Correlation among the heart rate variability indices in healthy children and those with atrial septal defect

Sağlıklı ve atriyal septal defektli çocuklarda kalp hızı değişkenliği indeksleri arasındaki korelasyon

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ABSTRACT

Objectives: Most researchers use the time domain and spectral analysis in the assessment of heart rate variability (HRV), while others use either the time or frequency domain measures. In this study, we investigated the presence of correlation between the time and frequency domain indices of HRV in normal healthy children and in patients with atrial septal defect (ASD).

Study design: A total of 60 children, 28 with ASD and 32 healthy children, were recruited. Time domain measures and frequency domain measures were analyzed from the 24-hour Holter ECG records. Correlation between time domain measures and frequency domain measures as well as correlation within the time domain measures was computed in each group.

Results: There was a positive correlation among all the measurements except the low- (LF) and high- (HF) frequency (LF/HF) ratio which was negatively correlated. The degree of correlation was stronger in some variables and weak in others.

Conclusion: We have shown that time domain measures are correlated with frequency domain measures in both ASD patients and in healthy children. Some of these indices are so strongly correlated with each other that they can be used interchangeably.

ÖZET

Amaç: Az sayıda araştırmacı kalp hızı değişkenliğinin (HRV) değerlendirilmesinde zaman veya frekans alan ölçümlerini, çoğu ise zaman alanı ve spektral analizi kullanmaktadır. Bu çalışmada, atriyal septal defektli (ASD) olgular ve sağlıklı çocuklarda HRV'nin zaman ve frekans alan indeksleri arasında korelasyon olup olmadığı araştırıldı.

Çalışma planı: ASD'li 28 ve sağlıklı 32 çocuk olmak üzere toplam 60 çocuk çalışmaya alındı. Zaman alan ölçümleri ve frekans alan ölçümleri 24 saatlik Holter EKG kayıtlarından yapıldı. Her bir grupta zaman alan ölçümlerinin kendi içinde ve frekans alan ölçümleri ile arasındaki korelasyon araştırıldı.

Bulgular: Düşük frekans/yüksek frekans (LF/HF) oranı hariç diğer tüm ölçümler arasında pozitif korelasyon saptandı. Çeşitli değişkenler arasındaki korelasyon derecesi bazılarında güçlü diğerlerinde zayıf olmak üzere farklı bulundu.

Sonuç: Çalışmamızda hem ASD'li hastalar hem de sağlıklı çocuklarda zaman alan ölçümleri ve frekans alan ölçümleri arasında korelasyon varlığı gösterildi. Aralarında güçlü bir korelasyon olan indekslerin bazıları birbirlerinin yerine kullanılabilir.

Heart rate variability (HRV) is a non-invasive index of the sympathetic and parasympathetic activity of the heart. It primarily measures the degree of heart rate fluctuation around mean heart rate during a given period of time.[1] HRV is altered in most cardiac and non-cardiac diseases in children. Recent research into HRV in children has focused on the variation in health and diseased states.[2-6] There are few studies comparing the correlation between time and frequency domain variables in children.[7] The aim of this study was to find the correlation between time domain HRV and frequency domain HRV as well as the

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correlation within the various time domain variables in both healthy children and patients with atrial septal defect (ASD).

PATIENTS AND METHODS

This study was conducted in the pediatric cardiology unit. Prior to subject recruitment, study protocol was reviewed and approved by the local ethics committee in accordance with the ethical principles for human investigations as outlined by the Second Declaration of Helsinki. Details of the study were explained to the parents and written informed consents were obtained. Patients who had been followed up with the diagnosis of ASD were recruited for the study. Children who were found to be normal both on physical examination and echocardiography were also recruited as a control group.

The recruitment criteria for the patients with ASD were: age 1-14, echocardiographic detection of ASD, evidence of right atrium and right ventricle dilatation on echocardiography, no signs of cardiac failure, no upper or lower respiratory tract infection, no evidence of arrhythmia on electrocardiography and not taking any medications.

The recruitment criteria for the normal children were: age 1-14, normal physical examination, electrocardiographic and echocardiographic findings and not taking any medications. Twenty-four-hour ambulatory electrocardiographs were obtained in all subjects using a miniature tape recorder (Del Mar Digicorder model 483). The data were gathered while the subjects were involved in their normal daily activities and normal sleep and wake pattern. The raw electrocardiographic data were digitized at a sampling rate of 128 Hz.

The 24-hour ambulatory electrocardiographs were replayed through a Del Mar Holter analyzer (Model 563 stratascan analyzer Del Mar Avionics) to detect the presence of arrhythmias. Abnormal beats, significant pauses and areas of artifacts were automatically and, later, manually identified and rejected. The whole process was done by the same qualified cardiologist. Recordings with significant arrhythmias, less than 18 hours recording or with less than 90% of the recording suitable for analysis were excluded to avoid effects caused by circadian variation in HRV. Measurements of heart rate variables were completed using only normal to normal intervals.

Time domain indices

Time domain measures were calculated for the entire duration of recording. The indices taken were:

Abbreviations:

ASD *Atrial septal defect*
HF *High frequency*
HRV *Heart rate variability*
LF *Low frequency*
VLF *Very low frequency*

• SDNN: standard deviation of all filtered RR intervals in the entire period of recording,

• SDANN: standard deviation of 5-minute averages of RR intervals for the entire analysis,

• SD: standard deviation of the differences between adjacent RR intervals,

• SDNNindex: mean of the standard deviation of all RR intervals for all the 5-minute segments of the entire recording,

• rMSSD: square root of the mean of the sum of square differences between adjacent filtered RR interval over the whole period of analysis, and

• PNN50: percentage of the difference between adjacent RR intervals greater than 50 milliseconds for the whole period of analysis.

Frequency domain indices

Frequency domain analysis was performed on 300-second segments which were free of abnormal data. We determined spectral power over three frequency regions of interest:

• Very low frequency (VLF) index (0.017 - 0.05 Hz)

• Low frequency (LF) index (0.05 - 0.15 Hz)

• High frequency (HF) index (0.15 - 0.50 Hz)

We also determined total power (all frequencies greater than 0.017 Hz) and the ratio between low and high frequency LF/HF ratio.

Statistical analysis

Pearson correlation coefficient was used to find the correlation between time domain and frequency domain as well as among the various time domain variables in ASD patients and normal children.

RESULTS

Table 1 shows the correlation between time and frequency domain variables in ASD patients. Table 2 shows the correlation within the time domain variables in ASD patients. Table 3 presents the correla-

Table 1. Correlation between time domain variables and frequency domain variables in ASD patients

	Total power (ms²)		VLF (ms²)		LF (ms²)		HF (ms²)		LF/HF ratio	
	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*
SDNN (ms)	0.6869	**<0.01**	0.6470	**<0.01**	0.5876	**<0.01**	0.5020	**<0.01**	0.0688	>0.05*
SDANN (ms)	0.4349	**<0.05**	0.4490	**<0.05**	0.2778	>0.05*	0.3810	**<0.05**	-0.0860	>0.05*
RMSSD (ms)	0.5284	**<0.01**	0.6419	**<0.01**	0.2397	>0.05*	0.4949	**<0.01**	-0.1162	>0.05*
SD (ms)	0.8094	**<0.01**	0.6489	**<0.01**	0.7394	**<0.01**	0.6238	**<0.01**	0.1429	>0.05*
SDNNindex	0.8239	**<0.01**	0.7461	**<0.01**	0.7783	**<0.01**	0.5506	**<0.01**	0.1875	>0.05*
PNN50%	0.8142	**<0.01**	0.7105	**<0.01**	0.6915	**<0.01**	0.6388	**<0.01**	0.0381	>0.05*

ASD: Atrial septal defect; SDNN: Standard deviation of all filtered RR intervals in the entire period of recording; SDANN: Standard deviation of 5-minute averages of RR intervals for the entire analysis; SD: Standard deviation of the differences between adjacent RR intervals; SDNNindex: Mean of the standard deviation of all RR intervals for all the 5-minute segments of the entire recording; rMSSD: Square root of the mean of the sum of square differences between adjacent filtered RR interval over the whole period of analysis; PNN50: Percentage of the difference between adjacent RR intervals that are greater than 50 milliseconds for the whole period of analysis; VLF: Very low frequency index; LF: Low frequency index; HF: High frequency index; MS: Millisecond; *Not significant.

tion between time and frequency domain variables in normal children. The time domain variables in normal children were presented within Table 4. Time and frequency domain indices are positively correlated except the LF/HF ratio, which is negatively correlated with the other HRV indices. The level of significance of the correlation was $p<0.01$ for most of the pairs. The degree of correlation (r value) differed considerably.

In patients with ASD, the correlation was stronger between SD, SDNNindex, PNN50 and total power ($r>0.8$). No correlation was found between SDANN, rMSSD, and the LF and between time domain variables and LF/HF ratio. There was a positive correlation between the various time domain variables. The correlation was strong ($r>0.78$) between SDNN and all other time domain variables. The correlation was strong ($r>0.9$) between SDNN and SDANN, SD, SDNNindex (Table 2).

In normal children, a positive correlation existed between total power, HF, LF, and all the time domain variables, with no correlation between VLF, LF/HF ratio and all the time domain variables. No correlation was found between LF and SD (Table 3). A significant correlation was observed between various time domain variables. The correlation was strong ($r>0.85$) between SDNN and all time domain variables as well as between SDNNindex and all time domain

Table 2. Correlation between time domain variables within the ASD patients

	PNN50%		SDNN (ms)		SDANN (ms)		rMSSD (ms)		SD (ms)		SDNN index (ms)
	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*	r
SDNN (ms)	0.7893	**<0.01**	NS	1.00	0.9283	**<0.01**	0.7879	**<0.01**	0.9098	**<0.01**	0.9147
SDANN (ms)	0.5976	**<0.01**	0.9283	**<0.01**	NS	1.00	0.7679	**<0.01**	0.7550	**<0.01**	0.7115
rMSSD (ms)	0.7655	**<0.01**	0.7879	**<0.01**	0.7679	**<0.01**	NS	1.00	0.6689	**<0.01**	0.7295
SD (ms)	0.7750	**<0.01**	0.9098	**<0.01**	0.7550	**<0.01**	0.6689	**<0.01**	NS	1.00	0.9449
SDNNindex	0.8577	**<0.01**	0.9147	**<0.01**	0.7115	**<0.01**	0.7295	**<0.01**	0.9449	**<0.01**	NS
PNN50%	NS	1.00	0.7893	**<0.01**	0.5976	**<0.01**	0.7655	**<0.01**	0.7750	**<0.01**	0.8577

ASD: Atrial septal defect; SDNN: Standard deviation of all filtered RR intervals in the entire period of recording; SDANN: Standard deviation of 5-minute averages of RR intervals for the entire analysis; SD: Standard deviation of the differences between adjacent RR intervals; SDNNindex: Mean of the standard deviation of all RR intervals for all the 5-minute segments of the entire recording; rMSSD: Square root of the mean of the sum of square differences between adjacent filtered RR interval over the whole period of analysis; PNN50: Percentage of the difference between adjacent RR intervals that are greater than 50 milliseconds for the whole period of analysis; ms: Millisecond; NS: Not significant.

Table 3. Correlation between time domain variables and frequency domain variables in normal children

	Total power (ms²)		VLF (ms²)		LF (ms²)		HF (ms²)		LF/HF (ms²)	
	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*
SDNN (ms)	0.6717	**<0.01**	0.1716	>0.05*	0.4613	**<0.01**	0.6434	**<0.01**	-0.2017	>0.05*
SDANN (ms)	0.5919	**<0.01**	0.1112	>0.05*	0.4214	**<0.05**	0.5429	**<0.01**	-0.2301	>0.05*
RMSSD (ms)	0.8181	**<0.01**	0.2058	>0.05*	0.4551	**<0.05**	0.8159	**<0.01**	-0.1885	>0.05*
SD (ms)	0.6720	**<0.01**	0.1332	>0.05*	0.3472	>0.05*	0.6835	**<0.01**	-0.1667	>0.05*
SDNNindex (ms)	0.7241	**<0.01**	0.1863	>0.05*	0.4324	**<0.05**	0.7084	**<0.01**	-0.1495	>0.05*
PNN50 (ms)	0.5988	**<0.01**	0.1429	>0.05*	0.4223	**<0.05**	0.5734	**<0.01**	-0.1380	>0.05*

SDNN: Standard deviation of all filtered RR intervals in the entire period of recording; SDANN: Standard deviation of 5-minute averages of RR intervals for the entire analysis; SD: Standard deviation of the differences between adjacent RR intervals; SDNNindex: Mean of the standard deviation of all RR intervals for all the 5-minute segments of the entire recording; rMSSD: Square root of the mean of the sum of square differences between adjacent filtered RR interval over the whole period of analysis; PNN50: Percentage of the difference between adjacent RR intervals that are greater than 50 milliseconds for the whole period of analysis; VLF: Very low frequency index; LF: Low frequency index; HF: High frequency index; ms: Millisecond; *Not significant.

variables. The correlation was also strong between rMSSD and SD, SDNNindex, and PNN50 (Table 4).

DISCUSSION

Heart rate variability, defined as degree of fluctuation of the beat-to-beat differences in cardiac rhythm, is a reliable, noninvasive marker of autonomic nervous system activity.[8] The loss of this beat-to-beat variability is indicative of various diseases.[9-14] Detection of such changes, especially for the evaluation of autonomic nervous system functions, may be used as a marker of underlying pathology.

Decreased HRV, which represents autonomic dysfunction, is associated with increased mortality and morbidity with various forms of heart disease. Several authors have reported the harmful effect of increased sympathetic activity and the protective role of vagal activity in patients with cardiovascular disease.[15] Treatment modalities decreasing the sympathetic activity and/or increasing parasympathetic activity by correcting the autonomic control of cardiovascular system have been suggested to lower cardiac death.[15]

Heart rate variability is a very useful and easy method to assess the sympathovagal balance or the modulation of the cardiovascular system.[16] It has been suggested in previous studies that frequency domain measures should be preferred to time domain measures when short time recordings are investigated.[16] It has also been reported that HF, rMSSD, and

Table 4. Correlation between time domain variables within normal children

	SDNN (ms)		SDANN (ms)		rMSSD (ms)		SD (ms)		SDNNindex (ms)		PNN50% (ms)	
	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*
SDNN (ms)	NS	1.00	0.9430	**<0.01**	0.8620	**<0.01**	0.8450	**<0.01**	0.8953	**<0.01**	0.8536	**<0.01**
SDANN (ms)	0.9430	**<0.01**	NS	1.00	0.6806	**<0.01**	0.7393	**<0.01**	0.9430	**<0.01**	0.6781	**<0.01**
rMSSD	0.8620	**<0.01**	0.6806	**<0.01**	NS	1.00	0.8194	**<0.01**	0.9642	**<0.01**	0.8194	**<0.01**
SD (ms)	0.8450	**<0.01**	0.7393	**<0.01**	0.8194	**<0.01**	NS	1.00	0.8288	**<0.01**	0.7172	**<0.01**
SDNNindex (ms)	0.8953	**<0.01**	0.7092	**<0.01**	0.9642	**<0.01**	0.8288	**<0.01**	NS	1.00	0.9830	**<0.01**
PNN50 (ms)	0.8536	**<0.01**	0.6781	**<0.01**	0.9027	**<0.01**	0.7172	**<0.01**	0.9830	**<0.01**	NS	1.00

SDNN: Standard deviation of all filtered RR intervals in the entire period of recording; SDANN: Standard deviation of 5-minute averages of RR intervals for the entire analysis; SD: Standard deviation of the differences between adjacent RR intervals; SDNNindex: Mean of the standard deviation of all RR intervals for all the 5-minute segments of the entire recording; rMSSD: Square root of the mean of the sum of square differences between adjacent filtered RR interval over the whole period of analysis; PNN50: Percentage of the difference between adjacent RR intervals that are greater than 50 milliseconds for the whole period of analysis; ms: Millisecond; Ns: Not significant.

PNN50 reflect short-term HRV and are predominantly influenced by parasympathetic tone whereas LF, SDNN, SDANN, SDNNindex are influenced by both sympathetic and parasympathetic tone and express long-term HRV. Some studies have demonstrated that there is a strong correlation between the time domain and frequency domain measures of HRV.[7,17,18] It has been said that the HF variables are clinically similar to the time domain short time variables while the LF was similar to the time domain long time variables. In our study, HF was strongly correlated with rMSSD in normal children and borderline correlated with PNN 50% in ASD patients. Goto et al.[4] also found a significant correlation between time domain measure of rMSSD and frequency domain measure of HF. Tsuji et al.[1] showed a very strong correlation among high frequency HF, PNN50 and rMSSD and a strong correlation among total power, VLF, LF and SDNN.

We found a significant correlation ($0.40<r<0.50$) between LF and SDNN, SDANN, rMSSD, SDNNindex and PNN50 in normal children. HF was strongly correlated with RMSSD ($r=0.815$) and borderline correlated with SDNN, SDANN, SDNNindex and PNN50 ($r>0.54$). In ASD group LF was strongly correlated with SDNNindex ($r=0.778$), weakly correlated with PNN50, SD, SDNN, and not correlated with rMSSD and SDANN. The HF was borderline correlated with SD, SDNNindex, and PNN50 and weakly correlated with rMSSD, SDNN and SDNN. No correlation was found between LF/HF ratio and time domain variables in both groups. Our results also show the clinical similarity between time domain and frequency domain measures; some of these can be used as a substitute for the other.

We found positive correlation within the time domain indices in both groups. The degree of this correlation differed greatly. In the patient group the correlation was strongest between SDNN and SDANN ($r=0.92$) and weakest between SDANN and PNN50 ($r=0.59$). In the normal group the strongest correlation was between SDNNindex and PNN50 ($r=0.98$) and weakest between rMSSD and SDANN ($r=0.68$). Massin reported that the variables calculated from differences between adjacent cycles such as rMSSD and PNN50 have correlation well above 0.9 and can be considered as surrogates for each other.[7] Overall measures such as SDNN and SDANN are highly correlated and are essentially equivalent. These results are similar to what we found in both groups. Massin concluded that the SDNN and SDANN can be used interchangeably to assess sympathetic tone and rMSSD, PNN50 and HF to assess parasympathetic tone in the 24-hour interval in healthy children and those with cardiac diseases.[7] In our study rMSSD and PNN50 were highly correlated with total power and HF in the normal children. In the patients with the ASD, rMSSD and PNN50 were highly correlated with total power and VLF.

In conclusion our study showed that HF is highly correlated with rMSSD and PNN50 and thus can be used interchangeably.

Limitations of the study

The sample size was relatively small was and conducted at a single center. Therefore, future large multi-center prospective cohort studies are needed to address this issue.

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Key words: Autonomic nervous system; blood pressure monitoring, ambulatory; child; electrocardiography; heart rate/physiology; heart septal defects, atrial.

Anahtar sözcükler: Otonom sinir sistemi; kan basıncı izlemesi, ambulatuvar; çocuk; elektrokardiyografi; kalp hızı/fizyoloji; atriyal septal defekt.