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Title: Evaluation of P-Wave Dispersion, Ventricular Functions and Atrial Electromechanical Coupling in children with Type 1 Diabetes Mellitus

Authors: Derya Aydın Şahin [1], Ahmet İrdem [1], Mehmet Kervancıoğlu [1], Osman Başpınar [1], Murat Sucu [2], Mehmet Keskin [3], Metin Kılınç [1]

Instutions: [1] Division of Pediatric Cardiology, Gaziantep University School of Medicine, Gaziantep, Turkey

[2] Department of Cardiology, Gaziantep University School of Medicine, Gaziantep, Turkey

[3] Division of Pediatric Endocrinology, Gaziantep University School of Medicine, Gaziantep, Turkey

Address for correspondence: Derya Aydın Şahin

E-mail: deryaaydin01@mynet.com

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Abstract

Objective: The present study aimed to evaluate ventricular diastolic function, inter- and intra-atrial conduction delay, and P wave dispersion in pediatric patients with type 1 diabetes mellitus (DM).

Methods: The study comprised 30 pediatric patients with type 1 DM and 30 healthy children served as the control group. Pd was measured on a 12-channel ECG. Both systolic and diastolic functions of

both ventricles were evaluated using conventional and tissue Doppler imaging (TDI) echocardiography (ECHO). Atrial electromechanical delay was measured by tissue doppler imaging (TDI) accompanied with electrocardiography (ECG).

Results: On conventional transthoracic echocardiography (ECHO), the mitral E/A ratio and isovolumetric relaxation times (IVRT) were different between the type 1 DM patients and the control group (1.67 ± 0.46 vs. 1.95 ±0.43, *P*=0.017 and 74.5 ± 7.0 vs. 63.3 ± 5.2, *P*<0.001, respectively). On Tissue Doppler Imaging (TDI), LV septal peak systolic (S_m) and early diastolic (E_m) velocities, and E_m/A_m ratio were found to be significantly lower in the type 1 DM patients than in the control group (*P* =0.047, *P* =0.003 and *P* =0.001, respectively). With regard to atrial electromechanical conduction, prolongation was detected in PA lateral, PA septal, PA tricuspid, and inter-atrial (PA lateral - PA tricuspid) and intra-atrial (PA septal - PA tricuspid) conduction delay (P<0.001, P<0.001, P<0.001, P<0.001, and P<0.05, respectively).

Conclusion: Our findings suggest that intra- and inter-atrial conduction delay, P wave dispersion, and ventricular diastolic functions are abnormal in type 1 DM patients.

Keywords: atrial electromechanical delay, children, diastolic function, left atrial mechanical function, type 1 diabetes mellitus

Introduction

Type 1 DM is one of the most common chronic diseases in adolescents and children. Poorly controlled type 1 DM is associated with many complications such as nephropathy, neuropathy, retinopathy and cardiovascular diseases. There is an increased risk of cardiovascular diseases such as ischemic heart diseases, systolic and diastolic heart failure, conduction system abnormalities and arrhythmias in patients with type 1 DM (1,2). Atrial fibrillation, which is associated with high mortality and morbidity, is frequently encountered in daily practice (3). It is known that prolonged intra- and inter-atrial conduction delay and non-homogenous distribution of sinus impulses increase predisposition to AF. Risk of this predisposition can be determined by noninvasive methods such as P wave dispersion (Pd) and TDI (4, 5).

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There are a few studies conducted on pediatric cases in the literature. Similar to the methodology and design of the previous study conducted by İrdem et al. (6) on pediatric patients with hypothyroidism, we aimed to evaluate ventricular diastolic function, inter- and intra-atrial conduction delay and P wave dispersion in pediatric patients with type 1 DM.

Materials and Methods

30 pediatric patients (18 females, 12 males, mean age 9.6±2.4 years) who have been diagnosed with type 1 DM in accordance with the criteria of the American Diabetes Association (7), who have received insulin therapy for at least one year and have been followed for a mean time period of 3.0±1.2 years in our clinic, as well as 30 healthy children (16 females, 14 males, mean age 8.4±3.6 years), as the control group, were enrolled in this study. Pediatric cases with hypertension, cardiomyopathy, valvular heart disease, branch block in ECG, atrioventricular conduction disorders, thyroid function disorder, kidney disease, lung disease, hypercholesterolemia and a bad presentation in ECG and TTE in both type 1 DM and control groups were excluded from the study. In addition, individuals in both groups were not using any drugs that could affect heart rhythm and they had sinusoidal heart rhythm. P wave dispersion was measured as described by Dilaveris et al. (8) in resting ECG. Individuals in both groups provided written informed consent and the approval of the local ethics committee was obtained before the study. We used the method from our previous study on pediatric patients with subclinical hypothyroidism while planning this study (6).

Transthoracic echocardiography (TTE) (Vivid S5 Pro device, GE, Horten, Norway, 2-4MHz phased-array transducer) was performed with 2-dimensional, M-mode, pulse and color flow Doppler imaging on all cases. A recording was made with one lead ECG throughout the TTE. Using conventional TTE, the mean values of the mitral and tricuspid early diastolic E wave, late diastolic A wave, IVRT, deceleration time (DT) and E/A ratio were calculated from three cycles obtained with Doppler and evaluated according to the American Echocardiography Association guidelines (9). Left atrial (LA) diameter was measured from the parasternal long axis, whereas left ventricular end diastolic diameter (LVEDd) and left ventricular end systolic diameter (LVEDs) as well as ejection fraction (EF) were measured using M-mode.

Atrial Electromechanical Coupling and tissue Doppler imaging assessments were performed using minimal optimal gain and adjusting spectral pulse Doppler signal filters until reaching Nyquist limit 0.15-0.20 m/s with transducer frequencies between 3.5-4 MHz in Tissue Doppler echocardiography.

LV lateral mitral annulus, septal mitral annulus and RV tricuspid annulus TDI measurements were obtained using pulse Doppler in the Apical 4 chamber. Atrial electromechanical delay (PA), the time interval from the onset of P wave to the beginning of the late diastolic (A_m) wave on surface ECG was measured in milliseconds from the LV lateral mitral annulus (PA lateral), septal mitral annulus (PA septal) and RV tricuspid annulus (PA tricuspid) (10). Values were calculated by averaging the measurements from 3 sequential beats. The difference between lateral and tricuspid PA (lateral PA-tricuspid PA) was defined as inter-atrial electromechanical delay, and the difference between septal PA and tricuspid PA (septal PA - tricuspid PA) was defined as intra-atrial electromechanical delay.

In calculating the P wave in 12-lead resting ECG, the beginning of the first positive wave deflecting upwards from the isoelectric line or the beginning of the first negative wave deflecting downwards from the isoelectric line was determined as the beginning of the P wave. The point where the wave returned to the isoelectric line was determined as the end of the P wave. The longest (P_{max}) and shortest (P_{min}) P wave in any derivation of the twelve-derivation ECG were measured in milliseconds in order to calculate P wave dispersion (P_d) ($P_d=P_{max}-P_{min}$). All measurements were performed by two experienced investigators who did not have any information about the clinical condition of the patients. Among the variables measured by two investigators, only those with less than 5% difference were included in the study.

Statistical Analysis

All analyses were performed using SPSS 11.0 (SPSS for Windows 9.0, Chicago, IL) software. All continuous variables were described as mean±standard deviation, and categorical variables as percentage. Categorical variables were compared with the Chi-square test. The relationship between the two variables was analyzed using the Pearson Correlation analysis. Student t test was used in comparing continuous variables between the two groups. $P<0.05$ was accepted as statistically significant.

Results

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Age, gender, body weight, height, body mass index, systolic and diastolic pressures, LA diameter, LVEDd, LVEDs and LV EF were similar in both groups (P>0.05) (Table 1). Maximum P wave duration and P_d values were found to be significantly higher in patients with type 1 DM (P<0.001) (Table 1). The mean HbA_{1c} level was 8.1±0.7% and the mean duration of the disease was 3.0±1.2 years in patients with type 1 DM.

IVRT was higher in the type 1 DM group as compared to the control group (P<0.001) (Table 2). Mitral and tricuspid E, A wave velocities and DT were similar in both groups (P>0.05) (Table 2). Mitral E/A ratio was significantly lower in the type 1 DM group as compared to the control group (P=0.017) (Table 2).

LV septal S_m, E_m velocities and E_m/A_m ratio were significantly lower in the type 1 DM group as compared to the control group (P= 0.047, P=0.003, P= 0.001, respectively) (Table 2). A_m velocity and E/E_m ratio, on the other hand, were significantly higher in patients with type 1 DM in comparison to the control group (P=0.010, P=0.038, respectively) (Table 2). LV lateral E_m velocity and E_m/A_m ratio were significantly lower in the type 1 DM group as compared to the control group (P= 0.009, P=0.012, respectively) (Table 2). A_m velocity and E/E_m ratio were similar in both groups (P= 0.906, P=0.068, respectively) (Table 2). In addition, RV lateral E_m velocity was significantly lower in the type 1 DM group as compared to the control group (P= 0.001) (Table 2). S_m, A_m velocities and E_m/A_m ratio were similar in both groups (P>0.05) (Table 2).

Patients with type 1 DM were found to exhibit a significantly prolonged PA lateral, PA septum, PA tricuspid, inter-atrial (PA lateral-PA tricuspid) and intra-atrial conduction delay (PA septum-PA tricuspid) in comparison to the control group (P<0.001, P<0.001, P=0.001, P<0.001, P<0.001, respectively) (Table 3).

No correlation was found between the duration of disease and HbA1c, atrial conduction delay (r=0.003, p=0.493; r=-0.092, p=0.315, respectively).

Discussion

It is known that type 1 DM constitutes a risk of heart disease. In addition, DM increases the risk of heart failure by directly affecting the heart without the presence of coronary heart disease and also causes functional and structural changes in individuals with impaired glucose tolerance without the presence of microvascular disease (11-13). Cardiac dynamic changes (increased heart rate, arrhythmia etc.) due to autonomic nervous system dysfunction, systolic and diastolic dysfunction in

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the heart, and cardiomyopathy can manifest in patients with DM (14, 15). Patients with DM can frequently have heart rhythm disorders with advancing age. The most common of such disorders is atrial fibrillation (AF) (16). Previous studies showed that conditions which cause left atrial enlargement lead to inter-atrial conduction delay (4, 5). Filtered P wave analysis is useful in detecting atrial electrophysiological abnormalities in paroxysmal AF. Atrial electromechanical delay can be measured by various methods (17, 18). Today, it is frequently measured by calculating the time interval between the onset of P wave on ECG and the onset of A_m wave in both ventricles on TDI in milliseconds while performing TTE. Studies have shown that patients with paroxysmal AF and mitral stenosis also had intra- and inter-atrial conduction delay (4, 5). There was intra- and inter-atrial conduction delay in our study despite the normal size of the left atrium.

The decrease in mitral or tricuspid early systolic A velocity correlated with reduced atrial contraction. Both parameters are affected by many cardiac conditions such as heart rate, preload and afterload (19). Previous studies have reported different results regarding left ventricular systolic and diastolic function in patients with DM; i.e. some of these studies reported systolic dysfunction whereas others reported diastolic dysfunction (20-23). However, impaired glucose tolerance leads to systolic and diastolic dysfunction in the heart also in the early phase of DM (13, 21, 24). Left ventricular systolic dysfunction may improve by itself if serum glucose concentrations return to normal levels (11). In our study, although ventricular systolic functions were normal in patients with type 1 DM, some parameters of the ventricular diastolic function were moderately impaired. The reason why our patients exhibited diastolic dysfunction in both ventricles and especially in the right ventricle, although mean duration of the disease was short, can be attributed to high HbA_{1c} levels.

Intra- and inter-atrial conduction time can be determined by calculating P wave dispersion and maximum P wave duration in twelve-lead ECG. It is known that non-homogenous sinus impulses constitute a risk factor for AF. It was reported that inter-atrial electromechanical delay measured using TDI has a correlation with P wave dispersion (10, 22). Increased atrial heterogenous electrical activity facilitates developing atrial fibrillation/atrial flutter by causing atrial reentry. Pd and Pmax have been used to predict the risk of AF development in many studies (3-5, 25). It is known that an increase in the left atrial diameter is significant for AF development. However, studies demonstrated that Pd increased in patients with AF, although the atrial diameter was normal. Our study also revealed that maximum P wave duration and P_d were significantly higher in patients with Type 1 DM, although LA diameter was normal. Consequently, patients with type 1 DM have higher atrial

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conduction delay in comparison to healthy individuals and this may indicate an increased risk of developing atrial rhythm disturbance in patients with type 1 DM.

Our study has more than one limitation. The limiting factors of this study include the low number of cases in the study, short duration of follow-up, lack of LV posterior wall thickness measurements and lack of LA mechanical measurements.

Conclusion

In our study, it was seen that there was atrial electromechanical delay, i.e. left atrium was affected in patients with type 1 DM. In addition, we found in tissue Doppler imaging that systolic and diastolic functions of the left ventricle were sub-clinically affected in patients with type 1 DM.

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Tables

Table 1: Clinical and laboratory characteristics of the patient and control groups

	Patients (n=30)	**Control (n=30)**	**P**
Age (Years)	9.6 ± 2.4	8.40 ± 3.6	0.120
Female (n, %)	18 (60%)	16 (53.3%)	0.602
Body mass index (kg/m^2)	16.3 ± 2.2	15.9 ± 3.7	0.615
Height (cm)	130.9 ± 12.0	124.5 ± 19.9	0.136
Systolic pressure (mmHg)	100.2 ± 7.9	97.9 ± 9.8	0.320
Diastolic pressure (mmHg)	61.5 ± 4.7	63.3 ± 5.6	0.200
Heart rate (beats/min)	90.75 ± 13.0	87.1 ± 16.7	0.352
P_{max} (ms)	106.2 ± 12.0	91.3 ± 8.0	<0.001
P_{min} (ms)	77.5 ± 9.9	74.3 ± 7.9	0.173

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P_d (ms)	28.6 ± 8.2	16.9 ± 7.3	<0.001
HbA_{1c} (%)	8.1 ± 0.7	--	
Duration of disease (years)	3.0 ± 1.2	--	

LVEDd, left ventricular end diastolic diameter; LVESd, left ventricular end systolic diameter; Pmax, maximum P-wave; Pmin, minimum P-wave; Pd, P-wave dispersion.

Table 2. Comparison of the variables measured using conventional and tissue Doppler imaging between patients and control groups

	Patients (n=30)	**Control (n=30)**	**P**
Conventional Doppler parameters			
Ejection fraction (%)	70.9 ± 3.7	70.2 ± 4.8	0.528
LVEDd (cm)	3.9 ± 0.3	3.7 ± 0.5	0.067
LVESd (cm)	2.4 ± 0	2.3 ± 0.3	0.087
Left atrial diameter (cm)	2.3 ± 0.2	2.2 ± 0.3	0.143
Mitral E velocity (m/s)	0.92 ± 0.16	0.99 ± 0.17	0.128
Mitral A velocity (m/s)	0.57 ± 0.09	0.54 ± 0.15	0.406
Mitral E/A	1.67 ± 0.46	1.95 ± 0.43	**0.017**
DT (ms)	160.4 ± 14.5	154.7 ± 14.2	0.132

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IVRT (ms)	74.5 ± 7.0	63.3 ± 5.2	**<0.001**
Tricuspid E velocity (m/s)	0.70 ± 0.12	0.65 ± 0.10	0.128
Tricuspid A velocity (m/s)	0.46 ± 0.09	0.44 ± 0.10	0.512
Tricuspid E/A	1.45 ± 0.18	1.46 ± 0.29	0.816
Tissue Doppler parameters			
Septal LV			
S_m (m/s)	0.09 ± 0.02	0.11 ± 0.01	**0.047**
A_m(m/s)	0.07 ± 0.01	0.06 ± 0.01	**0.010**
E_m(m/s)	0.12 ± 0.0	0.14 ± 0.0	**0.003**
E_m/A_m	1.7 ± 0.6	2.2 ± 0.5	**0.001**
E/E_m	7.8 ± 1.6	7.0 ± 1.2	**0.038**
Lateral LV			
S_m (m/s)	0.10 ± 0.02	0.08 ± 0.02	**0.001**
A_m(m/s)	0.07 ± 0.02	0.07 ± 0.02	0.906
E_m(m/s)	0.13 ± 0.04	0.15 ± 0.03	**0.009**
E_m/A_m	1.8 ± 0.6	2.1 ± 0.4	**0.012**
E/E_m	7.3 ± 1.7	6.5 ± 1.6	0.068
RV lateral annulus			
S_m (m/s)	0.12 ± 0.02	0.12 ± 0.0	0.813
A_m(m/s)	0.10 ± 0	0.11 ± 0.0	0.125
E_m(m/s)	0.13 ± 0.0	0.16 ± 0.02	**0.001**
E_m/A_m	1.4 ± 0.4	1.5 ± 0.4	0.243

DT, deceleration time; IVRT, isovolumetric relaxation time; LV, left ventricle; Sm, septal systolic velocity; Em, early diastolic velocity; Am, late diastolic velocity; RV, right ventricle.

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Table 3: Atrial electromechanical interval measurement results obtained from tissue Doppler

	Patient (n=30)	**Control (n=30)**	**P**
PA lateral (ms)	69.8 ± 4.8	53.2 ± 4.7	**<0.001**
PA septum (ms)	46.3 ± 2.3	41.1 ± 2.9	**<0.001**
PA tricuspid (ms)	40.6 ± 3.5	37.8 ± 3.1	**0.001**
PA lateral-PA tricuspid (ms)[a]	29.1 ± 6.1	15.4 ± 5.5	**<0.001**
PA septum-PA tricuspid (ms)[b]	5.6 ± 4.4	3.3 ± 3.9	**<0.001**

Data was provided in mean ± standard deviation. PA; the time interval from the onset of P wave to the beginning of the late diastolic wave (A_m) on ECG measured by tissue Doppler

a; inter-atrial electromechanical delay.

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b; intra-atrial electromechanical delay.

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