Atrial Electromechanical Delay and Left Atrial Functions in Children with Type 1 DM

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Abstract: Background: Arrhythmias and conduction abnormalities are increased in diabetic patients. Prolonged intra and interatrial electromechanical delays and in homogeneous propagation of sinus impulses are known electrophysiological characteristics to atria prone to atrial fibrillation **Aim:** evaluate atrial conduction times , atrial electromechanical coupling and left atrial mechanical functions in type 1 DM children **Methods:** 40 type 1 DM children and 40 age and sex matched controls were included .P wave dispersion (Pd) calculated from 12 lead ECG, atrial electromechanical coupling measured by TDI , Left atrial (LA) maximal, minimal, and presystolic volumes measured according to biplane area length method and LA mechanical function parameters calculated. **Results:** Pd and inter atrial electromechanical delay were higher in type 1 diabetic children than control (P<0.001). LA active emptying volume and LA emptying fraction were increased in patients than control (P<0.001). Interatrial electromechanical delay was negatively correlated with early diastolic trans-mitral velocity, left ventricular end diastolic diameter, and presystolic atrial velocity and positively correlated with the average systolic velocity of mitral annuli (P=0.025, P=0.05, P=0.005 and p= 0.017, respectively). The intra-atrial delay was negatively correlated with maximum LA velocity, minimum atrial velocity and total LA emptying volume (P=0.006, p=0.036 . p=0.038, respectively). Duration of illness and DM type 1 were independent predictors of interatrial electromechanical delay by multivariate analysis (p=0.001 and 0.0001). **Conclusion:** children with DM-1 demonstrated LV and RV diastolic dysfunction, increased Pd and inter atrial electromechanical delay which predispose them to develop AF. LA compensates for LV diastolic dysfunction by increased the LA active emptying volume.

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1. Introduction

Diabetes mellitus is a chronic multisystem disease associated with the development of specific long term organ damage caused by microvascular disease, which is referred to as diabetes complications [1]

The frequency of cardiovascular disease is increased in diabetic patients. Several studies have demonstrated evidence of preclinical left ventricular diastolic dysfunction in patients with diabetes mellitus independent of coronary disease .[2]

Recent findings indicate that atrial fibrillation may be relatively common in diabetic patients and should be regarded as a marker of adverse outcome, promoting aggressive management of all risk factors [3]

The prolongation of intra and interatrial electomechanical delays and the inhomogeneous propagation of sinus impulses are well known electrophysiologic characteristics of atria prone to fibrillation [4]

A previous study demonstrated that inter and intra-atrial electromechanical delays are prolonged and left atrial mechanical functions are impaired in adults with DM [5]

To our knowledge no study has evaluated atrial conduction times in children with DM type I.

Aim of the work:

The aim of this work is to evaluate the LA electromechanical function, left atrial electromechanical delay as well as left and right ventricular diastolic function in children with type I DM which can predispose them to AF.

2. Subjects and methods:

A cross sectional case control study conducted on 40 consecutive patients with DM type I diagnosed according to the American Diabetes Association criteria (Genuth *et al.,* 2003), recruited from the diabetes clinic, Children's hospital, Ain Shams University.[6]

Forty age and sex matched healthy children constituted the control group. All subjects were in sinus rhythm, none of them was receiving antiarrhythmic medication. After explaining the procedures of the study a written consent was obtained from the parents/ or the guardians of the all subjects.

Patients underwent full history taking, thorough clinical examination.

All studied subjects underwent:
- Anthropometric measurement to obtain the body mass index.
-Laboratory investigation to measure the glycosylated hemoglobin (Hb A1c)
-Twelve lead electrocardiogram (ECG): to obtain the maximum (Pmax) and minimum (Pmin) duration of the P wave and to measure the P wave dispersion (Pd).

Echocardiography:

ECG gated echocardiography using was done using vivid E9, GE, Horten, Norway, with 5S phased array transducer) applying the following modalities

Conventional doppler:

Pulsed doppler at tips of leaflets of mitral valve (MV) in apical four chamber view to obtain the early diastolic (E), late diastolic (A), E/A ratio and E wave deceleration time (E DT).

motion mode (m-mode) at level of papillary muscle to obtain the left ventricular end diastolic diameter (LVEDd), Left ventricular septal diameter in diastole (IVSDd), Left ventricular post wall thickness in diastole (PWTd), and ejection fraction (EF).

Assessment of LA mechanical functions:

LA volumes were determined at the mitral valve opening (maximal, V max), the onset of atrial systole (P wave of ECG, Vp) and the mitral valve closure (minimal, Vmin) according to the biplane area-length method from the apical 4 chamber views. The following LA emptying function parameters were calculated: LA passive emptying volume= Vmax-Vp, LA passive emptying fraction= (Vmax-Vp)/Vmax, LA active emptying volume= Vp-Vmin, LA active emptying fraction= (Vp-Vmin)/Vp, Conduit volume= [LV stroke volume-(Vmax-Vmin)] and LA total emptying volume= V max-Vmin .[7]

Tissue Doppler: tissue doppler echocardiography was done with transducer frequencies 4-7MHz by adjusting the spectral pulsed Doppler signal filters until a Nyquist limit of 15-20 cm/s was reached and by using the minimal optimal gain. The monitor sweep speed was set at 50-100 mm/s to optimize the spectral display of myocardial velocities

1-Atrial electromechanical coupling:

In apical four chamber view, the pulsed doppler sample volume was subsequently placed at the level of the LV lateral mitral annulus, septal mitral annulus, and right ventricular tricuspid annulus. The sampling window was positioned as parallel as possible to the myocardial segment of interest to ensure the optimal angel of imaging to measure atrial electromechanical coupling which is called (PA). The time interval from the onset of the P wave on the surface ECG to the beginning of the late diastolic wave (Am wave) was obtained from the lateral mitral annulus, septal mitral annulus, and right ventricular tricuspid annulus and termed PA lateral, PA septum and PA tricuspid respectively . [8]These values were corrected for heart rate by dividing with the square root of the R-R interval.[9] Values were averaged over 3 consecutive beats. The difference between corrected PA (cPA) lateral and cPA tricuspid was identified as interatrial electromechanical delay, and the difference between cPA septum and cPA tricuspid was defined as intra-atrial electromechanical delay.

2-Left and right ventricular functions:

Peak systolic (Sm) and early (Em) and late (Am) diastolic velocities were obtained at the lateral and septal mitral annuli, the Sm global, Em global, and Am global velocities were derived by averaging the velocities from the annular sites. Right ventricular Sm. Em and Am values were obtained at the lateral tricuspid annulus. Global E m/Am ration of left ventricle and Em/Am ratio of right ventricle were calculated. E/Em ratio also was calculated to provide an estimation of LV filling pressures.[10] The myocardial performance index (MPI), a non invasive measurement of global ventricular function incorporating both systolic and diastolic function was calculated by using TDI methods for right and left ventricles .[11]

Statistical analysis:

Data collected and analyzed using appropriate statistical methods, mean and standard deviation were used for parametric data and median and inter quartile range were used for non-parametric data. Results were identified as significant when P value is less than 0.05.

3. Results:

This study was conducted on 40 children diagnosed to have Type I DM. The mean of their ages was 9.85+3.00 y, the duration of their illness was 5.5+1.99y. The mean of their body mass index was 21.58+2.15kg/m^2 and their HbA1c was 6.63+0.58gm/dl. They were compared to forty healthy children with a mean age of 9.95+2.89y and a body mass index of 21.5+2.29 kg/m^2.

I-Ventricular function:

-The echocardiographic m-mode derived measurements of left ventricular dimensions and systolic functions of the patients and the control groups were comparable (Table 1).

Conventional doppler:

There was a statistically significant difference between the patients and the control group as regards the transmitral early diastolic velocity (E), late diastolic velocity (A), E/A ratio and isovolumetric relaxation time (Table 2).

Tissue Doppler:

The average value of mitral annuli A wave (Am mitral average) was significantly lower and the average mitral Em/Am ratio was significantly higher in patients as compared to the control group (Table 3). The global LV diastolic function E/Em ratio of the patients (4.87+0.35) was significantly lower than that of the control group (6.92+0.52), *P*<0.001. The early velocity of the lateral tricuspid annulus (Em tricuspid), as well as the Em/Am ratio of the lateral tricuspid annulus were significantly higher in diabetic patients as compared to the control group (Table 3)

II-LA mechanical function:

The data of the left atrial volume and mechanical function of the studied groups are presented in table (4) The LA active emptying volume as well as the LA active emptying fraction were significantly higher in patients as compared to the control group.

III- LA electromechanical delay

Twelve lead ECG showed that the P wave dispersion of the patients (47.81+0.90 msec) was significantly higher than that of the control group (44.48+1.15msec) *P*<0.001.

Tissue doppler:

Data of LA electromechanical coupling of the studied subjects are presented in table (5). The PA lateral as well as the interatrial delays were significantly increased in diabetic patients as compared to the control group.

The interatrial delay was negatively correlated with the Am mitral r=-0.500, *p*=0.025, left ventricular end diastolic diameter r=0.444, *p*=0.05 and presystolic atrial velocity r=0.606, *p*=0.005. It was positively correlated with the average systolic velocity of mitral annuli r=0.529, *p*=0.017.

The intra-atrial delay was negatively correlated with the max LA velocity r=-0.591, *p*=0.006, minimal LA velocity r=-0.472, *p*=0.036 and total LA emptying volume -0.467, *p*=0.038.

Table (1): Comparison between patients and control group as regards the M-mode derived left ventricular dimensions and systolic function:

Variables		Control Group		Patients Group		t/z value	*p* value
LVEDD(mm)	Mean±SD	45.38±1.41		45.53±1.35		0.354	0.723
	Median	45.00		45.50			
	IQR	44.50	46.93	44.50	46.93		
LVESD(mm)	Mean±SD	46.21±1.36		46.51±1.34		0.745	0.456
	Median	46.30		46.85			
	IQR	45.00	47.38	45.13	47.50		
IVS(mm)	Mean±SD	8.77±0.35		8.78±0.35		0.136	0.893
	Median	8.80		8.90			
	IQR	8.53	9.00	8.53	9.00		
LVPWT(mm)	Mean±SD	8.74±0.35		8.73±0.37		0.068	0.946
	Median	8.75		8.80			
	IQR	8.60	9.00	8.45	9.00		
EF%	Mean±SD	65.70±3.97		65.70±3.97		0.000	1.000
	Median	66.00		66.00			
	IQR	62.25	69.00	62.25	69.00		
LVMI(gm/m^2)	Mean±SD	85.66±2.87		85.60±2.98		0.095	0.924
	Median	85.50		85.50			
	IQR	83.00	87.75	82.88	87.75		

LVEDD=left ventricular end diastolic diameter, LVESD=left ventricular end systolic diameter, IVS=interventricular septal thickness, LVPWT=left ventricular posterior wall thickness, EF=ejection fraction, LVMI=left ventricular mass index, SD=standard deviation, IQR=interquartile range, P>0.05=non significant.

Table(2): Comparison between patient's and control group as regards transmitral diastolic flow parameters

Variables		Control Group		Patients Group		t/z value	*p* value
Mitral E Velocity (cm/s)	Mean±SD	94.05±1.71		82.75±2.72		5.413 MW	<0.001
	Median	94.00		82.00			
	IQR	93.00	95.00	80.68	84.80		
Mitral A Velocity (cm/sec)	Mean±SD	60.25±1.45		68.45±2.96		3.004 KS	<0.001
	Median	60.00		68.50			
	IQR	59.00	61.00	66.00	71.75		
E/A ratio	Mean±SD	1.55±0.04		0.83±0.05		50.325 ST	<0.001
	Median	1.55		0.83			
	IQR	1.50	1.60	0.80	0.87		
DT msec	Mean±SD	185.68±3.47		187.23±1.66		0.791 KS	0.560
	Median	186.00		187.00			
	IQR	184.25	188.00	186.00	188.00		
IVRT msec	Mean±SD	80.60±3.38		101.95±4.62		3.162 KS	<0.001
	Median	80.00		104.50			
	IQR	78.25	81.00	97.25	105.75		

MW=ManWittney test, KS= Kolmogorov-Smirnov, St=student T test, Mitral E velocity=velocity of the early diastolic transmitral flow, Mitral A velocity=velocity of the late diastolic transmitral flow, E/A ratio=ratio between early and late transmitral diastolic flow, DT= deceleration time of the E wave, IVRT=isovolumetric relaxation time.SD=standard deviation, IQR=interquartile range. msec=millisecond, cm/sec=centimeter per second. *P*<0.001=highly significant, *P*>0.05=non significant.

Table (3): Comparison between patients and control group as regards the tissue doppler derived left and right ventricular functions

Variables		Patients Group		Control Group		t/z value	*p* value
Sm- aver m (cm/sec)	Mean±SD	10.84±0.94		10.80±0.90		0.095 MW	0.924
	Median	10.85		10.75			
	IQR	10.20	11.65	10.13	11.38		
Em-aver m (cm/sec)	Mean±SD	13.66±0.95		14.09±0.79		1.762 MW	0.078
	Median	13.65		14.10			
	IQR	12.90	14.18	13.50	14.50		
Am-aver m (cm/sec)	Mean±SD	11.05±0.29		10.75±0.35		2.946 ST	0.005
	Median	11.05		10.80			
	IQR	10.83	11.30	10.43	11.00		
Em/Am-aver m (cm/sec)	Mean±SD	1.23±0.10		1.30±0.07		1.423 KS	0.035
	Median	1.24		1.30			
	IQR	1.15	1.30	1.26	1.33		
MPI-LV	Mean±SD	53.23±2.55		52.95±2.68		0.314 MW	0.754
	Median	53.00		52.50			
	IQR	51.00	55.75	50.00	55.75		
Sm- lat t (cm/sec)	Mean±SD	15.35±0.68		15.31±0.70		0.299 MW	0.765
	Median	15.55		15.50			
	IQR	14.73	15.98	14.70	15.98		
Em-lat t (cm/sec)	Mean±SD	14.99±0.61		15.31±0.41		2.158 MW	0.031
	Median	15.00		15.20			
	IQR	14.70	15.28	15.00	15.48		
Am-lat t (cm/sec)	Mean±SD	16.58±0.62		15.91±0.50		3.776 MW	<0.001
	Median	16.80		16.00			
	IQR	16.50	16.98	15.80	16.20		
Em/Am- lat t	Mean±SD	0.89±0.02		0.96±0.04		4.679 MW	<0.001
	Median	0.90		0.96			
	IQR	0.87	0.92	0.93	0.99		
MPI-RV	Mean±SD	49.50±2.98		50.00±2.18		0.232 MW	0.816
	Median	50.00		50.00			
	IQR	48.00	51.75	49.00	51.75		

Aver m=average value of mitral latral and septal annuli, Sm=systolic velocity of the myocardial velocity, Em=early diastolic myocardial velocity, Am=late diastolic myocardial velocity, lat t= lateral tricuspid annulus, MPI=myocardial performance index, LV=Left ventricle, RV= right ventricle, SD=standard deviation, IQR= interquartile range, cm/sec=centimeter per second, *P*<0.001= highly significant, *P*>0.05 non significant.MW=man Witney test, ST=student T test, KS= Kolmogorov-Smirnov.

Table (4): comparison between patients and control group as regards LA mechanical function parameters

Variables		Patients Group		Control Group		t/z value	p value
Vmax (mm)	Mean±SD	24.46+4.24		24.49+4.21		0.095 MW	0.925
	Median	24.70		24.80			
	IQR	20.65	28.15	20.60	28.03		
Vp (mm)	Mean±SD	13.22+1.28		13.20+1.31		0.054 MW	0.957
	Median	13.35		13.40			
	IQR	12.60	14.18	12.50	14.20		
Vmin (mm)	Mean±SD	7.07+0.97		7.08+0.99		0.027 MW	0.978
	Median	7.20		7.30			
	IQR	6.30	7.93	6.25	7.90		
LA passive emptying Volume (ml/m2)	Mean±SD	10.62+2.51		10.63+2.50		0.054 MW	0.957
	Median	10.50		10.55			
	IQR	8.55	12.50	8.50	12.55		
LA passive emptying Fraction (ml/m2)	Mean±SD	42.72+4.74		43.28+4.57		0.380 ST	0.706
	Median	43.35		43.50			
	IQR	38.10	47.50	38.55	47.75		
Conduit Volume (ml/m2)	Mean±SD	20.81+4.26		21.77+4.11		0.729 ST	0.471
	Median	21.75		20.85			
	IQR	17.38	24.93	18.18	25.90		
LA Active emptying volume (ml/m2)	Mean±SD	6.44+0.76		4.08+0.53		5.403 MW	<0.001
	Median	6.50		4.20			
	IQR	5.80	6.88	3.55	4.40		
LA active emptying fraction	Mean±SD	47.14+2.45		32.69+2.43		5.413 MW	<0.001
	Median	47.50		32.75			
	IQR	45.78	48.85	30.18	35.00		
LA total emptying volume (ml/m2)	Mean±SD	15.96+2.29		15.77+2.16		0.298 MW	0.766
	Median	16.25		15.95			
	IQR	13.63	17.88	13.70	17.55		

Vmax=maximum let atrial volume, VP=presystolic atrial volume, Vmin=minimal left atrial volume, SD=standard deviation, IQR= interquartile range, mm= millimeter, ml/m^2= millimeter per square meter, *P*<0.001= highly significant, *P*>0.05 non significant.MW=Man Witney test, ST=student T test, KS= Kolmogorov-Smirnov.

Table (5): Comparison between patients and the control group as regards the tissue doppler derived parameters of left atrial electromechanical delay

Variables		Control Group		Patients Group		t/z value	*p* value
PA Lateral	Mean±SD	47.50±2.46		55.71±2.08		5.413 MW	<0.001
	Median	47.50		55.75			
	IQR	45.50	49.65	53.75	57.80		
PA septum	Mean±SD	37.38±2.25		38.54±3.25		1.308 ST	0.199
	Median	38.00		38.35			
	IQR	35.28	38.98	36.55	40.68		
PA tricuspid	Mean±SD	50.82±71.51		35.56±2.55		0.953 ST	0.346
	Median	35.55		36.00			
	IQR	33.38	36.68	33.78	37.75		
PA lateral - PA tricuspid	Mean±SD	12.67±2.90		18.04±4.17		3.869 MW	<0.001
	Median	13.10		18.00			
	IQR	10.98	14.90	16.43	19.20		
PA septum - PA tricuspid	Mean±SD	2.43±0.63		3.00±1.41		1.651 AW	0.111
	Median	2.50		3.10			
	IQR	2.00	2.88	1.55	4.10		

PA=time interval between P wave on surface ECG and the late diastolic wave, Lateral=lateral mitral annulus, septum=septal mitral annulus, tricuspid=lateral tricuspid annulus, PA lateral-PA tricuspid=interatrial electro mechanical delay, PA septum-PA tricuspid=intra-atrial electromechanical delay, SD=standard deviation, IQR= interquartile range, *P*<0.001= highly significant, *P*>0.05 non significant.MW=ManWitney test, ST=student T test, KS= Kolmogorov-Smirnov

4. Discussion

Cardiac rhythm disorders are frequent in patients with diabetes mellitus [12]

In the current study the twelve lead ECG showed that the P wave dispersion of the patients (47.8 ±0..90) was significantly higher than that of the

control group (44.48 ± 1.15). P wave dispersion has been used to evaluate the intra and interatrial conduction times and the inhomogenous conduction of sinus impulses which are known electrophysiological markers for the prediction of paroxysmal AF [8,13,14]

Tissue doppler echocardiographic study of our diabetic patients revealed significant interatrial delay as well as significant prolongation of time interval between P wave on surface ECG and the late diastolic wave of mitral valve annulus. To our knowledge this is the first study to assess LA electromechanical delay in children with DM-1. Acar *et al.,* 2009, demonstrated prolonged intra and inter atrial electromechanical delay in adults with DM.[5] The demonstrated electromechanical abnormalities were associated with a higher risk of AF .[12]

Nichols *et al.,* 2009, reported that AF may be relatively common in diabetic patients and should be regarded as a marker of adverse outcome, promoting aggressive management of all risk factors.[3]

Although some studies found a relationship between left atrial dilatation and interatrial electromechanical delay , yet, such a relation was not observed in our study or the study done by Acar *et al.,* 2009[.9,5]

Left ventricular diastolic dysfunction in the form of decreased E/A ratio and increased isovolumetric relaxation time was observed in our studied diabetic patients. This agreed with Form *et al.,* who demonstration evidence of LV diastolic dysfunction in patients with diabetes independent of coronary artery disease or hypertension. [2]

In line with Karamitsos *et al.,* 2007, findings, our patients had impaired right ventricular diastolic function.[15]

The presence of diastolic dysfunction not only suggests that microvascular affection may play a part in development of decreased ventricular compliance, but also alludes to the role of autonomic disregulation and cardiac fibrosis in the etiology of diastolic dysfunction as both are well known consequences of DM.

Data from the strong heart study suggested that DM has independent adverse cardiac effects that may contribute to cardiovascular [16]

It has been suggested that a close relation could exist between glycemic control states and LV diastolic function in patients with DM-1 [17,18]. Moreover, Grandi *et al.,* 2006 reported that diastolic dysfunction can be prevented and reversed by tight glycemic control.[18]

Echocardiographic assessment of left atrial mechanical function of our studied diabetic patients revealed significant increase of LA active emptying volume as well as LA active emptying fraction as compared to the control group. Peterson *et al.,* 2006, demonstrated that in diabetic patients with impaired ventricular diastolic parameters, LA contribution to LV filling and LA systolic EF was increased as compared to the control group.[10]

LA mechanical function is an important determinant of LV filling in patients with diastolic dysfunction and demonstrated LV enlargement capacity .[19]

Conclusion: in the current study children with DM-1 demonstrated increased P wave dispersion as well as inter atrial electromechanical delay which can predispose them to develop AF. Diastolic dysfunction of LV as well as the RV exists in children with DM-1. The LA compensates for LV diastolic dysfunction by increased the LA active emptying volume.

Abbreviations

DM: diabetes mellitus;LA:left atrium ;AF:atrial fibrillation. Vmax=maximum let atrial volume, VP=presystolic atrial volume, Vmin=minimal left atrial volume, PA=time interval between P wave on surface ECG and the late diastolic wave, Lateral=lateral mitral annulus, septum=septal mitral annulus, tricuspid=lateral tricuspid annulus, PA lateral-PA tricuspid=interatrial electro mechanical delay, PA septum-PA tricuspid=intra-atrial electromechanical delay.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

NMH shared in data collection ,shared in echocardiography performance and editing of the manuscript, A A clinically assessed the patients ,shared in editing the manuscript ,OIY shared in echocardiography performance and data collection, did ECG analysis and interpretation of data and shared in editing the manuscript . All authors approved the manuscript

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