Decreased left ventricular longitudinal contraction in normotensive and normoalbuminuric patients with Type II diabetes mellitus: a Doppler tissue tracking and strain rate echocardiography study

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ABSTRACT

Type II diabetes mellitus is associated with congestive heart failure with preserved ejection fraction. This group of patients has been assumed to have isolated diastolic dysfunction; however, the longitudinal systolic contraction of the left ventricle has not been studied previously. The objective of the present study was to investigate the longitudinal contraction of the left ventricle in normotensive Type II diabetes mellitus patients with normal ejection fraction. We examined 32 normotensive patients with Type II diabetes mellitus with ejection fraction > 0.55 and fractional shortening > 0.25. Exclusion criteria were angina pectoris, cardiac valve disease, albuminuria, retinopathy or neuropathy. Normal subjects (n = 32) served as controls. A 16-segment model of motion amplitude assessed left ventricular longitudinal contraction and the average of the segments was calculated as the tissue tracking score index. Peak systolic velocity and strain rate was also obtained in each segment. Patients with Type II diabetes mellitus had a significantly lower tissue tracking score index compared with normal subjects (5.8 ± 1.6 mm compared with 7.7 ± 1.1 mm; P < 0.001). Mean peak systolic velocity was also significantly lower (4.3 ± 1.5 cm/s compared with 5.4 ± 1.0 cm/s; P < 0.001), as well as peak systolic strain rate (−1.2 ± 0.3 s⁻¹ compared with −1.6 ± 0.4 s⁻¹; P < 0.001). Patients with Type II diabetes mellitus and preserved diastolic function had a significantly lower tissue tracking score index compared with normal subjects (6.6 ± 1.5 mm; P < 0.001), but patients with diastolic dysfunction had an even more profound decrease in tissue tracking score index compared with patients without diastolic dysfunction (4.9 ± 0.9 mm; P < 0.01). In conclusion, the longitudinal systolic contraction was significantly decreased in normotensive patients with Type II diabetes mellitus with normal ejection fraction, which was most profound in patients with concomitant diastolic dysfunction.

Key words: echocardiography, left ventricle, systole, tissue Doppler, Type II diabetes mellitus.

Abbreviations: A-wave, peak atrial filling velocity; BMI, body mass index; CHF, congestive heart failure; EF, ejection fraction; E-wave, peak early mitral inflow velocity; DT, E-wave deceleration time; FS, Fractional shortening; HbA1c, glycosylated haemoglobin; LV, left ventricular; SR, strain rate; TT, tissue tracking; Vp, velocity flow propagation.

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INTRODUCTION

Clinical and epidemiological data indicate a significant association between diabetes mellitus and congestive heart failure (CHF) with normal ejection fraction (EF) [1–4]. Although these patients have a lower mortality risk than patients with decreased EF, they have a significantly increased mortality risk compared with age-matched controls without CHF [5].

The presence of left ventricular (LV) diastolic dysfunction seems to be an early complication in Type II diabetes mellitus and has been suggested to be the first stage in the development of the ‘diabetic cardiomyopathy’.

In recent Doppler echocardiographic studies with analysis of combined mitral and pulmonary venous flow and flow during the Valsalva manoeuvre [6,7], abnormal LV diastolic filling was demonstrated to be present in approx. 50% of normotensive patients with Type II diabetes mellitus with normal systolic function. However, LV systolic function is often described in terms of LVEF or fractional shortening (FS), reflecting global and radial shortening of the left ventricle, whereas the longitudinal systolic contraction of the outer and inner layer of the myocardium contributes less in these parameters. Tissue Doppler imaging has been introduced as a new method of quantifying segmental and global LV function by measuring systolic and diastolic tissue velocities. A derivative of tissue Doppler imaging is tissue tracking (TT), which allows assessment of the systolic baso-apical myocardial shortening, whereas strain rate (SR) imaging is a new method for detection of segmental myocardial contraction or stretching [8,9].

The aim of the present study was to describe the systolic longitudinal contraction of the left ventricle in normotensive Type II diabetes mellitus patients with normal LVEF and FS assessed by TT and SR imaging.

METHODS

Patients

The study population consisted of 32 patients with Type II diabetes mellitus admitted to the outpatient clinic. All patients had normal untreated arterial blood pressure (130/85 mmHg) and did not have any clinical signs of ischaemic heart disease. All patients were in sinus rhythm with a normal 12-lead ECG without signs of hypertrophy, ischaemia or right or left bundle branch block. LVEF was ≥55%, as measured by Simpson’s modified biplane method [10] based on three measurements. LV mass and volume measurements were corrected for body surface [10]. Endocardial border detection was enhanced by use of second harmonic imaging [11].

Pulsed Doppler recordings were performed in the apical four-chamber view and with the Doppler beam aligned perpendicular to the plane of the mitral annulus. The sample volume was placed between the tips of the mitral leaflets. Five consecutive beats during quiet respiration were used for calculation of the Doppler variables. Assessment of colour M-mode flow propagation recordings were performed in the apical four-chamber view and with the M-mode cursor aligned parallel with the LV inflow. Adjustments were made to obtain the longest column of flow from the mitral annulus to the apex of the left ventricle. The M-mode cursor was positioned through the centre of the inflow to avoid boundary regions. The velocity flow propagation was measured as the slope of the first aliasing velocity (41 cm/s) from the mitral annulus in early diastole to 4 cm distally into the ventricular cavity [12].

Diastolic filling was classified on the basis of the mitral inflow Doppler parameters and colour M-mode flow propagation. Peak early mitral inflow velocity (E-wave) deceleration time (DT) > 140 ms and ≤240 ms, an E-wave/peak atrial filling velocity (A-wave) ratio between 1 and 2 and velocity flow propagation (Vp) > 45 cm/s indicated normal diastolic filling, whereas abnormal filling was defined as DT > 240 ms and E-wave/A-wave ratio < 1, suggestive of impaired relaxation.
Cardiac dysfunction in Type II diabetes mellitus

Figure 1  Schematic drawing displaying the principals of TT echocardiography

Middle panel, a normal subject with all 7 colour bands displayed. TT wall index, 8.7 mm. Right-hand panel: a patient with Type II diabetes mellitus. TT wall index, 5 mm.

A DT > 140 ms and ≤ 240 ms with V_p ≤ 45 cm/s was suggestive of a pseudonormal filling, and DT < 140 ms was suggestive of a restrictive filling pattern. The cut-off points were chosen based on recent recommendations [13,14].

Tissue Doppler imaging

Tissue Doppler imaging was obtained from the four- and two-chamber apical views and the apical long axis view during end expiration apnoea. TT and systolic SR analysis were performed as special modalities of tissue Doppler imaging. TT displays the integral of tissue velocity during systole, which equals the distance of motion along the Doppler axis [15]. TT requires simultaneous ECG registration to define the beginning and the end of the systole. There are seven colour bands, which indicate different distances of motion with a stepwise increase in the distance of motion. The range of distance of motion displayed by the seven colour bands can be altered. The maximal distance of motion during systole was adjusted depending on the LV function to stretch the seven colour bands between the apex and the mitral annular level. When analysing the left ventricle in apical views, the lowest distance of motion is at the apex and the greatest distance at the mitral annulus. Figure 1 shows the principles of TT.

The left ventricle was divided into 16 segments, similar to the wall motion score analysis [10], and the motion distance for each segment was assessed. The average of the 16 segments was calculated and presented as the TT score index in mm.

Strain is originally defined as a dimensionless quantity produced by the application of a stress and it represents the fractional or percentage of change from the original or unstressed dimension. SR is equal to the temporal derivative of strain, and the total strain can therefore be determined by combining the SR values for a given interval [8,16,17].

The tissue Doppler technique used in the present study allowed processing of simultaneous systolic velocity, TT and SR from different myocardial segments in the same cineloop. The peak myocardial systolic velocities and SR were measured in each segment within the first 350 ms from the R-wave in the ECG. SRs and velocities were measured in the centre and basal one-third of each myocardial segment. Colour noise reduction was adjusted and a colour Doppler scanning frame rate was kept between 140 and 160 frames/s [18]. The average value of peak systolic velocity, SR and TT of the 16 segments was calculated. Analyses of TT score index and SR analyses were done separately and without knowledge of two-dimensional and pulsed Doppler recordings.

Statistics

Results are presented as means ± S.D., except for diabetes duration, which is presented as the geometric mean. Frequencies are expressed as percentages. Differences between groups were assessed by Student’s t test. Time of diabetes duration was log transformed to approximate normal distribution. Analysis of equal variance was used to detect differences between groups. Pearson’s correlation coefficient (r) was applied to estimate correlations between individual parameters. Categorical variables were compared using Fischer’s exact test or χ² whenever appropriate. A two-tailed P < 0.05 was considered significant.

RESULTS

Table 1 shows the clinical and demographic data. Mean systolic and diastolic blood pressure, lipid profile and serum creatinine in the diabetes mellitus patients were comparable with the control group. Body mass index (BMI), surface area and heart rate were significantly increased in patients with Type II diabetes mellitus.
Table 1 Clinical characteristics of 32 patients with Type II diabetes mellitus and matching controls

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Controls (n = 32)</th>
<th>Type II diabetes mellitus (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>53 ± 7</td>
<td>53 ± 7</td>
</tr>
<tr>
<td>Female (%)</td>
<td>44</td>
<td>44</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>120 ± 9</td>
<td>121 ± 7</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>80 ± 8</td>
<td>77 ± 7</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>67 ± 9</td>
<td>78 ± 13</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.9 ± 2.6</td>
<td>29.4 ± 5.3*</td>
</tr>
<tr>
<td>Surface area (m²)</td>
<td>1.88 ± 0.2</td>
<td>2.01 ± 0.3*</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>4.7 ± 0.4</td>
<td>4.9 ± 0.9</td>
</tr>
<tr>
<td>NEFA (mmol/l)</td>
<td>1.90 ± 1.7</td>
<td>2.1 ± 1.4</td>
</tr>
<tr>
<td>S-Creatinine (µmol/l)</td>
<td>83 ± 13</td>
<td>78 ± 12</td>
</tr>
<tr>
<td>Urine albumin (µmol/l)</td>
<td>12 ± 4</td>
<td>12 ± 4</td>
</tr>
<tr>
<td>UACR (mg/mmol)</td>
<td>1.5 ± 0.6</td>
<td>1.5 ± 0.6</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>5 (0.5–20)</td>
<td>5 (0.5–20)</td>
</tr>
<tr>
<td>Diabetes therapy (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dietary treatment</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Oral antihyperglycaemic agents</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Insulin therapy</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>HbA1c</td>
<td>0.0083 ± 0.002</td>
<td></td>
</tr>
<tr>
<td>Lipid-lowering therapy (%)</td>
<td>35</td>
<td></td>
</tr>
</tbody>
</table>

Echocardiographic data are shown in Table 2. Left atrial diameter, mitral A-wave velocity, DT and isovolumetric relaxation time were significantly higher, whereas E-wave/A-wave ratio and Vp were significantly decreased compared with the controls.

Table 3 shows the coherent values of regional systolic peak velocities, TT score index and SR. Mean peak systolic myocardial velocity for all 16 LV segments was significantly lower in patients with diabetes mellitus than in normal subjects (4.3 cm/s compared with 5.4 cm/s respectively; P < 0.001), as well as peak systolic SR (−1.2 s⁻¹ compared with −1.6 s⁻¹ respectively; P < 0.001). Mean TT score index was also significantly decreased in diabetes mellitus patients compared with normal subjects (5.8 mm compared with 7.7 mm respectively; P < 0.001).

Eighteen patients demonstrated a normal diastolic filling pattern (57%), whereas nine patients had impaired relaxation pattern (28%). Five patients had pseudo-normal filling patterns (15%), but we did not find patients with restrictive filling patterns. The overall prevalence of diastolic dysfunction was 43%. Age, gender distribution, duration of diabetes, diabetes treatment, glycated haemoglobin (HbA1c) and lipid profile were similar in the groups with and without diastolic dysfunction.

Patients with diabetes mellitus and preserved diastolic function had a significantly lower TT score index compared with normal subjects [6.6 ± 1.5 mm (range, 3.8–9.3 mm) compared with 7.7 ± 1.5 mm (range, 6–11.5 mm) respectively; P < 0.001], but patients with diastolic dysfunction had an even more profound decrease in TT score index [4.9 ± 0.9 mm (range, 3.0–6.3 mm)] compared with patients without diastolic dysfunction. This was significant compared with both controls and diabetes mellitus patients with normal diastolic filling (Figure 2). Peak systolic myocardial velocities and SRs were also lower in patients with impaired diastolic filling compared with patients with normal filling, but this was not significant (SR, −1.24 ± 0.36 s⁻¹ compared with −1.15 ± 0.5 s⁻¹ respectively; and peak systolic velocity, 4.4 ± 1.3 cm/s compared with 4.1 ± 1.6 cm/s respectively; P = 0.50).

The average SR, peak systolic myocardial velocities and TT from the basal segments alone were calculated in a separate analysis. We did not find any separation between patients with impaired diastolic filling and patients with normal diastolic filling in SR, peak systolic velocity or TT measurements [SR, −1.6 ± 1.0 s⁻¹ compared with −1.7 ± 0.7 s⁻¹ respectively (P = 0.5); peak systolic velocity, 5.3 ± 1.7 cm/s compared with 5.0 ± 1.0 cm/s respectively (P = 0.50); TT, 7.9 ± 2.0 mm compared with 9.8 ± 1.6 mm respectively (P = 0.1)].

Table 3 displays regional values of the three systolic tissue Doppler parameters.

Patients having insulin treatment were equally distributed among patients with normal and impaired
diastolic filling, and insulin-treated patients as a group did not have significantly lower longitudinal shortening than the rest of the patients (6.4 ± 1.1 mm compared with 5.8 ± 1.7 mm; \(P = 0.25\)). Likewise SRs and peak systolic myocardial velocities were also similar in insulin-treated patients compared with patients without insulin treatment \([\text{SR}, 1.3 \pm 0.4 \text{ compared with } -1.2 \pm 0.4 \text{ s}^{-1}\) respectively \((P = 0.50)\); peak systolic velocity, 4.6 ± 1.5 cm/s compared with 4.1 ± 1.4 cm/s \((P = 0.40)\).

**Correlation of peak systolic velocities, SR and TT score index**

No significant correlations were found with mean peak systolic myocardial velocities in either patients or controls. SR was significantly correlated to systolic blood pressure in diabetes mellitus patients \((\rho = -0.56, P < 0.01)\). No other correlations were found among demographic data or echocardiographic measurements. In control subjects, a significant negative correlation was...
found between the TT score index and age ($\rho = -0.48$, $P < 0.01$) and systolic blood pressure ($\rho = -0.43$, $P < 0.02$). In patients with Type II diabetes mellitus, no significant correlation was found between the TT score index and age, gender, heart rate, blood pressure, body surface, BMI, E-wave/A-wave ratio, DT, isovolumetric relaxation time, $V_p$, LV volume, FS or EF, anti-diabetic therapy, HbA$_{1c}$ or duration of the diabetes mellitus disease.

**DISCUSSION**

The prevalence of diabetes mellitus in the latest clinical trials of CHF is as high as 30% and this number will increase, as the number of Type II diabetes mellitus patients is escalating. The importance of assessing detailed information of LV myocardial performance is essential in understanding the development of CHF and gives physicians the opportunity to initiate therapeutic intervention at an early stage.

The impact of diabetes mellitus on LV systolic and diastolic function has been investigated previously in the Strong Heart study [19–21]. In that study, apparent implications of a specific diabetes mellitus effect on the myocardium were found in both hypertensive and normotensive patients. In normotensive diabetes mellitus patients, in particular, these changes were closely associated with the presence of microalbuminuria, which is a strong predictor of cardiovascular morbidity and mortality in diabetes mellitus patients.

In the present study, we found a high prevalence of diastolic dysfunction (43%) in normotensive and normoalbuminuric patients with Type II diabetes mellitus and normal FS and LVEF. This prevalence is equal to what other observational studies have found on similar populations [6,7]. We demonstrated significantly impaired longitudinal systolic contraction, since both SR and TT measurements, reflecting segmental myocardial longitudinal contraction, were significantly decreased, and we also found lower segmental myocardial systolic velocities; however, these results were less consistent when compared with SR and TT results. A possible explanation for this is that peak systolic myocardial velocity measurements describe the rate of movement of the myocardial segment, which is severely influenced by both frame rate and angle and also by tethering [8]. By combining TT with SR, a global image of the LV longitudinal contraction is obtained that discloses whether this is actual contraction or tethering, which pulsed tissue Doppler assessment does not.

A further important finding in the present study was that patients with assumed isolated diastolic dysfunction revealed a significant decrease in systolic longitudinal contraction compared with patients without diastolic involvement, confirming a significant interplay of both systolic and diastolic dysfunction in this particular patient group [22]. These findings were surprising, since this myocardial involvement seemed to precede any other complications known to be associated with CHF, such as hypertension and albuminuria, but support the original proposal of a diabetes-specific myocardial disease resulting in an increased susceptibility of diabetes mellitus patients to develop CHF [23]. This segregation between patients with and without diastolic impairment was not detectable with SR or peak systolic velocity assessment alone or even in the separate analysis of the basal segments.

**Potential mechanisms behind decreased longitudinal contraction**

It is well known that the presence of the metabolic syndrome, including obesity, insulin resistance and poor glycaemic control, predisposes individuals to the development of microangiopathy and also increases the risk of cardiovascular complications, including CHF [24–26]. Several trials have shown correlations between cardiovascular disease and elevated HbA$_{1c}$ levels or high-dose insulin treatment in this patient category [4,24,27], and it seems that long-term hyperglycaemia could be part of the cause, since hyperglycaemia is associated with impaired endothelium-dependent relaxation caused by abnormal glycosylation end-products and overproduction of free radicals [19,28]. Lack of this vasodilatative capacity will compromise myocardial performance [29]. In the present study, we did not find any evidence of the metabolic syndrome being of significant importance, since we did not find any difference in BMI, HbA$_{1c}$, diabetes duration or diabetes treatment between patients with and without diastolic dysfunction or any correlation with the decreased SR and TT score index. Neurohumeral activation is known to influence myocardial function. Pronounced myocardial conversion of angiotensin I into angiotensin II, which is shown in diabetes mellitus patients [30,31], has the potential to induce increased myocardial fibrosis in the interstitial tissue, and augmented necrosis and apoptosis of the myocytes will end in loss of contractile function. This can be aggravated by microangiopathy in the myocardial microcirculation, causing myocardial malperfusion that will increase diastolic filling pressures and enhance the extravascular component of coronary resistance. Such mechanisms can be demonstrated in the diabetic heart even in the absence of hypertension or coronary artery disease [32].

The longitudinal subendocardial layers of the left ventricle are also susceptible to macroangiopathy in the epicardial arteries. Previous tissue Doppler studies [33,34] have shown decreased segmental systolic and diastolic peak velocities, due to very severe ischaemia in patients with coronary heart disease. If these patients

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were affected by large vessel disease, we would have expected regional changes in SR and systolic velocities in areas supplied by the coronary arteries, but this was not found. The compromised longitudinal shortening was found to be global, affecting the entire myocardium.

It is more likely that the sum of interactions of structural alterations of myocardium, interstitium and coronary vasculature are likely to initiate and maintain a process of compromised myocardial perfusion, which can provoke functional depression of the myocardial performance.

Limitations
No coronary angiographies, myocardial scintigraphy or exercise test was performed in the present study, which is a limitation to our observational study. In addition, an analysis of TT and SR of 16 segments of the left ventricle can be performed within 5–10 min, which is relatively time consuming. However, these methods give important information that cannot be detected by conventional echocardiography. Some variation was found in the SR measurements in the apical segments. This was probably due to some difficulties in obtaining optimal echocardiographic windows in the small fraction of obese patients included in the study.

Conclusions
A decreased longitudinal contraction of the left ventricle was found in normotensive in patients with Type II diabetes mellitus despite normal EF and FS. The impairment of longitudinal LV systolic function was most pronounced in patients with co-existing diastolic dysfunction, which might lead to a reconsideration of the concept of isolated diastolic dysfunction in normotensive Type II diabetes mellitus. The analysis of LV systolic function assessed by TT and SR analysis gives new important insights into LV myocardial performance.

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