Assessment of left ventricular function in young type 1 diabetes mellitus patients by two-dimensional speckle tracking echocardiography: Relation to duration and control of diabetes

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Abstract
Background: The effect of type 1 diabetes mellitus (T1DM) on myocardial function is still controversial.
Aim: To examine the usefulness of speckle tracking echocardiography (STE) in detecting subclinical left ventricular (LV) dysfunction in asymptomatic T1DM patients and detect whether any LV abnormalities are related to duration or control of DM.
Methods: Sixty young T1DM patients and 30 controls were subjected to conventional echocardiography and STE. The left ventricular (LV) peak systolic (PS) global longitudinal strain (GLS)/strain rate (GLSR) and diastolic global strain rate during the isovolumic relaxation period (GSRivr), early diastole (GSRe) and late diastole (GSRa) were calculated as the average of the 12 myocardial segments of the four and two-chamber views while the mid circumferential strain (MCS) was calculated as the average of strains of the 6 LV segments of the mid LV cavity.
Results: In diabetic patients, the LV end diastolic dimension (LVEDD) was significantly lower ($p = 0.000$) while the LV myocardial performance index (LVMPI) and E/lateral E ratio were significantly higher ($p = 0.000$ and $p = 0.02$ respectively) compared to controls. By STE, only the GLS was significantly lower in diabetic patients compared to controls ($p = 0.000$). A significant

KEYWORDS
Left ventricular function; Speckle tracking echocardiography; Type 1 diabetes mellitus; Control of diabetes; Duration of diabetes

Abbreviations: A/C ratio, albumin/creatinine ratio; EF, ejection fraction; GLS, global longitudinal strain; GLSR, global longitudinal strain rate; GSRa, diastolic global strain rate during late diastole; GSRe, diastolic global strain rate during early diastole; GSRivr, diastolic global strain rate during the isovolumic relaxation period; HbA1c, glycosylated hemoglobin; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; LV, left ventricular; LVEDD, left ventricular end diastolic dimension; LVMPI, myocardial performance index; STE, speckle tracking echocardiography; T1DM, type 1 diabetes mellitus; TC, total cholesterol; TG, triglycerides
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negative correlation was detected between LDL-C and GLS ($r = -0.4; p = 0.002$). Multivariate logistic regression analysis identified HbA1c as the only independent predictor of GLS in patients (beta = $-0.34$, 95% CI: $-0.67$ to $-0.19; p = 0.001$).

**Conclusion:** STE is useful to detect subclinical LV dysfunction in asymptomatic patients with T1DM. Control of DM but not duration of disease was an independent predictor of LV systolic dysfunction.

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1. Introduction

Type 1 diabetes mellitus (T1DM) is potentially associated with serious microvascular and macrovascular complications, although these are usually subclinical during the pediatric and adolescent years. The duration of diabetes, glycemic control, age, and pubertal stage are critical factors contributing toward development of such complications.$^{1,2}$ T1DM is associated with at least 10-fold increase in cardiovascular disease as compared with an age matched non-diabetic population.$^{3,4}$ Diabetes does not only result in abnormalities of the vasculature but also induces structural and functional abnormalities of the myocardium “diabetic cardiomyopathy”.$^{5–7}$ The incidence of diabetic cardiomyopathy in the absence of coronary artery disease (CAD) or systemic hypertension (HTN) in T1DM however, is still controversial. Asymptomatic children and adolescents with T1DM showed evidence of subclinical right ventricle (RV) and left ventricle (LV) diastolic dysfunction that correlated with the degree of insulin resistance, duration of DM, and metabolic control.$^{8,9}$ Cardiac magnetic resonance performed on T1DM patients of the mega study Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) revealed that macroalbuminuria and mean glycosylated hemoglobin (HbA1c) were significantly associated with myocardial scar and alterations of LV structure and function.$^{10,11}$ In contrast to these results, a study of patients with long duration (>10 years) T1DM revealed no significant differences in echocardiographic diastolic or systolic LV function indices or serum level of N-terminal pro-B type natriuretic peptide (NT-pro BNP) between patients and non-diabetic controls despite historical changes typical of diabetes detected in hearts of some of the study deceased patients.$^{12}$ Speckle tracking echocardiography (STE) has emerged as an accurate quantitative technique to assess global and regional myocardial deformation parameters, being independent of both cardiac translation and insonation angle.$^{13,14}$ The assessment of myocardial deformation allows early detection of subclinical LV systolic and diastolic dysfunction in different cardiac diseases.$^{15–17}$ The aim of this study was to examine the usefulness of two-dimensional STE in detecting subclinical LV dysfunction in asymptomatic T1DM patients before overt clinical diabetic cardiomyopathy ensues and to detect whether any detected LV abnormalities are related to duration or control of DM.

2. Methods

2.1. Study population

We included in the study 60 asymptomatic T1DM patients without known cardiovascular disease, have never smoked and with an LV ejection fraction >55% by biplane Simpson’s method. T1DM was defined as being diagnosed in patients before the age of 30, and treated by insulin from the beginning of treatment.$^{18}$ We excluded patients with hypertension defined as blood pressure $\geq 140/90$, CAD, moderate to severe valvular heart disease, congenital heart disease and atrial fibrillation or other severe arrhythmias. The patients were recruited from those admitted in the National Institute of Diabetes and Endocrinology. The control group comprised 30 age and sex-matched, healthy non-diabetic, normotensive and never smoker subjects with no other comorbid conditions.

2.2. Methods

2.2.1. Clinical evaluation

All the patients and controls were subjected to full history taking, clinical examination and measurement of weight and height to calculate the body mass index (BMI). The BMI was calculated by the formula: $\text{BMI} = \text{weight in kilograms}/(\text{height in meters})^2$. Waist circumference (WC) was measured with a non-elastic tape at the mid distance between the top of the iliac crest and the bottom of the rib cage and as the average of one measurement taken after inspiration and one taken after expiration.

2.2.2. Laboratory investigations

A 14-h fasting peripheral venous blood sample was taken from patients and controls in order to measure total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), and triglycerides (TG). Low density lipoprotein cholesterol (LDL-C) was estimated using the Friedwald formula $[\text{LDL-C} = \text{TC} – (\text{HDL-C} + \text{TG}/5)]$ if the TG were $<400 \text{mg/dl}$. If the TG were $\geq400 \text{mg/dl}$, the LDL-C was directly determined. An 8-h peripheral venous blood sample was also taken in another day from all patients in order to measure fasting blood sugar (FBS). Serum urea, creatinine, HbA1c, and albumin creatinine (A/C) ratio in urine were also measured.

2.2.3. Conventional echocardiography and tissue Doppler imaging

All echocardiographic examinations were obtained using Mylab 60 XVision machine (Esaote, Italy) and performed according to the recommendations of American Society of Echocardiography.$^{20}$ The left atrium and aortic root dimensions were measured in the left parasternal long axis view. Left ventricular diameters and wall thicknesses were measured in the left parasternal long axis view at the level of the mitral valve tips, ensuring a measurement perpendicular to the long axis of the ventricle. Pulsed wave Doppler was used to record trans-mitral flow at the tips of the mitral leaflets in the
four-chamber (4-CH) apical view as well as the trans-aortic flow in the five-chamber (5-CH) apical view. Peak velocity of early (E) and late atrial (A) diastolic filling of the Doppler mitral flow, E/A ratio and E wave deceleration time (E-DT) were calculated. LVEF was determined using modified biplane Simpson’s method in the 4-CH and the two-chamber (2-CH) apical views. The tissue Doppler imaging (TDI) was performed using transducer frequencies of 3.5-4.0 MHZ, adjusting the spectral pulsed Doppler signal filters to obtain the Nyquist limit of 15 and 20 cm/s, and using the minimal optimal gain to minimize noise. TDI was recorded at 100 mm/s sweep speed. Meticulous care was taken to align the echocardiographic image to place the annular motion parallel to the TDI cursor (angle <15°). In the apical 4-CH view, a 5 mm Doppler sample volume was placed at the lateral border of the mitral annulus. From the TDI tracing, the following measurements were obtained:

- Peak diastolic velocity during early filling (E’), late filling (A’) and peak systolic velocity (S).
- Ratio between peak diastolic velocities of lateral annulus E’ and A’ waves or E’/A’ ratio.
- Isovolumic contraction time (IVCT) measured as the time interval between the end of late diastolic A’ wave and the onset of the systolic S wave.
- Isovolumic relaxation time (IVRT) measured as the time interval between the end of the systolic S wave and the onset of the early diastolic E’ wave.
- Ejection time (ET) measured as the time interval between the onset and the end of the S wave.
- Left ventricular myocardial performance index (MPI) was calculated according to the formula: MPI = IVRT / IVCT/ET.
- Doppler trans-mitral peak E wave velocity/tissue Doppler lateral mitral annulus peak E’ wave velocity ratio (E/E’ ratio).

2.2.4. Speckle tracking echocardiography

STE was used to measure different LV deformation parameters according to the recommendations of the American Society of Echocardiography.21 The machine ‘Esaote Mylab 60 Xvision’ we used in the current study uses a specific technology ‘velocity vector imaging’ to track the grayscale image speckles. Three consecutive end-expiratory cardiac cycles using high frame rate >80 s⁻¹ harmonic imaging were acquired in the apical 4-CH, 2-CH and the short-axis (SAX) mid-ventricular view at the level of the papillary muscles. The STE analysis was performed offline on grayscale images of the LV obtained in these views. The analysis was initiated by defining manually in the apical views three endocardial landmarks at the lateral and medial corners of the mitral annulus and the LV cardiac apex and in the mid ventricular SAX view, two landmarks at the inferior septum and the lateral wall. Thereafter, the endocardium and epicardium were delineated and the region of interest was divided into 6 segments automatically by the machine software. Manual adjustment of the segments of interest was performed when necessary. Once the regions of interest were optimized, the software generates automatically strain curves for different myocardial segments. From the apical 4-CH view, longitudinal strain/strain rate (LS/LSR) was assessed through basal, mid, apical inferior septal and basal, mid and apical antero-lateral wall segments. From the apical 2-CH view, LS/LSR was assessed through basal, mid, apical inferior wall and basal, mid, and apical anterior wall segments. The peak systolic (PS) global longitudinal strain/strain rate (GLS/GLSR) was calculated as the average of the LS/LSR of the 12 myocardial segments of the 4-CH and 2-CH views. The global peak diastolic SR during the isovolumic relaxation period (GSRivr), early diastole (GSRe) and late diastole (GSRa) was also calculated as the average of the SR of the 12 myocardial segments of the 4-CH and 2-CH views. From the short axis view at the level of the papillary muscles, the circumferential strain (CS) was assessed through the mid-segments of the antero-septal, anterior, antero-lateral, infero-lateral, inferior, and infero-septal walls. The PS mid circumferential strain (MCS) was calculated as the average of strains of the 6 LV segments of the mid LV cavity short axis view.

3. Statistical analysis

Normally distributed continuous variables were expressed as mean ± standard deviation (SD) while continuous variables with non-normal distribution were presented as median values and interquartile range (IQR). Categorical data were expressed as percentages. Differences between groups were assessed by unpaired 2-tailed t test and the Mann–Whitney U test for continuous variables, according to whether they were normally distributed or not. Categorical data and proportions were analyzed by the use of chi-square or Fisher’s exact test when required. Correlations were sought using the Spearman and Pearson correlation analyses where appropriate to determine correlation between different demographic, clinical and STE parameters. Univariate and multivariable linear regression analysis was used to investigate possible association between different clinical, laboratory, conventional echocardiographic, TDI parameters and STE LV deformation parameters in patients. All analyses were performed using SPSS software (SPSS system for Windows, version 20. Inc. Headquarters. Chicago, IL).

4. Results

4.1. Demographic and clinical data

The mean age of the patients was 21.08 ± 5.7 years. The mean duration of the disease was 9.5 ± 6.66 years. The patients had significantly lower weight, height, WC, and BMI compared to control subjects (p = 0.001, p = 0.001, p = 0.002 and p = 0.000 respectively). There was no statistically significant difference between patients and control subjects as regards age, gender, systolic or diastolic blood pressure (Table 1).

4.2. Laboratory data

The patients had significantly higher FBS, HbA1c, HDL-C and A/C ratio in urine compared to control subjects (p = 0.000, p = 0.000, p = 0.01 and p = 0.000 respectively). There was no statistically significant difference between patients and control subjects as regards serum urea, creatinine, TC, LDL-C and TG (Table 2). Thirty three (55%) out of 60
patients had no albuminuria. The remaining patients had micro or macro-albuminuria.

4.3. Conventional echocardiography and tissue Doppler imaging data

The patients had significantly lower aortic root dimensions and left ventricular end diastolic dimensions (LVEDD) compared to control subjects (both $p = 0.000$). There was no statistically significant difference between patients and control subjects as regards left ventricular end systolic dimensions (LVESD), interventricular septal thickness, posterior wall thickness, LV fractional shortening percent (FS%) or LV ejection fraction percent (EF%).

The patients had significantly higher Doppler trans-mitral peak A wave velocity and significantly lower E-DT compared to control subjects ($p = 0.003$ and $p = 0.000$ respectively). There was no statistically significant difference between patients and control subjects as regards trans-mitral peak E wave velocity and E/A ratio.

The patients had significantly higher tissue Doppler (TD) derived IVRT, IVCT, MPI and significantly lower ET compared to control subjects (all $p = 0.000$). The patients had significantly higher E/E' ratio compared to control subjects ($p = 0.017$). There was no statistically significant difference between patients and control subjects as regards mitral lateral annulus E', A', S wave peak velocities or E'/A' ratio (Table 3).

4.4. Speckle tracking echocardiography data

The patients had significantly lower GLS compared to control subjects ($p = 0.000$). There was no statistically significant difference between patients and control subjects as regards GLSR, MCS, GSRivr, GSRe and GSRa (Table 4) (Figs. 1–3).

4.5. Correlation analysis

Pearson correlation analysis was used to detect possible correlation between disease duration, TC, LDL-C, HDL-C, urinary albumin/creatinine ratio, HbA1c, LVEDD, peak A wave velocity, LV MPI, E/lateral E' ratio and GLS in patients. A significant negative correlation was detected between LDL-C and GLS ($r = -0.4; p = 0.002$). Multivariable logistic regression analysis identified HbA1c as the only independent predictor of GLS in patients (beta = -0.34, 95% CI: -0.67 to -0.19; $p = 0.001$).

Again, no significant correlation could be detected between duration of the disease or HbA1c and IVRT, E/lateral E' or LV MPI.

5. Discussion

In this study, we have demonstrated subclinical impairment of diastolic and systolic global LV function in young asymptomatic T1DM patients without evident cardiovascular disease. We also identified glycemic control as the only independent predictor of peak systolic GLS which was significantly reduced in diabetic patients compared to controls.

The patients with T1DM in our study had significantly lower weight, height, WC, and BMI compared to control subjects. This can be explained by the catabolic effect of DM in these young patients with poor glycemic control (mean HbA1c was 9.77 ± 1.42) and in whom diet control is usually difficult.2 The patients had significantly lower aortic root

### Table 1 Demographic and clinical data of patients and control subjects.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (N = 60)</th>
<th>Control subjects (N = 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>21.08 ± 5.7</td>
<td>23.60 ± 6.62</td>
<td>0.066</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>28/32</td>
<td>17/13</td>
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</tr>
<tr>
<td>Weight (Kg)</td>
<td>60.88 ± 11.05</td>
<td>73.02 ± 13.26</td>
<td>0.001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.99 ± 7.70</td>
<td>168.32 ± 7.0</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>22.87 ± 3.80</td>
<td>25.68 ± 3.83</td>
<td>0.000</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>80.95 ± 8.06</td>
<td>86.55 ± 9.6</td>
<td>0.002</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>120.50 ± 15.72</td>
<td>120.23 ± 7.23</td>
<td>0.95</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>77.33 ± 4.91</td>
<td>76.82 ± 5.61</td>
<td>0.62</td>
</tr>
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</table>


### Table 2 Laboratory data of patients and control subjects.

<table>
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<th>Patients (N = 60)</th>
<th>Control subjects (N = 30)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>FBG (mg/dl)</td>
<td>260.52 ± 68.65</td>
<td>79.55 ± 9.53</td>
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</tr>
<tr>
<td>Urea (mg/dl)</td>
<td>19.25 ± 8.31</td>
<td>18.36 ± 6.20</td>
<td>0.52</td>
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<tr>
<td>Creatinine (mg/dl)</td>
<td>1.18 ± 2.75</td>
<td>0.70 ± 0.128</td>
<td>0.41</td>
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<tr>
<td>TC (mg/dl)</td>
<td>198.73 ± 47.26</td>
<td>180.18 ± 44.36</td>
<td>0.07</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>107.92 ± 42.90</td>
<td>104.41 ± 41.26</td>
<td>0.09</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>61.75 ± 26.88</td>
<td>52.14 ± 11.96</td>
<td>0.01</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>135.38 ± 90.15</td>
<td>116.82 ± 58.45</td>
<td>0.42</td>
</tr>
<tr>
<td>A/C ratio (mg/gm)</td>
<td>184.26 ± 400.02</td>
<td>11.27 ± 1.78</td>
<td>0.000</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>9.77 ± 1.43</td>
<td>5.25 ± 0.16</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Conventional echocardiography and tissue Doppler imaging data of patients and control subjects.

<table>
<thead>
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<th>Variable</th>
<th>Patients (N = 60)</th>
<th>Control subjects (N = 30)</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td><strong>LA (cm)</strong></td>
<td>3.07 ± 0.43</td>
<td>3.09 ± 0.47</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>AO (cm)</strong></td>
<td>2.29 ± 0.294</td>
<td>2.59 ± 0.418</td>
<td>0.000</td>
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<tr>
<td><strong>LVDD (cm)</strong></td>
<td>4.39 ± 0.50</td>
<td>4.76 ± 0.38</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>LVESD (cm)</strong></td>
<td>2.855 ± 0.53</td>
<td>2.99 ± 0.48</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>IVST (cm)</strong></td>
<td>0.751 ± 0.124</td>
<td>0.71 ± 0.15</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>PWT (cm)</strong></td>
<td>0.716 ± 0.11</td>
<td>0.73 ± 0.16</td>
<td>0.64</td>
</tr>
<tr>
<td><strong>FS (%)</strong></td>
<td>38.87 ± 25.71</td>
<td>35.73 ± 4.59</td>
<td>0.23</td>
</tr>
<tr>
<td><strong>LVEF (%)</strong></td>
<td>64.72 ± 8.03</td>
<td>64.77 ± 6.09</td>
<td>0.76</td>
</tr>
<tr>
<td><strong>GLS (%)</strong></td>
<td>19.2 ± 2.02</td>
<td>0.000</td>
<td></td>
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Tissue doppler imaging

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (N = 60)</th>
<th>Control subjects (N = 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IVRT (ms)</strong></td>
<td>75.37 ± 19.06</td>
<td>56.59 ± 5.97</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>IVCT (ms)</strong></td>
<td>69.77 ± 17.34</td>
<td>56.32 ± 7.81</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>MTR (ms)</strong></td>
<td>251.32 ± 36.76</td>
<td>282.82 ± 22.34</td>
<td>0.000</td>
</tr>
<tr>
<td>** MPI**</td>
<td>0.58 ± 0.18</td>
<td>0.39 ± 0.04</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>IVRT</strong></td>
<td>17.5 ± 3.7</td>
<td>18.61 ± 4.1</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>IVCT</strong></td>
<td>9.75 ± 3.36</td>
<td>10.14 ± 2.23</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>E/A ratio</strong></td>
<td>1.76 ± 0.55</td>
<td>1.94 ± 0.68</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>IVRT</strong></td>
<td>13.0 ± 4.38</td>
<td>12.61 ± 2.36</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>IVCT</strong></td>
<td>5.14 ± 1.52</td>
<td>4.62 ± 0.89</td>
<td>0.02</td>
</tr>
</tbody>
</table>


GLS: global longitudinal strain. MCT: mean circunferential strain. GLSR: global longitudinal strain rate. GSRr: global strain rate during isovolumic relaxation period. GSR: global strain rate during early diastole. GSRa: global strain rate during late diastole.

As regards indices of LV systolic function, diabetic patients in our study had significantly higher trans-mitral Doppler peak A wave velocity, E/lateral E' ratio and IVRT compared to control subjects. These results were in agreement with the study by Wojcik et al.9 who used conventional Doppler echocardiography to demonstrate a significant prolongation of IVRT and decrease in the trans-mitral Doppler peak E wave velocity and E/A ratio despite normal systolic LV function in T1DM pubertal patients compared to controls. In their study, the abnormalities of diastolic function correlated with the degree of insulin resistance and DM duration in girls, and similarly as in boys, with the long term metabolic control of the disease as represented by the mean HbA1c over the entire treatment period. Using TDI, Salem et al.9 reached similar results by demonstrating significantly lower mitral annular E' velocity and E/A' ratio which were associated with higher HbA1c in T1DM patients compared to controls. Another TDI study24 revealed a significantly lower septal E', lateral E and significantly higher E/septal E' and E/lateral E' ratios in diabetic patients compared to controls. In this study, DM duration and complications but not HbA1c correlated with impaired LV diastolic parameters. A significantly increased E/E' ratio in T1DM patients compared to controls was also demonstrated to correlate significantly with advanced glycaion end products.27 In our study, we elected to measure the lateral E' velocity as it correlates better with LV filling pressure in the setting of a normal ejection fraction.28 We could not find however any significant correlation between DM duration or HbA1c and trans-mitral A wave, IVRT, or E/Lateral E' ratio in our patients. Similarly, de Simone et al.29 showed no correlation between presence of target organ damage, duration of disease or levels of glycosylated hemoglobin and LV diastolic abnormalities detected in T1DM patients. Discordant to our findings, certain studies did not recognize diastolic dysfunction in T1DM. Romanens et al.30 assessing T1DM patients described as being free of autonomic neuropathy, major micro or macrovascular complications and without evidence of ischemic heart disease or hypertension, found no evidence of diastolic dysfunction in these patients. In a study12 of T1DM patients with long disease duration (mean duration 23 years), none of the patients showed evidence of impaired diastolic function despite a statistically significant difference in the pulmonary venous S/D and the TDI E/E' ratios between patients and controls. There was also no significant difference in serum level of N-terminal pro-B type natriuretic peptide between patients and control subjects.

As regards indices of LV systolic function, diabetic patients in our study had significantly lower LV GLS despite similar
LV EF compared to controls. This finding was in agreement with the results of several studies. A study of T1DM patients without significant coronary stenosis by coronary angiography revealed a significantly reduced LV longitudinal strain by STE. They attributed this impaired LV longitudinal function to myocardial microangiopathy as evidenced by a significantly lower myocardial blood flow reserve detected by contrast echocardiography compared to controls. Abdel-Salam et al. demonstrated a significantly reduced GLS and GLSR in T1DM patients compared to controls despite similar global longitudinal early diastolic strain rate (GLSRe) in both groups. In the present study, we could not find as well a
significant difference in the diastolic deformation parameters GLSivr, GLSe or GLSa between patients and controls. A large study on 1065 T1DM patients revealed a significantly reduced GLS compared to controls. When the patients were stratified by degrees of albuminuria, this difference was shown to be driven solely by decreased GLS in T1DM patients with albuminuria. T1DM patients with no albuminuria had systolic myocardial function similar to healthy control subjects. In our study, 45% of the patients had some degree of albuminuria. We could not however, detect any correlation between the urinary A/C ratio and GLS. Kim and Kim assessing LV function of T1DM Korean children and adolescents, demonstrated a reduced regional strain and strain rates at the basal and mid septum of patients with DM duration > 4 years compared to patients with shorter disease duration. In the current study, we could identity metabolic control of DM as represented by HBA1c, but not diabetes duration as an independent predictor of GLS. Hyperglycemia has been shown to result in a dysfunctional sarcoplasmic reticulum (SR), leading to reduced sequestration of calcium into the SR causing a prolonged cardiac relaxation, reduced systolic calcium release and therefore a weaker cardiac contraction. Another explanation for this impaired longitudinal deformation is the effect of a diseased coronary microvasculature on the sub-endocardial region which is most vulnerable to ischemia. Since longitudinal myocardial fibers predominate in the sub-endocardial region, it is expected that longitudinal deformation abnormalities are both sensitive and specific for the early detection of subclinical LV dysfunction in these patients.

Finally, the current study showed an impairment of LV global function as evidenced by a significantly higher MPI in patients compared to control subjects. A higher LV MPI was similarly detected in the study of Salem et al. on T1DM children and adolescents. This higher MPI is a reflection of significantly higher IVRT and IVCT and significantly lower ejection time in our patients. The isovolumic contraction time corresponds to when calcium enters the myoplasm from the sarcolemma, while isovolumic relaxation time reflects the removal of Ca$^{2+}$ from the myoplasm by Ca$^{2+}$-ATPases. It seems that changes in cellular Ca$^{2+}$ handling in the myocardium which was found to be impaired in DM, underlie much of the abnormal contractility and relaxation. MPI is an index of combined systolic and diastolic function and was found to provide important prognostic information for the risk of future congestive heart failure, beyond other measurements of cardiac function and traditional heart failure risk factors.

6. Limitations

This study has some limitations. The first is the relatively small number of patients. The rigorous exclusion criteria that comprised hypertension and smoking (current or former) however may partly explain the small number of included patients. This relatively small number of patients did not allow us to divide them into 2 groups with longer and shorter disease duration. The second is not subjecting the patients to tests such as myocardial perfusion imaging or coronary angiography to exclude coronary affection as the underlying cause of the

Figure 3  Left ventricular circumferential strain of the different segments (each segment is represented by a different color) in the short axis view at the level of the papillary muscles. The white line represents the average strain of the different segments.
myocardial dysfunction rather than diabetic cardiomyopathy. We speculated that the patients included in the study are young (mean age 21.1 ± 5.7 years) and asymptomatic and consequently the possibility of coronary affliction must be low. The third is the cross-sectional nature of the study. A follow-up of the progression and the clinical impact of the subtle LV diastolic and systolic abnormalities detected in this study would have added important information to the development of cardiac complications and congestive heart failure in T1DM patients. Finally, we measured the left ventricular (LV) global longitudinal strain (GLS) as the average of the 12 segments in the apical 4 chamber and 2 chamber views and did not take into account the 6 segments of the apical 3 chamber view (apical long axis view). We thought that calculating the GLS in only 2 apical instead of 3 apical views would be valid in this young population (age: 21.08 ± 5.7) with no segmental wall motion abnormalities in the resting echocardiography and no history of coronary artery disease. We did not think adding analysis of additional segments would significantly change the results or affect the accuracy of the measurements which were compared to control subjects using the same methodology.

7. Conclusion

Young asymptomatic patients with T1DM have evidence of impaired left ventricular both diastolic and systolic function compared to control subjects. STE allowed early detection of abnormal systolic longitudinal deformation before overt impairment of indices of LV systolic function. The glycemic control as detected by HbA1c was the only independent predictor of abnormal LV longitudinal function.

Conflict of interest

We declare having no financial or personal relationships with other people or organizations that could inappropriately influence (bias) our work.

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