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Original Article

Heart Rate Variability in Children Receiving Palliative Care: An Exploratory Cross-Sectional Study

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ABSTRACT

Aim: Heart rate (HR) variability (HRV) is simply a measure of the variation in time between each heartbeat. This variation is controlled by the autonomic nervous system. The aim of this study was to evaluate HRV parameters in children who were hospitalized in palliative care.

Materials and Methods: Twenty-eight palliative patients and 30 age- and gender-matched healthy control participants were included in this study. 24-hour Holter monitoring results were compared.

Results: The minimum and mean HRs were significantly higher, while the maximum HR was significantly lower in the palliative-care patients. Additionally, PR duration was shorter in the palliative care patients than in the control participants. Moreover, all time and frequency domain HRV values were lower in the palliative-care patients compared to the control participants. Lastly, the low frequency/high frequency ratio was almost significantly higher in the palliative care patients than in the controls. In the analysis of only palliative cases, the mean root mean square of successive RR interval differences and the percentage of successive RR intervals which differed by more than 50 ms (pNN50) were significantly higher in those patients with tracheostomy, while the same parameters were significantly lower in those with gastrostomy.

Conclusion: HRV parameters may provide complementary information regarding autonomic regulation in pediatric palliative care settings.

Keywords: Heart rate variability, palliative care, children

Introduction

Heart rate (HR) variability (HRV) is a marker which provides information regarding the health of the autonomic nervous system. HRV has also been accepted as a parameter representing the complex interaction between the brain and the cardiovascular system (1). HRV consists of time and frequency domain parameters. Among these parameters, some of them, such as standard deviation of normal-to-normal intervals (SDNN) and low frequency (LF), indicate both sympathetic and parasympathetic health, while root mean square of successive RR interval differences (rMSSD), pNN50 and high frequency (HF) are more influenced by the parasympathetic system (2).

The autonomic nervous system can offer insights into the biological aspects of psychological states and coping in the context of palliative medicine, since it mediates the body's response to stressors (3). Studies on how HRV is affected in pediatric patients receiving palliative care are limited. However, the significant relationship between SDNN and acute well-being and also higher HRV values in

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adult patients discharged from palliative care have been reported (4,5). In addition, HRV has been used in a limited number of palliative care studies, primarily as a potential predictor of mortality (6,7).

In this study, it was aimed to determine whether the HRV parameters of children receiving palliative care differed from those of age- and gender-matched healthy children and also to evaluate the clinical importance of HRV in palliative care.

Materials and Methods

Study Design

This prospective cross-sectional study was conducted in children between eight and 18 years old. The inclusion criteria were as follows: a stay in a pediatric palliative care clinic for at least two weeks, full recovery from acute inflammation and infection, 24-hour Holter monitoring due to suspected rhythm problems on electrocardiography and voluntary participation in this study. Those patients with clinically significant arrhythmias, such as sustained atrial or ventricular arrhythmias, were excluded from this study. In addition, those patients with progressive neurological disease, fever, inflammatory disease, head trauma, those with a Glasgow coma score <13 and those using medication such as sedatives, opioids, antiepileptics, and beta-blockers were also excluded from this study. Age- and gender-matched healthy control groups were selected from asymptomatic patients who visited the pediatric cardiology outpatient clinic for examination before participating in sport, and had applied for 24-hour Holter monitoring due to their family history.

Written informed consent was obtained from the parents of all of the participants, and this study was approved by the University of Health Sciences Türkiye, Ankara Bilkent City Hospital Clinical Research Ethics Committee No. 2 (approval no.: E2-23-5880, date: 27.12.2023).

Data Collection

The patients' data were obtained from the electronic records. Age, gender, vital signs such as HR, respiratory rate, systolic and diastolic blood pressure (BP), primary and secondary pathology, the presence of tracheostomy, gastrostomy or medical device, Karnofsky/Lansky performance score, and hospital stay duration were noted. The Karnofsky and Burchenal (8) and Lansky Performance Scores (9) were obtained during their stay in the palliative care unit simultaneously with the 24-hour Holter monitoring.

24-Hour Holter Monitoring

The DM Software CardioScan 79A was used. All participants, including the control group, underwent Holter monitoring under standardized daily living conditions. They were instructed to maintain their usual routines while avoiding strenuous physical activity. Posture and activity-related variations were minimized by ensuring comparable daytime activity patterns and nighttime rest periods between the groups. All participants were instructed to maintain their usual daily activities during the monitoring period. However, they were specifically asked to avoid strenuous physical exercise, maintain similar daytime activity patterns, and follow their habitual sleep-wake schedule in order to minimize circadian and activity-related variability. In addition, parents/caregivers were instructed to ensure the consistency of daily routines as much as possible during the recording period. During HRV processing, ectopic beats and artifacts were identified and managed according to standard procedures. Specifically, segments containing frequent ectopic beats or artifacts were either automatically filtered by the analysis software or manually reviewed and excluded when necessary. Only NN intervals were used for HRV calculations in order to maintain data accuracy and consistency. 24-hour- Holter parameters including rhythm, PR, QTC duration, minimum, maximum and mean HR, and HRV parameters such as SDNN, SDANN (the standard deviation of all five-min interval means), SDNNi (mean of the standard deviation of all of the NN intervals for each five-minute segment), rMSSD, pNN50, triangular index, total power, very-LF, LF and HF were calculated and recorded.

Statistical Analysis

All data were analyzed using the Statistical Package for Social Sciences for Windows 25.0 program (IBM Corp., Armonk, N.Y., USA). After descriptive statistics and normality analysis, normally distributed continuous variables are reported as mean± standard deviation, non-normally distributed continuous variables are given as median with range, and categorical variables are shown as count with the percentage of the total. Chi-square or Fisher's exact test was used to compare categorical or ordinal variables, and Student's t-test or the Mann-Whitney U test was used to compare continuous variables.

Results

Twenty-eight palliative patients and 30 age- and gender-matched healthy control participants were included in

Table I. Clinical characteristics of the palliative care patients	
Data*	
Age (year)	9.05±5.99
Gender Male Female	 16 (57.1%) 12 (42.9%)
Height (cm)	117.71±40.37
Weight (kg)	28.37±21.93
Respiratory rate (per min)	25.43±7.66
BP systolic (mmHg)	98.79±19.55
BP diastolic (mmHg)	59.29±14.58
Primary pathology Trauma Syndromic disease Neurometabolic disease Operated CHD Malignancy Lupus PM, BPD	 10 (35.7%) 2 (7.1%) 4 (14.2%) 5 (17.8%) 5 (17.8%) 1 (3.6%) 1 (3.6%)
Hospitalization duration	30 (15-90)
Lansky-Karnofsky score	33.92±18.72
Tracheostomy	22 (78.6%)
Gastrostomy	4 (14.3%)
Medical device MV BIPAP	 11 (39.3%) 17 (60.7%)

*Data are presented as n (%) for categorical variables and median (interquartile range) or mean± standard deviation for continuous variables
CHD: Congenital heart disease, PM: Prematurity, BPD: Broncho pulmonary dysplasia, LRTI: Lower respiratory tract infection, MV: Mechanical ventilation, BIPAP: Bi-level positive airway pressure

this study. While 46.7% (n=14) of palliative patients were female, this rate was 57.1% (n=16) in the healthy control participants. The mean ages for the palliative patients and healthy control participants were 9.04±6.02 and 9.10±4.03, respectively. Table I shows the clinical characteristics of those patients who were hospitalized in the palliative care unit.

When comparing the palliative care patients to the healthy control participants, the minimum and mean HRs were significantly higher, while the maximum HR was significantly lower in the palliative care patients. Additionally, the PR duration was shorter in the palliative care patients than in the control participants. Moreover, all time and frequency domain HRV values were lower in the palliative care patients compared to the control participants. Lastly, the LF/HF ratio was almost significantly higher in the palliative care patients than in the control group. Detailed 24-hour Holter monitoring results are given in Table II.

When it comes to the analysis of only the palliative cases, median rMSSD and pNN50 were significantly higher in those patients with tracheostomy with a value of 32 (10-175) for rMSSD and of 7 (0-33) for pNN50, as opposed to 20 (10-29) and 1.5 (0-7) for those patients without this condition, as shown in Figure 1 (p=0.044 and 0.042, respectively). In addition, the medians of the same parameters were significantly lower in those with gastrostomy, with a value of 14 (10-3) versus 29 (10-175) for rMSSD and 1 (0-6) versus 7 (0-33), as shown in Figure 2 (p=0.037 and 0.043, respectively). Moreover, interesting differences were observed when those patients on mechanical ventilation were compared to those supported with Bi-level positive airway pressure (BIPAP). For instance, the former group's median rMSSD [48 (19-175)] was significantly higher than the latter group's [26 (10-45)], while the median SDNNi and pNN50 were almost significantly higher [52 (13-132) versus 29 (10-52) for SDNNi and 22 (0-33) versus 6 (0-19) for pNN50], as shown in Figure 3 (p=0.005, 0.057, 0.058, respectively). However, no correlations were found between the duration of hospital stay and the Karnofsky and Lansky scores and the HRV parameters.

Table II. Comparison of 24-holter monitoring

Data*	**Total (n=58)**	**Patients (n=28)**	**Control (n=30)**	**p value**
HR				
Minimum	56 (39-100)	64.50 (40-100)	51.5 (39-85)	**0.001****
Maximum	161.3±22.2	156.3±21.9	165.9±21.8	**0.049****
Mean	98.5±18.8	107.2±21.6	90.4±10.9	**0.001****
ECG				
PR duration (ms)	140 (100-200)	120 (100-160)	140 (120-180)	**0.049****
QTC (msn)	395.6±23.7	393.3±23.1	394.9±24.7	0.651

Table II. Continued				
Data*	**Total (n=58)**	**Patients (n=28)**	**Control (n=30)**	**p value**
Time domain parameters				
SDNN (msec)	122.5 (36-260)	73.5 (36-210)	155.0 (67-260)	**0.0001****
SDANN (msec)	102.5 (28-244)	61.5 (28-193)	123.5 (58-244)	**0.0001****
SDNNi (msec)	53.5 (10-215)	33.5 (10-132)	77.0 (33-215)	**0.0001****
rMSSD (msec)	44 (10-191)	27.5 (10-175)	73.5 (25-191)	**0.0001****
pNN50 (msec)	19 (1-71)	6.5 (0-33)	29.5 (4-71)	**0.0001****
Triangular index	27.7±13.3	21.0±13.4	33.9±9.9	**0.0001****
Frequency domain parameters				
TP (msec^2)	2,605.9 (43.4-7,936)	896.9 (43.4-4,463)	3,138.0 (893-7,936)	**0.0001****
VLF (msec^2)	1,234.5 (18.4-5,418)	571.0 (18.4-3204)	2,031.5 (495-5,418)	**0.0001****
LF (msec^2)	407.2 (10.1-1899)	179.7 (10.1-731)	608.5 (96-1,899)	**0.0001****
HF (msec^2)	300.1 (11.8-1,223)	68.1 (11.8-905)	558.7 (37.6-1,223)	**0.0001****
LF/HF ratio	2.06±1.31	2.48±1.62	1.66±0.78	0.058

*Data are presented as n (%) for categorical variables and median (minimum-maximum) or mean ± standard deviation for continuous variables
**Significant difference (p<0.05)
HRV: Heart rate variability, SDNN: Standard deviation of NN intervals, SDANN: The standard deviation of all 5-min interval means, SDNNi: Mean of the standard deviation of all the NN intervals for each 5-minute segment of a 24 hours HRV recording, rMSSD: Root mean square of successive RR interval differences, pNN50: Percentage of successive RR intervals that differ by more than 50 ms, TP: Total power, HF: High frequency, LF: Low frequency, VLF: Very-LF

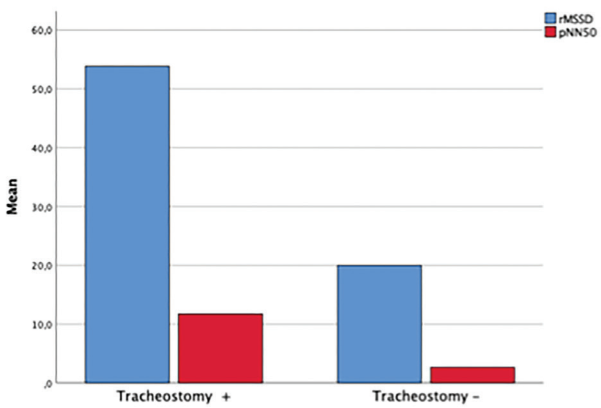

Figure 1. Comparison of rMSSD and pNN50 between patients with and without tracheostomy (p=0.044 and 0.042, respectively)
rMSSD: Root mean square of successive RR interval differences, pNN50: Percentage of successive RR intervals that differ by more than 50 ms

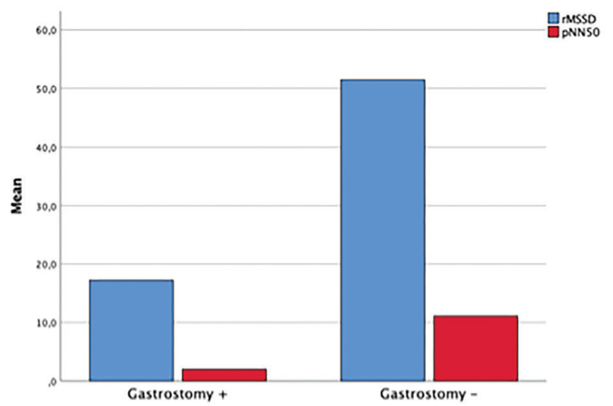

Figure 2. Comparison of rMSSD and pNN50 between patients with and without gastrostomy (p=0.037 and 0.043, respectively)
rMSSD: Root mean square of successive RR interval differences, pNN50: Percentage of successive RR intervals that differ by more than 50 ms

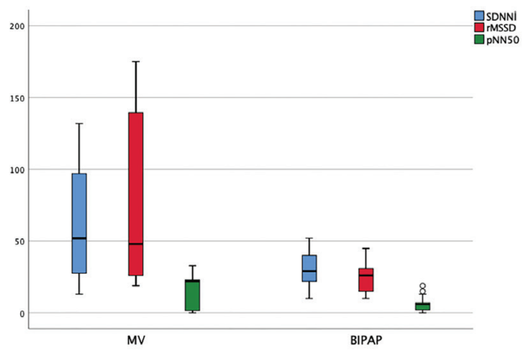

Figure 3. Comparison of rMSSD, pNN50 and SDNNi between mechanically ventilated and BIPAP patients (p=0.005, 0.057, 0.058, respectively)
rMSSD: Root mean square of successive RR interval differences, pNN50: Percentage of successive RR intervals that differ by more than 50 ms, SDNNi: Mean of the standard deviation of all the NN intervals for each 5-minute segment of a 24 hours HRV recording, BIPAP: Bi-level positive airway pressure, MV: Mechanical ventilation

Discussion

According to the current study, in those patients who were hospitalized in palliative care for at least 15 days, overall HRV parameters and maximum HR were found to be lower, minimum and mean HRs were higher and PR intervals were shorter than for those of the control participants. Analysis of only palliative care patients showed that while parasympathetic system-related parameters were higher in those with tracheostomy, the same parameters were lower in those with gastrostomy. In addition, similarly, parasympathetic system-related parameters were higher in those on mechanical ventilation compared to BIPAP.

The lower overall HRV parameters and the decreased difference between maximum and minimum HRs observed in this cohort may be consistent with altered autonomic regulation. However, given the heterogeneity of the underlying conditions and the cross-sectional design, it is not possible to determine whether these findings are attributable to the palliative care status itself, the primary diseases, or other clinical factors. Various factors, including trauma, cardiac surgery, and cancer, can impair HRV (10-12). Since most of the patients had conditions such as trauma, surgery, or cancer in their etiology, the decrease in HRV may be related to the primary etiology. In addition, hospitalization can cause anxiety and poorer sleep quality in the context of chronic stressor exposure and these conditions result in impaired HR regulation (13,14). On the other hand, a recent study reported that patients' posture does not have an effect on HRV parameters (15). Therefore, impaired HRV parameters in palliative care patients may be attributable to a combination of factors, including their primary illness and emotional state. In order to establish this, an assessment of the patients' emotional state with scales such as anxiety and sleep quality may be considered.

The finding that the mean HR and LF/HF ratios of palliative patients were higher than those of the control group may reflect a relative shift of autonomic balance toward sympathetic predominance. Since LF is affected by both the sympathetic and parasympathetic systems and HF is affected more by the parasympathetic system, an increase in the LF/HF ratio can be used as an indicator of sympathetic activity (16). A relatively more active sympathetic system in palliative care patients could be related to exposure to stressors such as pain and anxiety. However, it should be noted that the interpretation of the LF/HF ratio as a direct marker of sympathetic activity remains controversial in the current HRV literature (17,18) and should therefore be interpreted with caution. In addition, as HR increases, the PR interval tends to shorten (19), which may partly explain the shorter PR intervals observed in this cohort.

Another finding of this study was that the Karnofsky and Lansky scores used as performance scores were not associated with HRV parameters. These scores assess whether the patient is performing an activity, such as walking, playing, or performing basic needs, independently or with support. To the best of our knowledge, there are no studies investigating the relationship between performance scores and HRV. Our results may suggest that the level of functional independence alone does not necessarily correspond to differences in HRV parameters; however, this finding should be interpreted cautiously. Further studies with larger patient populations are needed in order to better understand this relationship.

The fact that parasympathetic system-related HRV parameters were lower in those with gastrostomy may be explained by vagal nerve influence. Vital aspects of autonomic physiology, such as breathing, HR, BP, and gut motility, as well as reflexes such as coughing and swallowing and survival behaviors such as eating, drinking, and reacting to illness, are all regulated by the vagus nerve, a body-brain connection (20). The link between vagus nerve activity and the HF component of HRV has been well-established (21). Patients with gastrostomy demonstrated lower rMSSD and pNN50 values. Although impaired vagal function may represent one possible explanation, the small subgroup size and potential influence of underlying neurological disease preclude definitive conclusions regarding the mechanisms involved. It has also been reported that vagus nerve stimulating devices can improve oral feeding in patients with gastrostomy (22). However, this association should be interpreted with caution, as the severity of the underlying neurological condition may also have contributed to reduced parasympathetic activity and the need for gastrostomy. Therefore, this association should be considered hypothesis-generating.

The most obvious difference between spontaneous breathing and mechanical ventilation is that intrathoracic volume decreases in spontaneous breathing, while it increases with mechanical ventilator support (23). During mechanical ventilation, the sudden expansion of the lungs activates the afferent arm of a depressor reflex, which produces negative inotropic and chronotropic responses, in addition to arterial vasodilation. The receptors are sensitive to stretch and the afferent pathway runs predominantly in the vagus nerves. Vagal feedback from pulmonary stretch receptors is obligatory for the generation of a neurally mediated respiratory sinus arrhythmia in awake individuals (24,25). Accordingly, the higher rMSSD and pNN50 values observed in those patients with tracheostomy and mechanical ventilation support may represent an exploratory observation which is potentially related to vagally mediated physiological mechanisms. However, given the limited sample size, these findings should be interpreted cautiously and require confirmation in larger studies.

Study Limitations

This study had several limitations. First, it was conducted at a single center with a relatively small sample size, which may limit the generalizability of the findings. Second, the heterogeneity of the underlying diagnoses in the palliative care population may have influenced HRV parameters, making it difficult to isolate the effects of palliative care itself from those of the primary disease. Although patients with conditions known to markedly affect autonomic function, such as head trauma and chronic inflammatory diseases, were excluded, the study cohort still comprised a range of clinical conditions, including neurological disorders, post-surgical states, and malignancies, each of which may affect autonomic regulation through different pathophysiological mechanisms. Therefore, residual confounding related to disease-specific effects cannot be excluded and may have contributed to variability in HRV measurements. In addition, the lack of disease-specific subgroup analyses further limits the ability to draw condition-specific conclusions. Subgroup analyses involving tracheostomy, gastrostomy, and respiratory support modalities were based on relatively small numbers of patients; therefore, these findings should be considered exploratory and hypothesis-generating rather than confirmatory. Future multicenter studies with larger and more homogeneous patient populations are needed in order to validate these observations. Third, emotional and psychological factors such as anxiety, pain perception, and sleep quality, all of which can affect autonomic function and HRV, were not systematically assessed or controlled for. Moreover, the cross-sectional design also precludes conclusions about causality or longitudinal changes in HRV over time. The wide age range of the pediatric participants may have influenced HRV parameters, as HRV is known to vary with age. Furthermore, the absence of follow-up data prevents assessment of whether HRV parameters are associated with clinical outcomes such as symptom burden, functional decline, or survival. Lastly, the selection of control participants who underwent Holter monitoring due to family history may have introduced a potential selection bias, which should be considered when interpreting the results.

Conclusion

In this exploratory study, children receiving palliative care demonstrated lower HRV parameters and higher mean HRs compared with healthy controls. These findings may be consistent with altered autonomic regulation; however, because of the heterogeneous patient population and cross-sectional design, the underlying mechanisms and clinical significance remain uncertain. Differences observed according to gastrostomy status, tracheostomy, and mechanical ventilatory support should be regarded as exploratory observations. Although physiological mechanisms involving vagal activity may contribute to these findings, larger studies are required before definitive interpretations can be made. HRV parameters may provide complementary information regarding autonomic regulation in pediatric palliative care settings; however, further studies are needed before their clinical utility can be established.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the University of Health Sciences Türkiye, Ankara Bilkent City Hospital Clinical Research Ethics Committee No. 2 (approval no.: E2-23-5880, date: 27.12.2023).

Informed Consent: Written informed consent was obtained from the parents of all of the participants.

Footnotes

Authorship Contributions

Concept: M.B., Design: M.B., Data Collection or Processing: G.A., Analysis or Interpretation: M.B., Literature Search: G.A., Writing: M.B.

Conflict of Interest: The authors declare no conflicts of interest.

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