Subclinical left ventricular dysfunction in asymptomatic patients with Type II diabetes mellitus, related to serum lipids and glycated haemoglobin

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ABSTRACT

The aim of the present study was to measure regional ventricular function at rest and during stress in order to assess if patients with Type II diabetes have subclinical myocardial dysfunction and if it is related to risk factors. Seventy subjects (35 patients with Type II diabetes with no symptoms, signs or history of heart disease, and 35 age- and sex-matched healthy controls) had echocardiography at rest and during dobutamine stress. Myocardial velocities were measured off-line from digital loops of colour tissue Doppler. Subendocardial function was assessed from the mean longitudinal velocities of four basal segments (apical views) and radial function from the velocities of the basal posterior wall (parasternal view). Systolic functional reserve was calculated as the increase in velocity from baseline. Longitudinal peak systolic velocity was lower in patients with diabetes, at rest (5.6 ± 1.4 compared with 6.5 ± 1.1 cm/s) and at peak stress (10.9 ± 2.8 compared with 14.3 ± 2.1 cm/s) (both \( P < 0.01 \)). Functional reserve was impaired in patients with diabetes (5.4 ± 2.0 compared with +7.7 ± 1.7 cm/s; \( P < 0.01 \)). Radial systolic velocity was higher in patients with diabetes (5.4 ± 1.3 compared with 4.7 ± 1.4 cm/s; \( P < 0.05 \)). Resting longitudinal systolic function correlated inversely with low-density lipoprotein–cholesterol (\( r = -0.53 \)), glycated haemoglobin (\( r = -0.48 \), age (\( r = -0.41 \)) and diastolic blood pressure (\( r = -0.38 \)) (all \( P < 0.05 \)). Peak stress systolic velocity correlated inversely with glycated haemoglobin (\( r = -0.46 \)) and age (\( r = -0.44 \)) (both \( P < 0.01 \)). In conclusion, patients with Type II diabetes and no clinical heart disease have impaired subendocardial function of the left ventricle at rest and peak stress, which is related to glycated haemoglobin and serum low-density lipoprotein–cholesterol.

INTRODUCTION

Diabetes is a risk factor in 10–30% of patients who develop heart failure [1]. In Type II diabetes, isolated abnormalities of diastolic relaxation in the absence of symptoms or signs of heart disease suggest a diagnosis of ‘diabetic cardiomyopathy’. This is thought to result from microangiopathy, deposition of collagen, decreased expression/activation of the K\(^+\) channel and Na\(^+\) pump and decreased myofilament Ca\(^2+\) sensitivity [2–4].

Key words: diabetes mellitus, stress echocardiography, tissue Doppler, ventricular function.

Abbreviations: A, peak atrial velocity; ATDE, velocity of myocardial motion during systole; CV, coefficient of variation; E, peak early velocity; Ea, peak diastolic velocity during mitral annular motion during early filling; ETDE, early diastolic velocity of myocardial motion; HbA1c, glycated haemoglobin; LV, left ventricular; LDL, low-density lipoprotein; PSV, peak systolic velocity; TDE, tissue Doppler echocardiography.

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In an animal model, hyperglycaemia was associated with increased deposition of collagen in the myocardium and a reduced peak velocity and prolonged deceleration time of early transmural flow [5]. These changes suggest a subclinical stage of diabetic cardiomyopathy. If this could be detected non-invasively, it might be possible to recognize patients at risk of heart failure before they develop overt left ventricular (LV) dysfunction and/or symptoms. The frequency of subclinical abnormalities and their rate of progression to clinically evident myocardial dysfunction are not yet established.

Heart disease in patients with Type II diabetes has been diagnosed from global diastolic dysfunction tested by conventional Doppler parameters of blood flow. These methods may give misleading results if there is 'pseudonormalization' of mitral inflow (a false-negative normal ratio of early to atrial phase flow (E/A) across the mitral valve when both left atrial and LV diastolic pressures are elevated) [4] (where E is peak early velocity and A is peak atrial velocity), and they are insensitive, since global mitral inflow becomes abnormal only after 50% of LV segments are diseased [6]. The new method of tissue Doppler echocardiography (TDE) may be much more sensitive [7], as it allows non-invasive assessment separately of radial and longitudinal, and systolic and diastolic, regional myocardial function.

Radial function of the left ventricle is due mainly to contraction of circumferential myocardial fibres in the mid-wall, whereas long-axis function is governed by longitudinal subendocardial fibres [8]. Since the subendocardium is more vulnerable to ischaemia and interstitial fibrosis [5], measurement of the velocity of longitudinal shortening of the ventricle by TDE may be a more sensitive marker of subclinical changes in LV performance in diabetes than assessment of global function by conventional echocardiographical methods.

The principal aim of this investigation was to study LV function in patients with Type II diabetes, at rest and during stress using conventional and new echocardiographic methods, in order to determine if they have reduced systolic function compared with controls. Secondly, we tested the hypothesis that subclinical dysfunction in diabetic subjects may be related to their overall glycaemic control.

**METHODS**

**Subjects**

Seventy subjects were studied: 35 patients with Type II diabetes, recruited consecutively from a specialist diabetic clinic, and 35 age- and sex-matched normal subjects.

The patients with diabetes had no symptoms or signs of heart disease, were in sinus rhythm and had a normal resting 12-lead ECG. Exclusion criteria were any history of coronary heart disease (stable angina, unstable angina, myocardial infarction or revascularization), more than mild (grade 1) arterial hypertension, impaired LV systolic function (ejection fraction < 50%, or any regional wall motion abnormality), heart valve disease, pericardial disease, severe diabetic neuropathy and/or retinopathy, renal failure (creatinine > 200 mmol/l) and/or proteinuria (> 1 g/24 h), contraindication to dobutamine or atropine, and possible pregnancy. Laboratory tests (triaclycerol (triglycerides), total cholesterol, low-density lipoprotein (LDL)–cholesterol, high-density lipoprotein–cholesterol, creatinine, glycated haemoglobin (HbA1c) and microalbuminuria) were performed in all patients within 1 week of the echocardiographic study.

Normal subjects, matched as case controls (same sex and age, ± 5 years), were selected from the MYDISE database [9]. This study was conducted in six west European countries (United Kingdom, Sweden, France, Belgium, Germany and Austria), and its database includes digitally stored dobutamine stress echocardiographic studies performed in normal subjects. Twenty-seven of the selected studies were from patients referred for assessment of atypical chest pain, but all of these had a normal maximal exercise ECG and normal coronary arteriography within 3 months of the echocardiographic study. The other eight selected studies were from healthy volunteers, all of whom had a normal maximal exercise ECG test, as well as a low predicted probability of coronary heart disease (< 10% over 10 years). None of the control subjects had any current or past history of heart disease, hypertension or diabetes.

The protocol was approved by the Local Research Ethics Committee, and each subject gave written informed consent.

**Baseline echocardiography**

Patients were studied in the left lateral decubitus position, using a commercially available ultrasound system equipped with tissue Doppler (Vingmed System 5; GE Vingmed, Horten, Norway), using a 1.5–2.5 MHz transducer. The ECG was recorded simultaneously. Digital echocardiographic data, containing a minimum of three consecutive beats, were acquired during passively held end-expiration and transferred on to a Macintosh computer for off-line measurement.

**Standard echocardiographic studies**

Standard echocardiographic studies consisted of M-mode, cross-sectional and Doppler blood flow measurements. M-mode tracings from the parasternal long-axis view were used to measure diameter of the aortic root, diameter of the left atrium, end-diastolic diameter of the right ventricle; and septal thickness, LV diameter and posterior wall thickness in systole and diastole. Cross-sectional images were recorded from the apex for measurement of end-diastolic and end-systolic areas.
Pulsed-wave Doppler of transmitral flow was used to assess global diastolic function. The sample volume was placed at the tips of the mitral leaflets in the apical four-chamber view. The following Doppler indices were measured: E, A, E-wave deceleration time, atrial wave duration and isovolumic relaxation time. E/A ratio was calculated. LV inflow was also recorded by colour M-mode echocardiography and flow propagation velocity was measured [10]. Pulmonary venous flow recordings were obtained from the apical four-chamber view, with the sample volume placed 1 cm into the right-upper pulmonary vein and the following parameters were measured: peak systolic velocity (PSV), peak diastolic velocity, A and atrial wave duration. All measurements were taken as the mean of three consecutive beats.

**Data analysis**

LV volumes, ejection fraction and LV mass were measured off-line and calculated. LV volumes and mass were indexed by body surface area. LV volumes and ejection fraction were calculated by the modified biplane Simpson’s method. LV mass was estimated by the method of Devereux with the application of the Penn convention [11].

**Long-axis function by pulsed tissue Doppler**

To record lateral mitral annular motion in the longitudinal axis, we used colour-guided pulsed-wave tissue Doppler from the apex. The pulsed sample volume was placed over the mitral annulus in systole. From the spectral traces we measured peak diastolic velocities of mitral annular motion during early filling (Ea) in order to calculate E/Ea ratio [12].

**Dobutamine stress echocardiography**

β-Blockers and Ca2+-channel blockers were stopped 48 h before the study. Dobutamine was infused intravenously for 3 min at successive doses of 5, 10, 20, 30 and 40 µg·min⁻¹·kg of body weight⁻¹. In patients who had not reached a target heart rate (>85% of (220−patient’s age in years)) or another end-point, the last dose was continued while incremental doses of atropine (0.25 mg) were given by intravenous bolus injection every minute to a maximum of 1 mg. Heart rate and rhythm were monitored continuously from a precordial ECG lead (modified lead I or II), and blood pressure was measured in the upper arm using an automated sphygmomanometer (705CP; Omron, Tokyo, Japan). A 12-lead ECG was recorded every 3 min. Symptoms were documented.

Predefined end-points included intolerable symptoms (such as chest pain), ≥ 2 mm of horizontal or downsloping ST-segment depression on the ECG, persistent arrhythmias, such as ventricular tachycardia or atrial fibrillation, and systemic hypotension (fall of systolic pressure > 30 mmHg) or bradycardia.

**Echocardiographic acquisition**

At baseline and then during the last 90 s of each stage of dobutamine infusion, digital echocardiographic images were acquired from each of four standard imaging planes: parasternal long-axis, parasternal short-axis, apical four-chamber and apical two-chamber views. A complete two-beat loop was edited to start before one QRS complex and to end after the third QRS complex. This loop was reviewed in ‘real-time’ to ensure that there was no significant translation of the heart on the image before being transferred on to a Macintosh computer. Grey-scale studies were performed routinely with harmonic imaging, but digital loops were acquired while displaying superimposed colour tissue Doppler images. In order to avoid aliasing during stress, the Nyquist limit was increased, usually to 25 cm/s. The depth of imaging and the sector angle in each view were adjusted to obtain the highest possible frame rate for colour tissue Doppler while keeping the whole left ventricle in view; the goal was a frame rate of more than 100/s.

**Off-line measurements**

Digital loops were retrieved and analysed at baseline and peak dose of dobutamine. Grey-scale images were analysed for wall motion abnormalities. Tissue Doppler measurements were made in nine myocardial segments: velocities of radial function were recorded from the parasternal long-axis view, whereas longitudinal function was assessed from the velocities of basal-septal and mid-septal and basal-lateral and mid-lateral segments (four-chamber view), and basal-anterior and mid-anterior and basal-inferior and mid-inferior segments (two-chamber view). In parasternal views, the cursor was positioned in the posterior wall so that it did not encompass the pericardium at any time during the cardiac cycle. In apical views, each LV ‘wall’ was divided into thirds, and the cursor was placed within the basal portion of each segment during systole; in the basal segments, it was positioned so that it never encompassed the mitral annulus during systole. No angle corrections were used. Measurements were taken from two consecutive beats and averaged. Myocardial velocities were measured off-line using customized software (Echopac TVI; GE Vingmed) (Figure 1).

PSV was defined as the maximal velocity (in cm/s) during systolic ejection. Myocardial early diastolic velocity of myocardial motion (ETDE) was defined as the maximal negative velocity during early diastole (in cm/s), excluding isovolumic relaxation, whereas the velocity of myocardial motion during atrial systole (ATDE) was defined as the maximal velocity during atrial contraction (in cm/s) just after the P wave on the ECG. When ETDE and ATDE were fused at rapid heart rates, a single diastolic velocity was measured.

The off-line measurements in normal subjects and diabetic patients were performed independently by two
observers (C. F. M. and D. V.), who were unaware of the results of the other investigations.

Data analysis
The velocities of four basal segments (septal, lateral, anterior, and inferior, studied in apical views) were averaged. Systolic functional reserve was calculated as the absolute or percentage increase in velocity from baseline.

Reproducibility
We have reported detailed studies of inter-observer agreement [13]. Ten randomly selected studies were analysed by nine observers and each pooled S. D. was divided by its corresponding mean value to give a coefficient of variation (CV; in %).

Statistical analysis
Statistical analysis was performed with SPSS software (version 11.0; SPSS Inc., Chicago, IL, U.S.A.). Results are presented as means ± S.D. Differences between groups were tested for significance using independent-samples Student's t test and χ² test. Analyses of univariate and multiple stepwise linear regression were performed to define the most important correlates of subclinical LV dysfunction. Multifactorial ANOVA was used to study the independent effects of diabetes and hypertension on regional ventricular function. A P < 0.05 for a two-tailed test was considered significant.

RESULTS

Subjects
General characteristics of the study groups are presented in Table 1. Patients with diabetes had a mean duration from the diagnosis of disease of 11 ± 7 years (range, 4–30 years). Twenty-two patients (63 %) were on oral treatment only, eight (23 %) on insulin and five (14 %) on both. From the 27 patients on oral treatment, 12 were on sulphonylureas, 23 on metformin, six on thiazolidinediones and one on nateglinidine. Twenty-seven patients (77 %) had no complications, five (14 %) had mild retinopathy, two (6 %) had mild peripheral neuropathy and one (3 %) had mild nephropathy (creatinine = 167 µmol/l). Fifteen patients (43 %) had associated grade 1 hypertension (blood pressure 140–159/90–99 mmHg) [14], and all of these were taking an ACE (angiotensin-converting-enzyme)-inhibitor. Eighteen patients (57 %) were on a statin, and 12 (34 %) on aspirin. The mean HbA1c level in the patients with diabetes was 9.2 ± 1.4 % (range, 6.9–12.3 %).

Table 1  Comparison of the study groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Type II diabetes</th>
<th>Normal subjects</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57 ± 10</td>
<td>56 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td>Male (%)</td>
<td>63</td>
<td>63</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30 ± 5</td>
<td>26 ± 4</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Triacylglycerols (mmol/l)</td>
<td>2.7 ± 1.4</td>
<td>1.8 ± 1.1</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>5.0 ± 1.1</td>
<td>5.0 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>LDL–cholesterol (mmol/l)</td>
<td>2.8 ± 1.0</td>
<td>3.0 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>HDL–cholesterol (mmol/l)</td>
<td>1.2 ± 0.3</td>
<td>1.3 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Current/ex smokers (%)</td>
<td>17/14</td>
<td>31/23</td>
<td>NS</td>
</tr>
<tr>
<td>Aortic diameter (mm)</td>
<td>34 ± 3</td>
<td>33 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>Left atrial diameter (mm)</td>
<td>40 ± 5</td>
<td>36 ± 6</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Septal thickness (diastole) (mm)</td>
<td>10 ± 2</td>
<td>10 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>EDVI (mm/m²)</td>
<td>27 ± 3</td>
<td>26 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>PW thickness (diastole) (mm)</td>
<td>10 ± 1</td>
<td>10 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td>ESVI (ml/m²)</td>
<td>90 ± 44</td>
<td>91 ± 35</td>
<td>NS</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>37 ± 17</td>
<td>35 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td>Right ventricular diameter (mm)</td>
<td>22 ± 3</td>
<td>20 ± 2</td>
<td>NS</td>
</tr>
</tbody>
</table>

Standard echocardiographic observations
Standard echocardiographic data are presented in Table 1. All patients had normal global systolic function (ejection fraction 50–77 %; mean ± S.D., 64 ± 7 %). Applying the guidelines of the European Study Group on Diastolic Heart Failure [15], 30 patients (86 %) had global diastolic dysfunction. However, none of the patients had an abnormal transmural E/A ratio, mitral E deceleration time or ratio of pulmonary venous systolic and diastolic velocities (Table 2). The commonest abnormalities were new criteria such as a colour M-mode flow propagation velocity < 45 cm/s (present in 60 %) and a peak early diastolic velocity of the lateral mitral annulus < 8 cm/s (present in 29 %) [16].

Dobutamine stress echocardiography
Haemodynamic measurements, end points and symptoms during dobutamine stress are shown in Table 3.
Table 2  Global diastolic dysfunction in patients with diabetes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Type II diabetes</th>
<th>Normal subjects</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>74 ± 11</td>
<td>72 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Peak</td>
<td>142 ± 17</td>
<td>137 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>Resting BP (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>145 ± 13</td>
<td>132 ± 16</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Diastolic</td>
<td>83 ± 11</td>
<td>76 ± 11</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Peak systolic BP (mmHg)</td>
<td>156 ± 28</td>
<td>143 ± 28</td>
<td>NS (0.06)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>64 ± 7</td>
<td>64 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>Peak</td>
<td>69 ± 10</td>
<td>72 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>Dobutamine 40 µg · kg⁻¹ · min⁻¹ (%)</td>
<td>5/20/29</td>
<td>0/14/40</td>
<td>NS</td>
</tr>
<tr>
<td>Dobutamine 40 µg · kg⁻¹ · min⁻¹ and atropine given (%)</td>
<td>46</td>
<td>46</td>
<td>NS</td>
</tr>
<tr>
<td>End points (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Achieved target heart rate</td>
<td>69</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Completed protocol</td>
<td>25</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>0</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

No patient developed typical chest pain, ECG changes of myocardial ischaemia or wall motion abnormalities. In one patient, the study was stopped prematurely, because of high blood pressure and his 'peak' stress echo data were excluded from the statistical analysis.

### Long-axis function by tissue Doppler

Longitudinal systolic velocities were lower in patients with diabetes for all the eight investigated segments both at rest and at peak stress (Figure 2). The four-site mean systolic velocities were also lower both at rest (5.6 ± 1.4 in patients with diabetes compared with 6.5 ± 1.1 cm/s in controls; P < 0.01) and at peak stress (10.9 ± 2.8 compared with 14.3 ± 2.1 cm/s; P < 0.001).

Longitudinal systolic functional reserve was impaired in patients with diabetes compared with normal controls: +5.4 ± 2.0 cm/s (+98 ± 37 %) compared with +7.7 ± 1.7 cm/s (+119 ± 31 %); P < 0.01.

At rest, longitudinal four-site mean early diastolic velocity (5.9 ± 2.3 compared with 7.6 ± 1.9 cm/s; P < 0.01) and E_TDE/A_TDE ratio (0.9 ± 0.4 compared with 1.2 ± 0.4, P < 0.05) were also lower in patients with diabetes.

### Short-axis function by tissue Doppler

Radial systolic velocities were higher in patients with diabetes (5.4 ± 1.3 compared with 4.7 ± 1.4 cm/s; P < 0.05), whereas peak systolic velocities (13.1 ± 3.3 compared with 12.1 ± 3.4 cm/s; not significant) and functional reserve (+7.6 ± 2.9 compared with +7.3 ± 3.3 cm/s; not significant) were similar to the normal subjects. Radial E_TDE/A_TDE ratio was lower in patients with diabetes (1.2 ± 0.8 compared with 2.4 ± 2.4; P < 0.05).
Correlates of subclinical LV dysfunction

By univariate analysis, LV systolic function at rest in patients with diabetes (measured as the mean velocity of long-axis shortening) correlated inversely with LDL–cholesterol \((r = -0.53)\), HbA\(_{1c}\) \((r = -0.48)\), age \((r = -0.41)\) and baseline diastolic blood pressure \((r = -0.38)\) (all \(P < 0.05)\). The maximal velocity at peak stress correlated inversely with HbA\(_{1c}\) \((r = -0.46)\) and age \((r = -0.44)\) (both \(P < 0.01\)). The strongest correlation of HbA\(_{1c}\) was found to be with the E/E\(_a\) ratio \((r = 0.66; P < 0.001; \text{Figure 3})\), which is a relatively preload-independent index of LV filling pressure [12].

By stepwise multivariate regression analysis, the determinants of longitudinal systolic function of the left ventricle at rest in patients with diabetes were LDL–cholesterol and baseline diastolic blood pressure \((r = 0.63, r^2 = 0.40; P < 0.001)\). At peak stress, longitudinal function of the left ventricle was predicted by age and HbA\(_{1c}\) \((r = 0.53, r^2 = 0.28; P < 0.05)\). Other factors studied, but not selected by the multivariate analyses, were systolic blood pressure, pulse pressure, body mass index, serum triacylglycerols and LV mass index.

Effects of diabetes and hypertension on regional LV function

By multifactorial ANOVA analysis performed in the whole study population, including control subjects and patients with Type II diabetes, the diagnosis of diabetes (as a dichotomous variable) was an independent contributor to LV longitudinal dysfunction, whereas the contribution of co-existing arterial hypertension was not significant (Table 4).

Reproducibility

CVs for measurements of PSV in basal segments were 8–13% at rest and 11–17% at peak stress [13]. For measurements of myocardial E velocities in basal segments at rest, CVs were 11–22%.

DISCUSSION

In the present study, we have shown that patients who have Type II diabetes but no clinically apparent heart disease, nonetheless have impaired longitudinal function of the left ventricle both in systole and diastole and both at rest and peak stress. Their systolic functional reserve is reduced. Longitudinal function is inversely related to increasing age and to the average glycaemic control (HbA\(_{1c}\)) and LDL–cholesterol.

TDE

TDE is an ultrasonic modality that measures the velocities of myocardial motion. During each cardiac cycle, distinct velocities can be recorded during systole, in early diastole (E\(_{TDE}\)) and during late diastolic filling after atrial contraction (A\(_{TDE}\)).

Table 4 Regional LV function in Type II diabetic patients with normal blood pressure and grade 1 hypertension compared with normal subjects

The relative effects of diabetes and of arterial hypertension on regional ventricular function are based on a multifactorial ANOVA analysis.

<table>
<thead>
<tr>
<th>LV function</th>
<th>Normotensive ((n = 20))</th>
<th>Hypertensive ((n = 15))</th>
<th>Normal subjects ((n = 35))</th>
<th>Effect of diabetes (P)</th>
<th>Effect of hypertension (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longitudinal systolic velocity ((\text{cm/s}))</td>
<td>5.6 ± 1.6</td>
<td>5.5 ± 1.1</td>
<td>6.5 ± 1.1</td>
<td>&lt; 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Radial systolic velocity ((\text{cm/s}))</td>
<td>5.4 ± 1.6</td>
<td>5.5 ± 0.8</td>
<td>4.7 ± 1.4</td>
<td>0.07</td>
<td>NS</td>
</tr>
<tr>
<td>Peak stress</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longitudinal systolic velocity ((\text{cm/s}))</td>
<td>11.1 ± 3.4</td>
<td>10.6 ± 1.8</td>
<td>14.3 ± 2.1</td>
<td>&lt; 0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Radial systolic velocity ((\text{cm/s}))</td>
<td>12.6 ± 3.8</td>
<td>13.7 ± 2.6</td>
<td>12.1 ± 3.4</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Functional reserve</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longitudinal ((\text{cm/s}))</td>
<td>+ 5.5 ± 2.3</td>
<td>+ 5.2 ± 1.6</td>
<td>+ 7.7 ± 1.7</td>
<td>&lt; 0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Radial ((\text{cm/s}))</td>
<td>+ 7.2 ± 3.1</td>
<td>+ 8.2 ± 2.3</td>
<td>+ 7.3 ± 3.3</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>
The subendocardial myocardial fibres are aligned longitudinally from apex to base, and so subendocardial function can be assessed by using TDE to measure longitudinal velocities of myocardial segments from apical views [12,17]. We have shown previously [18,19] in patients with chronic pressure or volume overload that TDE can diagnose subclinical longitudinal LV dysfunction. In a multicentre study of stress echocardiography, we showed that myocardial functional reserve can be measured accurately by tissue Doppler during dobutamine stress [9]. Therefore we applied the same techniques in order to diagnose subclinical changes in patients with suspected diabetic cardiomyopathy.

**Diabetic cardiomyopathy**

Since Rubler et al. [20] first suggested the existence of ‘diabetic cardiomyopathy’, there has been considerable additional support for the concept from experimental and clinical studies [21]. In experimental diabetes, abnormal mechanical properties of the myocardium include prolongation of contraction and relaxation, as well as considerable reduction of contraction and relaxation velocities [2,22]. Clinical studies using conventional echocardiography, however, have shown only global diastolic dysfunction, with a prevalence of about 60 % in patients with Type II diabetes who have no clinically detectable heart disease [4,23]. Annonu et al. [23] reported that patients with diabetes had a lower mean ejection fraction than control subjects, but they included some patients who already had dilated ventricles and impaired systolic function.

To our knowledge, the present study is the first to show that patients with Type II diabetes and normal global systolic function may have subclinical regional systolic dysfunction at rest and at peak stress affecting long-axis contraction. This can be demonstrated only using TDE to quantify regional myocardial function. Radial function appears to compensate with increased systolic velocities, and thereby global systolic function is preserved. Some of our patients, depending on the criterion used, also had global diastolic dysfunction, due to impaired myocardial relaxation in both longitudinal and radial directions.

Stress echocardiography predicts cardiac events in diabetic patients with known or suspected coronary artery disease when it is analysed to give a wall motion score index [24]. In the present study, we show that, when combined with tissue Doppler, it is useful also for assessing myocardial functional reserve and diagnosing subclinical changes in diabetic patients without known heart disease.

Two other recent studies have also applied TDE to the diagnosis of subclinical myocardial disease in diabetes mellitus [25,26]. Fang et al. [25] studied regional myocardial function at rest only in a mixed population of 93 diabetic patients (predominantly Type II) and in normal and hypertensive control subjects. They demonstrated average reductions of 8 % and 13 % in systolic function in normotensive diabetics compared with controls, using the parameters of strain and strain rate respectively [25]. In our present study, the average reduction in myocardial velocities at rest in the diabetic patients (14 %) was comparable, whereas we observed an increased difference at peak stress, when maximal systolic velocities were 24 % lower in diabetics than in controls. Hansen et al. [26] demonstrated only an insignificant trend to a reduced longitudinal systolic velocity at rest in diabetic patients compared with controls (by 9 %), but they studied only eight patients with Type I diabetes and a mean age of 28 years. They found no difference between patients and age-matched controls in the myocardial systolic response to intravenous dipyridamole, which suggests that dobutamine stress, as used in the present study, is much more useful for revealing impaired myocardial functional reserve (rather than regional ischaemia) in diabetic patients.

We have confirmed the findings of earlier studies using traditional echocardiographic assessment of global diastolic function [4,27] that early diastolic filling of the left ventricle is reduced in patients with diabetes mellitus early in the natural history of their cardiac disease. On average, resting longitudinal early diastolic myocardial velocities were 22 % lower in the diabetic patients compared with controls. Comparable reductions observed in the other recent studies were 29 % [25] and 12 % [26].

Taken together, these studies using TDE as a very sensitive non-invasive test of regional myocardial function all suggest that systolic and diastolic myocardial function are similarly impaired in diabetic patients without overt cardiac disease. Differences can be observed best in longitudinal myocardial motion or deformation, for example by measuring LV subendocardial function from apical echocardiographic windows. The reason why previous studies have demonstrated global diastolic dysfunction, but have failed to show systolic changes [27], may be our new observation that radial myocardial systolic function is increased in diabetic patients compared with controls. A subtle change in the end-diastolic shape of the left ventricle in diabetic subjects with preclinical heart disease could increase circumferential stretch and result in increased systolic radial velocities due to the Starling mechanism. This will maintain global ejection fraction, as we observed, in spite of reduced subendocardial systolic function.

Epidemiological studies have suggested that poor overall glycaemic control may be associated with an increased risk of heart failure among patients with diabetes: a HbA1c ⩾ 10, relative to < 7, implied a 1.56-fold greater risk of heart failure [28]. However, global diastolic dysfunction failed to correlate with HbA1c [4]. In the present study, we show from both univariate and multivariate analyses that HbA1c correlates inversely with, and thus
may be an important determinant of, longitudinal systolic velocities. This hypothesis has also been tested by other investigators [25], but they were unable to demonstrate a relationship probably because they studied patients with better average glycaemic control and a narrower range of results than in our study (mean HbA1c 7.4–7.9 % compared with 9.2 %). Furthermore, we observed that HbA1c correlates with the E/E′ ratio, which is a good parameter of LV relaxation and filling pressures, because it is relatively preload-independent and not affected by pseudo-normalization [12,16]. Hansen et al. [26] found a subclinical reduction in longitudinal early diastolic velocity that was inversely related to the duration of Type I diabetes. These observations extend an earlier report that global diastolic dysfunction is related to HbA1c and duration of diabetes [27].

The present study did not investigate the mechanisms of subclinical subendocardial dysfunction in diabetic patients, but reductions in myocardial velocities have been reported to correlate with the degree of interstitial myocardial fibrosis [29]. This could be triggered by subendocardial ischaemia related to endothelial and microvascular dysfunction [30]. We have reported recently [31] that subclinical LV dysfunction is inversely related to conduit arterial stiffness, and aortic stiffness is increased in diabetes even in young subjects who have no clinical cardiovascular disease [32].

**Clinical implications**

Our present results suggest that diagnosis of subclinical diabetic cardiomyopathy should be based on assessment of LV longitudinal function at rest and also at peak stress for the measurement of myocardial functional reserve. Simple measurement of ejection fraction or conventional Doppler assessment of transmitral flow may underestimate the severity of involvement of the heart. The prognostic importance of this subclinical dysfunction is not known, and further studies are warranted. Tissue Doppler should be used in clinical trials as a diagnostic test for subclinical changes of cardiac function in patients with Type II diabetes, since it will have the best power to show changes with new [26] or intensified treatment.

**Study limitations**

Patients with ‘uncomplicated’ Type II diabetes are difficult to find because of the high incidence of coexisting coronary heart disease and arterial hypertension. In this study, we attempted to rule out regional ischaemia by performing non-invasive tests such as quantitative stress echocardiography, which we have shown to be reliable in excluding coronary heart disease [9]. Thus, although the patients may have had some atherosclerosis, it is very unlikely that any patient had a significant epicardial coronary arterial stenosis. The other exclusions and the strict entry criteria meant that 77 % of patients had no evidence of any diabetic complications and 23 % had only minor complications. In our opinion, the population that was studied does not represent a group of diabetic patients at unusual risk, so the results do reflect early subclinical disease in a ‘well’ population, that can be extrapolated to other patients with Type II diabetes.

We included some patients with mild well-controlled arterial hypertension, which may have influenced our results because hypertension can cause subendocardial dysfunction [18], but we did not find significant effects on any of the examined echocardiographic parameters: regional systolic functional reserve was 5 % less in the mildly hypertensive diabetic subjects than in the normotensive diabetic subjects (Table 4). Multifactorial ANOVA suggested that, in our present study, Type II diabetes acted as an independent contributor to longitudinal dysfunction, whereas arterial hypertension (measured as systolic pressure) did not. Diastolic blood pressure was a factor selected by the multivariate regression. Our study was not designed to assess the interaction between diabetes and hypertension on subclinical LV dysfunction, however, and a recent study [25] that specifically addressed this question showed convincingly that there is a cumulative effect. The reduction in subendocardial systolic function at rest (measured as longitudinal strain) was similar in normotensive diabetic patients and age-matched hypertensive non-diabetic controls (both −8 %), while it was doubled (−15 %) in hypertensive diabetics [25].

**Conclusion**

Patients with Type II diabetes have subclinical subendocardial dysfunction both at rest and peak stress, which correlates with the overall glycaemic control of diabetes (HbA1c), lipid profile (LDL-cholesterol), diastolic blood pressure and age. This can be diagnosed easily by TDE, so it can be monitored during treatment to reduce cardiovascular complications of diabetes.

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