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Heart Rate Variability in Healthy Children Younger than 18 Months

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Abstract

Introduction: A normal Heart Rate Variability (HRV) is the result of a balanced relation between the sympathetic and parasympathetic system. A decreased HRV can be an indicator for cardiac diseases or an increased stress level. Changes in HRV might identify diseases that affect the heart rhythm *via* the autonomic nervous system. This applies to diseases that directly damage the autonomic nervous system and to diseases that influence the autonomic nervous system indirectly, e.g. through permanently increased metabolic stress. However, methods measuring the HRV are varying between the studies and normal values especially in infants are lacking. The current study is aimed to create reference values for the HRV in children aged younger than 18 months.

Methods: We analyzed ECG curves of 30 infants, who had a routine EEG due to non-epileptic paroxysmal events. To evaluate the HRV we calculated the RMSSD (Root Mean Square of the Successive Differences) and the SDNN (Standard Deviation of all Normal Sinus R/R Intervals). Analyses were performed for each patient and in a second step separately for patients from 0 -<12 months and from 12 -<18 months.

Results: We found no significant differences in the different age groups regarding the HRV. By means of linear regression, it was also shown that there were no other significant differences in HRV in children under 18 months of age. But compared to older children in the literature, HRV was found to be significantly lower.

Conclusion: Our results also indicate age-dependent differences when compared to previous findings in the literature and shows that it is important to have age-matching normal values.

Keywords: Heart Rate Variability (HRV) • Normal values • Infants • children • Autonomic nervous system

Abbreviations

ECG: Electrocardiogram; EEG: Electroencephalogram; HRV: Heart Rate Variability; RMSSD: Root Mean Square of the Successive Differences; SDNN: Standard Deviation of all Normal Sinus R/R Intervals; SUDEP: Sudden Unexpected Death in Epilepsy Patients

Introduction

A normal Heart Rate Variability (HRV) is the result of a balanced relation between the sympathetic and parasympathetic system. Therefore, a reduced HRV could be a sign of inadequate adaptability of the autonomic nervous system [1-3]. Variants in HRV are associated with various cardiac and non-cardiac diseases and a negative prognostic factor. There is also an association between changes in HRV and increased morbidity. This applies to diseases that directly damage the autonomic nervous system and to diseases that influence the autonomic nervous system indirectly, e.g. through permanently increased metabolic stress in both adults and children. However, methods measuring the HRV are varying between the studies and normal values especially in infants are lacking [4,5]. Three different approaches to analyze the HRV are described, namely the timeline approach, the frequency and the non- linear method. Another problem with the measurement of HRV is the different values in relation to age, fitness and activity during the measurement [6]. To our knowledge, there are no available normal values for HRV in children, especially in infants. All mentioned studies compared their data to a distinct control group. Therefore, we aimed to create reference values for the HRV in children aged younger than 18 months to improve the explanatory power of future studies. To this end, we analyzed the correlation between age and HRV in the first 18 months of life.

What is known?

1. A normal HRV is the result of a balanced relation between the sympathetic and parasympathetic system.
2. Little is known about normal HRV in infants and small children
3. Several diseases are thought to have an impact on the autonomic nervous system and could lead to an imbalance, but also to the medication which is administered has to be taken into account.

What is new?

1. We could present normal values of HRV in infants aged younger than 18 months.

Our results indicate age-dependent differences in HRV compared to older children in the literature.

Materials and Methods

This retrospective study was conducted on 30 infants aged younger than 18 months, who had a routine EEG (Electroencephalogram). The indication

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for EEG was given because of suspicious episodes. All examinations were carried out at the epilepsy unit of the Department of Pediatrics and Adolescent Medicine, Kepler University Hospital Linz between 03 February 2021 and 08 April 2022. Inclusion criteria were age younger than 18 months, an unafflicted EEG and the exclusion of any pathological cause of the episodes leading to clarification.

During the EEG-monitoring the heartrate was documented using ECG (Electrocardiogram) electrodes. We analyzed a period of 60 s of ECG for each patient. The duration of the episode was chosen because at this age patients rarely lie peacefully and care was taken to collect the section during a quiet waking period. Another reason for choosing this relaxed waking state was that sleep itself alters breathing and therefore the HRV. A sleep EEG is not performed on every child, especially if a non-epileptic etiology is likely. This was done by analyzing the recorded ECG curves in the used EEG program "Natus Database". The most artifact-free and calm phase possible was selected for this purpose. All R/R intervals were measured manually over 60 seconds.

To evaluate the HRV we calculated the RMSSD (Root Mean Square of the Successive Differences) using the definition of the Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology (ESC/NASPE) 1996: "The square root of the mean of the sum of the squares of differences between adjacent R/R intervals". This was performed for each patient. In a second step, we also calculated the median RMSSD, both for the whole study collective and separately for patients from 0-<12 months and from 12-<18 months.

Because the SDNN (Standard Deviation of all Normal Sinus R/R Intervals) is the "gold standard" for medical stratification of cardiac risk, we also calculated this value for each patient. Likewise, the median SDNN was calculated for the whole study collective and separately for patients from 0-<12 months and from 12-<18 months.

All demographic data were collected from patient records. We assessed age, gender, and the indication for EEG examination.

The intra-rater variability was a priori tested, the relevant ECG sections were then analyzed by an investigator (AP) for data analysis and we used SPSS 28. On the one hand, we determined the mean and the standard deviation by t-test. To describe the differences between the age groups regarding the HRV we used the chi-squared test. To better represent the relationship between age and HRV we used the linear regression analysis model.

Results

In total 30 patients younger than 18 months who had a routine EEG were retrospectively analyzed. The mean age was 8.7 months (± 4.83), range 1 to 17 months. 13 patients were male (43.33%) and 17 were female (56.67%) of all patients, 20 were aged younger than 12 months and 10 were aged between 12 and <18 months. For these subgroups, the mean age was 5.9 months (± 3.06) and 14.3 months (± 1.77) respectively. There were various indications for performing the EEG examination: Shuddering attacks, gastroesophageal reflux, BRUE (Brief Resolved Unexplained Event), rhythmic movement disorder, transient loss of tonus, breath-holding spells, vasovagal syncope, movement stereotypes, apnea, benign myoclonus of infancy, shaking chills, striking eye movements, paroxysmal movement disorder, emotional excitement, tonic upward gaze, pain-induced twitching and pronounced VitB12 deficiency. For a detailed presentation of indications and demographic data, shown in Table 1.

The median RMSSD in our study collective was 15.49 ± 5.25 ms (12.99–32.28 ms; 25% 14.0 ms–75% 21.7 ms). For patients aged<12 months, we found a median RMSSD of 15.28 ± 3.99 ms (12.99–27.66 ms; 25% 13.77 ms–75% 18.77 ms) and 18.72 ± 6.60 ms (13.61–32.28 ms; 25% 14.62 ms–75% 26.04 ms) for patients aged 12 to 17 months. SDNN values were 20.94 ± 7.49 ms (9.22–44.97 ms; 25% 18.82 ms–75% 27.97 ms) for all patients, 19.98± 6.72 ms (9.22–34.55 ms; 25% 17.02 ms-75% 26.29 ms) for patients aged<12 months, and 24.62 ± 8.43 ms (15.57–44.97 ms; 25% 18.87 ms–75% 29.15 ms) for patients aged 12 to <18 months. A graphical presentation of these data can be seen in Figures 1A-1C. We found no significant differences in the different age groups regarding the HRV (RMSSD p=0.414 and SDNN p=0.414). Using linear regression analysis and t test, it was also shown that there were no other significant differences in HRV in children under 18 months of age (p=0.252). A difference regarding gender could not be found.

Table 1. Demographic data.

Demographics	All patients (n=30)	Patients aged <12 months (n=20)	Patients aged 12 to <18 months (n=10)
Clinical characteristics			
Age months, mean + SD	8,7 ± 4,83	5,9 ± 3,06	14,3 ± 1,77
Age months, range	Jan-17	01-Nov	Dec-17
Gender male (%)	13 (43.33)	10 (50)	3 (30)
Gender female (%)	17 (56.67)	10 (50)	7 (70)
Indication for EEG, n (%)			
Shuddering attack	4 (13.33)	4 (20)	0 (0)
Gastroesophageal reflux	4 (13.33)	4 (20)	0 (0)
BRUE (Brief Resolved Unexplained Event)	3 (10)	2 (10)	1 (10)
Rhythmic movement disorder (head banging)	2 (6.67)	1 (5)	1 (10)
Transient loss of tonus	2 (6.67)	1 (5)	1 (10)
Breath-holding spells	2 (6.67)	1 (5)	1 (10)
Vasovagal syncope	2 (6.67)	0 (0)	2 (20)
Movement stereotypes	2 (6.67)	0 (0)	2 (20)
Apnea	1 (3.33)	1 (5)	0 (0)
Benign myoclonus of infancy	1 (3.33)	1 (5)	0 (0)
Shaking chills	1 (3.33)	1 (5)	0 (0)
Striking eye movements - e.g. Bell phenomenon	1 (3.33)	1 (5)	0 (0)
Paroxysmal movement disorder	1 (3.33)	0 (0)	1 (10)
Emotional excitement	1 (3.33)	1 (5)	0 (0)
Tonic upward gaze	1 (3.33)	0 (0)	1 (10)
Pain-induced twitching and restlessness	1 (3.33)	1 (5)	0 (0)
Developmental regression with pronounced VitB12 deficiency	1 (3.33)	1 (5)	0 (0)

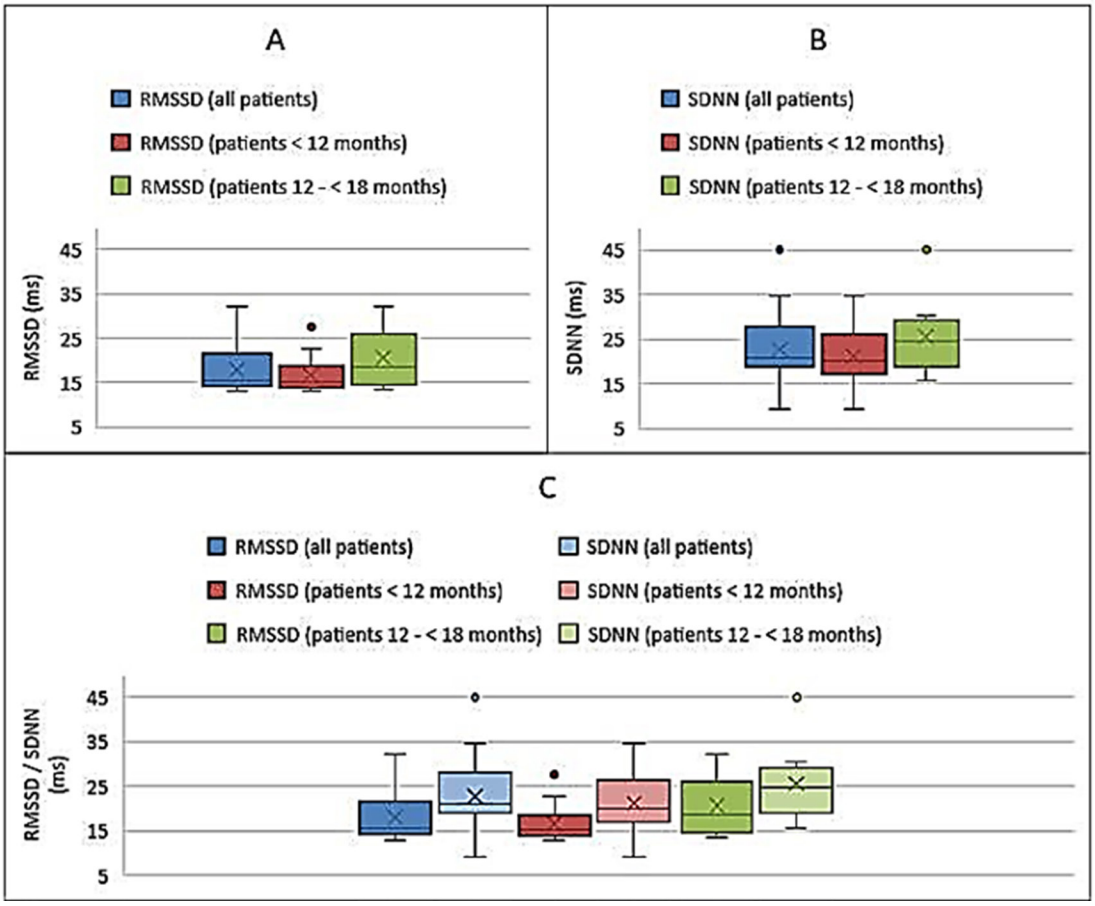

Figure 1. Heart rate variability–measures; (A) RMSSD compared between all patients, patients aged <12 months, and patients aged 12 to <18 months; (B) SDNN compared between all patients, patients aged <12 months and patients aged 12 to <18 months; (C) RMSSD and SDNN for all patients, patients aged <12 months, and patients aged 12 to <18 months.

Discussion

The aim of our study was to measure values of HRV in healthy infants with a method that is easy to apply in everyday life without additional mathematical programmes or skills, because it was previously shown, that age is an important parameter with a strong influence on HRV [7,8]. In order to better assess the different external influences, the standardized situation of routine EEG was chosen. The simple method of measurement and calculation arose from the desire to obtain the result promptly and to be able to advise the parents independently of devices, long-term cardiological examinations and mathematical programmes in the neurological outpatient clinic. The good feasibility is reflected in our interrater reliability. Immediate counselling of parents about a possible increased risk, even during the first counselling session in the context of the diagnostic interview, is essential because changes in HRV might be a cause of SUDEP (Sudden Unexpected Death in Epilepsy Patients) [1,9-12]. However, the value of the data collected can only be interpreted in conjunction with normal values. Other questions of our study were the correlation of HRV with age in the first 18 months of life and the evaluation of normal values in this age group. In our study, we could show a median RMSSD of 15.49 96 ± 5.25 ms and the median SDNN value was 20.94 ± 7.49 ms in healthy children aged younger than 18 months. In the age group we studied, there were no further gradations of HRV with age. A difference regarding gender could not be found. Other studies have already described HRV in healthy children, but not yet in a structured way in this age group. Hallioglu et al. reported RMSSD values of 70.4 ± 47.6 ms and SDNN values of 66.4 ± 33.7 ms in children with a mean age of 8.1 years [9]. Evrengül et al. found an RMSSD of 46.6 ± 33.2 ms and an SDNN of 91.7 ± 34.0 ms in healthy adults [3]. We showed that small children younger than 18 months have a lower HRV (RMSSD and SDNN) compared with older children or adults mentioned in other studies (RMSSD 15.5 vs. 46.6 vs. 70.4 ms, SDNN 20.9 vs. 91.7 vs. 66.4 ms) [3,9]. The reason why the children in the study of Hallioglu et al. score highest would not be explained in more detail in their work.

To take one of the most common diseases worldwide as an example, epilepsy is thought to have an impact on the autonomic nervous system and could lead to such an imbalance [2,3]. There is no distinctness concerning the effect of antiepileptic treatment on a reduced HRV. Lotufo et al. could not observe an improvement of a reduced HRV after establishing an antiepileptic drug therapy [2]. Other studies found a decrease in HRV in epilepsy patients with and without antiepileptic drug therapy compared to a control group [9]. In contrast, Berilgen et al. could show a positive effect of treatment on autonomic dysfunction in epilepsy patients [13]. Møller et al. found reduced HRV in patients with West syndrome when hypsarrhythmia is present in the Electroencephalography (EEG) [10]. Thus, it is evident that changes in HRV can be subject to a disease, but also to the medication which is administered. The knowledge about this is essential to inform the patients and families adequately about possible increased morbidity or mortality (e.g. due to SUDEP) and about side effects of the medication.

The main limitation of this study is the small sample size. Studies on healthy subjects are difficult at this age because parents do not make their healthy children available for examination. In other studies the sample size was also small [14]. For this reason, we used the ECG channels recorded during the EEG examination. Furthermore, the recording or measurement of 60 seconds is quite short. A longer recording, maybe over 24 hours might be constructive, especially as there might be changes in the HRV during different states of awareness. This could be particularly important to explain the underlying pathophysiology of Sudden Unexpected Death in Epilepsy Patients (SUDEP), which mostly occurs during sleep [1]. But there is also a benefit of the short measurement. Due to the short measurement,

we were able to create relatively uniform test conditions. Thus, variations due to different physical activities could be excluded compared to a longer measurement in daily life. Another limitation was that the calculations were performed manually. So there might be a bias due to manual imprecision, but anyway the simple method of measurement and calculation arose from the desire to obtain the result promptly.

Conclusion

We could present normal values of HRV in infants aged younger than 18 months. Furthermore, a sub-analysis shows corresponding data for children from 0-<12 months and 12-<18 months of age. Our results also indicate age-dependent differences when compared to previous findings in the literature and show that it is important to have age-matching normal values.

Declarations

Ethical approval

This study was supported by the Ethics Committees of Kepler University Hospital Linz affiliated with the medical faculty of Johannes Kepler University Linz, Austria.

Competing interests

The authors declare no competing interests.

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