Use of strain, strain rate, tissue velocity imaging, and endothelial function for early detection of cardiovascular involvement in young diabetics

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ABSTRACT

Background: Subtle structural and functional changes may precede the onset of overt global left ventricular (LV) dysfunction. Data pertaining to tissue velocity imaging (TVI) and strain imaging to assess regional myocardial function and flow mediated vasodilatation are limited in young patients with diabetes.

Materials: Conventional echocardiography, TVI parameters along with strain (S), and strain rate (SR) were measured in 50 young diabetics (15.16 ± 2.95 years, mean HBA1c 8.15 ± 1.37 g %) and 25 controls (15.60 ± 2.51 years). Flow-mediated dilation (FMD), nitrate-mediated dilatation (NMD), and carotid intima–media thickness were also assessed.

Results: Conventional echocardiography parameters were similar in patients and controls; however, deceleration time of the mitral inflow velocity (early deceleration time) was significantly shorter in patients when compared with controls (149.06 ± 31.66 ms vs. 184.56 ± 19.27 ms, P = 0.001). Patients had lower strain values at the basal lateral LV (21.39 ± 4.12 vs. 23.78 ± 2.02; P = 0.001), mid-lateral LV (21.43 ± 4.27 vs. 23.17 ± 1.92 P = 0.02), basal septum (20.59 ± 5.28 vs. 22.91 ± 2.00; P = 0.01), and midseptum (22.06 ± 4.75 vs. 24.10 ± 1.99; P = 0.01) as compared to controls. SR at the basal and midsegments of the lateral LV wall and at the basal septum was also significantly lower in diabetic patients. Diabetic children also had endothelial dysfunction with significantly lower FMD (8.36 ± 4.27 vs. 10.57 ± 4.12, P = 0.04).

Conclusions: LV strain indices and flow-mediated dilatation are impaired in asymptomatic children and adolescents with type 1 diabetes mellitus despite absence of overt heart failure and normal ejection fraction. Early detection of subclinical regional myocardial dysfunction by deformation analysis including strain and strain rate may be useful in the asymptomatic diabetic population.

Keywords: Diabetes, echocardiography, strain, strain rate, tissue doppler
INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a major cardiovascular risk factor associated with an excess of mortality due to important cardiovascular manifestations including coronary artery disease (CAD), heart failure, and hypertension. There is growing evidence that diabetes can lead to systolic and diastolic cardiac dysfunction and can cause diabetic cardiomyopathy even in the absence of overt CAD, hypertension, and valvular heart disease. Apart from accelerated atherosclerosis, factors associated with diabetic cardiomyopathy include metabolic disturbances, myocardial fibrosis, small vessel disease, and insulin resistance. Even though the existence of “diabetic cardiomyopathy” is often debated, the pathophysiological mechanisms underlying diabetes-associated nonischemic heart failure are poorly understood and clinical data on myocardial mechanics in early stages of diabetes with normal global left ventricular (LV) function are lacking.

Subtle structural and functional changes often occur early in the course of the disease and precede the onset of overt global left ventricular dysfunction and obvious reduction of ejection fraction (EF). Therefore, conventional echocardiographic parameters may often be inadequate to detect these early abnormalities of cardiac dysfunction in patients with diabetes especially if the global ventricular function is normal. Hence, it is important to assess these changes using echocardiographic techniques such as tissue velocity imaging (TVI), ventricular strain imaging (SI), and strain rate imaging (SRI) that are superior to routine echocardiographic techniques for analysis of regional and longitudinal myocardial function. Children and adolescents with uncomplicated diabetes serve as an ideal model to study the early effects of diabetic metabolic milieu on myocardial function in the absence of potentially confounding ischemic events. While some studies have reported subclinical cardiac dysfunction in young adults, children, and adolescents with type 1 DM, others have failed to show any differences in echocardiographic diastolic or systolic LV function indices between patients and non-diabetic controls.

The aims of the present prospective study were to assess conventional echocardiography parameters, tissue Doppler indices, and global and regional strain of the left and right ventricle in young patients (age <18 years) with type 1 DM and to compare them with matched controls. In addition, assessment of vascular function was done by measuring carotid intimal medial thickness and endothelial-dependent (FMD) and endothelial-independent (nitrate mediated dilatation [NMD]) function of the brachial artery.

METHODS

Patients with type 1 diabetes (n = 50, all on insulin therapy) were recruited after obtaining informed consent from the guardians/parents. Healthy age- and gender-matched controls (n = 25) were also studied. All patients underwent detailed history taking and clinical investigations including hemogram, HbA1C, renal function, liver function tests, and lipid analysis. Detailed clinical evaluation and anthropometric measurements such as height, weight, and body surface area (BSA) were done for all patients. Patients with congenital or rheumatic valvular heart disease, present or past history of heart failure, arrhythmias, or those on cardiac medications (including β-blocker, calcium channel blocker, angiotensin-converting enzyme inhibitor, or diuretics) were excluded.

Echocardiography

Detailed echocardiography was performed using a GE Vivid 7 ECHO machine (GE Healthcare, Waukesha, WI) by an operator who was blinded to the clinical data. Conventional echo-doppler parameters including LV end-diastolic dimensions and volumes (LVEDD, LVEDV), LV end-systolic dimensions and volumes (LVESD, LVESV), interventricular septal thickness (IVST), LV posterior wall thickness (LVPWT), LV fractional shortening (LVFS), LV stroke volume, and LV EF (LVEF) were measurements according to the American Society of Echocardiography guidelines. The LV dimensions were obtained from M mode parasternal long-axis views, while LV volumes were obtained from the apical four- and two-chamber views using standard transducer positions. Using the modified Simpson’s method, EF was automatically calculated as the difference between end-diastolic volume and end-systolic volume normalized to end-diastolic volume. The corrected LV mass (g) was calculated as 0.8 × (1.04 \{LVEDD + LVPWT + IVST\}^3 - LVIDD^3) + 0.6 and indexed LVM (LV massi) as LVM/body surface area.

LV work (in mm Hg × L/min) was calculated as LV stroke volume times heart rate times arterial blood pressure (BP) at end systole (Pes), which was calculated as follows: Pes = 2/3 systolic BP + 1/3 diastolic BP measured by sphygmomanometer.

Diastolic doppler parameters were recorded including early and late transmitral diastolic velocities (Evel and Avel) and their ratio (E/A) and early deceleration time (EDT) of the transmitral diastolic flow. Tei index or myocardial performance index (MPI), an echocardiography Doppler load independent index of combined systolic and diastolic function, was calculated as isovolumic relaxation time plus isovolumic contraction time divided by ejection time. Measurements were performed over three heart beats and average of the three measurements was taken.
**Tissue velocity imaging measures**

TVI analysis of the mitral annulus was performed in the apical four-chamber window. A 5 mm sample volume was placed at the desired area of interest and systolic myocardial velocities at the basal segments of the lateral LV wall (LV-Sm), septal wall (septal-Sm), early and late diastolic myocardial velocities (Em, Am), and their ratio (Em/Am) of the same basal segments of lateral LV wall (i.e. LV-Em, LV-Am and LV-Em/Am for the basal lateral LV segment) and septal wall (septal-Em, septal-Am and septal-Em/Am for the basal septal segment) were also recorded. All velocities in text and tables were expressed in cm/sec.

**Strain imaging and strain rate imaging measures**

The apical 4-chamber view was used to record the cardiac cycle in tissue Doppler imaging mode at a frame rate of more than 100/s, following which 2 mm volume samples were placed at 4 segments of the LV and 2 segments of the RV in apical 4-chamber view for strain analysis. Strain and strain rate imaging measures included longitudinal systolic strain and strain rate at the basal and mid segments of the lateral LV wall (S-LV-Basal, S-LV-Mid and SR-LV-Basal, SR-LV-Mid), basal and mid-septum (S-Septal-Basal, S-Septal-Mid and SR-Septal-Basal, SR-Septal-Mid) and basal and mid-RV (S-RV-Basal, S-RV-Mid and SR-RV-Basal, SR-RV-Mid). The TVI, strain, and strain rate imaging measures were obtained from the recorded loops. Strain values were expressed as the negative percentage values and the strain rate was expressed as negative 1/s values.

All measurements were made from three consecutive beats at end expiration and the results were averaged to get the final value. End diastole was defined by the peak of the R and the end systole was defined by the end of the T wave on the ECG. The intra-observer variability for strain parameters was observed to be 3.0% ± 2.1%, while the inter-observer variability was 5.3% ± 2.9%.

**Vascular studies**

Arterial endothelial function of the brachial artery was assessed noninvasively by ultrasound examination of the vasodilation response to endothelium dependent and independent stimuli, as previously reported. The right brachial artery, proximal to the antecubital fossa, was imaged longitudinally using the linear array transducer. Flow-mediated endothelium-dependent vasodilatation was assessed by measuring the brachial artery diameter at baseline and during reactive hyperemia. Reactive hyperemia was induced by deflating a cuff previously inflated to 300 mm Hg pressure over 4-5 min. Arterial flow velocity was measured at baseline and during reactive hyperemia using pulsed-wave Doppler. After 10-15 min, the endothelium-independent response (NMD) was assessed by the change in artery diameter at 3–4 min after a 5 mg dose of sublingual glyceryl trinitrate. The parameters were measured for three consecutive cardiac cycles, and the average was taken.

**Carotid intimal medial thickness (CIMT)**

For the measurement of carotid intima–media thickness (CIMT), the subject was made to lie supine with the neck turned contra laterally to the side being examined. The measurement was taken in the 1 cm segment of the common carotid artery (CCA) proximal to the carotid bulb, which was defined as the point of the deviation of the far wall from the parallel plane of the distal CCA. The CIMT was measured by the caliper as the distance between the inner echogenic line representing the intima blood interface and the outer echogenic line representing the adventitia-media junction. Measurements were repeated three times unfreezing the image on each occasion and relocating the position of the maximal intima–media thickness. The mean value of the each set of the readings represented the mean CIMT that was taken for the final analysis. The intra-observer variability for CIMT was 5.8% ± 3.7%, while the inter-observer variability was 7.6% ± 4.2%.

**Ethics**

Participants were included and studied after obtaining consent and institutional ethical clearance.

**Statistical analysis**

The data were expressed as the mean ± standard deviation. Statistical analysis was performed using the Statistical Package for the Social Sciences, version 20, for Windows (SPSS, Chicago, Illinois, USA). The independent t-test and Chi-square test were used for comparison of the continuous and categorical variables between groups, respectively. To study correlations, Pearson’s and Spearman’s coefficients were used for continuous and categorical variables, respectively. P < 0.05 was considered significant.

**RESULTS**

The study included 50 diabetic patients (22 males, mean age 15.16 ± 2.95 years) and 25 healthy subjects (12 males, mean age 15.60 ± 2.51 years). The baseline characteristics are summarized in Table 1; mean age, gender distribution, height, weight and body surface area (BSA), heart rate, systolic and diastolic BPs, and biochemical profile were comparable. The mean HbA1C level in diabetic patients was 8.15 ± 1.37 g% (range, 6.20–13.20), while the mean duration of diabetes was 4.92 ± 1.86 years (range, 3–10 years).

Conventional echocardiography parameters including LV dimensions, LV volumes, EF, E/A velocity, and MPI were not significantly different among the patients and controls [Table 2]. The LVEF (60.05 ± 5.62 vs.
61.79 ± 16.56% was also similar in patients vs. controls and none of the patients had global LVEF <50%. The absolute LV mass (154.36 ± 38.32 vs. 149.91 ± 29.62 gm, \( P = 0.58 \)) and indexed LV mass (127.47 ± 36.04 vs. 122.19 ± 25.20 g/m², \( P = 0.46 \)), although slightly higher in diabetics, the difference was not statistically significant. The deceleration time of the mitral inflow velocity (EDT) was significantly shorter in patients when compared with controls (149.06 ± 31.66 vs. 184.56 ± 19.27 ms, \( P = 0.001 \)).

**TVI parameters**

The systolic (Septal Sm) and diastolic velocities at the basal segments of the septal LV wall (septal-Am) and the ratio septal-Em/Am were not statistically different among the two groups (although early diastolic septal-Em velocity at the basal segment of septal LV was significantly higher). However, velocities at the basal segments of the lateral LV wall revealed significant differences in patients and controls. Despite similar systolic velocity at the basal portion of lateral LV wall (LV-Sm) in the two groups, lateral early diastolic myocardial velocity (LV-Em) was significantly lower, lateral late diastolic myocardial velocity (LV-Am) significantly higher than controls, leading to significantly lower ratio of early/late diastolic velocity at the basal segment of lateral LV (LV-Em/Am) in diabetics [Table 3].

**Strain parameters**

Values of LV strain [Table 4] at the basal (21.39 ± 4.12 vs. 23.78 ± 2.02) and midevent (21.43 ± 4.27 vs. 23.17 ± 1.92 respectively) of the lateral LV wall (S-LV-Basal and S-LV-Mid) were significantly lower in diabetics. Similarly, strain values at the basal septum (20.59 ± 5.28 vs. 22.91 ± 2.00) and midevent (22.06 ± 4.75 vs. 24.10 ± 1.99, S-Septal-Basal and S-Septal-Mid) were significantly lower in the patients as compared to controls. The strain parameters at basal and mid-RV wall were not significantly different among the two groups [Figure 1: patient vs. control of strain].

**SR imaging**

In keeping with the strain values, SRI measures [Table 5] also revealed similar trends. The SRI values at the mid-lateral LV wall (SR-LV-Mid) , basal septum (SR-Septal-Basal) and RV basal (SR-RV-Basal) were all significantly lower in the patients. The SRI value at basal lateral wall (SR-LV-Basal), midevent wall (SR-Septal-Mid), and RV midwall (SR-RV-Mid) although lesser in patients, but did not achieve statistical significance. [Figure 2: patient vs. control of strain rate].

**Vascular studies**

The carotid IMT was similar between the patients and healthy subjects (0.36 ± 0.13 vs. 0.39 ± 0.34, \( P = 0.17 \)). In contrast, vascular endothelium-dependent FMD was significantly impaired compared with controls (8.36 ± 4.27 vs. 10.57 ± 4.12, \( P = 0.04 \)), while endothelium-independent

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**Table 1: Baseline characteristics of the patient and the control group**

| Parameter | Patients (50) | Controls (25) | \( P \) |
|-----------|--------------|---------------|--------|
| Sex (male:female) | 22:28 | 12:13 | 0.73 |
| Age (years) | 15.16±2.95 | 15.60±2.51 | 0.67 |
| Height (cm) | 142.28±10.27 | 141.84±3.65 | 0.79 |
| Weight (kg) | 38.68±7.64 | 38±1.71 | 0.81 |
| Body surface area (m²) | 1.24±0.202 | 1.23±0.03 | 0.84 |
| Hemoglobin (g/dl) | 12.72±0.79 | 12.70±0.69 | 0.91 |
| Serum creatinine (mg/dl) | 0.61±0.13 | 0.63±0.16 | 0.71 |
| Systolic BP (mm Hg) | 105.6±3.61 | 105.92±3.61 | 0.75 |
| Diastolic BP (mm Hg) | 75.00±3.61 | 74.72±3.55 | 0.76 |
| Mean HbA1C (%) | 8.15±1.37 | -- | -- |
| Fasting blood sugar (mg/dl) | 120.67±10.12 | 80.65±9.99 | <0.01 |
| Duration of diabetes (years) | 4.92±1.86 | -- | -- |
| HbA1C: Glycated haemoglobin, BP: Blood pressure |

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**Table 2: Conventional (systolic and diastolic) echocardiography parameters of patients and controls**

| Parameter | Patients | Controls | \( P \) |
|-----------|----------|----------|--------|
| Left atrial diameter (mm) | 26.40±3.86 | 26.92±2.74 | 0.52 |
| Aortic diameter (mm) | 20.36±3.01 | 20.80±2.86 | 0.44 |
| LVEDD (mm) | 38.44±3.28 | 38.12±2.56 | 0.645 |
| LVESD (mm) | 21.96±2.32 | 20.52±1.59 | 0.002 |
| IVS thickness (mm) | 8.08±1.15 | 8.24±1.16 | 0.53 |
| Posterior wall thickness (mm) | 7.68±1.21 | 7.44±1.15 | 0.41 |
| LVEDV (ml) | 65.46±18.77 | 64.96±9.32 | 0.88 |
| LVESV (ml) | 26.12±8.13 | 24.40±9.43 | 0.44 |
| LV mass (g) | 30.94±13.95 | 39.56±12.66 | 0.69 |
| LV mass (g/m²) | 60.05±5.62 | 61.79±16.56 | 0.61 |
| LV mass (g/m²) | 145.36±38.32 | 149.91±29.62 | 0.58 |
| LV mass, (g/m²) | 26.47±36.04 | 122.19±25.20 | 0.46 |
| E/e’ (ms) | 1.15±0.18 | 1.10±0.19 | 0.32 |
| Avel (m/s) | 0.73±0.243 | 0.729±0.172 | 0.90 |
| Avel/Avel ratio | 1.66±0.412 | 1.584±0.419 | 0.43 |
| EDT (s) | 149.06±31.66 | 184.56±19.27 | 0.001 |
| MPI | 0.348±0.028 | 0.342±0.078 | 0.72 |
| LV work (mmHg x L/min) | 322,109.89±97,029.04 | 337,829.80±107,533.98 | 0.54 |

LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, IVS: Interventricular septal thickness, LVPWT: Left ventricular posterior wall thickness, LVEDV: Left ventricular end-diastolic volume, LVESV: Left ventricular end-systolic volume, LVSV: Left ventricular stroke volume, LVEF: Left ventricular ejection fraction, LV mass: Left ventricular mass (g), LV mass; Left ventricular mass index to body surface area (g/m²), E/e’: Transmitial early flow velocity, Avel: Transmitial late flow velocity, EDT: Early deceleration time, MPI: Myocardial performance index (Tei index), LV work (mmHg x L/min)
NMD was not significantly different among the two groups (13.37 ± 4.23 vs. 13.09 ± 5.06, P = 0.80).

The % of patients with FMD < 5.5% in patients versus controls was 16/50 (32%) versus 1/25 (4%), respectively, P < 0.01.

**Table 3: Left ventricular tissue velocity imaging (cm/s) parameters of the patients and controls**

| Parameter | Patients   | Controls  | P   |
|-----------|------------|-----------|-----|
| Septal systolic myocardial velocity (septal-Sm) | 10.73±1.55 | 11.10±0.95 | 0.2 |
| Septal early diastolic myocardial velocity (septal-Em) | 11.60±2.67 | 10.39±1.92 | 0.03 |
| Septal late diastolic myocardial velocity (septal-Am) | 8.22±1.87 | 7.75±2.01 | 0.35 |
| Septal early/late diastolic myocardial velocity ratio (septal Em/Am) | 1.46±0.39 | 1.46±0.56 | 0.97 |
| Lateral systolic myocardial velocity (LV-Sm) | 10.08±1.80 | 10.24±1.64 | 0.69 |
| Lateral early diastolic myocardial velocity (LV-Em) | 10.30±0.99 | 11.67±3.21 | 0.05 |
| Lateral late diastolic myocardial velocity (LV-Am) | 11.73±1.44 | 8.82±1.69 | < 0.05 |
| Lateral early/late diastolic myocardial velocity ratio (LV-Em/Am) | 0.89±0.15 | 1.41±0.64 | < 0.05 |

LV: Left ventricular

In patients with mean duration of diabetes more than 6 years, serum HbA1C levels had a significant positive correlation with lateral LV Am velocity, (r = 0.4, P ≤ 0.05), while a negative correlation was noted with lateral Em/Am ratio (r = −0.43, P = 0.04), basal lateral LV-strain (r = −0.192, P = 0.04), and midlateral LV strain (r = −0.32, P = 0.032). Negative correlation was also seen between HbA1C levels and FMD (r = −0.327, P = 0.017).

In patients with mean HbA1C levels > 8.5 g%, FMD had significant negative correlation with duration of diabetes (r = −0.38, P = 0.008), HbA1C (r = −0.83, P = 0.04), LV mass (r = −0.17, P = 0.05), and LV work (r = −0.43, P = 0.038), while a positive correlation was found with RV midstrain (r = 45, P = 0.05), RV midstrain rate (r = 0.49, P = 0.03), and RV basal strain rate (r = 0.57, P = 0.01).

LV mass index (LV mass) showed a positive correlation with septal Em velocity (r = 0.357, P = 0.03) and Am velocity (r = 0.327, P = 0.03) and basal septal strain rate (r = 0.605, P = 0.006), while it had negative correlation with mean HbA1C levels (r = −0.42, P = 0.05) and mean duration of diabetes (r = −0.61, P = 0.04).
Table 4: Strain (S in %) parameters of the patients and controls

| Parameter                          | Patients     | Controls    | P   |
|------------------------------------|--------------|-------------|-----|
| Basal lateral wall (S-LV-basal)    | −21.39±4.12  | −23.78±2.02 | 0.001|
| Mid-lateral wall (S-LV-mid)        | −21.43±4.27  | −23.17±1.92 | 0.02 |
| Basal septal wall (S-septal-basal) | −20.59±5.28  | −22.91±2.00 | 0.01 |
| Mid-septal wall (S-septal-mid)     | −22.06±4.75  | −24.10±1.99 | 0.01 |
| RV basal wall (S-RV-basal)         | −22.32±3.48  | −23.43±1.94 | 0.08 |
| RV midwall (S-RV-mid)              | −24.13±7.25  | −23.43±1.94 | 0.09 |

RV: Right ventricular

Table 5: Strain rate imaging (SR in 1/s) parameters of the patients and controls

| Parameter                          | Patients     | Controls    | P   |
|------------------------------------|--------------|-------------|-----|
| Basal lateral wall (SR-LV-basal)   | −0.7214±0.3326 | −0.8896±0.2576 | 0.08 |
| (SR-LV-mid)                        | −0.7676±0.2194 | −0.8768±0.1995 | 0.04 |
| Basal septal wall (SR-septal-basal) | −0.7214±0.3326 | −0.9016±0.2573 | 0.02 |
| (SR-septal-mid)                    | −0.7328±0.2937 | −0.7712±0.2765 | 0.59 |
| RV basal wall (SR-RV-basal)        | −1.1426±0.6715 | −1.4868±0.2831 | 0.04 |
| RV midwall (SR-RV-mid)             | −1.0772±0.7235 | −1.2844±0.2064 | 0.07 |

SR: Strain rate, RV: Right ventricular, LV: Left ventricular

DISCUSSION

In this study of 50 children (mean age 15.16 ± 2.95 years, diabetes duration 4.92 ± 1.86 years) with Type 1 DM, conventional echocardiography analysis revealed no significant difference in systolic or diastolic function as compared to controls. Although diabetic patients had higher LV mass as compared to controls, this did not reach statistical significance. Most parameters of diastolic function were not altered significantly, except for slight shortening of EDT in patients with DM. Although previous studies have documented abnormalities in indices of LV diastolic function including higher trans-mitral Doppler peak A wave velocity, E/lateral E ratio, and IVRT [13–23] similar to our observations, others have also documented that global LV diastolic function might be well preserved till late in the course of the disease necessitating more sensitive echocardiography techniques to detect subtle abnormalities of cardiac function.[14,24,25]

TVI analysis: We found that while septal velocity profile among diabetic patients was similar to controls, diabetics had significantly lower early diastolic velocity, higher late diastolic velocity, and significantly lower early/late diastolic myocardial velocity ratio at the lateral LV as compared to controls. The impaired mitral annular or basal LV velocities reflect the abnormalities in the long-axis motion of the ventricle, which is an important component of LV systolic and diastolic function. Comparison of individual TVI parameters among patients with DM also revealed interesting trends. While the overall systolic velocity at the septal (Septal-Sm, 10.73 ± 1.56) and lateral LV wall (LV-Sm: 10.08 ± 1.80) was not significantly different, the late diastolic myocardial velocity at the lateral LV wall was significantly higher (LV-Am, 11.73 ± 1.44 vs. 8.22 ± 1.87, P < 0.01). Therefore, the ratio Em/Am was also much lower in the lateral LV (0.89 ± 0.15) as compared to the septal LV (1.46 ± 0.39). Hence, the TVI spectral analysis suggested that despite an overall normal LVEF, there was a differential abnormality of TVI in the lateral versus the septal LV regions in patients with diabetes, with the lateral area demonstrating subtle abnormalities. Although previous studies have also shown impairment of tissue velocity imaging parameters with lower mitral annular and lateral velocity and E/A ratio in diabetics, this septolateral differential variation in velocity parameters is not commonly reported.[11,12] Similar to our analysis, Abd-El Aziz et al. also reported impaired TVI parameters in young diabetics although detailed strain rate analysis was not performed.[13]

Assessment of strain and strain rate: Strain and strain rate are quantitative measures for the echocardiographic assessment of myocardial deformation; while strain is an index of deformation describing the % change from the original dimension, strain rate is the rate at which this change happens. As a measure of myocardial deformation in diabetic patients strain rate is a more robust index of LV myocardial contractility in contrast to strain as it is less dependent on confounding factors such as pre- and afterload and more closely reflects global ventricular function than EF.[26,27]

In our study, we observed that LV strain at the basal and mid segments of the lateral LV wall as well as at the basal and midseptum was significantly lower in diabetic patients. Strain rate imaging values were also impaired in patients with diabetes throughout the basal and mid segment of the lateral LV wall as well as at the basal septum. Hodzig et al. also reported impaired longitudinal strain as well as peak systolic strain in the septal wall in diabetic children; however, strain analysis at the lateral LV segments was not analyzed.[23] In contrast, Kim and Kim reported reduction in regional strain and strain rates at the basal and midseptum only in patients with DM duration >4 years, while those with shorter disease duration had no significant impairment.[13] Longitudinal strain which is primarily controlled by subendocardial longitudinal myofibers plays an important role in cardiac pump function. These fibers are more susceptible to fibrosis and ischemia and hence impairment of longitudinal strain is often the first anomaly seen prior to onset of overt global heart failure.

Vascular analysis: Although we did not observe any differences in CIMT in patients versus controls, FMD was significantly more impaired in patients with DM and a
negative correlation was also seen between HbA1C levels and FMD. This is similar to previously reported data, which has demonstrated impaired vascular homeostasis and endothelial dysfunction in type 1 diabetes.\(^{28-30}\) Significantly more diabetic patients (32\%) had abnormal FMD (<5.5\%) as compared to controls (1\%). No differences in NMD were noted in the two groups confirming the fact that non endothelium-dependent vasodilatation is preserved. The genesis of altered vascular stiffness in patients with DM is postulated to be increased oxidative stress, decreased local nitric oxide availability, presumably due to superoxide-mediated nitric oxide destruction, endothelial dysfunction with disruption and fragmentation of vascular elastic lamellae, and cell apoptosis.\(^{31,32}\) Although carotid IMT and arterial stiffness both indicate vascular function, endothelial dysfunction and arterial stiffening may be affected earlier on in the course of vascular involvement in DM. Hence, CIMT measurement may be normal and therefore not reflect early vascular changes which may be better detected by FMD assessment.

In our patients with mean duration of diabetes >6 years, serum HbA1C levels had a significant negative correlation with lateral Em/Am ratio, basal lateral and mid-lateral LV strain, as well as FMD. Previous studies have also demonstrated that strain indices of the LV were significantly lower among patients with longer diabetes duration or poorer glycemic control.\(^{11,12,23,33}\) There are studies which have failed to consistently demonstrate this association.\(^{10,13,21,25,34}\) The impairment of myocardial deformation as reflected in altered strain indices is thought to be linked to hyperglycemia, which results in dysfunctional sarcoplasmic reticulum, altered cellular Ca2+ handling, and reduction in sequestration of calcium into the sarcoplasmic reticulum.\(^{35}\) Changes in LV mechanics may also occur secondary to deposition of advanced glycation end products and cardiac fibrosis.\(^{36}\) Such changes are often too subtle to be identified with load-dependent indicators, such as EF, and hence need application of sensitive techniques like strain imaging.

Our study demonstrates that regional rather than global functional impairment as detected by TDI and strain imaging may occur in young diabetics reflecting the often patchy and nonhomogeneous abnormalities of myocardial deformation. Our observations further suggest that strain imaging is not only more superior to conventional echocardiographic parameters such as LVEF and LVFS, but also better than tissue Doppler parameters (TVI) in the detection of regional myocardial function. Despite all our patients having normal LVEF, analysis of TVI detected abnormal velocity parameters only at the lateral LV wall, while septal parameters were not different from controls. In contrast, SI and SRI detected lower systolic strain and strain rate both at the septal as well as the lateral across both the basal and mid segments. Evidence of endothelial dysfunction with impaired FMD was also common in diabetic children in this study.

**CONCLUSION**

LV strain indices are impaired in asymptomatic children and adolescents with type 1 DM despite absence of overt heart failure and normal EF. Early detection of subclinical regional myocardial dysfunction by deformation analysis including strain and strain rate may be useful in the asymptomatic diabetic population. In addition, evidence of endothelial dysfunction in the form of impaired flow mediated vasodilatation was observed in the diabetic children. In developing countries like ours where the burden of DM is high with resultant adverse cardiovascular events, our study adds to the existent literature confirming the use of strain imaging to detect subtle myocardial dysfunction in patients with DM early in the course of their disease.

**Limitations**

A small number of patients (\(n = 50\)) represents an obvious limitation and more studies with larger number of patients are needed to help further define the role of these echocardiography parameters in assessment of LV function in patients with diabetes. A single echocardiogram analysis is another important limitation and serial studies with measurement of parameters in follow-up are necessary to clarify if these abnormalities are progressive or reversible with better glycemic control. Tagged magnetic resonance imaging (MRI) and MRI stress spectroscopy have also been used to quantify altered LV mechanics and strain secondary to abnormal myocardial energetics in young adults with uncomplicated T1DM. However, we did not use MRI due to cost logistics. More studies with larger patient numbers and long-term follow-up with echocardiography studies are required to further study these issues.

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**Conflicts of interest**

There are no conflicts of interest.

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