Visual assessment of heart rate variability patterns associated with neonatal infection in preterm infants

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Highlights

- Heart rate variability in 15 preterm infants is compared with clinical signs as well as C-reactive protein levels and blood culture results.
- Preterm babies with positive bacterial blood cultures mostly had low heart rate variability assessed visually.
- A display of heart rate variation may help identifying infants at risk of developing infection.

Abstract

Early identification of neonatal sepsis may help reduce morbidity. From Heart Rate Variability (HRV) visually assessed in preterm infants, eight of nine recordings in babies with positive blood cultures had low HRV and six infants without positive cultures had normal HRV. Straightforward HRV display could help identify infection in infants.

Keywords: newborn infant, infection, heart rate

Abbreviations

CRP	C-reactive protein
CTG	Cardiotocograph
EEG	Electroencephalogram
HRC	Heart Rate Characteristics
HRV	Heart Rate Variability
SpO_2	Pulse oximetry arterial oxygen saturation

Introduction

Late onset sepsis is a leading cause of morbidity and mortality in preterm infants undergoing intensive care [1]. Currently detection is based largely on clinical signs which may only be evident when the infection has taken hold; early identification would allow prompt treatment which could help to reduce serious effects of infection. In adults early non-specific signs of infection such as fatigue can be seen in the prodromal phase of infection but this would be difficult to assess in the neonatal intensive care setting unless a surrogate indicator could be identified.

Over recent years there has been interest in investigating heart rate variability (HRV) changes associated with infection [2, 3]. Heart Rate Characteristics (HRC) monitoring uses an algorithm combining heart rate variability, decelerations and entropy to form a numerical value to estimate the chance of sepsis [4 - 7]. However, its effectiveness in detecting neonatal bloodstream infection has been questioned [8]. Thus it is unclear whether physiological monitoring could provide a reliable means of identifying possible infection. Assessment of heart rate patterns from cardiotocograph (CTG) traces has been shown to be useful in intrapartum monitoring with abnormal baseline heart rate, reduced heart rate variability, decelerations and lack of accelerations being key indicators of possible foetal compromise [9]. HRV can change with transition between sleep states and so the period over which the assessment is made is likely to be important for potential detection of abnormalities.

Aim

To examine if visual assessment of heart rate variability can aid identification of infants who develop clinically significant infection.

Method

Physiological data (heart rate, respiratory rate and SpO_2) were acquired from fifteen preterm infants undergoing varying levels of intensive care treatment a tertiary care neonatal unit; this retrospective audit of anonymised data was approved by the Clinical Governance in the Hospital Neonatal Services Department.

The patients were selected over a 6 month period from summary diagnoses of proven or suspected sepsis. As the study is retrospective the blood sample timing was not chosen but for each case CRP_a is a routine blood test that comes as close as possible to the beginning of the second trace. CRP_b is the highest in the second study time period. Blood cultures are taken as might be expected close to the time of clinical suspicion of sepsis or shortly following the finding of a CRP rise.

The data were collected using standard cotside monitors (GEC Solar) which downloaded automatically at one minute intervals into Metavision, a patient electronic record system (iMDsoft, Israel). The recordings were exported from Metavison to spreadsheet files and randomised. Heart rate traces were no less than 15 hours in length and were from approximately equal numbers of infants with and without positive bacterial blood cultures. For each infant shown in table 1 the heart rate traces 1 and 2 were taken respectively from the period before suspected sepsis and during the period of suspected sepsis. For one baby with early onset sepsis trace 1 was during the time of suspected sepsis and the second trace

during recovery; this is consistent with the high initial CRP and second lower, recovery CRP. We developed software using MATLAB (The MathWorks Inc., USA) to assess and display heart rate changes in sections of 5 hours duration. One recording from an infant with known infection was compared with one recording from an infant with no infection to form a test data set. The test data indicated a clear difference in heart rate patterns; the case with infection had little heart rate variability (HRV) with occasional decelerations and the case with no infection indicated clear HRV. Hence for all the other recordings which had been randomised, heart rate was assessed as being either of normal variability or of low variability without knowledge of clinical condition of the babies; the assessments were repeated in order to check intra-observer variability. Low HRV was defined as variability below 10 beats/minute with or without decelerations and lasting for at least five hours; the level of 10 beats/minute was taken from consideration of the test data and the recording lengths as well as in view of less than 5 beats/minute being considered to indicate reduced variability in CTG monitoring (9). The heart rate analysis was compared with clinical signs of infection as well as C-reactive protein levels and blood culture results. Descriptive statistics, Fisher's Exact test and plotting of additional heart rate graphs from the MATLAB analysis were performed using Minitab v18 (Minitab Inc., USA).

Results

Data were analysed on 15 infants with suspected infection due to abnormal clinical signs and raised C-reactive protein (CRP); a summary of the clinical signs suggestive of infection is given in Table 1. The median (range) gestation at birth was 26 (24-30) completed weeks. The segments of data analysed commenced from a median (range) age of 8 (0 to 78) days. For 14 babies two data periods were analysed; the first was just prior to clinically identified infection and the second when there were documented clinical signs of sepsis and a CRP rise.

Nine infants went on to have positive bacterial blood cultures and one infant had positive bacterial cultures from a wound swab; the HRV was normal for the infant with a wound infection. Table 1 gives the CRP levels corresponding to the recordings and details of the infections detected. The CRP levels are higher in the second sample compared with the first recorded value except for one case of early onset sepsis and 3 cases where no prior CRP value was available. There were two cases for whom the clinical indication of infection included acidosis at the same time as low HRV; the other infant with acidosis had a low HRV the day before clinically suspected infection. There was no clear association between HRV and administration of morphine in the analysed data.

Examples of low HRV and normal HRV patterns are shown in Figure 1. Comparing the assessments of heart rate pattern with clinically identified infection, 8 of 9 recordings in babies with positive blood cultures had low HRV at the time of elevated CRP levels and of 6 infants without positive blood cultures all had normal HRV; hence low HRV was more likely in infants with positive blood cultures, $p = 0.001$ (Fisher's Exact test). Furthermore 15 of 20 recordings prior to clinically identified infection or in babies without proven bacterial sepsis

had normal HRV. There was no obvious association between gestation and the occurrence of low HRV. Repeated HRV assessments showed very good agreement.

Conclusion

The reasons for the difference in HRV associated with infection compared with absence of infection are not clear; it may be that as infection is associated with more fatigue in adults, in newborn infants this is manifested by a greater degree of quiet sleep and sleep is known to affect HRV. Although sleep states may not be well defined in very preterm infants, it seems likely that there are still variations in activity. Sleep cycling would thus be expected to affect both foetal [9] and neonatal heart rate variability and thus a minimum recording length needs to take into account sleep wake cycling; in this study we displayed heart rate changes in sections of 5 hours duration and used a minimum recording length of 15 hours.

Two babies with acidosis as a sign suggestive of infection had concomitant low HRV; respiratory acidosis is associated with a reversible increase in EEG discontinuity in preterm infants [10] and this may also suggest an effect on sleep wake cycling. We did not observe an association between gestation or morphine administration and the occurrence of low HRV in the recordings in this study; it is possible that morphine administration may be expected to affect sleep cycling particularly in the first few days after birth and hence could have an effect on HRV.

Instead of giving a number to the heart rate features on the trace, we utilised a visual pattern recognition approach. Although open to interpretation, we suggest that the underlying heart rate changes can easily be recognised. Visual assessment of heart rate also has the advantage of allowing identification of recording artefacts. Most babies with positive bacterial blood cultures had low heart rate variability, thus the results of this pilot study suggest that a straightforward display of heart rate variation over several hours may allow early non-invasive, cotside identification of preterm infants at risk of developing

infection. Thus the advantages of our approach are the simplicity and straightforward implementation, knowing exactly how the assessment is reached as well as being able to recognise artefact easily. Further studies are required to investigate how the start of reduced HRV might be related to the onset of infection.

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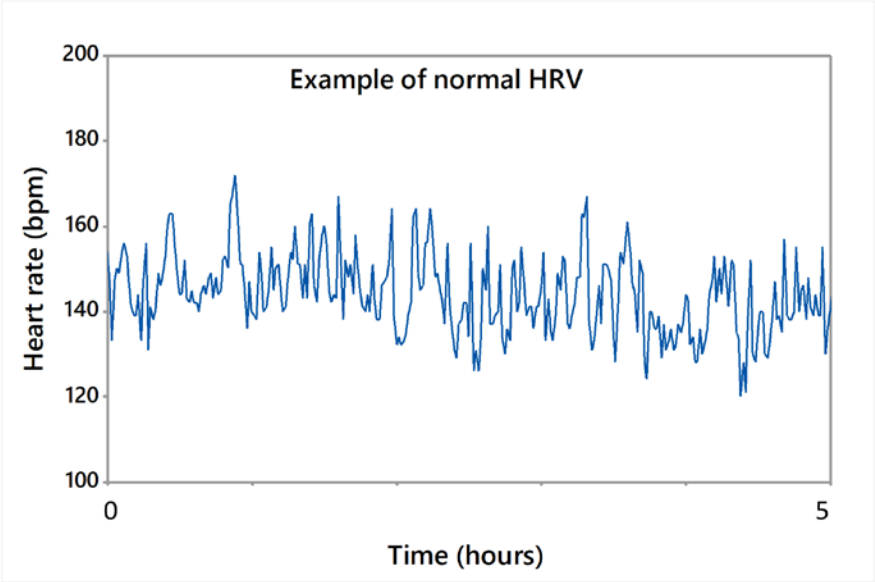
Gestation (weeks)	Postnatal age 1st and 2nd trace (days)	HRV 1	HRV 2	CRP_a	CRP_b	Postnatal age (days) CRP_a	CRP_b	Clinical Signs	Blood Culture Result (day)
27^{+3}	8, 11	normal	low	0.9	23	11	12	Temperature instabililty, SpO2 desaturations	Coagulase negative staphylococcus (11)
30^{+3}	1, 2	low	normal	1.3	23.8	2	4	Acidosis, hypotension	Bacillus Cereus (5)
26^{+2}	2, 5	low	low	0.3 (m)	35.8 (m)	5	7	Hypotension	Pseudomonas species (7)
25^{+4}	0, 4	low	low	0.5 (m)	37.7 (m)	4	6	Acidosis, hyperglycaemia	Escherichia Coli (6)
26^{+3}	11, 12	normal	low	not known	78.9		12	SpO2 desaturations	Staphylococcus haemolyticus
25^{+5}	7, 11	normal	low	2.7	119.5	11	12	SpO2 desaturations, bradycardias	B. Cereus (11)
24^{+3}	5, 9	low	low	4.3 (m)	181 (m)	9	12	Increased FiO2, acidosis	Enterococcus faecalis (7)
24^{+5}	19, 24	normal	low	3.6 (m)	198.8 (m)	24	27	Temperature instability, SpO2 desaturations	Pseudomonas species (26)
29^{+6}	1, 6	low	normal	95.2 (m)	21.5 (m)	1	6	Hypotension, increased FiO2	Escherichia Coli (Early onset sepsis)
24^{+3}	28, 33	normal	normal	not known	35.4		33	Temperature instability, 2 days post PDA repair	Staphylococcus aureus (wound swab) (33)
26^{+3}	78, 83	normal	normal	0.5	8.7	83	87	Temperature instability, quiet	No proven infection (87)
26^{+3}	28, 33	normal	normal	not known (m)	18.8 (m)	28	33	No clinical changes	No proven infection (33)
24^{+3}	4, 11	normal	normal	2.2 (m)	27.1 (m)	11	16	Pyrexial	No proven infection (11)
28^{+0}	24, 29	short recording	normal	4.2	30.7	29	30	SpO2 desaturations, apnoea, bradycardias	No proven infection (29)
24^{+5}	68, 76	normal	normal	0.3	38.3	76	82	Bradycardias and SpO2 desaturations	No blood culture taken (Laser surgery) (81)

Table 1: Summary of clinical data from the 15 babies in the study. The table includes signs suggestive of infection in the infants as well as bacteria detected and CRP values; (m) following the CRP level, indicates the infant was receiving a morphine infusion for sedation whilst being mechanically ventilated. The postnatal ages when the CRP levels and cultures were taken are also given except where obtained at the referring hospital. The first nine rows (in red) indicate infants where clinically significant infection and positive blood cultures were present.


Example of normal HRV
Heart rate (bpm)
200
180
160
140
120
100
0
5
Time (hours)

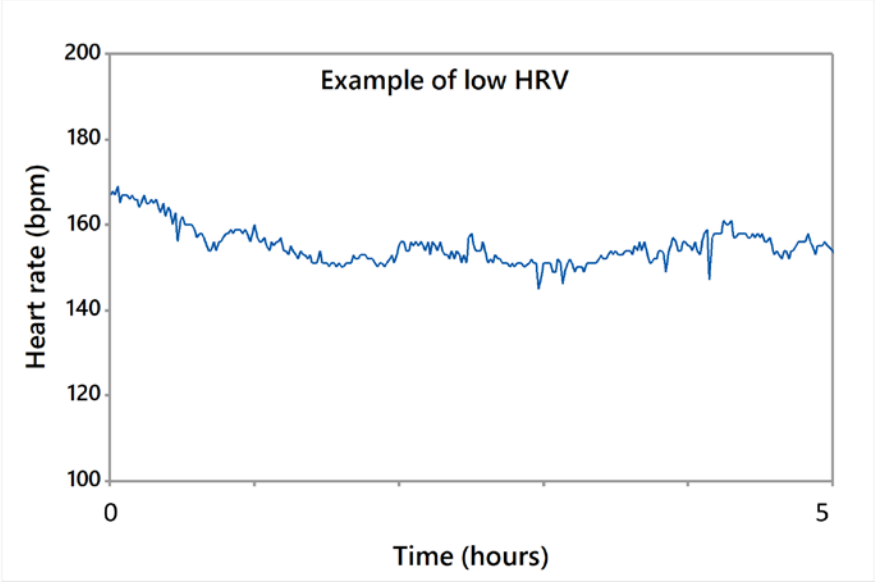

Example of low HRV
Heart rate (bpm)
200
180
160
140
120
100
0
5
Time (hours)

Figure 1. Example of normal heart rate variability pattern (upper trace) and low heart rate variability pattern (lower trace) both with a section length of five hours plotted using Minitab v18. The baseline heart rates are similar for both these traces. Note that the low heart rate variability trace also shows some decelerations.