Mid-term assessment of cardiac autonomic functions in children with transposition of the great arteries after arterial switch operation

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Abstract

Objective: It has been documented that impaired heart rate variability (HRV) is related to life threatening arrhythmias in children with surgically repaired congenital heart disease. We aimed to analyze the balance of the cardiac autonomic functions by assessing HRV in children with arterial switch operation (ASO).

Methods: In this observational cohort study, HRV analysis using 24-h Holter electrocardiography recordings was examined in 22 patients (mean age: 59.5±38.7 months, 18 male, 4 female) who had undergone ASO during the newborn period and 22 healthy children (mean age: 65.1±39.4 months, 18 male, 4 female). After Kolmogorov-Smirnov testing for normality, Student t-test and Mann-Whitney U test were used when appropriate. Chi-square was used for categorical data.

Results: In 24-h HRV analysis showed that SDANN and VLF were significantly higher in patient group. Awake SDNN, rMSSD, pNN50, TP and VLF levels of patient group were significantly higher than those of control subjects. Awake LF/HF ratio in patient group was significantly higher than their counterpart in asleep group. In the patient group, awake rMSSD, pNN50, TP, LF and HF were significantly lower than their counterpart in the asleep group.

Conclusion: Children with transposition of the great arteries (TGA) following ASO have not decreased levels of time and frequency HRV parameters in the mid-term follow-up period. All HRV parameters reflecting vagal tone were increased in the patient group. It is suggested that vagal tone is more predominant than sympathetic tone for children with ASO. *(Anadolu Kardiyol Derg 2014; 14: 735-40)*

Key words: transposition of the great arteries, cardiac autonomic functions, heart rate variability

Introduction

Transposition of the great arteries (TGA) is the most frequently seen cyanotic congenital heart disease in newborn and infants with a 0.45 cases per 1,000 live births (1). Arterial switch operation (ASO) has become an accepted surgical procedure of infants with complete TGA (1). Since Jatene et al. (2) developed first successful ASO in 1975, several surgeons such as Lecompte et al. (3) have been tried to reduce the mortality and morbidity by modifications in surgical approach, aimed to decrease the possibility of pulmonary outflow obstruction. Data regarding late results of ASO revealed that sinus rhythm and good ventricular functions are preserved compared to the atrial switch procedure (4).

Heart rate variability, characterizing the beat-to-beat change in cardiac cycle, noninvasively evaluates autonomic nervous system, and reduced HRV has been documented as an indicator of severity of heart disease (5-7). It is well established that HRV is impaired in children with various cardiac diseases, and impaired HRV has been recognized to relate with life threatening arrhythmias in children with surgically repaired congenital heart disease (8-11).

To our knowledge, limited data are available on HRV of children with ASO. Therefore, it was our aim to analyze the balance of the autonomic nervous system in children with ASO by assessing HRV.

Methods

Study design and subjects

In this observational cohort study, we enrolled 22 patients with ASO due to TGA who were admitted to İzmir Dr. Behcet Uz

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Children's Hospital pediatric cardiology outpatient clinic between June 2012-December 2012. Inclusion criteria for current study include: Patients over the age of 12 months, patients without arrhythmia and patients not using any medications. Heart rate variability analysis using 24-h Holter electrocardiography (ECG) recordings were examined in all subjects. Age-sex matched 22 children with innocent murmur and normal cardiovascular examination were referred to as control group. We took informed consent from all participant's parents, and the research was approved by the Ethics Committee of our hospital.

Echocardiographic examination

Each subject was examined using a Vivid S6 Echocardiography System (General Electric's Healthcare, Milwaukee, WI) equipped with a M4S-RS broadband transducer (General Electric's Healthcare Japan Corporation, Hino-shi, Tokyo) with second harmonic capability.

HRV analysis

Using DMS 303A V11a Holter recorder (DMS Inc., New York, United States of America), 24-h Holter ECG recordings were obtained from all subjects. The recordings included a complete awake (06.00-22.00) and asleep (22.00-06.00) cycle. All subjects refrained from coffee and tea from 10 pm to evening before the recording. All recordings were analyzed using DMS Cardioscan program (DMS Cardioscan 11 Holter analysis program, DMS Inc.), and QRS complexes were identified as artifacts, ectopic and normal beats. Noisy data, artifacts, ectopic and arrhythmia beats, pauses were excluded from analysis. Holter tapes were re-evaluated by a pediatric cardiologist.

The following time-domain indices were calculated: Standard deviation of all normal sinus R-R intervals (SDNN); mean of the standard deviations of all normal sinus R-R intervals for all 5-minute segments of the entire recording (SDNNi); standard deviation of the averages of R-R intervals in all 5-minute segments of the entire recording (SDANN); root mean square of the successive normal sinus R-R interval difference (rMSSD); and the percentage of successive normal sinus R-R intervals longer than 50 milliseconds (pNN50%). The calculated frequency-domain indices were: Variance of all R-R intervals - total power (TP); power in the very low frequency range - very low frequency (VLF, 0.003-0.04 Hz); power in the low frequency range-low frequency (LF, 0.04-0.15 Hz); low frequency power in normalized units-normalized low frequency; power in the high frequency range-high frequency (HF, 0.15-0.40 Hz); and high frequency power in normalized units-normalized high frequency and the ratio of low frequency to high frequency (LF/HF).

Statistical analysis

Statistical Package for the Social Sciences (SPSS Version 18, SPSS Inc., Chicago, IL, USA) for Windows program was used to perform the analysis. Kolmogorov-Smirnov test was used to check the normality assumption. Values are expressed as mean±SD or median (interquartile range) as appropriate. The student's t-test was used for normally distributed data and the Mann-Whitney U test for not normally distributed data. Chi-square analysis was used for comparison of categorical data. A p value <0.05 was considered significant.

Results

Demographic and echocardiographic characteristics

Twenty-two patient (mean age: 59.5±38.7 months, 18 male, 4 female) who had undergone ASO during the newborn period, and 22 healthy children (mean age: 65.1±39.4, 18 male, 4 female) who were admitted to our cardiology outpatient clinic for the evaluation of murmur were included in this study. There was no statistical difference in mean age or distribution of ages between patient and healthy children (p>0.05). Transthoracic echocardiography showed that all patients had simple TGA; however, six of them had ventricular septal defect (VSD) which did not necessitate additional surgical procedure. Demographic, and echocardiographic characteristics of the patients are summarized in Table 1. Mean operation time was 7±4.8 days (range 2-19 days) after birth and mean follow-up duration was equal to patient's mean age.

HRV analysis

Heart rate parameters are listed in Table 2. There was no significant difference in minimum, maximum and average heart rate, mean RR duration and mean recording time between two groups. All 24-h time and frequency domain indexes were higher in patient group than healthy subjects; however, only SDANN and VLF in patient group were found to be statistically higher than of the control group (Table 3). Awake SDNN, rMSSD, pNN50, TP and VLF levels of patient group were significantly higher when compared with those of the control subjects (Table 4). There was no significant difference between patient and control groups in terms of asleep HRV parameters (Table 5). Awake SDNN and LF/HF in patient group were higher than their counterpart in the asleep group; however, statistical significance was observed regarding only LF/HF ratio (Table 6). In the study group, awake rMSSD, pNN50, TP, LF and HF were significantly lower than their counterpart in the asleep group. We observed similar findings, when awake HRV parameters were compared to asleep HRV parameters in healthy subjects.

Discussion

We found that children with TGA following ASO have increased time and frequency HRV parameters in mid-term follow-up period. Statistical significance was observed only regarding SDANN and VLF variables. We also found that all awake time-domain HRV parameters reflecting vagal tone (SDNN, rMSSD, pNN50) and some awake frequency-domain HRV parameters such as TP and VLF were increased in patient group. Based on these findings, we may suggest that vagal tone is more predominant than sympathetic tone for children with ASO, to the best our knowledge, it has not been reported.

Table 1. Demographic and echocardiographic characteristics of the patients

Patient no.	Age, months	Sex	Pre-op echocardiography	Operation time, day	Follow up echocardiography
1	12	Male	d-TGA, PFO, PDA, VSD (muscular, restrictive)	6	Mild neoaortic valve regurgitation, Mild neopulmonary valve stenosis
2	90	Male	d-TGA, PFO, PDA	8	Normal
3	68	Female	d-TGA, PFO, PDA	4	Moderate neoaortic valve regurgitation
4	62	Male	d-TGA, PFO, PDA	7	Mild neoaortic valve regurgitation
5	71	Male	d-TGA, PFO, PDA	4	Moderate neoaortic valve regurgitation
6	88	Male	d-TGA, PFO, PDA	15	Moderate neopulmonary valve stenosis
7	40	Male	d-TGA, PFO, PDA	3	Normal
8	24	Female	d-TGA, PFO, PDA, VSD (muscular, restrictive)	5	Normal
9	25	Male	d-TGA, PFO, PDA, VSD (perimembranous, restrictive)	7	Mild neoaortic valve regurgitation, VSD (perimembranous, restrictive)
10	49	Male	d-TGA, PFO, PDA, VSD (muscular, restrictive)	12	Mild neoaortic valve regurgitation, VSD (muscular, restrictive)
11	29	Male	d-TGA, PFO, PDA	4	Normal
12	59	Male	d-TGA, PFO, PDA	5	Normal
13	43	Female	d-TGA, PFO, PDA	4	Mild neopulmonary valve stenosis
14	84	Male	d-TGA, PFO, PDA, VSD (muscular, restrictive)	15	Mild neoaortic valve regurgitation
15	24	Female	d-TGA, PFO, PDA	3	Normal
16	188	Male	d-TGA, PFO, PDA	19	Mild neoaortic valve regurgitation, Moderate neopulmonary valve stenosis
17	54	Male	d-TGA, PFO, PDA	2	Mild neoaortic valve regurgitation, Mild neopulmonary valve stenosis
18	119	Male	d-TGA, PFO, PDA, VSD (muscular, restrictive)	8	Mild neopulmonary valve stenosis, VSD (muscular, restrictive)
19	42	Male	d-TGA, PFO, PDA	2	Mild neoaortic valve regurgitation
20	62	Male	d-TGA, PFO, PDA	14	Normal
21	42	Male	d-TGA, PFO, PDA	6	Mild neoaortic valve regurgitation
22	37	Male	d-TGA, PFO, PDA	3	Mild neoaortic valve regurgitation

d-TGA - transposition of the great arteries; PDA - patent ductus arteriosus; PFO - patent foramen ovale; VSD - ventricular septal defect

Table 2. Comparison of heart rate parameters

Heart rate parameters	Study group (mean±SD)	Control group (mean±SD)	*P*†
Mean heart rate, bpm	94.3±14.5	98.2±16.4	0.25
Minimum heart rate, bpm	53.9±8.6	56.6±8.27	0.76
Maximum heart rate, bpm	167.5±22.8	168.2±19.4	0.81
Mean RR, ms	561.7±105.7	541.7±101.9	0.13
Mean recording time, min	1290.7±165	1340.8±130	0.51

†: p is calculated with Student-T Test, SD - standard deviation

One possible explanation of parasympathetic predominance can be a surgical technique. The ASO produces a suture line through the ascending aorta and pulmonary trunk as well as around the coronary ostia. It is known that the majority of the sympathetic nerves extend to the heart through the great arteries (12). Therefore, a large proportion of the sympathetic nervous inflow is injured at the time of surgery. Denervation super sensitivity could be a possible explanation of increased incidence of sudden death without obvious coronary occlusion (13).

Kondo et al. (14) reported that cardiac sympathetic nerves are reinnervated late after arterial switch operation. Similarly, it has been shown that one year after heart transplantation there was increased norepinephrine (NE) uptake, indicating reinnervation of cardiac sympathetic nerves (15). Consistent with this data, studies on piglets exposed to ASO showed increased sensitivity to circulating NE 6-7 weeks following surgery, possibly due to defective re-uptake (16). Most of the released NE (>%80) is recaptured into the sympathetic nerve vesicles by the uptake mechanism (17). Falkenberg et al. (18) showed that spillover of NE into plasma from cardiac sympathetic nerves was lower in the ASO patients than in the healthy subjects. Decrease

Table 3. Comparison of the 24 hours time- and freguency-domain HRV parameters

HRV parameters	Study group	Control group	*P*
SDNN, ms	128±37	105±37	0.50†
SDANN, ms	112 (65)*	87 (37)*	0.040‡
SDNNi, ms	61 (30)*	47 (19)*	0.082‡
rMSSD, ms	42±16	34±15	0.90†
pNN50, %	20 (20)*	9 (11)*	0.052‡
TP, ms^2	3616 (3000)*	2078 (1792)*	0.067‡
VLF, ms^2	2667 (1935)*	1291 (1353)*	0.049‡
LF, ms^2	640 (523)*	492 (360)*	0.096‡
HF, ms^2	290 (426)*	252 (168)*	0.453‡
LF/HF	2.5±1.1	2.1±0.75	0.272†

HF - power in the high frequency range - high frequency; LF - power in the low frequency range - low frequency; LF/HF - the ratio of low frequency to high frequency; NS - not significant; pNN50% - The percentage of successive normal sinus; R - R intervals longer than 50 milliseconds; rMSSD - root mean square of the successive normal sinus; R - R interval difference; SDANN - standard deviation of the averages of R-R intervals in all 5-minute segments of the entire recording; SDNN - standard deviation of all normal sinus R-R intervals; SDNNi - mean of the standard deviations of all normal sinus R-R intervals for all 5-minute segments of the entire recording; TP - variance of all R-R intervals - total power; VLF - power in the very low frequency range -very low frequency.
*:Data are given as median (interquartile range)
†:*P* is calculated with Student-t Test
‡:*P* is calculated with Mann-Whitney U Test

Table 4. Comparison of the awake time- and freguency-domain HRV parameters

HRV parameters	Study group	Control group	*P*
SDNN, ms	113 (35)*	85 (29)*	0.02‡
rMSSD, ms	38 (21)*	26 (13)*	0.019‡
pNN50, %	13 (14)*	6 (8)*	0.015‡
TP, ms^2	3293 (2280)*	1797 (1077)*	0.046‡
VLF, ms^2	2416 (1655)*	1213 (817)*	0.044‡
LF, ms^2	607 (327)*	429 (192)*	0.067‡
HF, ms^2	279 (231)*	186 (131)*	0.213‡
LF/HF	2.7±1.2	2.5±0.8	0.647†

HF - power in the high frequency range - high frequency; LF - power in the low frequency range - low frequency; LF/HF - the ratio of low frequency to high frequency; NS - not significant; pNN50% - The percentage of successive normal sinus R-R intervals longer than 50 milliseconds; rMSSD - root mean square of the successive normal sinus R-R interval difference; SDNN - standard deviation of all normal sinus R-R intervals; TP - variance of all R-R intervals - total power; VLF - power in the very low frequency range - very low frequency.
*:Data are given as median (interquartile range)
†:*P* is calculated with Student-t Test
‡:*P* is calculated with Mann-Whitney U Test

in the specific activity of tritiated NE from arterial to coronary sinus was 35% slighter than that in the control group (18). Falkenberg et al. (18) concluded from their data that NE reuptake in ASO patients is impaired, and neonatal ASO did not alter cardiac vagal functions as we found in the current study.

Previous studies suggest that the HRV is an useful predictor of mortality in patients with cardiovascular disease and HRV is impaired in children with congenital heart disease (8-11). Gordon et al. (19) showed reduced post-operative frequency domain indices in children with congenital heart disease. In a study comparing the HRV before and after surgery of congenital heart disease, Heragu et al. (9) demonstrated a reduction in time and frequency domain indices in children with congenital heart disease when compared to controls, and HRV is further decreased postoperatively. However, their postoperative measurements were performed on average 5.8 days after surgery. It has been shown that patients with repaired tetralogy of Fallot (TOF) had reduced HRV (20, 21). To our knowledge, HRV was not studied in children with

Table 5. Comparison of the asleep time- and freguency-domain HRV parameters

HRV parameters	Study group	Control group	*P*‡
SDNN, ms	98 (51)*	75 (44)*	0.084
rMSSD, ms	43 (39)*	37 (24)*	0.280
pNN50, %	26 (27)*	15 (22)*	0.124
TP, ms^2	3673 (4062)*	2780 (2685)*	0.103
VLF, ms^2	2522 (2762)*	1358 (1703)*	0.241
LF, ms^2	655 (776)*	624 (706)*	0.622
Normalized LF, %	55 (18)*	59 (12)*	0.814
HF, ms^2	369 (631)*	406 (363)*	0.953
Normalized HF, %	36 (21)*	37 (14)*	0.869
LF/HF	1.64 (1.5)*	1.6 (0.95)*	0.851

HF - power in the high frequency range - high frequency; LF - power in the low frequency range - low frequency; LF/HF - the ratio of low frequency to high frequency; NS - not significant; pNN50% - the percentage of successive normal sinus R-R intervals longer than 50 milliseconds; rMSSD - root mean square of the successive normal sinus R-R interval difference; SDNN - standard deviation of all normal sinus R-R intervals; TP - variance of all R-R intervals - total power; VLF - power in the very low frequency range - very low frequency.
*:Data are given as median (interquartile range)
‡:*P* is calculated with Mann-Whitney U Test

Table 6. Comparison of the awake time- and freguency-domain HRV parameters with the asleep time- and freguency-domain HRV parameters in the study group

HRV parameters	Awake	Asleep	*P*
SDNN, ms	111±26	103±36	0.245†
rMSSD, ms	36 (21)*	43 (39)*	0.002‡
pNN50, %	14±9	28±16	0.000†
TP, ms^2	3293 (2280)*	3673 (4062)*	0.011‡
VLF, ms^2	2416 (1655)*	2522 (2762)*	0.099‡
LF, ms^2	607 (327)*	655 (776)*	0.019‡
HF, ms^2	279 (231)*	369 (631)*	0.001‡
LF/HF	2.7±1.2	1.95±1.1	0.001†

HF - power in the high frequency range - high frequency; LF - power in the low frequency range - low frequency; LF/HF - the ratio of low frequency to high frequency; NS - not significant; pNN50% - the percentage of successive normal sinus; R-R intervals longer than 50 milliseconds; rMSSD - root mean square of the successive normal sinus; R-R interval difference; SDNN - standard deviation of all normal sinus R-R intervals; TP - variance of all R-R intervals - total power; VLF - power in the very low frequency range - very low frequency.
*:Data are given as median (interquartile range)
†:*P* is calculated with paired samples t-test
‡:*P* is calculated with Wilcoxon Signed Ranks Test

d-TGA who had undergone ASO. Kondo et al. (14) studied metaiodobenzylguanidine (MIBG) uptake in patients with complete transposition. They hypothesized that the heart was sympathetically denervated shortly after, and reinnervated late after the ASO. They also showed that impaired cardiovascular responses on peak exercise were more often seen in the patients with absent MIBG uptake than in those with positive uptake. In the current study, cardiac autonomic system as measured by HRV affected following surgery in children with TGA. Our average follow-up duration was 59.5±38.7 months. We found no significant differences in asleep HRV parameters between patient and healthy children. In the current study, we also observed awake LF/HF ratio, asleep time and frequency domain indices of study group were significantly higher in agreement to data evaluating heart rate and HRV in healthy children. These findings suggest that circadian rhythm did not alter in children with ASO (22).

Study limitations

The power of the study for variables, which did not differ significantly between patient and control group was nearly 30%. The power for variables which differ significantly between night and day time was over 80%, except for normalized HF which power was found to be 0.51. Since mean values of parameters for patients and controls are closed to each other, a relatively high beta type error risk is found between patient and controls. Any additional clinical benefit is not expected with increasing number of subjects as for the similar mean and standard deviation. Since this study did not have prospective cohort design, we did not have HRV recording data before and after operation, especially at first year of life. Although our patient with ASO did not suffer major complication after early surgery, we did not have detailed record about their postoperative arrhythmic events.

Conclusion

In children with congenital heart disease, HRV is reduced compared to normal controls and is predictive of sudden cardiac death (23, 24). Following cardiac surgery for congenital heart disease, HRV is further reduced and may remain reduced years after operation (23, 25, 26). In our study, we found that HRV did not decrease following ASO, and children with ASO have predominant vagal tone. However, a large scale study would be necessary to better understand these findings.

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References

1. Hong SJ, Choi HJ, Kim YH, Hyun MC, Lee SB, Cho JY. Clinical features and surgical outcomes of complete transposition of the great arteries. Korean J Pediatr 2012; 55: 377-82. [CrossRef]
2. Jatene AD, Fontes VF, Paulista PP, de Souza LC, Neger F, Galantier M, et al. Successful anatomic correction of transposition of the great vessels: A preliminary report. Arq Bras Cardiol 1975; 28: 461-4.
3. Lecompte Y, Zannini L, Hazan E, Jarreau MM, Bex JP, Tu TV, et al. Anatomic correction of transposition of the great arteries. J Thorac Cardiovasc Surg 1981; 82: 629-31.
4. Losay J, Touchot A, Serraf A, Litvinova A, Lambert V, Piot JD, et al. Late outcome after arterial switch operation for transposition of the great arteries. Circulation 2001; 104: 121-6. [CrossRef]
5. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 1996; 93: 1043-65. [CrossRef]
6. Tulppo MP, Kiviniemi AM, Hautala AJ, Kallio M, Seppänen T, Mäkikallio TH, et al. Physiological background of the loss of fractal heart rate dynamics. Circulation 2005; 112: 314-9. [CrossRef]
7. Sharshenova AA, Majikova EJ, Kasimov OT, Kudaiberdieva G. Effects of gender and altitude on short-term heart rate variability in children. Anadolu Kardiyol Derg 2006; 6: 335-9.
8. Butera G, Bonnet D, Sidi D, Kachaner J, Chessa M, Bossone E, et al. Patients operated for tetralogy of Fallot and with non-sustained ventricular tachycardia have reduced heart rate variability. Herz 2004; 29: 304-9. [CrossRef]
9. Heragu NP, Scott WA. Heart rate variability in healthy children and in those with congenital heart disease before and after operation. Am J Cardiol 1999; 83: 1654-7. [CrossRef]
10. Massin M, von Bernuth G. Clinical and haemodynamic correlates of heart rate variability in children with congenital heart disease. Eur J Pediatr 1998; 157: 967-71. [CrossRef]
11. Ohuchi H, Suzuki H, Toyohara K, Tatsumi K, Ono Y, Arakaki Y, et al. Abnormal cardiac autonomic nervous activity after right ventricular outflow tract reconstruction. Circulation 2000; 102: 2732-8. [CrossRef]
12. Janes RD, Brandys JC, Hopkins DA, Johnstone DE, Murphy DA, Armour JA. Anatomy of human extrinsic cardiac nerves and ganglia. Am J Cardiol 1986; 57: 299-309. [CrossRef]
13. Tamisier D, Ouaknine R, Pouard P, Mauriat P, Lefebvre D, Sidi D, et al. Neonatal arterial switch operation: coronary artery patterns and coronary events. Eur J Cardiothorac Surg 1997; 11: 810-7. [CrossRef]
14. Kondo C, Nakazawa M, Momma K, Kusakabe K. Sympathetic denervation and reinnervation after arterial switch operation for complete transposition. Circulation 1998; 97: 2414-9. [CrossRef]
15. Rundquist B, Eisenhofer G, Dakak NA, ElamM, Waagstein F, Friberg P. Cardiac noradrenergic function one year following cardiac transplantation. Blood Press 1993; 2: 252-61. [CrossRef]
16. Falkenberg C, Hallhagen S, Nilsson K, Nilsson B, Ostman-Smith I. A study of the physiological consequences of sympathetic denervation of the heart caused by the arterial switch procedure. Cardiol Young 2010; 20: 150-8. [CrossRef]
17. Eisenhofer G, Esler MD, Meredith IT, Dart A, Cannon RO 3rd, Quyyumi AA, et al. Sympathetic nervous function in human heart as assessed by cardiac spillovers of dihydroxyphenylglycol and norepinephrine. Circulation 1992; 85: 1775-85. [CrossRef]
18. Falkenberg C, Ostman-Smith I, Gilljam T, Lambert G, Friberg P. Cardiac autonomic function in adolescents operated by arterial switch surgery. Int J Cardiol 2013. [CrossRef]

19. Gordon D, Herrera VL, McAlpine L, Cohen RJ, Akselrod S, Lang P, et al. Heart rate spectral analysis: a noninvasive probe of cardiovascular regulation in critically ill children with heart disease. Pediatr Cardiol 1988; 9: 69-77. [CrossRef]
20. McLeod KA, Hillis WS, Houston AB, Wilson N, Trainer A, Neilson J, et al. Reduced heart rate variability following repair of tetralogy of Fallot. Heart 1999; 8: 656-60.
21. Silvilairat S, Wongsathikun J, Sittiwangkul R, Pongprot Y, Chattipakorn N. Heart rate variability and exercise capacity of patients with repaired tetralogy of Fallot. Pediatr Cardiol 2011; 32: 1158-63. [CrossRef]
22. Massin MM, Maeyns K, Withofs N, Ravet F, Gérard P. Circadian rhythm of heart rate and heart rate variability. Arch Dis Child 2000; 83: 179-82. [CrossRef]
23. McGlone L, Patel N, Young D, Danton MD. Impaired cardiac autonomic nervous control after cardiac bypass surgery for congenital heart disease. Interact Cardiovasc Thorac Surg 2009; 9: 218-22. [CrossRef]
24. Brouwer J, van Veldhuisen DJ, Man in 't Veld AJ, Haaksma J, Dijk WA, Visser KR, et al. Prognostic value of heart rate variability during long-term follow-up in patients with mild to moderate heart failure. The Dutch Ibopamine Multicenter Trial Study Group. J Am Coll Cardiol 1996; 28: 1183-9. [CrossRef]
25. La Rovere MT, Pinna GD, Maestri R, Mortara A, Capomolla S, Febo O, et al. Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. Circulation 2003; 107: 565-70. [CrossRef]
26. Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987; 59: 256-62. [CrossRef]