October 31, 2023, related to sepsis and heart rate variability. There is no restriction on study design or language on our search. The six databases include PubMed, Web of Science, Embase, Cochrane Library, Wanfang, and CNKI, using the following terms for our search strategy: (((((((Infants, Newborn) OR (Newborn Infant)) OR (Newborn Infants)) OR (Newborns)) OR (Newborn)) OR (Neonate)) OR (Neonates)) AND ((((((((((((((((Sepsis) OR (Bloodstream Infection)) OR (Bloodstream Infections)) OR (Infection, Bloodstream)) OR (Pyemia)) OR (Pyemias)) OR (Pyohemia)) OR (Pyohemias)) OR (Pyaemia)) OR (Pyaemias)) OR (Septicemia)) OR (Septicemias)) OR (Poisoning, Blood)) OR (Blood Poisoning)) OR (Blood Poisonings)) OR (Poisonings, Blood)) OR (Severe Sepsis)) OR (Sepsis, Severe))) AND (Heart Rate Variability)(((((((Infants, Newborn) OR (Newborn Infant)) OR (Newborn Infants)) OR (Newborns)) OR (Newborn)) OR (Neonate)) OR (Neonates)) AND ((((((((((((((((((Sepsis) OR (Bloodstream Infection)) OR (Bloodstream Infections)) OR (Infection, Bloodstream)) OR (Pyemia)) OR (Pyemias)) OR (Pyohemia)) OR (Pyohemias)) OR (Pyaemia)) OR (Pyaemias)) OR (Septicemia)) OR (Septicemias)) OR (Poisoning, Blood)) OR (Blood Poisoning)) OR (Blood Poisonings)) OR (Poisonings, Blood)) OR (Severe Sepsis)) OR (Sepsis, Severe))) AND (Heart Rate Variability). The flowchart showing the literature retrieval and screening process was shown in Fig. 1.

General profile of premature infection

Neonatal sepsis refers to a systemic inflammatory response syndrome caused by infection, which can lead to changes in metabolism, inflammation, immunity, and endocrine function. This change is closely related to the regulation of the nervous system. According to estimates, worldwide, approximately 23.4% of newborns die from

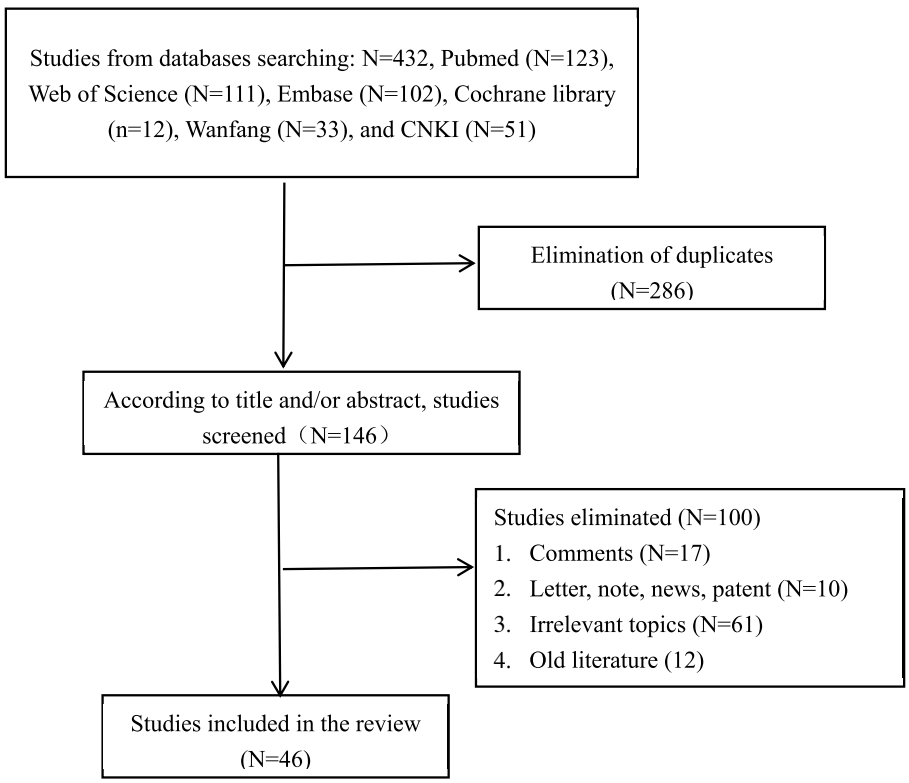

Fig. 1 Flowchart showing the literature retrieval and screening process

infection every year [2]. In developed countries, despite more advanced medical conditions and health facilities, neonatal infection is still common, especially in premature infants and low birth weight infants. In the neonatal period, 1/4 of preterm infants with a gestational age of less than 32 weeks will develop severe infection [3]. With the widespread implementation of hand hygiene in China, the care for umbilical cord and skin as well as aseptic operation has been strengthened, and the incidence of neonatal sepsis has decreased, but its incidence still accounts for 1–8‰ of live births, up to 164‰ in very low birth weight infants, and up to 300‰ in long-term hospitalization. It is the third leading cause of neonatal death, second only to the suffocation of premature and neonatal infants [4].

Due to the immaturity of their immune system, organ and function development, and the fewer gestational age, the lower the body weight, the longer the premature will stay in neonatal intensive care unit (NICU), and the risk of infection and complications development, mortality, and development of permanent nervous system damage will be much higher [2]. Currently, the clinical manifestations of infection in premature infants are diverse and lack of specificity. There are some limitations in relying on the existing laboratory tests (such as blood routine, c-reactive protein, procalcitonin) for diagnosis; on one hand, the sensitivity and specificity of diagnosis are not high, and on the other hand, the lag of diagnosis makes it difficult to identify sepsis in the early stage [5]. Blood culture is currently the gold standard for the diagnosis of sepsis, but there are many factors that affect the results of blood culture, such as low volume of blood for culture, prenatal use of antibiotics, low colony counts in the blood or in the interval of bacteria discharge, can lead to low positive blood culture, and time-consuming [6]. As a result, the clinical symptoms often deteriorate at the time of diagnosis, and the best treatment opportunities are missed, leading to an increased probability of death and severe long-term neurological sequelae. Although the empirical use of antibiotics has reduced the mortality of sepsis to some extent, it has also brought many side effects, such as the overuse of antibiotics, increasing the risk of development of drug-resistant bacteria. Therefore, there is an urgent clinical need to find a method that can detect sepsis early when the clinical manifestations are not obvious, which will help to reduce premature mortality and the development of serious complications.

Relationship between infection and heart rate variability

Heart rate variability (HRV) is the variation of heart rate. By analyzing the minute time change and regularities of a cardiac cycle, we will be able to identify the continuous and instantaneous fluctuation of heart rate. The concept of HRV was first proposed in 1965 by Obstetricians Hon and Lee, who found that a decrease in heart rate variability could indicate fetal distress. Over 10 years ago, Griffin et al. found that before clinical symptoms of sepsis appeared, newborns would experience the same reduction in heart rate variability and temporary deceleration of heart rate as fetuses during distress, and this abnormal change occurred 12–24 h prior to the clinical diagnosis of sepsis [7]. Ahmad et al. found an average 25% reduction in the baseline amplitude of HRV within 35 h prior to the diagnosis of sepsis [8]. All of these provide diagnostic ideas for early detection and identification of sepsis. In addition, Moneme et al. reported that the HRV reduced in the infants with congenital gastric wall defects based on the clinical heart rate data from 2009 to 2020, which was detected in the early stage of the disease, and proposed that the cause may be related to intestinal inflammation [9].

HRV analysis methods are still evolving; currently, the available analysis methods include time-domain analysis, frequency-domain analysis, and nonlinear analysis. In time-domain analysis, the RR intervals of all sinus beats mainly reflect the changes of the overall sympathetic and parasympathetic nervous system, and the standard deviation of the mean RR intervals reflects the changes of the tension of the sympathetic nervous system. In the frequency-domain analysis index, the heart rate change signal is decomposed into different frequency components, and its relative intensity is quantified as power, which provides the power spectrum measurement of various frequency components, and the cardiac sympathetic and vagal activity can be evaluated simultaneously. It has been shown that the heart rate of the mice slowed after endotoxin was injected intraperitoneally in mice, and this change occurs to the neonates after they develop sepsis, and HRV decreases in both the time and frequency domains as well as its high and low frequencies [10]. Continuous monitoring of HRV reveals that significant changes in HRV parameters occurred 24–40 h prior to clinical diagnosis of infection [8]. Time-domain analysis and frequency-domain analysis are widely used in clinics, and there are many factors that can affect the analysis of HRV time domain or frequency domain alone, and the combination of these two methods can increase the accuracy. Among the nonlinear analysis, the scatter plot being most studied contains the linear and nonlinear trend of HRV and is more sensitive and more individualized than the time-domain index of HRV [11].

Dysfunction of autonomic nervous system in premature infants with infection

HRV is dominated by sympathetic nerve and parasympathetic nerve of autonomic nervous system, which cause

heart rate to accelerate and decelerate [12], and sympathetic nervous system plays an important role in the regulation of homeostasis [13]. The physiological basis of HRV is attributed to the sympathetic vagus system, in which the vagus nerve plays a major role in determining HRV. Therefore, when the vagus nerve functions normally, there is a significant degree of heart rate variability; when the vagus nerve function is impaired, the degree of heart rate variability is reduced. During sepsis, the inflammatory response activates the sympathetic nervous system, triggering the activation of adrenergic receptors, leading to an increase in catecholamine levels in the blood. In severe cases, excessive activation of the sympathetic nervous system can cause dysfunction in certain organs, with the heart being the most susceptible, resulting in myocardial ischemia, arrhythmias, and impaired diastolic function. Inhibition of vagal excitation in sepsis causes a decrease in the cholinergic anti-inflammatory reflex [14, 15]. Studies have shown that there is an association between deceleration of heart rate and increased vagal nerve input induced by pathogens [16]. HRV refers to the variations of RR interval of ECG, which can be influenced by diseases affecting cardiac autonomic function [17]. It has been established that reduced heart rate variability is a poor prognostic factor for many diseases [18].

Sepsis can reduce the release of efferent signals from the vagus nerve and decrease the responsiveness of vagus nerve, resulting in a mild reduction in HRV. On the other hand, during sepsis, cholinergic anti-inflammatory response activation may theoretically decrease heart rate by enhancing efferent signals from the vagus nerve, thus increasing HRV. These dual effects explain the decrease in HRV and intermittent, transient reductions in heart rate observed in premature infants with sepsis. Kox et al. [19] injected endotoxin into 40 volunteers, 12 of whom were reinjected with lipopolysaccharide in two weeks to observe HRV before and within 8 h after lipopolysaccharide injection, and plasma cytokine levels were measured at different times. The results found that although HRV changed after lipopolysaccharide (LPS) injection, the inflammatory response did not change with HRV.

In animal models of sepsis, vagus nerve transection has been shown to increase cytokine production and mortality rates. Conversely, electrical stimulation of the vagus nerve or administration of pharmacological therapies such as nicotine or nicotinic acetylcholine receptor agonists can reduce cytokine production and decrease mortality rates [20]. In a study of 3000 randomized subjects, Moorman et al. [21] found that HRV monitoring could significantly reduce mortality in low birth weight infants. During sepsis, the inhibition of HRV by inflammatory cytokines may reflect impaired normal autonomic nervous system balance [22]. The exact mechanisms underlying this phenomenon are not well understood, but there is evidence suggesting abnormalities in both sympathetic and parasympathetic nerve tone during sepsis. Increasing evidence indicates that systemic inflammatory response, especially inflammatory cytokines, plays an important role in lowering HRV during sepsis and other diseases. When *Escherichia coli* endotoxin was administered, it was found that HRV decreased in a dose-dependent manner, and the levels of various cytokines were increased in the serum. When dexamethasone was used to inhibit the production of cytokines, abnormal HRV disappeared, and administration of a single cytokine, such as tumor necrosis factor, can also reduce HRV [10]. Based on the above studies, abnormal HRV is a physiological marker of sepsis. HRV, as a noninvasive detection predominantly assessing cardiac autonomic function, holds significant clinical value in the early diagnosis of sepsis. Timely correction of factors contributing to autonomic dysfunction and improvement of autonomic function is crucial for enhancing the prognosis of septic patients.

Application of HRV in the diagnosis of sepsis in premature infants

In clinical practice, transient deceleration of heart rate in pediatric sepsis patients is often not easily detected by healthcare professionals. Transient deceleration of heart rate typically does not fall below the minimum alarm threshold of the monitor (usually set clinically at 100 bpm). Therefore, quantifying the characteristics of abnormal HRV is particularly important to facilitate assessment by healthcare professionals. Prior to pediatric patients transitioning from a normal state to clinically suspected sepsis, there is a gradual increase in transient lengthening of the RR interval (transient deceleration of heart rate), and this phenomenon becomes increasingly frequent. The distribution histogram of RR intervals indicates a gradual shift towards asymmetric distribution. There is a noticeable decrease in heart rate acceleration [7]. It was reported that the asymmetry of RR interval began to increase on 3–4 days prior to the emergence of clinical presentation of sepsis, rose sharply within the 24 h of sepsis onset, and decreased to the baseline level in the recovery period after clinical treatment [23]. In addition, a new time-series complexity measure method proposed by Richman et al., sample entropy, utilizes RR interval sample entropy to measure the irregularity of RR intervals. They found that the decrease in sample entropy values occurs earlier than clinical manifestations and is tolerant to data loss. Therefore, they propose that RR interval sample entropy can serve as an indicator for assessing abnormal HRV characteristics [24]. It is also

reported that there is a significant association between sepsis in preterm infants and HRV in neonatal NICU, and the application of HRV in predicting neonatal sepsis as an independent tool has been partially validated [25].

Other researchers extracted the RR interval data from the ECG monitor and obtained the heart rate characteristic index through a series of algorithms, to predict the risk of sepsis in the next 24 h [26]. In a study of more than 300 cases of late-onset neonatal sepsis, Griffin et al. found that the characteristics of the HRV were associated with the development of sepsis [27], and that an increase in the HRV index occurred earlier than the clinical manifestations of sepsis [28]. According to a prospective study conducted between September 2020 and May 2021 in NICU, HRV assessment can improve the prognosis of neonates and predict the occurrence of hospital infection [29]. Moorman et al. conducted a multicenter randomized controlled trial between 2004 and 2010 to continuously monitor 3003 very low birth weight infants hospitalized in the NICU using the HeRO monitor and randomly selected half of the subjects as experimental group, the remaining half as the control group. The results showed that there was a significant difference in mortality between the two groups, with the mortality rate in the experimental group decreasing from 10.2 to 8.1% ($p = 0.04$) [21]. In recent years, there have also been studies that combined HRV with assessment of respiratory and motor characteristics to predict neonatal sepsis [30]. The relevant studies were summarized in Table 1.

Drawbacks of HRV in prediction of sepsis in premature infants

Premature infants, as a unique population, have immature autonomic nervous systems [32]. Premature detachment from the maternal environment exposes them to adverse external factors such as brain injury, mechanical ventilation, oxygen therapy, infections, and painful stimuli. These factors often disrupt the normal maturation process of the autonomic nervous system. Moreover, premature infants exhibit a wide range of gestational ages and multiple complications, leading to numerous confounding factors. Consequently, research on HRV in premature infants is currently limited and yields inconsistent results, making it susceptible to bias [33]. HRV monitoring is a noninvasive method that can detect changes before abnormal laboratory test results appear, providing a basis for early diagnosis of neonatal sepsis. However, there are still certain limitations in clinical practice. HRV is regulated by the autonomic nervous system, and besides sepsis, there are other diseases that can cause dysfunction of the autonomic nervous system, including diseases of the autonomic nervous system itself, acute brain injury, and stress states (including hypoglycemia, shock, neonatal respiratory distress syndrome, intestinal perforation, acute hemorrhage). Research has also shown that the use of certain medications such as glucocorticoids, sedatives like phenobarbital, and midazolam can interfere with autonomic nervous system function. In a mouse experiment using dexamethasone, increased heart rate variability was observed regardless of the presence or absence of inflammatory stimuli, and it was possible that administration of dexamethasone improved regulatory function of mouse autonomic nervous system [10]. During septic shock, patients with adrenal insufficiency show a significant decrease in HRV, but administration of exogenous glucocorticoid partially improves the reduction in HRV [34]. Glucocorticoid can increase HRV, but the specific mechanism underlying glucocorticoid increasing HRV needs further exploration. In preterm infants, administration of dobutamine can also affect HRV [28]. In addition, neonatal hemolysis, major surgery, trauma, tissue ischemia-reperfusion injury, and hypoxia can also trigger the inflammatory response [35] and then affect HRV. It was reported that HRV was associated with normal physiological status, such as respiratory [36], hear rate [37], blood pressure [38], oxygenation [39], frequency of crying [40], body fat percentage [41], race [42], ratio of body height to age, and neonatal behavior assessment scale [43] In addition, the gestational age and day of life in preterm infants can also produce effects on HRV [22]. Therefore, the utility of HRV in the clinical practice should take full account of the above factors [44]. Besides, some researchers pointed out that there was no consistency in the report and calculation methods with the increasing interest in neonatal HRV; this may be due to a lack of expert consensus and relevant neonatal HRV guidelines [45].

Summary and prospect

The utility of HRV monitoring in premature infants with infection can make it possible for clinicians to identify, diagnose, and treat sepsis early prior to the deterioration of the condition of premature infants. The significance of HRV utility is not only to reduce premature infant mortality and neurological damage but also to reduce unnecessary administration of antibiotics. Due to the limitation of HRV monitoring conditions and its underlying physiological mechanisms being unknown, it is needed to further standardize HRV analysis methods, control influencing factors, and optimize detection indicators. HRV analysis, a noninvasive monitoring technique, will show its clinical value and promising prospects. HRV monitoring is a noninvasive method and can present change prior to the manifestation laboratory variables, which can provide evidence for early diagnosis of premature infection. Although

Table 1 Studies evaluating the application of HRV index in neonatal sepsis

Author	Year of study	Study population	Aims of study	Results
Kurul S. et al.	2022	A gestational age at birth of < 32 weeks in the period January 2016–June 2020 ($n = 1135$; $n = 515$ pre-implementation, $n = 620$ post-implementation)	To investigate the association between the implementation of a local HRV monitoring guidelines combined with determination of inflammatory biomarkers and mortality, measures of sepsis severity	The nSOFA course during a sepsis episode was significantly lower in the post-implementation group ($P = 0.01$)
León C. et al.	2021	HRV data on 49 premature infants in NICU	Predictive value of visible graphic features for the diagnosis of late-onset sepsis in preterm infants	Visible graphic indicators are useful in predicting sepsis in newborns during HRV analysis
Israeli-Mendlovic H. et al. [31]	2020	32 preterm infants gestational age between 28 weeks and 32 weeks	To determine the reproducibility and MDC of HRV and assess postnatal changes in HRV measures between 32 and 35 weeks	At the 32nd week, the ICC for HRV were statistically significant. By the 35th week, HRV parameters showed a significant increase, exceeding the MDC
Moorman et al.	2011	3003 VLBW neonates in 9 NICUs	Comparing number of days alive and ventilator-free for 120 days post randomization between neonates with and without HRC monitoring	2% mortality reduction rate in infants with HRC monitoring displayed (10.2 to 8.1%, $P = 0.04$), with increased days alive and ventilator-free (95.9 days compared to 93.6 days in control subjects, $P = 0.08$)
Griffin et al.	2005	1022 infants in 2 NICUs, of which 458 were VLBW infants	To evaluate the use of continuous HRC index monitoring as a risk index to identify infants who are at increased risk of sepsis, urinary tract infections, or death in the NICU	Neonates with high-risk HRC index and abnormal laboratory test results had an 11% incidence of adverse outcomes compared with 2% in neonates with normal HRC and normal laboratory test results ($P < 0.001$). High HRC with an abnormal laboratory test result have a 6- to 7-fold increase in relative risk compared to high HRC without abnormal laboratory test results ($P < 0.001$)
Griffin et al.	2003	633 infants in 2 NICUs, of which 270 were VLBW infants	To derive and validate multivariable statistical models involving HRC to predict for sepsis and sepsis-like illness in newborn infants	Regression models involving the use of HRC index is highly predictive for sepsis and sepsis-like illness in both NICUs ($P < 0.001$) and added significantly to demographic information of birth weight, gestational age, and days of postnatal age ($P < 0.001$). Regression models including HRC index performed better with a ROC curve of 0.77, as compared to 0.72 without HRC index

the utility of HRV in the field of infection of premature infants is still in its exploratory stage, and it needs a large number of samples and multicenter clinical data before it can be widely applied in clinical practice, the prospects of HRV utility in the field of infection of premature infants are around the corner.

Conclusion

The application of HRV, a noninvasive monitoring method, to the identification and diagnosis of sepsis in premature infants can enable clinicians to identify, diagnose, and treat children with sepsis early, thereby reducing the mortality of premature infants and neurological damage. In the diagnostic criteria for sepsis in premature infants, the vital signs and laboratory tests are influenced by gestational age and postnatal age (the smaller the gestational age, the faster the heart rate), and the identification of tachycardia needs to exclude other external factors such as cardiac malformations, congenital heart defect, pain stimuli, and chronic medication; meanwhile, tachycardia cannot be explained by other reasons, and heart rate increase should last approximately over 1 h. Although the application of HRV in the field of identification and diagnosis of sepsis in premature infants is not yet fully understood, the physiological mechanism underlying remains unclear, and it is necessary to further standardize the analysis methods, control the influencing factors, and optimize the detection indicators. HRV analysis, as a noninvasive monitoring technique, would undoubtedly show its clinical value and promising prospects.

Abbreviations

HRV	Heart rate variability
NICU	Neonatal intensive care unit
LPS	Lipopolysaccharide
ICC	Intra-class correlation coefficient
VLBW	Very low birth weight
MDC	Minimum detectable change
nSOFA	Neonatal Sequential Organ Failure Assessment
HRC	Heart rate characteristics
ROC	Receiver operating characteristic

Acknowledgements

Not applicable

Authors' contributions

YFZ conceptualized the study and revised and reviewed the manuscript. DC, WXG, JJL, WHG, and YW collected and interpreted the data and contributed to the draft of the manuscript. All authors read and approved the final manuscript.

Funding

Not applicable

Availability of data and materials

Not applicable

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

Received: 5 February 2024 Accepted: 20 March 2024
Published online: 12 June 2024

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