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Prognostic Value of Heart Rate Turbulence and Heart Rate Variability in Children with Dilated Cardiomyopathy

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ABSTRACT

The aim of our study is to evaluate the prognostic value of heart rate turbulence (HRT) and heart rate variability (HRV) in children with dilated cardiomyopathy.

Methods: Twenty-five children with dilated cardiomyopathy (DCM) and 25 healthy children who were admitted to our hospital between January 2002-September 2004 were enrolled in this prospective study. After echocardiographic examination, three-channel 24 hour ambulatory ECG recordings were obtained in all patients with DCM and control group. Time domain HRV parameters were obtained in both groups. Heart rate turbulence was measured in DCM patients, but not in the control group due to the lack of premature ventricular contractions in 24 hour ECG monitoring.

Results: The mean follow-up period of DCM group was 13.4 months (3–26 months). Five patients died (20%) during the follow-up period. Triangular index, turbulence slope (TS), age and availability of non-sustained VT on 24 hour ECG monitoring were prognostic factors according to the correlation analyses. Only triangle index was detected as independend risk determining factor among the prognostic factors according to the logistic regression analyses.

Conclusion: This study assessed prognostic value of heart HRT and HRV in children with DCM. Further studies are needed to investigate prognostic value of HRT.

KEYWORDS

Heart rate turbulence, heart rate variability, dilated cardiomyopathy

Dilate Kardiyomiyopatili Çocuklarda Kalp Hızı Türbülansı ile Kalp Hızı Değişkenliğinin Prognostik Önemi

ÖZET

Dilate kardiyomiyopatili (DKM) hastaların yıllık ölüm hızları %5–45 arasında değişmektedir. Bu hastalarda ani ölüm açısından yüksek riskli hastaların belirlenmesi amacıyla bir çok noninvaziv parametre çalışılmıştır. Bunlardan kalp hızı türbülansının prediktif değerinin diğer prognostik faktörlerden üstün olduğu saptanmıştır.

Amaç: Dilate kardiyomiyopatili çocuklarda kalp hızı türbülansının prognostik değerinin araştırlımasıdır.

Metod: Haziran 2002-Eylül 2004 tarihleri arasında başvuran etyolojik araştıma sonucu neden bulunamayan 25 dilate kardiyomiyopatili hasta 24 sağlıklı çocuk çalışmaya dahil edildi. Ekokardiyografik değerlendirmeden sonra tüm hastalar ve kontrol grubunda yer alan çocuklar üç kanallı 24 saat ambulatuar EKG ile değerlendirildiler. Her iki grup için time domain KHD parametreleri belirlendi. Dilate kardiyomiyopati grubunda yer alan hastalarda KHT değerlendirildi. Kontrol grubunda yer alan çocuklarda ventriküler ekstrasistol saptanamadığı için KHT değerlendirilemedi. Çalışma sonunda orelasyon analizi ve regresyon analizi ile KHD ve KHT parametrelerinin prognozla olan ilişkisi değerlendirildi.

Sonuç: İzlem süresi içerisinde olguların 5'i (%20) kaybedildi.Korelasyon analizi uygulandığında triangle indeks, türbülans eğimi, yaş ve 24 saatlik ambulatuar EKG'de ventriküler taşikardi bulunmasının prognostik açıdan değerli faktörler olduğu, bu faktörler arasında sadece triangle indeksin bağımsız risk belirleyici faktör olduğu tespit edildi.

Bu çalışmada dilate kardiyomiyopatili çocuklarda KHT ve KHD'nin prognostik değeri değerlendirilmiştir. Çocuklarda KHT'ın prognostik değerlendirilmesi için daha fazla çalışmaya ihtiyaç vardır.

ANAHTAR KELİMELER

Kalp hızı turbulansı, kalp hızı değişkenliği, dilate kardiyomiyopati

İLETİŞİM ADRESİ

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Prognosis of dilated cardiomyopathy is poor with annual death rates between 5% and 45%. Sudden death resulting from arrhythmias are the main reason of sudden death in approximately half of these patients (1,2).

Identification of patients who are at high risk of cardiac events is an important clinical point. Numerous studies have attempted to define the prognostic factors especially in adult patients with dilated cardiomyopathy (DCM) after myocardial infarction. Various parameters including ST segment and T wave analysis, ventricular arrhythmias, heart rate variability, late potentials, QT dispersion are assessed by standard ECG or 24 hour ambulatory ECG for prognostic purposes in adult patients with dilated cardiomyopathy (3,4,5). Recently, it has been reported that decreased baroreflex sensitivity and reduced heart rate variability are associated with adverse prognosis after myocardial infarction (6).

In 1999, Schmidt et al presented heart rate turbulence (HRT) for risk prediction following myocardial infarction (7). In adult patients, the predictive value of HRT is comparable or superior, to known prognostic factors. In contrast to the large number of studies involving adult patients, only limited data is available on prognostic factors in children with dilated cardiomyopathy and HRT has not been evaluated in children with dilated cardiomyopathy so far.

The aim of our study is to evaluate the prognostic value of heart rate turbulence and heart rate variability in children with dilated cardiomyopathy. This is the first report assessing the prognostic value of HRT in children with dilated cardiomyopathy.

Materials and Methods

Twenty-five children with DCM and 25 healthy children admitted to our hospital between January 2002-September 2004 were enrolled in this prospective study. The diagnosis of dilated cardiomyopathy was made after etiological screening including history, physical examination, ECG, telecardiogram, hematological tests, biochemistry, serum carnitene level, cardiac enzymes (Troponin-I, CK-MB), viral serological screening, urine-blood amino asides, M-Mode, 2D and Doppler echocardiographic studies. At the end of these screenings, the patients who had no other reasons for systolic dysfunctionwho are in sinus rhythm wer selected for our study. Two patients were excluded from study because of rhythms other than sinus rhythm.

The control group consisted of 24 children with normal physical examination and echocardiographic analysis who were not taking any medications at least for a month and did not have any diseases.

Echocardiographic examination

The diagnosis of DCM was based on M-mode; 2-D and Doppler echocardiographic evaluation which was performed using a commercially available ultrasonic system (HP Sonos 1000). Left ventricular internal dimensions at end diastole and end systole were measured; ejection fraction and fractional shortening were calculated according to the standards of American Society of Echocardiography guidelines (8). Ejection fraction was calculated by the following formula EF (%): End diastolic volume–end systolic volume / end diastolic volume x 100. Fractional shortening was calculated by the formula: FS (%): End diastolic volume – end systolic diameter / end diastolic diameter x 100. Left ventricular dimensions and volume measurements were indexed according to body surface area.

Twenty-four hour ambulatory ECG monitoring

After the skin preparation, electrodes were placed to record leads II, V1 and V5. Three-channel 24 ambulatory ECG recordings were obtained in all patients with dilated cardiomyopathy and in the control group. All recordings were analyzed with computerized commercial 24 hours ambulatory ECG scanner (Pathfinder 700 series, Reynolds Medical Ltd, Hertford, UK).

Average hourly heart rates, maximum, minimum and mean 24-hour heart rates with standard deviations were calculated for each subject. Measurement and physiological interpretations of time domain heart rate variability (HRV) parameters were performed according to the standards of the Task Force of European Society of Cardiology and North American Society of Pacing and Electrophysiology (9).

Heart-rate turbulence

After the elimination of the artifacts and assessment of arrhythmia and heart rate variability, heart rate turbulence was calculated using the HRT view program on a computer. In brief, all VPCs that occurred in isolation (preceded and followed by >20 normal sinus beats) were selected by a computer algorithm and confirmed manually. Turbulence onset is defined as the difference between the mean duration of the first two sinus beats following VPC and the mean duration of the last two sinus beats preceding VPC, divided by the mean duration of the last two sinus beats preceding VPC. Turbulence onset is expressed as %. Turbulence slope was calculated as maximum positive slope of the regression line over any sequence of 5 sinus-rhythm RR intervals after a VPC. The value of the turbulence slope is expressed in millisecond/RR interval (7). We couldn't calculate heart rate turbulence in control group owing to no VPC in 24 hour ECG monitoring in this group.

Follow-up

Patients with DCM were hospitalized for at least 1 week on admission. Then, they were followed at 1 week, 1st month and after this period every 3 months. Evaluation included routine clinical examination, chest X-ray, ECG, and echocardiography.

Statistical analysis

All statistical analyses were performed using SPSS 9.0 (SPSS Inc, Chicago, Illinois). Chi-square test was performed to compare the HRV values between the dilated cardiomyopathy group and control group. A p value <0.05 was considered significant value. Correlation analysis was performed to determine correlation between studied parameters and mortality. After the correlation test, statistically significant parameters compared between the living and dead dilated cardiomyopathy patients using Mann Whitney U test. In addition, we used logistic regression models to evaluate the association between the mortality and statistically significant parameters according to the correlation test. The cut off point for parameters studied in this study was calculated using ROC analysis (receiver operator characteristic curve). According to these defined cut-off values, Kaplan-Meier survival analysis was applied.

Patients and Results

Our study was conducted between January 2002- October 2004 at Dr Sami Ulus Children's Hospital. Twenty-five patients with dilated cardiomyopathy and 24 healthy children were enrolled in this study. Two patients were excluded from study because of rhythms other than sinus rhythm.

In the DCM group, 16 patients were girls (64%), 9 patient were boys (36%), and their ages ranged from 3 months and 14 years (mean 5.4 ±4,5 years). In control group; 15 of the children were girls (62%), 9 of them were boys (38%), their ages ranged from 6 months and 13 years (mean 5.8 ±3, 5 years). There was no statistical significance determined between ages and sex of both groups (p >0.05).The characteristics of patients involved in the DCM group are shown in table 1.

The main complaint on admission was coug, fatigue, exercise intolerance, and edema in eyes and legs. The time between symptoms and admission ranged between 2 months and five years (mean 11.2 months). The number of patients who had severe heart failure was 6 (24%). Chest X-ray examination of patients revealed cardiomegaly in all patients.

TABLE 1

Characteristics of patients with DCM (N:25).

Age (years)	5.4 ±4,5 years (3 months–14 years)
Sex	
Girl	16 (64%)
Boy	9 (36%)
Duration of symptoms	11,2 months (2 months–5 years)
Chest X-ray	
Cardiomegalia	25 (100%)
ECG	
Normal	13 (52%)
Right axis	1 (4%)
Left axis	2 (8%)
Left ventricular hypertrophy.	6 (24%)
VES	2 (8%)
SVE	1 (4%)
Treatment	
Digoxin	25 (100%)
ACE inhibitors	25 (100%)
Diuretics	25 (100%)
Aspirin	25 (100%)
Coenzyme Q10	25 (100%)
Amiodaron	4 (16%)
Dopamine + Dobutamin	6 (24%)
Low molecular weight heparin	2 (8%)
Follow-up period (month)	13,4 (3–26)
Prognosis	
Live	20 (80%)
Exitus	5 (20%)

ECG was normal in 13 patients, 1 patient had right axis deviation, 2 had left axis deviation, 6 had left ventricular hypertrophy, 2 had ventricular extrasystoly and one had supraventricular extrasystol. On echocardiographic analysis; left ventricular ejection fraction was found to be between 20%and 48%(mean 35.1 ±7.8 %), and fractional shortening between 10 %and 28 %(mean 17.2 ±4.4 %) in the patient group. Left ventricular end diastolic diameter (LVEDD) ranged from 30 mm and 63 mm (mean 49.6 ±10 mm). The mean indexed LVEDD as cm/m^2 was 8.47 ±3.3 (3.75–15.3 cm /m^2). Left ventricular end-systolic diameter (LVESD) ranged from 24 mm and 55 mm (mean 37.9 ±8.2 mm). The mean indexed LVESD as cm/m^2 was 37.9 ±8.2 (24–55 cm/m^2). The mean end- diastolic volume (EDV) was 36.4 ±208 ml (36.4–208 ml) and 168.4 ±82.2 ml/m^2 (53.3–372 ml/m^2). End systolic volume (ESV) was calculated as 69.2 ±37.5 ml (17.9–157 ml) and 6.42 ±2.5 ml /m^2 (2.14–12.9 ml/m^2).

In addition to impairment of left ventricular systolic functions, thrombus was detected in left ventricle of 2 patients with DCM; first degree mitral insufficiency in 24 patients, second degree mitral insufficiency in one, first degree tricuspid insufficiency in 22 patients and second degree tricuspid insuffiency in one patient.

Twenty-four hour ambulatory ECG monitoring of DCM group revealed rare VES in 20 patients, bigeminy and trigeminy in 3 patients, couplet in 1, frequent VES in 1, SVE in 1 and nonsustained VES in 3 patients. The results of 24 hour ECG monitoring of DCM patient are shown in details in Table 2.

TABLE 2

Echocardiography and 24 hour ambulatory ECG characteristic of patients.

Echocardiographic measurement		
LVEF	(%)	35,1 ±7.8 (20–48)
LVSF	(%)	17.2 ±4.4 (10–28)
LVEDD	(mm)	49.6 ±10.0 (30–63)
	(cm/m^2)	8.47 ±3.3 (3.75–15.3)
LVESD	(mm)	37.9 ±8.2 (24–55)
	(cm/m^2)	6.42 ±2.5 (2.14–12.9)
EDV	(ml)	113,1 ±52,5 (36,4–208)
	(ml/m^2)	168.4 ±82.2 (53.3–372)
ESV	(ml)	69,2 ±37,5 (17,9–157)
	(ml/m^2)	110.8 ±50.9 (40.6–235.1)
Mitral insufficiency		
	1. degree	24 (95%)
	2. degree	1 (5%)
Tricüspit insufficiency		
	1. degree	22 (80%)
	2. degree	2 (20%)
Trombus		2 (8%)
24 Hour Ambulatuar ECG		
Minimum heart rate		87.7 ±22.7 (53–132)
Maximum heart rate		157.9 ±21 (126–203)
Rare VES		20 (80%)
Bigeminy, trıgeminy		3 (12%)
Ventricular tachycardia		3 (12%)
Couplet		1 (4%)
Frequent VES		1 (4%)
SVE		1 (4%)

Among the HRV parameters; minimum heart rate (p <0.01), mean and maximum heart rate (p <0.05) values were significantly higher in the DCM group. HRV values of DCM and group are shown in details in Table 3.

In heart rate turbulence analysis, turbulence onset (TO) value was <0%in 11 patients. and >%0 in 14 patients. Turbulence slope (TS) was found to be <1.2 ms/RR interval in 10 patients and >1.2 ms/RR interval in 15 patient. We did not detect any corelation between the TO and TS, EF and FS (p >0.05).

The mean follow-up period of DCM group was 13.4 months (3–26 months). Five patients died (20%) in this period. Three of them were girls, two of them were boys. The mean age of patients who died was 9.4 years (3 months-14 years). Three of them died in hospital, the other two patients died at home. Of the patients who died, two had bigeminy and trigeminy and one had rare VES.. Twenty-four hour ambulatory monitoring of two patients who died revealed non-sustained VT. We consider that two patients who died at home were because of arrhythmias. The prescence of non-sustained VT on 24 hour ambulatory ECG monitoring was a sta-

TABLE 3

Heart rate variability values of DCM and control group.

	DCM group n:25		Control n:24		p
Parameters	**Mean**	**Standard deviation**	**Mean**	**Standard deviation**	
Minimum HR	87,7	22,7	66,5	12,7	<0.01
Mean HR	114,5	21,2	95,1	19,2	<0.05
Maximum HR	157,9	21,0	143,3	14,6	<0.05
Mean RR	539,7	103,5	684,2	108,0	<0.01
sNN50 increase	6184,5	6547,2	17591,0	7770,9	<0.01
sNN50 decrease	6155,6	7178,0	19410,3	8941,8	<0.01
sNN50 total	12340,0	13663,3	36794,1	16540,1	<0.01
sNN6%increase	10017,6	8807,1	21193,7	7328,9	<0.01
sNN6%decrease	8411,0	8623,3	21357,2	7720,4	<0.01
sNN6%total	19150,3	17542,2	43220,0	15489,1	<0.01
SDNN	73,4	38,4	131,9	42,5	<0.01
SDNNi	37,1	25,9	76,0	29,1	<0.01
SDANN	61,8	30,0	113,5	29,8	<0.01
RMSSD	33,0	27,9	71,7	32,4	<0.01
Triangle index	16,3	6,9	36,7	14,0	<0.01

tisticaly significant prognostic factor according to the correlation analyses ($p < 0.05$, r^2 0.16)

Triangle index, turbulence slope, age and the prescence of non-sustained VT on 24 hour ECG monitoring were prognostic factors according to the correlation analysis. Table 6 shows the factors affecting mortality. The age of patients who died was statisticaly higher than who did not ($p > 0.05$). Among the HRV data, triangular index was correlated with prognosis ($p < 0.05$, r^2: -0,22). When the cut-off value of triangle index was taken at 15, p value was detected as <0.01. In survival analysis of patients whose triangle index value was <15, mortality increased in the first 10 months. While survival rate at the 4th month was 81 %, and 6 th months was 52.9% (Fig. 1a).

Among the heart rate turbulence parameters, we could not detect any correlation between the prognosis and TO ($p > 0.05$, r^2 -0.02). We detected a meaningful statistical correlation between the prognosis and TS ($p < 0.05$, r^2: -0.21). When cut-off value was taken as 1.2 ms/RR interval, p value was detected to be more meaningful ($p < 0.01$). Survival analyses of patients whose TS value <1.2 ms/RR interval, survival rate was

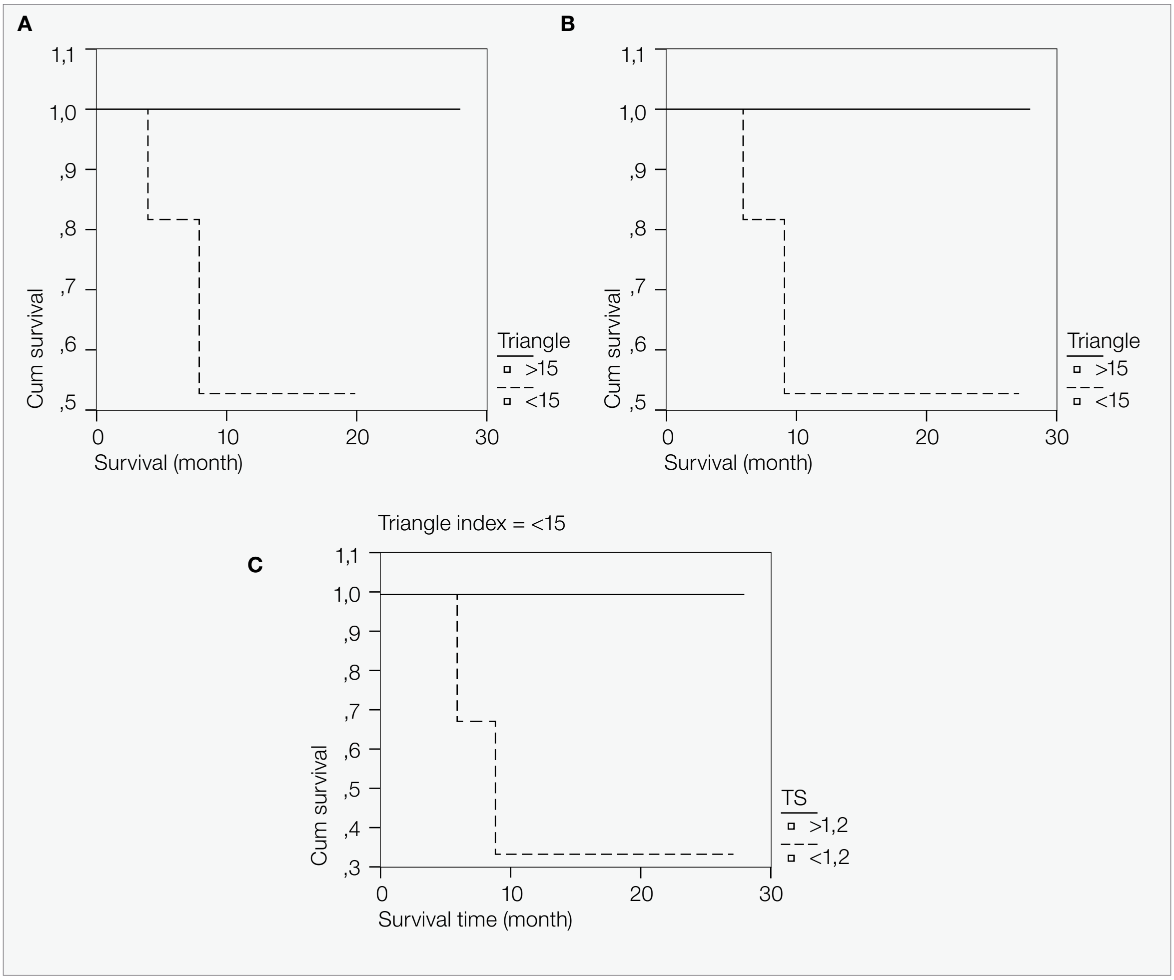

FIGURE 1A–C

Kaplan–Meier survival curve according to the triangle index (a), turbulence slope (b) and their combinations (c).

80%at 3 th month, 50%was 6 th month (Figure 1b). In evaluaton of triangle index <15 and TS <1.2 ms/RR interval group median life expectancy was 6.8 month, and probability of mortality was 85%at 6 th month (Fig. 1c).

Logistic regression analysis revealed that only triangular index was an independent risk factor for prognosis. P value of triangle index is <0.05 and risk ratio is 4.4 (minimum 0.64 maximum 1.0032, 95%confidence interval). Percent of correct prediction of triangle index was 80 %in living and 40%in died group. Overall correct prediction of triangle index was 76%. P value of TS was detected as 0,59, risk ratio was 2.27.

Discussion

DCM is characterised by ventrıcular dilation and impaired ventricular function. The most common cause is idiopathic, followed by metabolic disorders, ischemic, toxic, infectious causes and familial dilated cardiomyopathy (10). The prognosis of DCM is poor. About two-thirds of patients die from intractable heart failure within 4 years after the onset of symptoms of congestive heart failure (11).

The main reason of sudden death is caused by ventricular tachycardia, ventricular fibrillation, primary bradyarrhythmia, or electromechanical dissociation (1).

Arrhythmia risk stratification has been an important research area in adult patients for identification of patients who are at high risk of cardiac events. Becker et al (12) showed that nonsustained VT on Holter recordings is an independent risk factor. Grimm et al (4) assessed arrhythmia risk stratification in idiopathic dilated cardiomyopathy based on echocardiography and 12- lead, signal-averaged, and 24-hour holter electrocardiography. They revealed that the combination of left ventricular ejection fraction <30%and nonsustained VT on Holter, identify a subgroup of patients with idiopathic DCM with a 14-fold risk for subsequent arrhythmic events. In our study, non sustained VT was detected in 3 patients and statisticaly significant corelation determined between mortality and nonsustained VT ($p < 0.05$, r^2 0,40).

Autonomic dysfunction in chronic heart failure is reflected by neurohumoral activation, baroreflex dysfunction, and depressed heart rate variaibility (13). Time domain and frequency domain analysis of heart rate variability is a non invasive technique capable of providing information on autonomic modulation of the sinus node and stratifying risk for the cardiac events. Prognostic value of time domain parameters and geometric indexes has been consistently confirmed. Cut-off values of <70 ms for SDNN, <55 ms for SDANN, <30 ms for SDNNIDX and 20 units for triangle index have been utilized in several studies and proven effective to identify patients who carrying high risk (9,14,15). Decreased HRV by itself is only modest predictor of poor outcome (16). Heart rate variability and baroreflex sensitivity may represent important prognostic markers in patients with idiopathic dilated cardiomyopathy and chronic heart failure (17).

In our study, all HRV parameters except heart rate decreased suggesting increased neurohumoral activity. Among HRV parameters traingle index is a independent and most powerful risk predictor.

Schmidt et al presented a new method, heart rate turbulence, for risk prediction after the myocardial infarction. The physiology of early acceleration and late decelaration of heart rate after a ventricular premature beat mediated by baroreflex mechanism. Therefore it can be used as a non-invasive method for autonomic nervous system. Several studies including adult patients revealed that the predictictive value of TO and TS were comparable or superior and combination of TO and TS was the stongest indpendent variable for mortality (7). Reduced heart rate variability and attenuated baroreflex sensitivity after myocardial infarction and in patients with chronic congestive heart failure are associated with poor prognosis.

In contrast to a large number studies including adult patients, only limited data is available on prognostic factors in children with DCM and neither HRV nor HRT has been evaluated in these patients.

HRT is believed to be under control of the autonomic nervous system.The drop of systolic and diastolic blood pressure after a VPB lead to arteriel baroreseptor unloading.The drop of blood pressure is prolonged in healthy subjects for the first few post-VPB beats and its responsible for an early acceleration of heart rate after VPB. After that there is an increase of blod pressure with subsequent baroreceptors loading and vagal nerve activity is increased. This response is responsible late deceleration of heart rate (18,19).

In our study five patients (20%) died during the follow-up period. Among the studied parameters, triangle index, turbulence slope, age and the prescence of non-sustained VT on 24 hour ECG monitoring were prognostic factors according to the correlation analyses. Only triangular index was detected as an independent risk factor among the prognostic factors according to the logistic regression analyses. P value of triangle index is <0.05 and risk ratio is 4.4 (minimum 0.64, maximum 1.0032 for 95%confidence interval). Percent of correct prediction of triangle index was 80 %in living and 40%in died group. Overall correct prediction of triangle index was 76%. P value of TS was detected as 0,59, risk ratio was 2.27. We found that significant correlation between the turbulence onset and minimum heart rate (r^2 -1.47, p 0.18), mean heart rate (r^2 – 2,25, p:0.02), maximum heart rate (r^2 -1,75, p:0.2). We also found significant correlation between the turbulence slope and triangle index (r^2 -1.47, p:0.16). This suggests that heart turbulence closely related to autonomic nervous system same as heart rate variability.

Study limitations

Our study group was small when compared with large scale adult patients. We consider that turbulence slope may be an independent risk factor if HRT were evaluated in large groups consisting of children with dilated cardiomyopathy.

Conclusion

This study assessed prognostic value of heart rate turbluence and heart rate variability in children with dilated cardiomyopathy. Further studies are needed to investigate prognostic value of heart rate turbulence.

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