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Left ventricular filling patterns and its relation to left ventricular untwist in patients with type 1 diabetes and normal ejection fraction

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ABSTRACT

Background: We evaluated young patients with type 1 diabetes (T1DM) who had normal left ventricular (LV) ejection fraction and used speckle tracking echocardiography to assess changes in LV untwisting. We used cardiac magnetic resonance imaging (MRI) to assess the LV filling patterns in these subjects.
Methods: We recruited 33 T1DM patients and 32 age-matched healthy controls (HC) into the study. Study participants underwent echocardiography, cardiac MRI and metabolic exercise testing.
Results: The early peak LV untwisting rate (E) was similar in T1DM and HC (-11.9 ± 4.6 0/cm/s vs -11.3 ± 4.7 0/cm/s, $P=0.29$) but the late peak LV untwisting rate (A) was significantly increased in T1DM (-6.2 ± 3 0/cm/s vs -4.9 ± 3.9 0/cm/s, $P<0.05$). The time to early peak untwisting rate was not different ($50.9\pm9.6\%$ vs $48.4\pm7.3\%$, $P=0.12$) but the time to late peak untwisting rate was significantly delayed in T1DM patients ($80.4\pm12.5\%$ vs $72.7\pm14.6\%$, $P<0.05$). The LV filling patterns demonstrated a significantly increased left atrial (LA) contribution to LV filling in T1DM. On linear regression peak late filling rate ($r=0.60$, $P<0.000$), trans-mitral A wave ($r=0.25$, $P<0.05$) and A′ ($r=0.30$, $P<0.01$) were predictors of LA contribution to LV filling.
Conclusion: We demonstrate for the first time using speckle tracking that LV untwisting rate E is preserved and untwisting rate A is increased and delayed in young patients with uncomplicated T1DM. The LA contribution to LV filling is increased in these patients and is directly related to increases in other indices of LA function like peak late filling rate, trans-mitral A wave and A′.

1. Introduction

Diabetes is a metabolic disorder characterized by hyperglycemia and insulin deficiency. The prevalence of type 2 diabetes (T2DM) in particular is rapidly increasing throughout the western world [1–3]. Heart failure occurs more frequently in diabetes [4] and although frequently due to coronary artery disease (CAD) [5–7] and/or hypertension, may occur in the absence of these, when it is termed diabetic cardiomyopathy. Although there is increasing evidence for the presence of diabetic cardiomyopathy as a separate entity, detection of early changes in the myocardium is challenging in patients with diabetes. Previous studies with 2D and tissue Doppler echocardiography have demonstrated abnormalities in various diastolic parameters prior to the onset of overt systolic dysfunction [8–10]. Echocardiographic trans-mitral pulsed wave Doppler demonstrates abnormalities in mitral inflow velocity and deceleration time (DecT), isovolumetric relaxation time and filling patterns [11]. In healthy young subjects the majority of left ventricular (LV) filling is accomplished in the early filling phase and the left atrium (LA) contributes the remainder. In heart failure the early phase of filling is hampered by the stiff ventricle [12,13]. In this situation the LA contributes significantly more to LV filling. Similarly there is increased reliance on the LA for LV filling in the presence of diastolic dysfunction. We demonstrated recently that increased LA filling compensates for impaired early relaxation during exercise in patients with heart failure with preserved ejection fraction [14]. LA function may be an important factor in maintaining ejection fraction in the early stages of diabetic cardiomyopathy. Loss of atrial function with the onset of atrial fibrillation may precipitate worsening heart failure in any of the above situations.

In this study we investigated various aspects of LV diastolic function in young T1DM subjects with no underlying heart failure or CAD. Speckle tracking echocardiography has recently been used to measure LV torsion and untwisting. LV untwisting, which follows LV

Abbreviations: T1DM, type 1 diabetes; LV, left ventricular; MRI, magnetic resonance imaging; LA, left atrial; HC, healthy controls; T2DM, type 2 diabetes; CAD, coronary artery disease; DecT, deceleration time; EF, ejection fraction; EDV, end-diastolic volume; ESV, end-systolic volume; PFR, peak filling rates.

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torsion contributes significantly to LV filling. We studied the untwisting patterns in patients with T1DM using speckle tracking echocardiography. The early untwisting corresponds to the early phase of filling and late untwisting corresponds to the LA filling phase. We used cardiac MRI to directly measure LV volumes during the cardiac cycle and hence LV filling patterns in these subjects.

1.1. Aims of the study

1. To assess the LV untwisting patterns and other parameters of diastolic function in type 1 diabetes patients in the absence of CAD and heart failure.
2. To assess the LV diastolic filling patterns in these subjects as compared to healthy controls and calculate the LA contribution to LV filling.
3. To assess the relationship between LA contribution to LV filling and other parameters of LA function and LV diastolic function.

1.2. Hypotheses of the study

1. LV torsion and untwist are altered in patients with type 1 diabetes prior to onset of overt heart failure.
2. Increased reliance on LA for LV filling which is related to the diastolic dysfunction in these subjects with no overt heart failure.
3. Study of LV untwisting patterns and LV filling will provide insights into early changes in diastolic function in diabetes.

2. Methods

This was a prospective study in patients with type 1 diabetes as compared to HC. All subjects were fasted overnight and fasting blood samples were taken. Following this, subjects were allowed to have a light breakfast and the diabetes patients had their morning dose of insulin. All subjects then underwent echocardiography, cardiac MRI and metabolic testing on the same day which completed their participation in the study. All the investigations were undertaken in the University of Birmingham and the project was approved by Multicenter Regional Ethics Committee in Birmingham. Data on LV torsion in these subjects have been published previously by our group [15].

2.1. Patients

We recruited 33 subjects who met the following criteria from the Heart of England NHS Foundation Trust and University Hospital Birmingham NHS Trust, Birmingham, UK:

2.2. Inclusion criteria

- Patients with T1DM according to WHO definition with HbA1C < 10%.
- No history of chest pain or breathlessness.
- No evidence of CAD or heart failure based on history, 12 lead electrocardiogram, a normal ejection fraction (EF) on echocardiography and metabolic exercise testing.
- Above 18 years of age.
- Able to provide informed consent.

2.3. Exclusion criteria

- Less than 18 years of age or unable to provide informed consent.
- Previous history of CAD, heart failure or renal failure.
- Pregnant subjects.

2.4. Healthy controls

32 age and sex matched controls with no cardiac history or diabetes mellitus were recruited. All HC had a normal 12 lead electrocardiogram, echocardiogram and metabolic exercise test. HC were recruited by general adverts in the University of Birmingham and blood banks.

2.5. Echocardiography

Echocardiography was performed with participants in the left lateral decubitus position with a Vivid 7 (GE Vingmed) echocardiographic machine and a 2.5-MHz transducer. Standard echocardiographic views were obtained from parasternal (short axis gray scale images at mitral, papillary and apical levels) and apical (4 and 2 chamber views) windows. Trans-mitral flow profiles and tissue Doppler measurements of mitral annular velocities were performed. The ejection fraction was calculated with Simpson's rule [16]. The left atrial volume was determined using the area-length method. The gray scale images obtained in the parasternal short axis view were used to compute LV rotation using commercially available speckle tracking software on an Echopac system.

2.6. Metabolic exercise testing

Subjects underwent a symptom-limited erect treadmill exercise testing using a standard ramp protocol with simultaneous respiratory gas analysis on a Schiller CS-200 Ergo-Spiro exercise machine. Samplings of expired gases were performed continuously, and data were expressed as 30-second means. Minute ventilation, oxygen consumption, carbon dioxide production, and respiratory exchange ratio (RER) were obtained. Peak oxygen consumption (VO_2 max) was defined as the highest value of oxygen consumption measured during the exercise period. Blood pressure and ECG were monitored throughout. Subjects were encouraged to exercise to exhaustion with a minimal requirement of RER > 1.

2.7. Cardiac MRI

Cardiac MRI was performed on a 3 T Phillips Achieva MRI scanner. The subjects were positioned supine with a dedicated cardiac sense coil wrapped around the chest. The subjects were positioned in the scanner with their heart at the isocenter of the magnet. Survey images were obtained and the short axis images were planned from this. The LV was divided into slices of 8 mm with a gap of 2 mm. A total of 12 slices ensured complete coverage of the LV from apex to base. Short axis cine images were acquired at breath hold using sense cine sequences.

3. Analysis

3.1. Speckle tracking echocardiography (STE)

Myocardial deformation was measured using a commercially available speckle tracking system on an ECHOPAC (version 4.2.0) workstation. In this system, the displacement of speckles of myocardium in each spot was analyzed and tracked from frame to frame. We selected the best-quality digital two-dimensional image and the LV endocardium was traced at end-systole. The region of interest width was adjusted as required to fit the wall thickness. The software package then automatically tracked the motion through the rest of the cardiac cycle. The onset of the QRS complex was taken as the beginning of systole. Adequate tracking was verified in real time. Counter-clockwise rotation was marked as a positive value and clockwise rotation as a negative value when viewed from the apex. In order to calculate LV torsion, torsion rate and untwist rates, the rotation traces of the basal and apical LV cross-sections were exported into DPlot graph software (Version 2.2.1.4, HydeSoft Computing, LLC, Vicksburg, USA). The LV twist curve was generated by calculating the difference between apical and basal rotations at each corresponding time point. LV untwist rates were derived from the first derivative of the LV twist curve (Fig. 1). Peak LV torsion was derived from LV twist divided by LV diastolic longitudinal length. In order to adjust for the differences in heart rate between individuals the RR interval was normalized to 100%. Of the 65 subjects in the study, 61 (94%) subjects had both adequate LV basal and apical images for speckle tracking to complete analysis of all LV rotational parameters.

3.2. Reproducibility of STE

Reproducibility of STE determined within our department using a randomly selected group of 10 controls has been published previously [17]. Inter-observer measurement variability was determined by two independent observers who measured LV torsion in the 10 controls. To obtain the intra-observer variability, the first observer performed the analysis on two separate occasions 1 month apart. We performed Bland–Altman plots to assess variability of measurement. Our results showed that for LV torsion, intra-observer reproducibility was 0.24 ± 0.58 (bias $\pm$ 1.96 standard deviation of the difference (SD)) and inter-observer reproducibility was 0.15 ± 0.69 (bias $\pm$ 1.96 SD), which are acceptable.

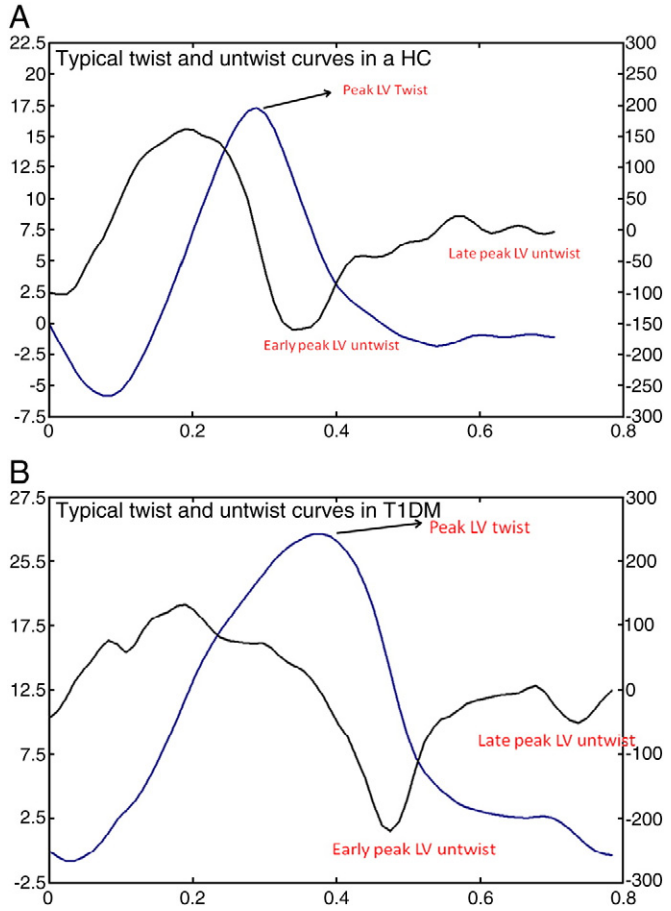

Fig. 1. A typical twist and untwist curve in HC (A) as compared to T1DM (B) HC-healthy control, T1DM – type 1 diabetes mellitus patient.

3.3. LV volumes

LV volumes were computed from the short axis cine MRI images. The images were analyzed on Viewforum software version 5.0. The endocardial and epicardial borders were traced at end diastole in each slice and propagated through the rest of the cardiac cycle. The software generated LV volumes at each phase of the cardiac cycle incorporating all the slices. The LV volume time curves were exported to graphical software Dplot (Fig. 2). The first derivative of the LV volume curve was computed to represent the rate of LV volume changes. Stroke volume (SV) was defined as the difference between end-diastolic volume (EDV) and end-systolic volume (ESV). Early and late peak filling rates (PFR) were defined as the first and second positive peaks of the first derivative curve during diastole. The early and late (atrial) components of LV filling were measured from the corresponding LV volume segments. The early and late (atrial) contributions to LV filling were expressed as percentage of stroke volume (% SV).

4. Statistics

Continuous variables are expressed as means ± standard deviation. Comparison between means was performed using unpaired Student T-tests. Categorical variables were compared with Pearson Chi-Square test. A P value of <0.05 was considered to indicate statistical significance. Variances of data sets were determined using F-test. Pearson correlation coefficient (r) was used to describe the relationship between variables. Variables of interest that were found to correlate with the dependent variable on univariate analysis were included in a stepwise linear regression analysis to identify independent predictors. SPSS (v15.0) was used to perform the statistical operations.

5. Results

The baseline characteristics are summarized in Table 1. LV ejection fraction was 60.7 ± 5% in the T1DM subjects and VO_2 max was 38.5 ± 9.9 ml/kg/min. In the HC, the corresponding values were 61.4 ± 5% (P = 0.29 vs T1DM) and 44.1 ± 7.2 ml/kg/min (P<0.01 vs T1DM), respectively. The mean HBA1c in the diabetic patients was 8 ± 1%. The trans-mitral pulsed wave and tissue Doppler results are summarized in Table 2. Tissue Doppler analysis demonstrated a statistically significant reduction in E′ and E′/A′ with an increase in E/E′ indicating early relaxation abnormality in T1DM subjects as compared to HC. There were also statistically significant increases in trans-mitral A wave velocity and mitral annular A′. The left atrial volume index was significantly increased in T1DM as compared to HC (left atrial volume corrected for body surface area).

5.1. LV untwist

Peak LV torsion was significantly increased in the T1DM as compared to HC (1.9 ± 0.6 vs 1.4 ± 0.7, P<0.01). We noted increase in LV apical rotation and LV twist in T1DM compared with HC (Table 3). The early peak LV untwisting rate was similar in T1DM and HC (−11.9 ± 4.6 0/cm/s vs −11.3 ± 4.7 0/cm/s, P = 0.29). The late peak LV untwisting rate was significantly increased in T1DM (−6.2 ± 3 0/cm/s vs −4.9 ± 3.9 0/cm/s, P<0.05). The time to early peak untwisting rate was not different (50.9 ± 9.6% vs 48.4 ± 7.3%, P = 0.12) but the late peak untwisting rate was significantly delayed in T1DM patients (80.4 ± 12.5% vs 72.7 ± 14.6%, P<0.05).

5.2. LV volumes

The results from the cardiac MRI are summarized in Table 4. The LV ejection fraction and stroke volume were similar in T1DM and HC. The early peak filling rate was slightly higher where as the late peak filling rate was significantly higher in the T1DM as compared to HC. The LV filling patterns demonstrated a significantly increased LA contribution to LV filling in T1DM. Although the total diastolic period (as a percentage of the RR interval) was similar, T1DM patients spent less time in early filling and significantly longer time in atrial filling.

5.3. Correlation and linear regression

Left atrial contribution to LV filling correlated positively with LV torsion (r = 0.39, P<0.05), trans-mitral A wave (r = 0.58, P<0.00), A′ (r = 0.56, P<0.00), E/E′ (r = 0.32, P<0.05), and peak late filling rate (r = 0.80, P<0.000) and negatively with E′/A′ (r = −0.54, P<0.000) and E′ (r = −0.40, P<0.01). On linear regression peak late filling rate (r = 0.60, P<0.000), trans-mitral A wave (r = 0.25, P<0.05) and A′ (r = 0.30, P<0.01) were predictors of left atrial contribution to LV filling.

6. Discussion

The principal findings in this study are as follows: a) LV untwist rate A and time to LV untwist rate A were increased in young patients with T1DM as well as other indices of left atrial function (trans-mitral A wave and A′), b) left atrial contribution to LV filling was increased in these patients, and c) peak late filling rate, trans-mitral A wave and A′ were predictors of the left atrial contribution to LV filling.

LV torsion is the net result of counter-clockwise rotation of the base with respect to clockwise rotation of the apex along the long axis of the LV. Normally LV torsion contributes significantly to an energy-efficient ejection during systole [18,19]. LV untwisting which follows LV twist is a key determinant of LV filling. It helps to generate the intra-ventricular pressure gradient during isovolumetric

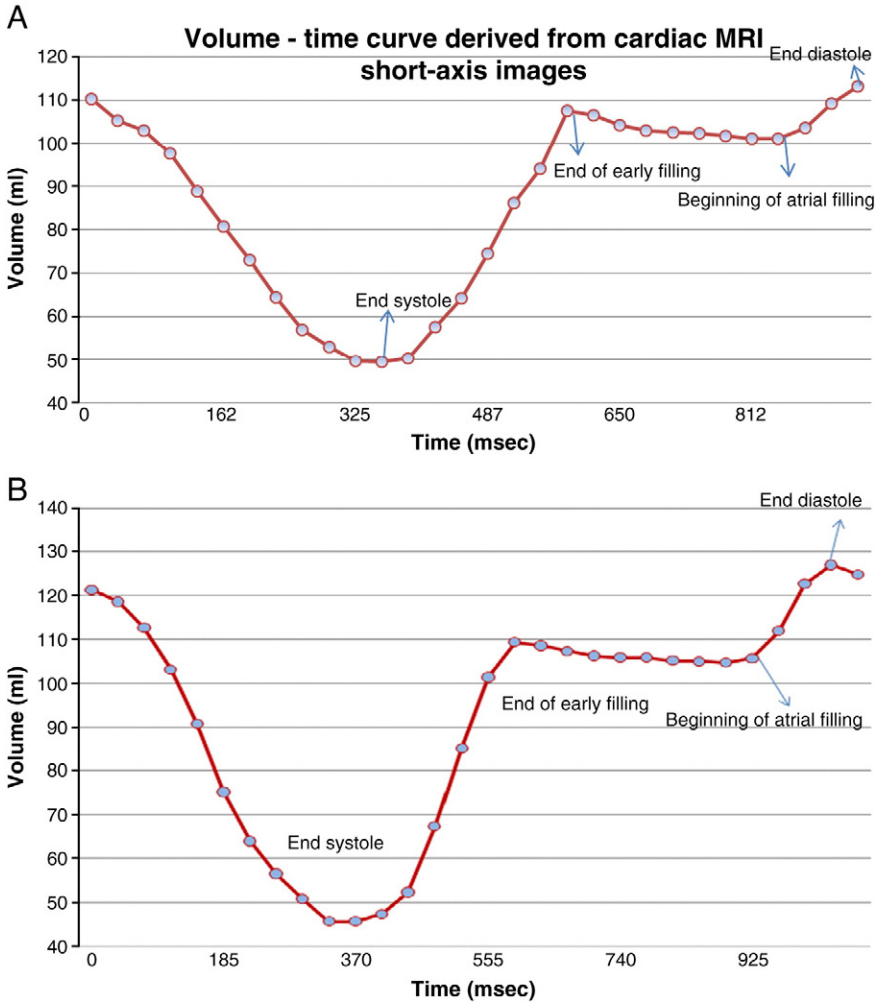

Fig. 2. Typical left ventricular filling curves in a healthy control (A) as compared with type 1 diabetes patient (B).

relaxation thus creating a suction effect to allow early diastolic filling to occur once the mitral valve opens [20]. In this study, we found that early LV untwist was preserved. This might be as a direct result of increased LV torsion which creates the potential energy for early untwisting. The late LV untwist was increased indicating augmented atrial contraction. In a previous study in diabetes patients the transmitral A wave was increased in subjects associated with impaired relaxation [11]. This is similar to our findings of increased indices of atrial function like increased trans-mitral A wave and A′. Also a recent study in T1DM patients demonstrated changes in LA transport function suggesting increased reliance on LA for LV filling [21].

Our study has demonstrated abnormalities in early diastolic filling. This is suggested by a reduced E′ and E′/A′ and an increased E/E′ on tissue Doppler analysis. Previously various studies have demonstrated early relaxation abnormalities as the precursors of heart failure in diabetes [9,10,22]. A recent study has demonstrated that E/E′ is a predictor of mortality in diabetic patients without heart failure who were

Table 1
Baseline characteristics and results in T1DM patients as compared with HC. The results are expressed as mean ± standard deviation.

Variable	T1DM	HC	P value
Number	33	32	ns
Female gender (%)	11 (33)	10(31)	ns
Age, years	33 ± 9	30 ± 8	0.13
BMI, kg/m^2	24 ± 3	25 ± 3	0.25
Resting heart rate, beats/min	82 ± 16	77 ± 11	0.09
Systolic blood pressure, mm Hg	119 ± 13	112 ± 10	<0.05
Diastolic blood pressure, mm Hg	75 ± 10	70 ± 10	0.06
VO_2 max, ml/kg/min	38.5 ± 9.9	44.1 ± 7.2	<0.01
VO_2 max, percentage predicted	98.6 ± 16	112.2 ± 16	<0.001
RER	1.2	1.2	0.12
Ejection fraction, %	60.7 ± 5	61.4 ± 5	0.29
HbA1C, %	8 ± 1	–	–
Duration of diabetes, years	13.5 ± 9.3	–	–
Fasting plasma glucose, mmol/l	8.6 ± 3.3	4.5 ± 0.4	<0.000
Total cholesterol, mmol/l	4.4 ± 0.9	4.9 ± 0.9	<0.05
HDL, mmol/l	1.6 ± 0.4	1.7 ± 0.6	0.44

P < 0.05 was considered as statistically significant.

Table 2
Mitral and tissue Doppler measurements in T1DM patients as compared with HC. The results are expressed as mean ± standard deviation.

Variable	T1DM	HC	P value
Ejection fraction, %	60.7 ± 5	61.4 ± 5	0.29
LA volume index, ml/m^2	25 ± 6.9	21.7 ± 4.9	<0.05
MV E velocity, cm/s	79.7 ± 13	77.4 ± 15	0.26
MV A velocity, cm/s	58.4 ± 15	49.1 ± 10	<0.01
E/A ratio	1.4 ± 0.5	1.6 ± 0.5	0.06
Dec time, ms	252 ± 57	248 ± 66	0.38
IVRT, ms	72 ± 11	72 ± 12	0.47
TDI peak S, cm/s	8.9 ± 2	9.4 ± 2	0.19
TDI peak E′, cm/s	10.6 ± 2	12.2 ± 2	<0.01
TDI peak A′, cm/s	8.6 ± 2	7.8 ± 2	0.05
E/E′	7.7 ± 1	6.4 ± 2	<0.001
E′/A′	1.8 ± 0.6	2.1 ± 0.8	<0.05

P < 0.05 was considered as statistically significant.

Table 3
LV torsion and untwist measurements in T1DM patients as compared with HC. The results are expressed as mean ± standard deviation.

Variables	T1DM	HC	P
Peak apical rotation, °	11.3 ± 4.4	8.5 ± 4	<0.01
Peak basal rotation, °	−5.8 ± 2.6	−4.9 ± 2.5	0.09
Peak LV twist, °	15.3 ± 4.4	11.3 ± 6	<0.01
Peak LV torsion, °/cm	1.9 ± 0.6	1.4 ± 0.7	<0.01
Peak twist rate S, °/s	12.7 ± 5.1	10.9 ± 4.8	0.08
Peak untwist rate E, °/s	−11.9 ± 4.6	−11.3 ± 4.7	0.29
Peak untwist rate A, °/s	−6.2 ± 3	−5 ± 3.9	<0.05
Time to untwist rate E, %[a]	50.9 ± 9.6	48.4 ± 7.3	0.12
Time to untwist rate A, %[a]	80.4 ± 12.5	72.7 ± 14.6	<0.05

P<0.05 was considered as statistically significant.
[a] Expressed as % of RR interval.

followed up for more than 10 years [23]. The early relaxation abnormalities result in impaired early LV filling and probably represent one of the earliest functional changes in the left ventricle.

To the best of our knowledge this is the first study that investigates the LV filling patterns in T1DM patients with normal ejection fraction using LV volumes measured by cardiac MRI. The ejection fraction, stroke volume, end-diastolic and end systolic volume were all similar in both T1DM patients and HC. However the late peak filling rate was significantly increased in T1DM patients suggesting increased trans-mitral gradient produced by augmented LA contraction. This resulted in increased LA contribution to LV filling. This increased contribution of LA to LV filling helps to maintain adequate LV filling and hence generate appropriate stroke volume. Hence the ejection fraction is maintained at this time despite abnormal early filling. The augmented LA function appears to be the key compensatory mechanism at this point. The early relaxation abnormality is likely to worsen on exercise and hence the reliance on LA for LV filling will only increase. The increase in LA function is noticed in early stages of heart failure. However, with worsening LV dysfunction LA dilates and this compensation is lost worsening the situation. We hereby demonstrate the key role LA may play in the pathogenesis of cardiac dysfunction in T1DM patients.

6.1. Clinical implications

Development of heart failure in diabetes is a complex process and is affected by many secondary factors like hypertension, CAD, renal disease and hyperlipidemia. We have shown in our study that LA probably plays a key functional role in compensating early relaxation abnormalities in patients who still have normal ejection fraction. Therefore assessment of left atrial function is an important step in evaluating these patients. Loss of atrial function may predict the onset of overt heart failure.

Table 4
LV volume results in T1DM (whole group) as compared with HC expressed as mean ± standard deviation.

Variables	T1DM	HC	P
Peak emptying rate, ml/ms	0.35 ± 0.1	0.31 ± 0.1	0.08
Time to peak emptying rate, ms	148 ± 30	166 ± 0.2	<**0.05**
Peak early filling rate, ml/ms	0.44 ± 0.14	0.40 ± 0.10	0.19
Peak late filling rate, ml/ms	0.19 ± 0.07	0.15 ± 0.05	<**0.05**
Early filling contribution, %	75.6 ± 8.9	80.7 ± 7.1	<**0.05**
Late filling contribution, %	24.4 ± 8.9	19.3 ± 7.1	<**0.05**
Total systolic time, %	37.5 ± 5.1	37.5 ± 5.5	0.48
Total diastolic time, %	62.5 ± 5.1	62.5 ± 5.5	0.48
Total early filling time, % of diastole	71.6 ± 7.2	76.9 ± 4.8	<**0.01**
Total late filling time, % of diastole	28.4 ± 7.2	23.1 ± 4.8	<**0.01**
Ejection fraction, %	60.3 ± 6.7	59.7 ± 4	0.14
End diastolic volume, ml	117.1 ± 29	113 ± 20	0.30
End systolic volume, ml	47.4 ± 17.1	45.9 ± 10.9	0.36
Stroke volume, ml	69.6 ± 14.6	67.1 ± 11.4	0.26
Cardiac output, l/min	4.5 ± 1.3	4.1 ± 0.69	0.07
Left ventricular mass	98.2 ± 27.2	95.3 ± 22	0.33

P<0.05 was considered as significant.
LV — left ventricle, T1DM — type 1 diabetes mellitus, HC — healthy control.

6.2. Study limitations

One of the main drawbacks of the study was the small sample size of the study population. Also patients were studied at rest. It will be interesting to study LA function on exercise.

Disclosures

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