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Assessment of general movements and heart rate variability in prediction of neurodevelopmental outcome in preterm infants

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ABSTRACT

Background: Adverse neurologic outcome in preterm infants could be associated with abnormal heart rate (HR) characteristics as well as with abnormal general movements (GMs) in the 1st month of life.
Aims: To demonstrate to what extent GMs assessment can predict neurological outcome in preterm infants in our clinical setting; and to assess the clinical usefulness of time-domain indices of heart rate variability (HRV) in improving predictive value of poor repertoire (PR) GMs in writhing period.
Study design: Qualitative assessment of GMs at 1 and 3 months corrected age; 24 h electrocardiography (ECG) recordings and analyzing HRV at 1 month corrected age.
Subjects: Seventy nine premature infants at risk of neurodevelopmental impairments were included prospectively.
Outcome measures: Neurodevelopmental outcome was assessed at the age of 2 years corrected. Children were classified as having normal neurodevelopmental status, minor neurologic dysfunction (MND), or cerebral palsy (CP).
Results: We found that GMs in writhing period (1 month corrected age) predicted CP at 2 years with sensitivity of 100%, and specificity of 72.1%. Our results demonstrated the excellent predictive value of cramped synchronized (CS) GMs, but not of PR pattern. Analyzing separately a group of infants with PR GMs we found significantly lower values of HRV parameters in infants who later developed CP or MND vs. infants with PR GMs who had normal outcome.
Conclusions: The quality of GMs was predictive for neurodevelopmental outcome at 2 years. Prediction of PR GMs was significantly enhanced with analyzing HRV parameters.

1. Introduction

In recent decades, major advances in neonatal medicine have led to the increase of survival rates of preterm-born infants [1]. With survival rates of preterm and/or low-birth weight infants improving, there is an increase in the number of these infants developing motor, sensory, cognitive, and many other neurodevelopmental problems later in life. Motor problems can range from developmental coordination disorders to cerebral palsy (CP) [2]. Consequently, it is of paramount importance to identify motor dysfunction in infants at an early stage so that appropriate interventions can be implemented [2,3].

There are a number of assessments that enable the motor development of preterm infants during the first year of life to be discriminated, predicted and evaluated. At present, it is estimated that Prechtl's method on the qualitative assessment of general movements (GMs) is one of the best methods for evaluating neurologic function in young infants and has a high predictive value for future neurologic deficits [4–7]. GMs as complex, endogenously generated movements involving the whole body are present from early foetal life until the end of the second month after term. Throughout this period, general movements have a writhing character: they are ellipsoid and create the impression

Abbreviations: GMs, general movements; HR, heart rate; HRV, heart rate variability; MND, minor neurologic dysfunction; CP, cerebral palsy; NN intervals, the length between two successive heart beats; SDNN, standard deviation of all NN intervals; SDANN, standard deviation of the averages of NN intervals in all five-minute segments; RMSSD, square root of the mean of the sum of the squares of the differences between adjacent NN intervals.

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that the infant is writhing. Usually 2 months after term the writhing GMs are gradually replaced by fidgety GMs. The characteristics of fidgety movements are: small amplitude, moderate speed, and variable acceleration of the neck, trunk and limbs in all directions. These movements are present up to 5 months after term [8,9].

GMs in the writhing period in at-risk and brain-damaged infants lose their complex and variable character and have either a poor repertoire (PR) or are cramped-synchronized (CS) or chaotic (Ch). Fidgety movements can be either abnormal or absent.

In the writhing period it is only the abnormal pattern of CS GMs that has a high predictive value for later spastic CP. The abnormal pattern of PR GMs is frequent in preterm infants, but has a low predictive value, so it is highly recommended to assess fidgety movements in these infants. It is only the presence or absence of fidgety movements that has a high predictive value for the neurological outcome [10–12].

Investigations regarding CP and neurodevelopmental disturbances are focused on central nervous system (CNS) damage, while studies of the function of the autonomic nervous system (ANS) have been virtually overlooked. There are a small number of studies describing heart autonomic irregularity among children with CP [13–14].

The ANS is a crucial regulator of the homeostasis of the circulatory and respiratory system. Parasympathetic and sympathetic controls of heart rate (HR) constantly mature with gestational age. After birth, there is a progressive HR decrease and heart rate variability (HRV) indices increase. Maturation of the ANS, on the one hand, allows the full-term newborn to adapt its respiratory and haemodynamic responses to internal and external environments. The premature newborn, on the other hand, may inappropriately adapt to environmental, nutritional or iatrogenic external conditions due to ANS immaturity. There is significantly lower ANS activity in premature than in term infants [15].

HR and HRV are powerful tools that allow not only the cardiovascular system but also the CNS to be studied. One of the clinical applications of HRV measurements in preterm infants is the prediction of neurological outcome [16].

In our previous study, we demonstrated that HRV could be helpful clinically as well as a prognostic tool in infants with developmental coordination disorders. This study was the first to report the relationship between 24 h HRV time-domain indices and the infant neurodevelopmental status as well as their neurodevelopmental outcome, favouring a hypothesis of enhanced sympathetic and low parasympathetic nervous system activity in infants with neurodevelopmental abnormalities [17,18].

The purpose of the current study was to demonstrate the extent to which GM assessment can predict neurological outcome in preterm infants in our clinical setting; and to assess the clinical usefulness of time-domain indices of HRV in improving the predictive value of PR GMs in the writhing period.

2. Methods

We collected the consecutive sample of 94 children, born at a gestational age of below 37 weeks, admitted at the tertiary referred Paediatric Rehabilitation Department of the University Hospital from July 2011 to December 2013. The reasons for admission were a high risk of neurodevelopmental problems or abnormal findings in paediatric examinations (such as hypotonia, hypertonia, abnormal reflexes, abnormal postural responses, abnormal posture, asymmetry, abnormal findings of cranial ultrasound etc.). At the admission to our institution all children were near the term age (37–41 weeks post-menstrual age (PMA)).

During the study 15 children were excluded due to: presence of congenital anomalies – 4; incorrect video recording of GMs – 2; incorrect ECG – 1; lost to follow-up – 7; and one child died. Finally, 79 children were included in the study. The study was performed in accordance with the Declaration of Helsinki and under the principles of Good Clinical Practice. The local ethic board approved the study and written informed consent was obtained from the parents or caregivers of each infant. The protocol consisted of the following assessments: a) video recordings and evaluation of GMs, b) 24 h ECG Holter monitoring and HRV analyses, c) neurological examination.

a) Video recordings and evaluation of GMs. Two digital video recordings were made of each infant: at 1 month corrected age, for assessment of writhing movements, and the second at 3 months after term, the age at which fidgety movements should be present. During recordings, the infant was lying on an uncoloured underlay, in the supine position, wearing only a nappy with their face clearly visible. The duration of the recording was at least 10 min with the infant in adequate behavioural state 4 (eyes open, not crying, irregular respiration, movements present). The recordings were evaluated by the observer, who had successfully participated in both a basic and an advanced GM training course. She had several years of experience in rating children by Prechtl's method in clinical practice. For this study she was blind to clinical history details, and she used the same standardized rating sheet that was used during the training courses with indications of the age of the child, the case number and the different rating possibilities:
For writhing period: N = normal writhing GMs (the movements are complex, variable, fluent, elegant, the entire body involved, with variable sequences of the arms, legs, neck and trunk); PR = poor repertoire GMs (the sequence of the successive movement components is monotonous and the movements of the different body parts do not occur in the normal rich and complex sequence); Ch = chaotic GMs (movements of all limbs are of large amplitude and occur in a chaotic order without any fluency or smoothness, and consistently appear to be abrupt); CS = cramped-synchronized GMs (movements appear stiff and rigid, without normal smooth and fluent character, all limb and trunk muscles contract and relax almost simultaneously).
For fidgety period: F = normal fidgety GMs (elegant movements of small amplitude, moderate speed, and variable acceleration of the neck, trunk and limbs in all directions, present continually or intermittently in the awake infant); AF = abnormal fidgety GMs (excessive amplitude, speed and jerkiness); and F− = absent fidgety GMs (no fidgety movements).
b) 24 h ECG Holter monitoring and HRV analyses. 24 h ECG–Holter monitoring was performed by small, ambulatory, portable device (Cardiolight FMC.A, Medset and Medizintechnik, Hamburg, Germany) at the age of 1 month after term. To determine HRV parameters, appropriate Holter software was used. Before HRV analyses we checked the precision of computer-assisted methods, and whether premature QRS complexes were excluded from HRV software analyses. The method of QRS detection was than overread by a physician, and all remaining ectopic beats, noisy data and artefacts were manually identified, and thus excluded from the HRV analysis. Only the normal NN intervals (the length between two successive heart beats) over a period of at least 18 h of analysable signal were analysed using the time-domain method. Observed time-domain parameters included: standard deviation of all NN intervals (SDNN), standard deviation of the averages of NN intervals in all 5-min segments (SDANN), and the square root of the mean of the sum of the squares of the differences between adjacent NN intervals (RMSSD). An HRV analysis was performed by one of the authors who was unaware of infants' neurological findings.
c) Neurological examination. At age 24 months corrected, a structured neurological examination was performed by a neurologist employed at the Paediatric neurology Department, well experienced and educated in the field of child neurology, for assessment of posture, reflexes, muscular tone and movements. The neurologic status was categorized as: Normal (completely normal neurologic status); Unspecific signs or MND (minor neurologic dysfunction) according to Touwen's criteria [19,20], but no definite signs of CP; and CP

Table 1
Characteristics of the subjects.

	Number of infants
Male:female ratio	41:38
Gestation	
Extremely preterm <25 weeks	0
Very preterm 25.0–31.6 weeks	18
Moderately preterm 32.0–33.6 weeks	25
Late preterm 34.0–36.0 weeks	36
Birth weight	
Extremely low birth weight (ELBW) <1000 g	4
Very Low Birth Weight (VLBW) 1000–1500 g	16
Low Birth Weight (LBW) 1500–2500 g	58
Normal Birth Weight >2500 g	1
Perinatal conditions (potential risk factors) -recorded	
Twins	19 (24.05%)
Sectio caesarean	34 (43.03%)
Asphyxia	18 (22.78%)
Septicaemia	11 (13.92%)
Respiratory distress syndrome (RDS)	14 (17.72%)
Nonatal seizures	18 (22.78%)
Hypoglicaemia	19 (24.05%)
Two or more risk factors	42 (53.16%)

(signs of CP present as defined by the SCPE (Surveillance of Cerebral Palsy in Europe) working group) [21].

3. Statistics

Descriptive statistics of clinical variables were presented as median and interquartile range (IQR) or percentage as appropriate. Time-domain parameters of HRV were presented as mean values with standard deviation (SD). One-way ANOVA was used for comparison of HRV parameters between different groups.

The discriminative performances of models for the prediction of CP development as outcome were evaluated with sensitivity, specificity, positive predictive rates, negative predictive rates and receiver operating characteristic curves (ROC). Significance was calculated using Fisher's exact test. Results of area under ROC curves were presented as 95% confidence intervals (CI).

A value of $p < 0.05$ was considered statistically significant. All statistical analysis was performed with software STATA, version 12 (Stata Corp. LP, USA).

4. Results

4.1. Population characteristics

The analysed group consisted of 79 infants: 38 female (48.1%) and 41 male (51.9%). The infants' gestational age, birth weight and perinatal conditions (potential risk factors) are shown on Table 1. All of the perinatal risk factor in patients included in study was transient and resolved by the 40th gestational weeks when the HRV examinations were performed. Median Apgar score at the 1st minute was 7 (IQR 7–9) and at the 5th minute 9 (IQR 8–9). Forty-four infants (55.7%) had a normal brain ultrasound; 18 infants (22.78%) had isolated ventricular dilatation, or periventricular echodensity lasting for <14 days, or intraventricular haemorrhage grades I and II according to Volpe [22]; 10 infants (12.66%) had bilateral periventricular echodensity lasting for >14 days; 4 infants (5.06%) had intraventricular haemorrhage grade III according to Volpe; and 3 infants (3.8%) had cystic periventricular leukomalacia or unilateral intraparenchymal echodensity.

4.2. Neurological outcome

At 2 years of age, 57 children were neurologically normal (72.15%), MND was observed in 11 (13.92%), and 11 (13.92%) developed spastic CP (9 bilateral and 2 unilateral).

Among infants with normal outcome, 8 were born very preterm (<31.6 weeks), 16 were born moderately preterm (32.0–33.6 weeks) and 33 were born late preterm (34.0–36.6 weeks). Among infants with MND, 4 were born very preterm, 5 were born moderately preterm and 2 were born late preterm. Among infants who developed CP, 6 were born very preterm, 4 were moderately preterm and 1 was born late preterm.

4.3. Assessment of GMs

At 1 month corrected age, 49 (62%) infants had N, 20 (25.3%) had PR and 10 (12.65%) had CS. At 3 months, 58 (73.4%) infants had normal F+, 7 (8.86%) had AF and 14 (17.72%) had F−. The longitudinal assessment of GMs showed 48 (60.75%) infants with Nor-Nor trajectory, 1 (1.26%) with Nor-Abn trajectory, 10 (12.66%) with Abn-Nor trajectory and 20 (25.32%) with Abn-Abn trajectory. Among the 10 infants with Abn-Nor trajectory, all 10 had PR. Among the 20 infants with Abn-Abn trajectory, 10 had PR at 1 month followed by AF in 5 cases and F− in 5 cases; 10 had CS at 1 month followed by AF in 1 case and by F− in 9 cases. Only one infant had N GMs at 1 month followed by AF at 3 months. Details of the relation between GMs and outcome are shown in Table 2.

The sensitivity and specificity of GMs predicting neurological outcome (CP at 2 years) are presented in Table 3. The finding of PR in the writhing period has the worst predictive characteristics for neurodevelopmental outcome at 2 years (sensitivity 18.2%, specificity 73.5%).

4.4. HR and HRV assessment

The summarized values of time-domain parameters (SDNN, SDANN and RMSSD) and average HR in infants in the writhing period (1 month corrected age) are presented in Table 4. In infants with abnormal patterns of GMs (PR and CS) we found significantly lower values ($p < 0.05$) of all 3 parameters than in infants with N GMs. For infants with PR GMs we separately analysed mean values with standard deviations of all 3 parameters (Table 5). We found significantly lower values of all 3 parameters in infants with PR who later developed CP than in infants with PR and normal outcome.

In 20 patients with PR GMs, HRV parameters significantly improved the prediction of neurological outcome at 2 years, with AUC of 0.861, 0.861 and 0.958 for SDNN, SDANN and RMSSD, respectively. For SDNN, the best estimation was achieved for the criterion ≤47 ms

Table 2
General movements and outcome at 2 years.

OUTCOME	Writhing			Fidgety			Trajectory			
	N ($n = 49$)	PR ($n = 20$)	CS ($n = 10$)	F ($n = 58$)	AF ($n = 7$)	F− ($n = 14$)	Nor-Nor ($n = 48$)	Nor-Abn ($n = 1$)	Abn- Nor ($n = 10$)	Abn-Abn ($n = 20$)
Normal	47 (95.92%)	10 (50%)	0	56 (96.55%)	1 (14.29%)	0	47 (97.92%)	0	9 (90%)	1 (5%)
Minor neurologic dysfunction	2 (4.08%)	8 (40%)	1 (10%)	2 (3.45%)	6 (85.71%)	3 (21.43%)	1 (2.08)	1 (100%)	1 (10%)	8 (40%)
Cerebral palsy	0	2 (10%)	9 (90%)	0	0	11 (78.57%)	0	0	0	11 (55%)

N = normal writhing; PR = poor repertoire; CS = cramped synchronized; F = normal fidgety; AF = abnormal fidgety; F− = absent fidgety; Nor–Nor = Normal–Normal; Nor–Abn = Normal–Abnormal; Abn–Nor = Abnormal–Normal; Abn–Abn = Abnormal–Abnormal.

Table 3
Sensitivity and specificity of GMS predicting neurological outcome (CP at 2 years).

General movement	CP/No CP					
	Sensitivity	Specificity	PPV	NPV	Area under ROC	*p* value*
Writhing period						
PR	18.2%	73.5%	10.1%	84.7%	0.459	0.434
CS	81.8%	98.5%	90.1%	97.1%	0.902	0.00
Any abnormal findings (PR or CS)	100%	72.1%	36.8%	100%	0.86	0.00
Fidgety period						
Ab F	0%	89.7%	0%	84.6%	0.449	0.334
F−	100%	95.6%	78.7%	100%	0.978	0.00
Any abnormal findings (Ab F or F−)	100%	85.3%	52.5%	100%	0.926	0.00
Trajectories						
Nor - Nor	0%	29.4%	0%	64.4%	0.147	0.00
Nor- Abn	0%	98.5%	0%	85.8%	0.493	0.861
Abn- Nor	0%	85.3%	0%	84%	0.426	0.202
Abn- Abn	100%	86.8%	55.2%	100%	0.934	0.00
Any abnormal trajectory	100%	70.6%	35.6%	100%	0.853	0.00

N = normal writhing; PR = poor repertoire; CS = cramped synchronized; F = normal fidgety; AF = abnormal fidgety; F− = absent fidgety; Nor–Nor = Normal–Normal; Nor–Abn = Normal–Abnormal; Abn–Nor = Abnormal–Normal; Abn–Abn = Abnormal–Abnormal; PPV = positive predictive value; NPV = negative predictive value; ROC = receiver operating characteristic curves.
* 1-sided Fisher's exact test.

(sensitivity 100%, specificity 83.3%, Fig. 1); for SDANN, the best estimation was achieved for the criterion ≤38 ms (sensitivity 100%, specificity 83.3%, Fig. 2); and for RMSSD, the best estimation was achieved for the criterion ≤14 ms (sensitivity 100%, specificity 88.9%, Fig. 3).

5. Discussion

For >15 years, observation of the quality of GMs has been widely used in the neurological assessment of neonates, but the current study is the first done in Serbia. The results of our study demonstrated a strong relationship between GMs at 1st and 3rd months of age and neurodevelopmental outcome at 2 years.

Our findings support the results of numerous previous studies that indicate that the qualitative assessment of GMs offers the opportunity to identify infants with neurological deficits at an early age [23–26]. GMs have the best predictive validity for CP and, with similar significance, for normal neurological outcome. Furthermore, the assessment of GMs is quick, inexpensive, non-invasive and nonintrusive [10–11,23,27].

It was recognised that the presence of CS patterns in the writhing period and absence of fidgety movements at 3 months post-term are highly predictive for CP. The current study confirmed that qualitative assessment of GMs in the writhing period can predict later neurodevelopmental outcome. We found that GMs in the writhing period (1 month corrected age) predicted CP at 2 years with a sensitivity of 100%, and specificity of 72.1%. Our results demonstrated the excellent predictive value of CS, but not of PR. Among 20 infants with PR GMs at 1 month, 50% had normal outcome, 40% had MND and 10% (2 infants) deteriorated from PR to CS and developed CP at 2 years. This clearly demonstrates that PR GMs have a low predictive value. These findings are similar to the results of other studies and they indicated that the prognostic value of GM assessment for PR patterns during the writhing period is less clear [12,23,27].

Nakajima et al. concluded that even detailed analysis of the different aspects and components of poor repertoire GMs could not improve the predictive value of this abnormal GM pattern [12]. They suggested that it remains obligatory to assess the fidgety movements of those infants with PR GMs in the writhing period because it is only the presence or absence of fidgety movements that can have a high predictive value for the neurological outcome. Some studies reported an association between PR GMs and lower developmental level at 2 years [27,28].

Our results suggest that HRV could improve prediction of neurodevelopmental outcome in children with PR GMs. The results showed no significantly higher average HR in infants with an abnormal pattern of GMs as well as significantly lower values of HRV parameters (SDNN, SDANN and RMSSD) at the age of 1 month, compared to infants with normal GMs. When analysing separately a group of infants with PR GMs we also found significantly lower values of HRV parameters in infants who later developed CP or MND than in infants with PR GMs who had normal outcome. Furthermore, we demonstrated independent predictive values of all 3 parameters in infants who subsequently developed CP.

The fact that HRV alterations were found in the preterm infants who subsequently develop CP, raises the hypothesis that the alteration of autonomic maturation in our group of patients could be explained by neurological injuries. Namely, the prediction of the outcome in this group of patients with PR GMs is uncertain because PR in writhing period may be followed by normal fidgety GMs, suggesting that it just reflects a temporary dysfunction, or followed by abnormal/absent fidgety movements suggesting permanent dysfunction and adverse neurological outcome. Since spontaneous movements are essential in

Table 5
Summarized time-domain parameters and heart rate of infants with poor repertoire ($n = 20$) according to neurodevelopmental outcome.

HRV parameters	OUTCOME		
	N ($n = 20$)	MND ($n = 8$)	CP ($n = 2$)
Average HR (beats/min) n.s	137.1 ± 3.57	143.5 ± 10.20	142 ± 12.73
SDNN (ms)**	66.5 ± 5.99	48.75 ± 9.56	43.5 ± 4.95
SDANN (ms)**	59.2 ± 8.27	38.63 ± 9.88	34.5 ± 4.95
RMSSD (ms)**	22.3 ± 3.27	17.37 ± 3.16	12.5 ± 2.12

N = normal; MND = minor neurologic dysfunction; CP = cerebral palsy; SDNN- standard deviation of all NN intervals SDANN- standard deviation of the averages of NN intervals in all five-minute segments; RMSSD- square root of the mean of the sum of the squares of the differences between adjacent NN intervals.
Comparisons between groups by one way ANOVA, n.s- not significant.
** $p < 0.05$.

Table 4
Summarized time-domain parameters of infants in writhing period (expressed as mean values with SD- standard deviation) and their average HR.

HRV parameters	GMs-writhing period			Comparison between groups*	
	N ($n = 49$)	PR ($n = 20$)	CS ($n = 10$)	F	*p*
Average HR (beats/min)	133 ± 9.34	140.15 ± 7.93	143.1 ± 16.6	1.89	0.02
SDNN (ms)	66.12 ± 11.68	58.6 ± 13.39	42.1 ± 12.40	3.21	<0.001
SDANN (ms)	54.47 ± 11.48	48.5 ± 13.84	34.6 ± 11.93	3.02	<0.001
RMSSD (ms)	22.84 ± 7.84	19.35 ± 4.49	16 ± 1.94	2.91	<0.001

N = normal writhing; PR = poor repertoire; CS = cramped synchronized; SDNN- standard deviation of all NN intervals; SDANN- standard deviation of the averages of NN intervals in all five-minute segments; RMSSD- square root of the mean of the sum of the squares of the differences between adjacent NN intervals.
* One-way ANOVA.

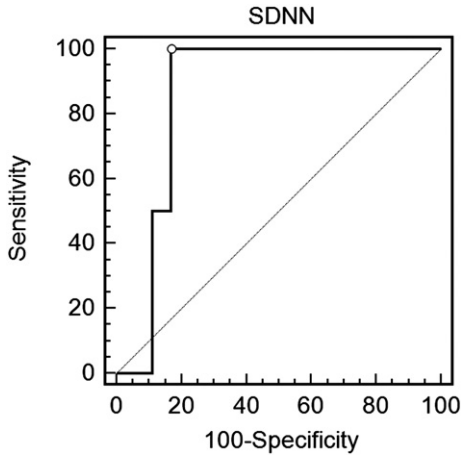

Fig. 1. A receiver operating characteristic curve (ROC) for SDNN parameter with area under the curve in patient with PR repertoire in writhing period. *Footnote*: Area under the ROC curve (AUC) 0.861, SE = 0.108, 95% CI 0.634 to 0.971, z = 3.332, $p = 0.0009$. Best estimation for criterion ≤47 m, Sensitivity 100%, Specificity 83.3%.

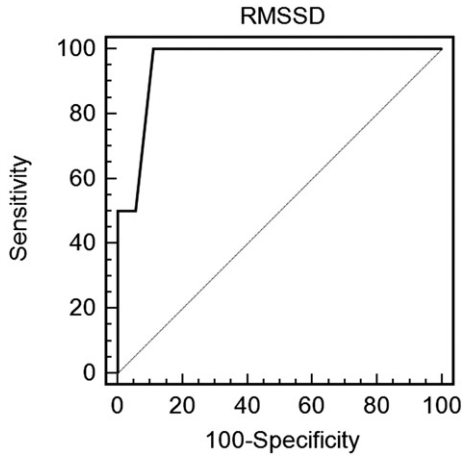

Fig. 3. A receiver operating characteristic curve (ROC) for RMSSD parameter with area under the curve in patient with PR repertoire in writhing period. Footnote: Area under the ROC curve (AUC) 0.958, SE 0.049, 95% CI 0.763 to 0.991, z = 9.344, $p = 0.0001$. Best estimation for criterion ≤14 ms, Sensitivity 100%, Specificity 88%.

developing the neuronal networks that precede voluntary mobility, it is currently theorized that the complexity and variation in general movements are generated by the transiently present cortical subplate and mediated by its motor efferent connections [23]. Additionally, it is hypothesized that abnormal GMs are the result of damage or dysfunction of the subplate and its efferent motor connections in the periventricular white matter [29]. As studying the HRV characteristics of premature infant can be used to assess the function of the nervous system, which may or may not be presenting physical signs of damage [16], one could hypothesize that early autonomic dysfunction in writhing period may reflect neurologic outcome.

Over the last decades HRV analysis has been extensively used to obtain prognostic information on different brain pathologies giving insight preferably on central sympathovagal balance [30,31]. There have been few reports on the usefulness of HRV analyses in infants at high risk showing in general reduced overall HRV in those with adverse neurological outcome [15–17,32]. It was demonstrated that evaluation of neural regulation of the heart provides useful information not only on sympathetic or parasympathetic activity but also on functional integrity of the CNS.

Our results suggest a potential values of HRV analysis in group of infants with PR GMs, which is frequently observed abnormal GMs but with low predictive values for the neurological outcome. Since 24 h ECG recording is non-invasive, safe and it is unaffected by active motor movements, we recommend this methodology as a potentially helpful clinical tool in everyday clinical practice when assessing the functional integrity of CNS in this group of patients. Due to potential high predictive value of HRV parameters in this clinical setting it would be useful to determine cut of values, enough sensitive and specific for adverse neurological outcome in all infants with PR GMs. In this regard, further well-designed clinical studies, with larger samples, are needed for external validity and to determine exact clinical applicability.

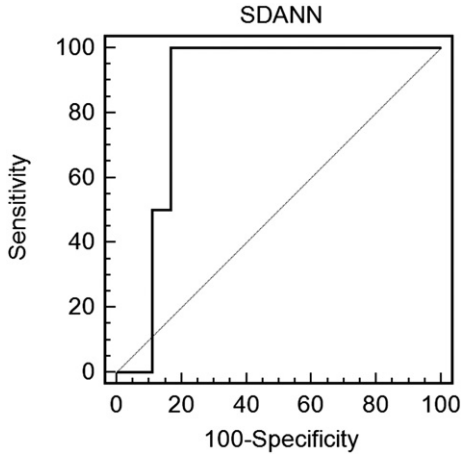

Fig. 2. A receiver operating characteristic curve (ROC) for SDANN parameter with area under the curve in patient with PR repertoire in writhing period. Footnote: Area under the ROC curve (AUC) 0.861, SE = 0.108, 95% CI 0.634 to 0.971, z = 3.332, $p = 0.0009$. Best estimation for criterion ≤47 m, Sensitivity 100%, Specificity 83.3%.

6. Study limitations

Interpretation of the data should take into account some potential limitations. First, external validity of our findings could be limited by the characteristics of the study population and the restriction to the university based Paediatric Rehabilitation Department. Although we have included in the study a large consecutive sample of preterm infants, the proportion of participants with PR GMs who developed CP is rather small. Hence, the results may not necessarily be applicable to other types of population. Also, potential limitation of our study is the fact that we lack detailed neuroimaging data. Magnetic resonance imaging of neonatal brain provides detailed high quality anatomical data but is expensive and needs sedation of infant [26]. In this study we performed MRI on infants with definitely abnormal GMs and severe abnormalities recorded on cranial ultrasound.

Second, abnormal HR characteristics are commonly associated with systemic pathologies (infection, inflammation, apnoea, acidosis), occurring in the first month after preterm born and could be one of the study limitations. However, all subjects included in the study were patients under the care by a neonatologist and no one has obvious clinical signs of systemic pathology at the moment of HRV analysis. We cannot undeniably exclude influence of potential subclinical infection or inflammation on HRV findings, but we consider that as less likely.

Third, it is also important to keep in mind that for the assessment of predictive values of HRV measurements we used only CP development as outcome. This traditional binary logic may not be always applicable in the real life and not reflect complexity of motor, sensory, cognitive, and many other neurodevelopmental problems later in life. Hence, further studies may consider some alternative outcomes and/or approaches like fuzzy logic where the truth value may range between completely true and completely false.

Finally, study accessed outcome at 24 months of corrected age. Although all clinical procedure in our study have been performed by physicians with adequate time and skills and not different from usually clinical practice, at the age of 24 months the clinical presentation may not be always completely clear. Also some minor developmental disabilities may become recognizable at school age [33] and further studies should consider this limitation.

7. Conclusion

The quality of GMs was predictive for neurodevelopmental outcome at 2 years. Our results indicate that HRV may improve the prediction of neurodevelopmental outcome in infants with PR GMs. Further studies with a greater sample size and different clinical settings are warranted.

Conflict of interest

The author declares no conflict of interest.

References

[1] A.F. Bos, E. Roze, Neurodevelopmental outcome in preterm infants, Dev. Med. Child Neurol. 53 (2011) 35–39.
[2] A.J. Spittle, L.W. Doyle, R.N. Boyd, A systematic review of the clinimetric properties of neuromotor assessments for preterm infants during the first year of life, Dev. Med. Child Neurol. 50 (2008) 254–266.
[3] T. Hielkema, C.H. Blauw-Hospers, T. Dirks, M. Drijver-Messelink, A.F. Bos, M. Hadders-Algra, Does physiotherapeutic intervention affect motor outcome in high-risk infants? An approach combining a randomized controlled trial and process evaluation, Dev. Med. Child Neurol. 53 (2011) e8–e15.
[4] C. Brogna, D.M. Romeo, C. Cervesi, L. Scrofani, M.G. Romeo, E. Mercuri, A. Guzzetta, Prognostic value of the qualitative assessments of general movements in late-preterm infants, Early Hum. Dev. 89 (2013) 1063–1066.
[5] L. Zuk, Fetal and infant spontaneous general movements as predictors of developmental disabilities, Dev. Disabil. Res. Rev. 17 (2011) 93–101.
[6] C. Einspieler, H. Prechtl, Prechtl's assessment of general movements: a diagnostic tool for the functional assessment of the young nervous system, Ment. Retard. Dev. Disabil. 11 (2005) 61–67.
[7] L. Snider, A. Majnemer, B. Mazer, S. Campbell, A. Bos, A comparison of the general movements assessment with traditional approaches to newborn and infant assessment: concurrent validity, Early Hum. Dev. 84 (2008) 297–303.
[8] C. Einspieler, H. Prechtl, A. Bos, F. Ferrari, G. Cioni, Prechtl's Method on the Qualitative Assessment of General Movements in Preterm, Term and Young Infants, first ed. Mac Keith Press, London, UK, 2004.
[9] H. Prechtl, Qualitative changes of spontaneous movements in fetus and preterm infant are a marker of neurological dysfunction, Early Hum. Dev. 23 (1990) 151–158.
[10] L. Adde, M. Rygg, K. Lossius, G.K. Oberg, R. Stoen, General movement assessment: predicting cerebral palsy in clinical practise, Early Hum. Dev. 83 (2007) 13–18.
[11] M. Burger, Q.A. Louw, The predictive validity of general movements – a systematic review, Eur. J. Paediatr. Neurol. 13 (2009) 408–420.
[12] Y. Nakajima, C. Einspieler, P. Marschik, A.F. Bos, H. Prechtl, Does a detailed assessment of poor repertoire general movements to identify those infants who will develop normally? Early Hum. Dev. 82 (2006) 53–59.
[13] T. Amichai, M. Katz-Leurer, Heart rate variability in children with cerebral palsy: review of the literature and meta-analysis, Neurorehabilitation 35 (2014) 113–122.
[14] H. Israeli-Mendlovic, J. Mendlovic, M. Katz-Leurer, Heart rate and heart rate variability parameters at rest, during activity and passive standing among children with cerebral palsy GMFCS IV-V, Dev. Neurorehabil. 17 (2014) 398–402.
[15] H. Patural, V. Pichot, F. Jaziri, G. Teyssier, J.M. Gaspoz, F. Roche, J.C. Barthelemy, Autonomic cardiac control of very preterm newborns: a prolonged dysfunction, Early Hum. Dev. 84 (2008) 681–687.
[16] G. Thieriez, C. Mougey, D. Varmeylen, V. Wermenbol, J.P. Lanquart, J.S. Lin, P. Franco, Altered autonomic control in preterm newborns with impaired neurological outcomes, Clin. Auton. Res. 25 (2015) 233–242.
[17] B. Bjelakovic, S. Ilic, L. Dimitrijevic, B. Milovanovic, G. Kostic, L. Bjelakovic, S. Lukic, Heart rate variability in infants with central coordination disturbance, Early Hum. Dev. 86 (2010) 77–81.
[18] S. Lukic, Z. Cojbasic, N. Jovic, M. Popovic, B. Bjelakovic, L. Dimitrijevic, L. Bjelakovic, Artificial neural networks based prediction of cerebral palsy in infants with central coordination disturbance, Early Hum. Dev. 88 (2012) 547–553.
[19] M. Hadders-Algra, K. Heineman, A. Bos, K. Middelburg, The assessment of minor neurological dysfunction in infancy using Touwen infant neurological examination: strengths and limitations, Dev. Med. Child Neurol. 52 (2010) 87–92.
[20] B.C.L. Touwen, Examination of the Child with Minor Neurological Dysfunction, second ed. William Heinemann Medical Books. Ltd, London, UK, 1979.
[21] Surveillance of Cerebral Palsy in Europe (SCPE). Prevalence and characteristics of children with cerebral palsy in Europe, Dev. Med. Child Neurol. 44 (2002) 633–640.
[22] J.J. Volpe, Neurology of the Newborn, fifth ed. PA:Saunders Elsevier, Philadelphia, 2008.
[23] V. Darsaklis, L. Snider, A. Majnemer, B. Mazer, Predictive validity of Prechtl's method on the qualitative assessment of general movements: a systematic review of evidence, Dev. Med. Child Neurol. 53 (2011) 896–906.
[24] A. Spittle, M. Spencer-Smith, J. Cheong, A. Eeles, K. Lee, P. Anderson, L. Doyle, General movements in very preterm children and neurodevelopment at 2 and 4 years, Pediatrics 132 (2013) e452–e458.
[25] F. Soleimani, R. Badv, A. Momayezi, A. Biglarian, A. Marzban, General movements as a predictive tool of the neurological outcome in term born infants with hypoxic ischemic encephalopathy, Early Hum. Dev. 91 (2015) 479–482.
[26] B. Skiold, C. Eriksson, A. Eliasson, U. Aden, B. Vollmer, General movements and magnetic resonance imaging in the prediction of neuromotor outcome in children born extremely preterm, Early Hum. Dev. 89 (2013) 467–472.
[27] E. Beccaria, M. Martino, E. Briatore, B. Podesta, G. Pomero, R. Micciolo, G. Espa, S. Calzolari, Poor repertoire general movements predict some aspects of development outcome at 2 years in very preterm infants, Early Hum. Dev. 88 (2012) 393–396.
[28] J. Kodric, B. Susteric, D. Poro-Panjan, Assessment of general movements and 2.5 year developmental outcomes: pilot results in a diverse preterm group, Eur. J. Pediatr Neurol 14 (2010) 131–137.
[29] M. Hadders-Algra, Putative neural substrate of normal and abnormal general movements, Neurosci. Biobehav. Rev. 31 (2007) 1181–1190.
[30] K. Addison, P. Griffin, R. Moorman, E. Lake, M. O'Shea, Heart rate characteristics and neurodevelopmental outcome in very low birth weight infants, J. Perinatol. 1-7 (2009).
[31] U. Felderhoff-Mueser, C. Buhrer, Clinical measures to preserve cerebral integrity in preterm infants, Early Hum. Dev. 81 (2005) 237–244.
[32] K. Fairchild, R. Sinkin, F. Davalian, A. Blackman, J. Swanson, J. Matsumoto, D. Lake, J. Moorman, J. Blackman, Abnormal heart rate characteristics are associated with abnormal neuroimaging and outcomes in extremely low birth weight infants, J. Perinatol. 34 (2014) 375–379.
[33] E. Arpi, F. Ferrari, Preterm birth and behaviour problems in infants and preschool-age children: a review of the recent literature, Dev. Med. Child Neurol. 55 (2013) 788–796.