Chapter 7
Heart Rate Variability in Newborns with Hypoxic Brain Injury

Vladimir Matić, Perumpillichira J. Cherian, Devy Widjaja, Katrien Jansen, Gunnar Naulaers, Sabine Van Huffel, and Maarten De Vos

Abstract In neonatal intensive care units, there is a need for continuous monitoring of sick newborns with perinatal hypoxic ischemic brain injury (HIE). We assessed the utility of heart rate variability (HRV) in newborns with acute HIE undergoing simultaneous continuous EEG (cEEG) and ECG monitoring. HIE was classified using clinical criteria as well as visual grading of cEEG. Newborns were divided into two groups depending on the severity of the hypoxic injury and outcome. Various HRV parameters were compared between these groups, and significantly decreased HRV was found in neonates with severe HIE. As HRV is affected by many factors, it is difficult to attribute this difference solely to HIE. However, this study suggests that further investigation of HRV as a monitoring tool for acute neonatal hypoxic injury is warranted.

V. Matić (✉) • D. Widjaja • S. Van Huffel
Department of Electrical Engineering (ESAT-SCD), Katholieke Universiteit Leuven, Leuven, Belgium

iMinds Future Health Department, Leuven, Belgium
e-mail: Vladimir.Matic@esat.kuleuven.be

P.J. Cherian
Section of Clinical Neurophysiology, Department of Neurology, Erasmus MC, Rotterdam, the Netherlands

K. Jansen
Department of Pediatrics, University Hospital Gasthuisberg, Leuven, Belgium

G. Naulaers
Neonatal Intensive Care Unit, University Hospital Gasthuisberg, Leuven, Belgium

M. De Vos
Department of Electrical Engineering (ESAT-SCD), Katholieke Universiteit Leuven, Leuven, Belgium

iMinds Future Health Department, Leuven, Belgium

Department of Psychology, University of Oldenburg, Oldenburg, Germany

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7.1 Introduction

Perinatal hypoxic ischemic encephalopathy (HIE) represents one of the major causes of morbidity and mortality in newborns. The sequelae in survivors include cerebral palsy, sensory and cognitive problems, and epilepsy. Acute hypoxic brain injury is dynamic and evolves over time. Both recovery and worsening of the encephalopathy can occur. Monitoring of the brain function within 24–72 h postpartum is necessary to assess the evolution of the injury. This helps to guide treatment and predict neurodevelopmental outcome.

In clinical practice, several monitoring tools are used to assess the severity of hypoxic injury. A well-suited bedside tool for noninvasive assessment of brain function is the continuously recorded electroencephalogram (EEG). However, the expertise required to register and interpret EEG is not available in most neonatal intensive care units (NICUs). As an alternative, many NICUs use aEEG (amplitude integrated electroencephalogram) as a device to monitor brain function, due to its ease of application and interpretation [1, 2].

Apart from the evolution of the background EEG activity [1], it is also known that heart rate variability (HRV) may be affected in HIE. This can be due to direct effect of asphyxia on the heart or due to impaired central (cerebral and brain stem) regulation of heart rate, or both, and may help in prediction of outcome.

An earlier study investigated HRV in term asphyxiated newborns [3]. In that study HRV was examined 7 days postpartum. Therefore, although valuable for estimation of the outcome, that study does not show HRV properties at an early stage of the injury (first 3 days postpartum) when treatment interventions are expected to be maximally effective.

The aim of the present study is to examine the use of HRV obtained by continuous electrocardiogram (ECG) monitoring done simultaneously with continuous EEG registrations (cEEG) in patients with HIE as a diagnostic tool. We compare heart rate parameters between two groups of neonates, group I with mild HIE and group II with moderate to severe HIE, using long-term ECG recordings. Although many factors influence HRV parameters, our goal is to examine whether the differences in HRV parameters are sufficiently discriminative between these two groups of newborns. To test these differences, a linear discriminant analysis (LDA) classifier was used.

7.2 Dataset

All data were recorded at Sophia Children's Hospital, Erasmus MC (Rotterdam, the Netherlands). We studied 19 newborns with HIE and without recorded epileptic seizures. They were preselected from a larger set of 119 newborns who underwent continuous EEG video monitoring. Sampling frequency of the simultaneously recorded ECG signal was 256 Hz.

Continuous 2-h artifact-free ECG recordings were selected. In total, we analyzed 36 ECG segments recorded within 18–48 h after birth. The number of analyzed segments ranged from 1 to 4 per patient. The severity of encephalopathy was assessed using both clinical grading (Sarnat scores) and grades of background EEG activity [1]. The scoring of the background EEG was performed by an experienced clinical neurophysiologist (PJC). Newborns were divided into two groups: group I ($n=10$) with mild HIE and good outcome and group II ($n=9$) with moderate to severe HIE and poor outcome. Outcome was classified into good outcome [normal or mild disability – minimal abnormalities at neurological examination or mild cerebral palsy; the Gross Motor Functional Classification System (GMFCS 1–2)] and poor outcome [death or Mental Developmental Index (MDI) < 70 or severe cerebral palsy (GMFCS 3–5)].

In these datasets we selected 2-h ECG recordings, as this was the longest artifact-free period we could find. This duration of ECG recordings was sufficient to accurately calculate and estimate long-term HRV parameters [4]. In total, we had 22 ECG segments from group I with a good outcome and 14 ECG segments from group II with a poor outcome.

7.3 Methods

To calculate HRV parameters the first step is to detect R peaks within the QRS complex of the ECG signal. We improved the accuracy of the HRV parameters by upsampling the ECG signal to 1,000 Hz and used it for further analysis. The Pan-Tompkins algorithm was applied for R peak detection. This way, we obtained a tachogram signal, also known as the RR interval. All 2-h ECG segments were visually inspected to ensure that there were no missed R peaks or false-positive R peak detections. In this way, we obtained an NN interval (normal-to-normal beat [4]).

Three groups of HRV parameters were calculated: time, geometry, and frequency domain parameters. All these parameters are calculated as proposed in [4]. As the first time domain parameter, mean NN interval is calculated. Variable SDNN is based on the standard deviation of NN time series and reflects the total power of the HRV spectra. By increasing the duration of the ECG recordings, the SDNN parameter increases as well. Therefore, it is important to compare this parameter using the ECG recordings of the same duration. The SDANN parameter reflects changes in NN time series using 5-min epochs. It represents the standard deviation of average NN intervals calculated over 5 min of recordings. Additionally, the SDNN index is calculated as a mean value of the 5-min standard deviations calculated over 2 h.

A commonly used time domain parameter is the RMSSD, the square root of the mean squared differences of successive NN intervals. pNN25 is the number of interval differences of successive NN intervals ≥ 25 ms divided by the total number of NN intervals and multiplied by 100. Finally, we calculated SDSD, the standard deviation of differences between adjacent NN intervals.

Additionally, we calculated standard geometric parameters as proposed in [4]. Triangular index, related to the histogram of the NN intervals and parameters SD1 and SD2 of the Poincaré plots, was calculated.

To calculate frequency parameters, we interpolated NN intervals using a 4-Hz sampling frequency. Thus, we obtained an equidistantly sampled signal. We then calculated power spectral density using Welch's periodogram.

Three frequency bands were defined (VLF, LF, and HF) of which the spectral power was expressed in absolute values (in ms^2) and in normalized units (n.u.) which represent the relative value of each power component in proportion to the total power minus the VLF component. The frequency bands were adapted to the newborn's heart rate: 0.01–0.04 Hz, 0.04–0.2 Hz, and 0.2–2 Hz, as proposed in [5].

The goal of this study is to examine whether HRV parameters from 2-h ECG are discriminative enough, i.e., to verify whether the outcome group can be predicted accurately using only parameters derived from the ECG signal. For this purpose, the leave-one-out method was applied in these experiments. We used ECG segments and corresponding HRV parameters from a single patient as an input to an LDA classifier. The classifier was trained using the HRV parameters obtained from the remaining patients. As the output, the classifier is expected to estimate the appropriate group of the patient, i.e., good or poor outcome.

Input features into the LDA classifier represented a subset of all calculated HRV parameters. As we did not know a priori which features would be the most discriminative, we combined features into different subsets to increase the discriminative power. The number of features was relatively low, and we were able to create subsets of various sizes and use an exhaustive combinatorial search to determine an optimal set of parameters.

7.4 Results

In total, 24 HRV parameters were calculated as proposed in [4], and they were used as input features into the LDA classifier. The best set of parameters achieved an accuracy of 80 % in discriminating the two groups of newborns. The most descriptive parameters were standard deviation of the heart rate signal (SDNN index), low-frequency power of the heart rate spectra (LF), and SD2 parameter of the Poincaré plot. Normalized values of these parameters are shown in Fig. 7.1. More importantly, there was a reduced HRV in the patient group with more severe HIE.

7.5 Discussion

In patients with HIE it is important to estimate the degree of hypoxic injury at an early stage. The most informative tool is the cEEG, and in this study we wanted to examine the use of continuously recorded ECG signal and HRV as a potential

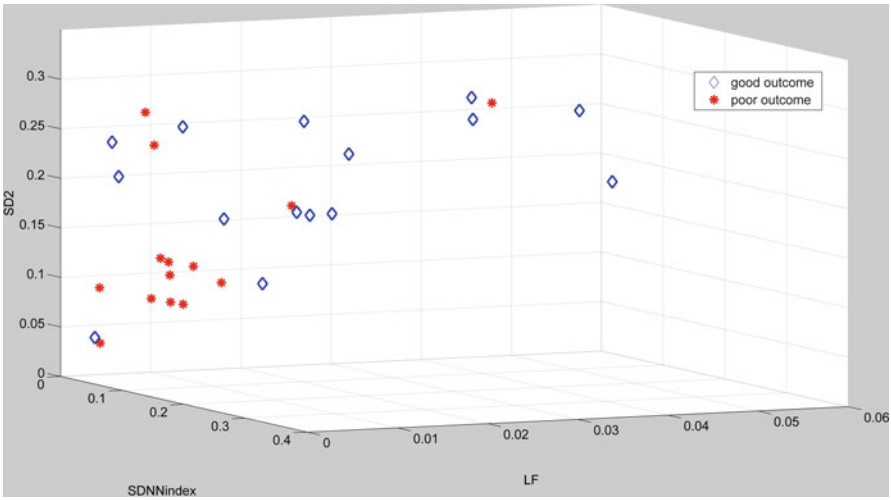

Fig. 7.1 Subset of HRV parameters that achieved the best discrimination between groups with good and poor outcome. All parameters are depicted using normalized values

additional tool. Advantage of the ECG signal is its well-defined morphology and straightforward and easy calculation of HRV parameters. A difficulty can arise in interpretation of the HRV parameters.

In this study, we tried to make our database as homogenous as possible by excluding patients who were treated with antiepileptic drugs. Many patients were excluded from the present study because the monitoring started more than 48 h postpartum or because the ECG recordings were corrupted by artifacts. Additionally, there is an inherent difficulty in making a new, better controlled study. Start of the ECG and EEG recordings is influenced by many medical and logistic factors that are often difficult to control.

In addition to hypoxic injury, HRV is influenced by many factors such as autonomic nervous system dysfunction, changes in blood pressure, temperature, respiration, and administered medications. Hence, in the present study it is difficult to draw definite conclusions about HIE as the major determinant of the HRV findings.

Despite these limitations, our results show that there is a significant relationship between the severity of HIE as graded clinically and by cEEG and HRV.

In [3], reduced HRV was also reported in term asphyxiated newborns 7 days after birth; in that study the Sarnat score was used to classify the patient groups. In our study, we used both the Sarnat score and the evolution of the background EEG to better classify encephalopathy. This is important because hypoxic injury usually evolves and brain function can recover or deteriorate over time. Additionally, we used the brain injury patterns seen on MRI scans done in the first week after birth and neurodevelopmental outcome in survivors at follow-up after 2 years. This made the classification of patients into two outcome groups more reliable.

For future study, more insight into HRV in perinatal HIE can be obtained by comparing HRV parameters at specific time points, such as 12, 24, 48, and 72 h postpartum. In that way maturational effects of the central nervous system as encountered in studies done after 1–2 weeks postpartum can be avoided. Such investigations would be valuable to confirm the possibility to use HRV as a tool to monitor the evolution of HIE recovery as well as to identify neonates requiring additional interventions or neuroprotection. In the case that correlations and dynamics do exist between HRV parameters and parameters derived from the cEEG (e.g., duration of inter-burst intervals), they can contribute to improve the assessment and monitoring of perinatal hypoxic brain injury.

Inclusion of a larger number of neonates with varying degrees of HIE, as well as studying HRV evolution over a longer period of time, would help to clarify the application of these parameters in the refinement of the assessment and prediction of outcome after perinatal hypoxic injury.

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