Early Detection of Left Ventricular Dysfunction in Type II Diabetic Patients by 2D Speckle Tracking Echocardiography

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To assess Left ventricular (LV) systolic dysfunction using 2D speckle tracking echocardiography (STE) in asymptomatic type II Diabetic patients. We acquired three LV short-axis, and three LV apical views in 100 asymptomatic diabetic patients with normal LV ejection fraction (EF) and 25 age-matched healthy volunteers. We measured end-systolic longitudinal strain (LS), radial strain (RS), and circumferential strain (CS) in 18 LV segments. There were no significant differences in LVEF between two groups. Diabetic patients had more advanced diastolic dysfunction and increased LV mass compared with control group. Basal, middle, and apical LSs were significantly lower in diabetic patients compared with control subjects, with 43% (43/100) of the diabetic patients showing abnormal global LS values (cut-off value: 217.2 mean 2SD in control subjects

Conclusion: Detecting subclinical LV systolic dysfunction by using 2D speckle tracking echocardiography (STE) might provide useful information of the risk stratification in an asymptomatic diabetic population.

Keywords: left ventricle; Speckle tracking; longitudinal function; Strain; Diabetes mellitus

INTRODUCTION

DM is often associated with coronary risk factors, resulting in significant cardiac morbidity and mortality.( Bell DS,2007) The Early detection of diabetic heart disease is of paramount importance, because timely life-style modifications and medical interventions could prevent or delay the subsequent development of heart failure which is considered one of major burdens for health insurance costs.( Fang ZY et al., 2005) Diabetic patients with normal left ventricular ejection fraction (LVEF) are frequently associated with diastolic dysfunction.( Galderisi M,2006) However, LVEF was not a sensitive marker for the detection of subclinical LV systolic dysfunction.( Sanderson JE et al., 2006) The Early manifestation of diabetic LV systolic dysfunction can be appeared longitudinally, because subendocardial fibers, which are prone to vulnerable to myocardial ischaemia, have a longitudinal trajectory.( Greenbaum RA et al., 1981) Presence of impaired longitudinal function in diabetic patients has been reported when using tissue Doppler imaging,( Fang ZY et al.,2004) But tissue Doppler imaging has its own limitations including angle dependency and the 1D nature of its measurement. The recent development of 2D speckle tracking echocardiography (STE) overcomes some of these limitations, and its accuracy (Cho GY et al., 2006) and clinical usefulness (Wang J et al., 2008) has been reported. Assessment of longitudinal strain (LS) profile curve also provides information on post-systolic shortening (PSS), which is considered as a marker of myocardial dysfunction. (Voigt JU et al., 2003) Thus, the aim of this study was mainly to measure LS, radial strain (RS), and circumferential strain (CS) in asymptomatic diabetic patients using 2DSTE, to determine which LV strain is preferentially impaired, and finally to elucidate the characteristics of PSS in a diabetic population.

PATIENTS AND METHODS

Study population

Our study included 100 patients with type II diabetes mellitus (54 males and 46 females: mean age 53±12 years). All patients had normal LVEF with no regional wall motion abnormalities on 2D echocardiography. Exclusion
criteria included a history of coronary artery disease, the presence of moderate-to-severe valvular heart disease, and/or significant rhythm disturbances. We also enrolled 25 healthy control subjects (15 males and 10 females: mean age 52±11 years) from our database for normal subjects. Healthy subjects were predominantly hospital employee or their relatives and/or friends. Because ageing affects diastolic function, we selected control subjects in order to adjust the same range of age. The Ethics Committee of the hospital approved the protocol and informed consent was obtained in every subject.

Echocardiography

The Echocardiography was performed using commercially available ultrasound equipment (M3S probe, Vivid S7). All 2D grey-scale echoangiographic images were obtained using second harmonic imaging. LV volumes and EF was measured using the modified Simpson method from the apical four- and two-chamber views. For the assessment of LV RS and CS, three LV short-axis planes were acquired at the basal, middle, and apical levels of the LV at high frame rates (range: 67–92 frame/s; mean 81±5 frame/s). Care was taken to ensure that the basal short-axis views were obtained at the level of the mitral valve, the middle planes at the level of the papillary muscles, and apical planes distal to the papillary muscles. For LS assessment, three LV apical views, apical four-chamber, two chamber, and long-axis views were acquired at high frame rates (range: 59–82 frame/s; mean 72±6 frame/s). In each plane, three consecutive cardiac cycles were acquired during a breath hold and digitally stored in a hard disk for off-line analysis.

Two-dimensional speckle tracking analysis

By using commercially available 2D strain software (Echopac PC, version 6.0), the endocardial border in the end-systolic frame was manually traced. A region of interest was then drawn to include the entire myocardium. The software algorithm automatically segmented the LV into six equidistant segments and selected suitable speckles in the myocardium for tracking. The software algorithm then tracked the speckle patterns on a frame-by-frame basis using the sum of absolute difference algorithm. Finally, the software automatically generated time-domain LV strain profiles for each of the six segments of each view, from which end-systolic strain was measured. The average value of strain at each level (basal, middle, and apical) and global strain obtained from averaging the strain values of 18 LV segments was calculated. We also evaluated longitudinal PSS. From time-domain LS waveforms throughout the cardiac cycle, we measured strain at end-systole (LSe) as well as post-systolic peak LS (LSpss). The post-systolic index (PSI) was calculated as (LSpss - LSe)/LSpss x 100 (%) in each segment, and these values displayed in a parametric bull’s eye map (Figure 1). Whenever PSS was not present, PSI value of 0 was given.

Upper three panels show longitudinal regional strain curve of six segments from the apical four-chamber, two-chamber, and long-axis views in a diabetic patient. The vertical line denotes aortic valve closure. In addition to longitudinal strain values at end-systole, post-systolic peak longitudinal strain was measured, if the regional strain curve reached its peak after the aortic valve closure. Lower panels show parametric image of end-systolic stain and post-systolic index. Note that post-systolic index was observed in the basal part of the myocardium.
Statistical analysis

Our study was designed with 90% power to detect a significant difference in global LS between diabetic patients and control subjects with a ¼ 0.05. A difference in global LS between two groups of 3.0% was defined as clinically important, with an estimated SD of 3.0%. Due to reliability of multivariate analysis in diabetic patients, we enrolled 100 diabetic patients. Data were expressed as mean values ± SD or median values (inter-quartile range). Frequencies were expressed as percentages. All statistical analysis was carried out using commercially available statistical software (JMP, version 7.0 SAS). Categorical variables were compared using Fisher’s exact test or x2 test whenever appropriate. Linear regression analysis was used to investigate the relation between two parameters. Univariate and multivariate analyses were performed to determine independent predictors between LS and clinical and echocardiographic parameters. A P-value less than 0.05 were considered significant.

RESULTS

1. Clinical and standard echocardiographic characteristics

Table (1) shows the clinical characteristics of both groups. The mean diabetic duration was 8.7 years.

Table (2) shows standard echocardiographic parameters. Although LVEF was not different between groups, LV mass index, relative wall thickness, and left atrial volume index were significantly higher in diabetic patients. Peak systolic and early diastolic annular velocity (E0) was significantly lower in the diabetic group, resulting in a higher E/E0 compared with control subjects.

Table 1: Clinical characteristics of diabetic patients and control subjects

<table>
<thead>
<tr>
<th></th>
<th>Diabetic patients (n = 100)</th>
<th>Control subjects (n = 25)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53 ± 12</td>
<td>52 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, male/female (N)</td>
<td>54/46</td>
<td>15/10</td>
<td>NS</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.60 ± 0.19</td>
<td>1.61 ± 0.15</td>
<td>NS</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>73 ± 13</td>
<td>67 ± 9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>47 (47)</td>
<td>8 (32)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD; N, number; BSA, body surface area; HR, heart rate.

Table 2: Standard echocardiographic data:

<table>
<thead>
<tr>
<th></th>
<th>Diabetic patients (n = 100)</th>
<th>Control subjects (n = 25)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVS (mm)</td>
<td>11.2 ± 1.6</td>
<td>9.4 ± 0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PW (mm)</td>
<td>10.8 ± 1.5</td>
<td>9.5 ± 1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVDD (mm)</td>
<td>46 ± 6</td>
<td>44 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>LVDs (mm)</td>
<td>29 ± 5</td>
<td>28 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDV (mL)</td>
<td>71.7 ± 20.7</td>
<td>81.2 ± 17.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LVESV (mL)</td>
<td>26.2 ± 11.3</td>
<td>29.1 ± 7.6</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>64.4 ± 7.2</td>
<td>64.2 ± 5.7</td>
<td>NS</td>
</tr>
<tr>
<td>LVMi (M-mode) (g/m²)</td>
<td>115 ± 30</td>
<td>80 ± 16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RWT</td>
<td>0.49 ± 0.10</td>
<td>0.43 ± 0.05</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>LAVI (mL/m²)</td>
<td>38.1 ± 11.4</td>
<td>26.7 ± 4.6</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>E (cm/s)</td>
<td>64 ± 17</td>
<td>66 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td>A (cm/s)</td>
<td>82 ± 20</td>
<td>67 ± 13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DcT (ms)</td>
<td>243 ± 68</td>
<td>215 ± 64</td>
<td>NS</td>
</tr>
<tr>
<td>E/A</td>
<td>0.8 ± 0.3</td>
<td>1.0 ± 0.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>IVCT (ms)</td>
<td>104.7 ± 23.7</td>
<td>88.3 ± 14.7</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>S′velocity (cm/s)</td>
<td>6.9 ± 1.8</td>
<td>8.0 ± 1.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>E′velocity (cm/s)</td>
<td>5.6 ± 2.0</td>
<td>7.5 ± 1.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E/ E′</td>
<td>12.9 ± 5.1</td>
<td>9.1 ± 2.4</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

A, mitral late diastolic peak velocity; DcT, deceleration time of the E-wave velocity; E, mitral early diastole velocity; E’, peak mitral annular velocity during early diastole; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; IVS, interventricular septum; LAVI, left atrial volume index; LVDD, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVMi, left ventricular mass index; NS, not significant; PW, posterior wall; RWT, relative wall thickness; S’, peak mitral annular velocity during systole.

End-systolic strain values

The global and regional three-principal strain values are shown in Figure 2. Global and regional LSs at the base-, mid-, and apical-LV levels were significantly lower in diabetic patients compared with control subjects. Global LS in control subject was 220.8±1.8. These data were used to establish abnormal cut-off value of global LS. This was calculated as the value of the mean 2 2SD. Using the cut-off value of 217.2, 43% (26/60) of the diabetic patients showed abnormal global LS value. CS at the base- and the mid-LV levels did not differ between groups. However, CS at the apical level was significantly lower in diabetic patients, resulting in a significant reduction in global CS. Diabetic patients had also significantly lower regional RS at the basal level and global RS compared with control.
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Similar results were obtained when diabetic patients with LV hypertrophy on 2D echocardiography were excluded from the analysis. No significant correlation was noted between LVEF and global LS (r = 0.20.05, P = 0.005) or RS (r = 0.24, P = 0.05). A weak albeit significant negative correlation was noted between LVEF and global CS (r = 0.38, P < 0.005).

Figure 2: showing global and regional strain values of diabetic patients (red columns) and control subjects (blue columns). Numerical values are represented as mean ± SD. In each box plot, upper and lower bars represent 90th and 10th percentiles. Top of the box represents 75th percentile, line in the box median value and bottom of the box means 25th percentile.

Univariate analysis revealed that the reduction of global LS was independently associated with E0 (P = 0.0001), relative wall thickness (P = 0.0001), duration of diabetic disease (P = 0.0006), albuminuria (P = 0.0037), and E-wave velocity (P = 0.0257). No correlation was noted between the reduction of global LS and fasting blood glucose (P = 0.7489) or glycosylated haemoglobin (P = 0.7524). Multivariate linear regression analysis demonstrated that diabetic duration was the only independent predictor for LS reduction (t = 2.22, P = 0.0313). When dividing diabetic patients into two groups according to the duration of disease (≤5 and >5 years), global LS was significantly lower in the diabetic group with longer disease duration (216.7±3.0) compared with the short diabetic duration group (218.2±1.9, P < 0.05). Although no significant differences in global RS (46.0±11.7 vs. 44.9±11.7) and CS (223.1±3.9 vs. 222.2±3.5) were noted, RS at the apical level (38.4±18.7 vs. 27.5±16.0, P < 0.05) and CS at the middle level (223.5±4.2 vs. 221.2±3.6, P < 0.05) were significantly higher in the diabetic group with prolonged disease duration compared with the short duration group.

Post-systolic shortening:

Figure 3 shows the PSS indices in both groups. The PSI value was significantly larger in diabetic patients compared with control subjects. PSI was significantly larger at the basal level compared with the middle or apical LV levels in both groups. Parametric PSS maps revealed that the distribution did not correlate with the perfusion territory of any coronary artery. PSI values significantly correlated with end systolic LS in all subjects (n = 85, r = 0.69, P < 0.001) as well as diabetic patients (n = 60, r = 0.64, P < 0.001).

Figure 3: Post-systolic index between the two groups.

DISCUSSION

The major findings of this study can be summarized as follows: (i) the reduction in LS was more prominent and evenly distributed throughout the LV. (ii) the duration of diabetic disease was the only independent predictor for the decrease in LS. (iii) Diabetic patients had more evidence for PSS index, and its distribution did not match the vascular territory of any coronary artery.

Two-dimensional strain

Identification of early manifestations of diabetic heart disease would allow the institution of timely medical
interventions to prevent the development of heart failure. Although diastolic dysfunction has been described as an early stage in diabetic heart disease progression in patients with normal LVEF, (Galderisi M.2006) isolated diastolic dysfunction is usually rare, (Sanderson JE et al., 2006) and when present, it often associated with subclinical systolic dysfunction. Systolic dysfunction might be initially apparent in the longitudinal direction, because subendocardial fibres, which are the ones more vulnerable to myocardial ischaemia and fibrosis, are longitudinally oriented. (Greenbaum RA et al., 1981) Several studies have demonstrated that systolic longitudinal dysfunction can be identified using tissue Doppler imaging in patients with hypertension, (Nishikage T et al., 2008) diabetes, (Andersen NH et al., 2003) and diastolic dysfunction. (Yip G et al., 2002) However, this method provides information in a single direction from a fixed transducer position. This method is also dependent on the angle between the beam and myocardial motion. In contrast, 2DSTE has the advantage that it allows the measurement of all principal LV strains in an angle independent manner, thus eliminating the major limitation of tissue Doppler imaging. Similar to previous tissue Doppler studies, (Andersen NH et al., 2003) we observed that global and regional LSs were significantly reduced in diabetic patients, with 40% of the patients showing abnormal LS values compared with the normal range obtained from our control group of age-matched subjects. In addition, global RS and CS were also reduced in diabetic patients, a finding which is in agreement with a previous magnetic resonance imaging study. (Fonseca CG et al., 2004) On the contrary, Fang et al., (2004) using tissue Doppler imaging reported that reduced longitudinal function was compensated by the augmentation of radial function in diabetic patients. Differences between study populations and in the method of measuring strain could have accounted for the discrepancies between Fang's and our study. Our results suggest that abnormal function is more widespread than just in the longitudinal direction in diabetic patients. We found that the reduction in global LS was independently associated with diabetic duration as well as early diastolic indices (E-wave velocity and E'), relative wall thickness, and albuminuria. Significant correlation between global LS and E' confirms the link between systole and diastole, which has been confirmed in previous studies. (Vinereanu D et al., 2004) Albuminuria is independently associated with systolic and diastolic dysfunction in diabetic patients. (Liu JE et al., 2003) The present study showed that diabetic duration was the only independent predictor for the reduction in LS. This highlights the relationship between long-term hyperglycemia and the impairment of LS. Although global LS was reduced, regional RS and CS were paradoxically increased in diabetic patients of long-term duration. This augmentation in regional RS and CS might reflect a compensation to maintain LVEF in diabetic patients with a long history of disease.

Post-systolic shortening

Myocardial shortening after aortic valve closure, i.e. PSS, has been suggested as a sensitive marker of regional myocardial dysfunction. (Voigt JU et al., 2003) However, PSS may also occur in healthy subjects. To discriminate between pathological and physiological PSS, Voigt et al., (2003) described that the timing and the magnitude are different between these two situations. The present study showed that PSS was significantly larger in diabetic patients compared with control subjects. Pathological PSS is usually associated with a reduction in systolic strain. The finding that PSI was negatively correlated with LS in our study supports this concept. Thus, we propose that PSS with reduced LS is a marker of myocardial dysfunction in diabetic patients with preserved LVEF. Interestingly, the distribution of PSS in both diabetic patients and control subjects was mainly observed in the basal myocardium. We also noted that its distribution did not correlate with the vascular territory of the coronary arteries. Although the precise mechanism of why PSS is preferentially observed in the basal myocardium is unknown, PSS observed in this study is not related to myocardial ischaemia induced by epicardial coronary artery stenosis.

STUDY LIMITATIONS

The study size was relatively small. Thus, our results cannot be extrapolated to the general diabetic population. The majority of diabetic patients had concomitant hypertension, which also affects longitudinal function. However, exclusion of hypertensive diabetic patients would produce significant bias in our results. Diabetic patients were considered to have a low probability of coronary artery disease based on clinical grounds and normal resting echocardiography.

CONCLUSIONS

2DSTE has the potential for detecting subclinical LV systolic dysfunction, and it might provide useful information for the risk stratification of an asymptomatic diabetic population. LVEF is not a sensitive indicator for the detection of subclinical systolic dysfunction in our study. Diabetic duration was the only independent predictor for the reduction of global LS.

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