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ORIGINAL ARTICLE

Does transcatheter ventricular septal defect closure affect heart rate variability in children?

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KEYWORDS
Heart rate variability;
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Abstract
Background: Heart rate variability (HRV) is a sign of the cardiac autonomic nervous system. Its evaluation in pediatric ventricular septal defect (VSD) cases before and after transcatheter closure contributes to an understanding of cardiac autonomic control.
Methods: Nineteen children with VSDs treated with transcatheter closure and 18 healthy children were enrolled in this study. A 24-h Holter rhythm monitor was applied to all patients before VSD closure and to those in the control group. Holter rhythm monitoring was repeated at three months in the patient group. HRV parameters were measured using the Cardio Scan Premier 12® program. Frequency-domain (total power; very-low-frequency, low-frequency (LF), and high-frequency (HF) indices; and the LF/HF ratio) and time-domain (standard deviation of all RR intervals (SDNN), standard deviation of 5-min averages of RR intervals (SDANN), the SDNN index, percentage of the difference between adjacent RR intervals, and the square root of the mean of the sum of square differences between adjacent filtered RR intervals) parameters were assessed.
Results: Before the procedure, SDNN, SDANN, and total power values were lower in the patient group than in the control group; other parameters were similar in the two groups. No significant difference in the SDNN, SDANN, or total power was detected between the patient and control groups in the third month, indicating that autonomic control of patients' hearts became normal during the third postoperative month. No correlation was detected between any hemodynamic parameters and any time-domain or frequency-domain parameters before closure.
Conclusion: This study showed that transcatheter closure of VSDs changed HRV parameters in pediatric patients.

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PALAVRAS-CHAVE
Variabilidade da frequência cardíaca;
Comunicação interventricular;
Pediatria;
Cardiopatia congénita

O encerramento percutâneo da comunicação interventricular afeta a variabilidade da frequência cardíaca em crianças?

Resumo
Introdução: A variabilidade da frequência cardíaca (VFC) é uma manifestação do sistema nervoso autónomo cardíaco. A sua avaliação em casos pediátricos de comunicação interventricular (CIV) antes e após o encerramento percutâneo contribui para a compreensão do controlo autonómico cardíaco.
Métodos: Neste estudo foram incluídas 19 crianças com CIV tratadas com encerramento percutâneo e 18 crianças saudáveis. Foi utilizado um ECG de Holter de 24 horas em todos os doentes antes do encerramento da CIV e no grupo de controlo. A monitoração com ECG de Holter foi repetida aos três meses no grupo de doentes. Os parâmetros de VFC foram medidos utilizando o programa Cardio Scan Premier 12®. Domínio de frequência [potência total; índices de frequência muito baixa, de frequência baixa (FB), de frequência alta (FA) e relação FB/FA]. Domínio temporal [desvio-padrão de todos os intervalos RR (SDNN), desvio-padrão de médias de 5 minutos de intervalos RR (SDANN), índice SDNN, percentagem da diferença entre intervalos RR adjacentes e a raiz quadrada da média da soma das diferenças quadradas entre intervalos RR filtrados adjacentes].
Resultados: Antes do procedimento, os valores SDNN, SDANN e da potência total foram mais baixos no grupo de doentes do que no grupo controlo; os outros parâmetros foram semelhantes nos dois grupos. Não foi detetada qualquer diferença significativa nos valores de SDNN, SDANN ou na potência total entre os doentes e o grupo controlo ao terceiro mês, indicando que o controlo autónomo dos corações dos doentes se tornou normal no pós-operatório. Não foi detetada qualquer correlação entre qualquer parâmetro hemodinâmico e qualquer parâmetro de domínio temporal ou de domínio de frequência antes do encerramento.
Conclusão: Este estudo demonstrou que o encerramento percutâneo da CIV alterou os parâmetros da VFC em doentes pediátricos.

Introduction

Heart rate variability (HRV) is a noninvasive tool for the assessment of the autonomic balance of the heart and evaluation of differences between the intervals of consecutive heartbeats. It is a marker of morbidity and mortality in many diseases, particularly cardiovascular diseases (i.e., coronary artery disease and heart failure). A decrease in HRV has been reported to reflect parasympathetic-sympathetic system imbalance and has a poor prognosis.[1–3]Autonomic imbalance emerges in congenital and acquired heart diseases.[4] In many studies, patients with atrial septal defects (ASDs) have been found to have reduced HRV, which has been improved after treatment (transcatheter procedure or surgery). Increased volume and pressure on the right side of the heart are thought to impair autonomic control and reduce HRV.[5,6]

Ventricular septal defects (VSDs) are the second most common congenital heart condition in the world, after bicuspid aortic valves.[7,8] Whereas the right atrium and right ventricle enlarge in patients with ASDs, enlargement occurs on the left side of the heart in patients with VSDs. Enlargement of the right side structures occurs in patients with VSDs only when severe pulmonary hypertension and Eisenmenger syndrome have developed. Additionally, heart failure, pulmonary hypertension, and pulmonary vascular disease are more significant in patients with VSDs. Left ventricular dysfunction is associated with a decrease in HRV, which in turn indicates a poor prognosis.[9] Thus, the effect of a VSD on the autonomic balance of the heart differs from that of an ASD.[10]

The most common treatment method for VSDs is surgery. Heiberg et al.[11,12] reported that patients with VSDs treated surgically in childhood have permanent chronotropic impairment (i.e., inadequate heart rate response to exercise) and decreased HRV as adults. This decrease is related to right bundle branch block and right ventricular dysfunction, and thus may not be seen after transcatheter closure.

The transcatheter method is not a complete alternative to surgery, but it has been applied widely and safely to anatomically suitable VSDs instead of surgery. No study has assessed the change in autonomic balance in patients with VSDs treated with the transcatheter method. We hypothesized that autonomic imbalance occurs in patients with VSDs due to heart failure and increased pulmonary artery pressure, and that this imbalance normalizes rapidly after transcatheter treatment.

Method

This prospective case-controlled study was carried out in the Pediatric Cardiology Department of Erciyes University Medical Faculty between April 2016 and April 2017. The

Institutional Review Board of Erciyes University approved the study protocol on 24 January 2014 (report no. 2014/39). All parents were informed about the study and provided written consent before the study commenced. All demographic data were recorded for the patient and control groups.

Nineteen consecutive pediatric patients with VSDs treated using the transcatheter method were included in the study. The inclusion criteria were VSD diameter <6 mm, significant left-to-right shunt, and left atrial and ventricular enlargement detected by echocardiography or a pulmonary flow (Q_p)/systemic flow (Q_s) ratio >1.5.

Transcatheter closure was performed in the pediatric catheterization laboratory under general anesthesia. The hemodynamic parameters, blood gas analysis data, and peripheral oxygen saturation were recorded before closure. The Q_p/Q_s ratio and pulmonary and systemic vascular resistance were calculated.

A 24-h Holter rhythm monitor was applied to each patient after VSD closure was planned. The procedure was performed one or two weeks later. Holter rhythm monitoring was repeated at three months. The patients and their families were encouraged to continue their daily physical activities during Holter recording.

Holter monitoring was also applied to 18 healthy children who were referred to our department with murmurs and had normal electrocardiographic and echocardiographic features. As with patients at three months, these children and their families were advised to continue their daily routine physical activities during monitoring.

Cardiac rhythm evaluation by Holter monitoring

A three-channel DMS 300-3A® Holter device was used for all patients and controls. All records were appraised using the Cardio Scan Premier 12® program. Significant artifacts and ectopic beats were detected automatically and manually and excluded from the evaluation. Patients with at least 23 h artifact-free Holter recording were included in the study. A single pediatric cardiologist performed all evaluations.

Patients with inconsistent Holter records were not enrolled in the study.

The following time-domain and frequency-domain parameters were determined following the Task Force report.[11]

Time-domain analysis

The following time-domain indices were calculated for entire Holter recordings after the exclusion of ectopic beats and artifacts:

- standard deviation of all filtered RR intervals (SDNN);
- standard deviation of 5-min averages of RR intervals (SDANN);
- mean of the standard deviation of all RR intervals for all 5-min segments (SDNN index);
- square root of the mean of the sum of square differences between adjacent filtered RR intervals (rMSSD);
- percentage of the difference between adjacent RR intervals >50 ms (pNN50).

Frequency-domain analysis

We determined spectral power over three frequencies for calculation of the following:

- Very-low-frequency (VLF; 0.003–0.04 Hz) index;
- low-frequency (LF; 0.04–0.15 Hz) index;
- high-frequency (HF; 0.15–0.40 Hz) index;
- variance of all NN intervals approximately <0.4 Hz (total power);
- LF/HF ratio.

Statistical analysis

The normality of the distribution of HRV parameters and hemodynamic measurements was assessed using the Kolmogorov–Smirnov test. Results are expressed as means for continuous variables and medians for ordinal variables. Demographic data and HRV parameters were compared between groups using the Mann–Whitney *U* test. HRV parameters in the patient group before the procedure and after the third month were compared using Friedman's test. Relationships between HRV parameters and hemodynamic measurements were assessed using Spearman's correlation analysis. $p<0.05$ was considered to be significant. All statistical analyses were performed using the Statistical Package for the Social Sciences (Version 22.0; SPSS Inc., Chicago, IL, USA).

Results

Nineteen patients with percutaneously closed VSDs were included in the patient group, and 18 healthy children were enrolled in the control group. The female/male ratios in the patient and control groups were 10:9 and 9:9, respectively. The mean age of patients was 96 ± 40 months and that of controls was 119 ± 39 months. The mean body weight of patients was 26.02 ± 13.83 kg and that of controls was 36.15 ± 16.89 kg. No significant difference in the demographic data was observed between groups (Table 1).

The mean pulmonary arterial pressure (mPAP) was 20.68 ± 4.13 mmHg. The Q_p/Q_s ratio was 2.01 ± 0.32, and all ratios were >1.5. Pulmonary vascular resistance was 1.8 (1.55–2.5) (U/m^2) and the pulmonary/systemic vascular resistance ratio was 0.18 ± 0.08. One patient had muscular VSD and the others had perimembranous VSDs. We used the Amplatzer duct occluder-II (ADO II) for 16 patients and the Amplatzer duct occluder-II additional sizes (ADO II AS) for three patients. Seven of the ADO II devices were 4 mm × 4 mm, six were 5 mm × 4 mm, and three were 4 mm × 6 mm. Two ADO II AS devices were 4 mm × 4 mm and one was 4 mm × 6 mm.

Two patients had Down's syndrome, two patients had minimal mitral regurgitation, and one patient had minimal aortic regurgitation. The patients had no congenital heart defect other than VSD.

Table 1 Characteristics of patient and control groups.

	Patient group (n: 19)	Control group (n: 18)	p value
Body weight (kg)	25 (16–29)	31 (19.5–47.25)	0.105
Age (month)	96 ± 40	119 ± 39	0.081
Female/male ratio	10/9	9/9	0.873
MPAP (mmHg)	20.68 ± 4.13		
PVR (wood units)	1.8 (1.55–2.5)		
PVR/SVR	0.18 ± 0.08		
Q_p/Q_s	2.01 ± 0.32		
VSD types			
Perimembraneous	18		
Muscular	1		
Devices			
ADO I	Ø		
ADO II	16		
ADO II AS	3		

ADO I: amplatzet duct occluder I; ADO II: amplatzet duct occluder II; ADO II AS: amplatzet duct occluder II additional sizes; MPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; SVR: systemic vascular resistance.

Table 2 Comparison of heart rate variability parameters between patient and control groups (0–3 months).

	Patient group, (0 month)	Patient group, 3rd month	Control group	p value (0–control)	p value (0–3 months)	p value (3 months–control)
SDNN	82 (71–114)	126 (100–144)	125.5 (105.5–143.75)	0.039	0.023	0.822
SDANN	68 (56–106)	102 (82–130)	105 (87.75–125.5)	0.03	0.02	0.73
SDNNi	51.63 ± 16.19	57 (47–65)	62.94 ± 17.31	0.057	0.477	0.169
PNN50	15 (8–19)	13 (10–20)	22.5 (11.75–27)	0.284	0.705	0.343
rMSSD	36.68 ± 10.81	38 (34–43)	40.5 ± 15.97	0.398	0.864	0.707
Total power	2367 (1497.9–4151.8)	3159.3 (2421.8–3950.6)	4236.0 (2675.7–4806.1)	0.039	0.185	0.20
VLF	1234.0 (860.1–2780.0)	1927.3 (1387.9–2566.0)	2455.3 (1565.9–3257.4)	0.052	0.21	0.248
LF	622.6 (335.1–998.0)	709.6 (538.8–1117.0)	2455.3 (1565.9–3257.4)	0.68	0.18	0.224
HF	358.0 (233.5–497.2)	448.4 (348.9–648.5)	499.8 (292.0–716.3)	0.11	0.073	0.84
LF/HF ratio	1.69 (1.43–2.46)	1.64 (1.15–1.98)	1.93 (1.3–3.02)	0.66	0.195	0.22

HF: high frequency index; LF: low frequency; PNN50: percentage of the difference between adjacent RR intervals greater than 50 milliseconds; rMSSD: square root of the mean of the sum of square differences between adjacent filtered RR interval; SDANN: standard deviation of 5-minute averages of RR intervals; SDNN: standard deviation of all filtered RR intervals; SDNN index: mean of the standard deviation of all RR intervals for all the 5-minute segments; VLF: very low frequency.

Twenty-four hour Holter monitoring

Time-domain parameters

The HRV parameters obtained in the patient group before closure and in the control group were compared. SDNN and SDANN values were significantly lower in the patient than in the control group 82 (71–114) vs. 125.5 (105.5–143.75), p=0.039 and 68 (56–106) vs. 105 (87.75–125.5), p=0.03, respectively), whereas SDDNi, pNN50, and rMSSD were similar in the two groups (Table 2).

No significant difference in the time-domain parameters obtained in the patient group at three months and in the control group was observed (Table 2). In the patient group, the SDNN and SDANN values were significantly higher than baseline at 3 months in the patient group (126 [100–144] vs. 82 [71–114], p=0.023 and 102 [82–130] vs. 68 [56–106], p=0.02, respectively). No other change in parameter from pre-closure was observed at 3 months in the patient group (Table 2).

No correlation between the time-domain parameters and hemodynamic measurements was detected (Table 3).

Frequency-domain parameters

The total power was lower in the patient group before closure than in the control group (2367 (1497.9–4151.8) vs. 4236.0 (2675.7–4806.1), p=0.039). VLF and HF indices and the LF/HF ratio were similar in the two groups. The frequency-domain parameters were similar in the two groups after 3 months, with no observation of low total power in the patient group (Table 2).

No relationship was observed between the other frequency-domain parameters and the hemodynamic parameters (Table 3).

Table 3 Correlation between heart rate variability parameters and hemodynamic measurements.

	MPAP		PVR		PVR/SVR		Q_p/Q_s	
	r	p	r	p	r	p	r	p
SDNN	0.248	0.305	−0.267	0.269	0.109	0.657	0.383	0.106
SDANN	0.278	0.249	−0.018	0.943	0.198	0.416	0.284	0.239
SDNNi	0.287	0.233	−0.356	0.135	0.10	0.682	0.339	0.156
PNN50	0.375	0.114	−0.029	0.906	0.421	0.073	0.063	0.799
rMSSD	0.018	0.941	0.013	0.957	0.328	0.170	0.231	0.288
Total power	0.424	0.071	−0.79	0.747	0.259	0.285	0.350	0.142
VLF	0.441	0.059	−0.053	0.830	0.237	0.329	0.357	0.133
LF	−0.008	0.974	−0.033	0.892	0.302	0.209	0.329	0.169
HF	0.361	0.129	−0.114	0.641	0.224	0.357	0.369	0.120
LF/HF ratio	0.12	0.624	−0.032	0.898	0.258	0.286	−0.156	0.523

ADO I: amplatzet duct occluder I; ADO II: amplatzet duct occluder II; ADO II AS: amplatzet duct occluder II additional sizes; HF: high frequency index; LF: low frequency; MPAP: mean pulmonary artery pressure; PNN50: percentage of the difference between adjacent RR intervals greater than 50 milliseconds; PVR: pulmonary vascular resistance; rMSSD: square root of the mean of the sum of square differences between adjacent filtered RR interval; SDANN: standard deviation of 5-minute averages of RR intervals; SDNN: standard deviation of all filtered RR intervals; SDNN index: mean of the standard deviation of all RR intervals for all the 5-minute segments; SVR: systemic vascular resistance; VLF: very low frequency.

One patient developed a complete atrioventricular (AV) block after transcatheter closure and was excluded from the study. Two patients developed varying degrees of AV block during the procedure, but these blocks did not persist after the procedure. A rare (<1%) single monomorphic ventricular extrasystole was detected in one patient before the procedure and at 3 months. These patients were included in the study, but a statistically separate group could not be formed.

Discussion

Heart rate variability is defined as the changeability between consecutive heartbeats.[11] It maintains autonomic control of the heart and is influenced by sympathetic and vagal activity. In patients with congenital heart diseases, particularly significant left-to-right shunts, sympathetic activity is elevated, creating a sympathetic–parasympathetic imbalance that disturbs autonomic control of the heart.[12–14] Massin et al.[15] showed that HRV decreases in many patients with congenital heart diseases in proportion to the New York Heart Association functional class.

Ventricular septal defect is a common heart defect that can cause congestive heart failure and pulmonary hypertension.[16] A left-to-right shunt causes increased end-diastolic left ventricular pressure and cardiac output.[14] The main compensatory mechanism for increased cardiac output is an increase in sympathetic tone. When the heart cannot achieve this increase, the balance decays in the direction of sympathetic activation, which may reduce HRV. In this study, following this mechanism, the HRV parameters SDNN and SDANN were lower in patients than in controls. SDNN and SDANN are time-domain HRV parameters that reflect long-term sympathetic–parasympathetic activity.[17]

Although our patients had small and medium VSDs and mild pulmonary hypertension, even small and medium left-to-right shunts can cause ventricular dysfunction and impair autonomic balance in infants and young children. The pulmonary blood flow and left ventricular end-diastolic volume decrease after the percutaneous closure of a left-to-right shunt, enabling the reduction of sympathetic activity and improvement of autonomic balance. In this study, patient's SDNN and SDANN had returned to levels seen in the control group at three months after closure. In contrast, Robinson et al.[20] reported that SDNN values were significantly lower than age-specific normal values after the closure of multiple muscular VSDs in pediatric and adult patients. This discrepancy in study findings may reflect the performance of Holter examination for <1 week after closure in that study,[18] or differences in VSD anatomy and size. No difference in the other HRV time-domain parameters (SDNNi, rMSSD, and pNN50) was observed between groups in this. This result is not consistent with those of other VSD studies, possibly due to the inclusion of small numbers of patients with heart failure in this and other studies.[19,20]

Congestive heart failure and pulmonary hypertension have been considered when defining the indications for VSD closure.[21] However, the effect of surgical or transcatheter VSD closure on autonomic balance remains unclear. Heiberg et al.[22,23] reported that surgical closure causes permanent chronotropic impairment and decreased HRV, possibly in association with right bundle branch block and right ventricular dysfunction. Although the need for a permanent pacemaker is greater after transcatheter closure, right bundle branch block and right ventricular dysfunction are less common after this procedure than after surgical closure.[24] Thus, transcatheter closure may contribute to the improvement of HRV and autonomic balance in the presence of appropriate indications and in selected patients, as shown in our study. However, in many centers, including ours, whereas surgery is the preferred method for younger children with larger defects and more severe heart failure, transcatheter closure is applied to older children with smaller defects.[25,26] Although we saw the benefit of transcatheter closure in our study, randomized

controlled studies comparing groups treated with the transcatheter approach and a surgical method with similar demographic characteristics and anatomical VSD characteristics are needed to strengthen our claim.

Frequency-domain analysis is another means by which to express HRV. HF represents parasympathetic activity and is affected by respiratory sinus arrhythmia.[27,28] The LF index reflects the baroreceptor reflex at a low breathing rate and is not affected by sympathetic activity.[28] The VLF index reflects sympathetic and parasympathetic activity, and more effectively predicts morbidity and mortality than the LF and HF indices.[29] Although controversial, low LF/HF ratios are taken to reflect parasympathetic dominance and high LF/HF ratios are taken to indicate sympathetic dominance.[28] Studies of congenital heart disease have shown that these parameters change, and this change is called sympathetic–parasympathetic blindness. However, the pathophysiology of congenital heart disease differs. Thus, autonomic control is dissimilar. The size of the shunt and level of HF also differ. Tadayoshi et al.[10] showed that HF is less frequent in patients with ASDs than in those with VSDs. Aletti et al.[20] reported that the LF, LF+HF, and total power values are higher in patients with congenital heart disease. In our study, the total power level was lower in patients than in controls, but other frequency-domain parameters were similar in the two groups. The total power level in patients at three months was similar to that in the control group.

Other consequences of congenital heart disease with left-to-right shunt are pulmonary arterial hypertension and pulmonary vascular disease. Many studies have shown that autonomic control is impaired and HRV decreases in cases of pulmonary hypertension.[29–32] In some studies, pulmonary arterial pressure correlated negatively with HRV parameters. In our small cohort study, no negative correlation was detected between the pulmonary arterial pressure and other hemodynamic parameters or HRV parameters, possibly due to the small number of patients included and the lack of cases of severe pulmonary hypertension and right heart failure. In addition, our patients had pulmonary hypertension due to left-to-right shunt, whereas patients with idiopathic pulmonary arterial hypertension (IPAH) were included in other studies.[29,30,32]

The pathophysiology of these diseases differs. Whereas right heart failure is present in IPAH, left-to-right shunt-related pulmonary arterial hypertension leads to left heart failure unless the defect is too large, and the treatment is administered too late.

Although the transcatheter closure of VSDs contributes to autonomic balance, the risk of a permanent AV block after such closure should not be forgotten. This risk is 0.07% after surgical closure, whereas Fu et al.[33] reported one case in 35 and Carminati et al.[34] reported three cases in 84 after transcatheter closure.[35] In our series, a permanent complete AV block developed in one of 49 cases, and a permanent pacemaker was implanted in this patient.[25] We believe that this complication was caused by intraoperative trauma to the conduction tissue and compression by the implanted devices. This complication can be avoided by passing the defect with a floppy catheter during the procedure and implanting the smallest possible device.[34]

In conclusion, our study shows that the transcatheter closure of VSDs altered HRV parameters, despite the lack of severe congestive heart failure and pulmonary hypertension. Further studies should be conducted with a larger case series and longer follow-up periods.

Conflict of interest

The authors report that they have no conflict of interest.

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