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Impaired myocardial function in newly onset Type 2 diabetes associates with arterial stiffness☆

Antti Loimaala [a,*], Kaj Groundstroem [b], Silja Majahalme [c], Arja Nenonen [d], Ilkka Vuori [a]

[a] *Clinical Physiology and Nuclear Medicine, Seinäjoki Central Hospital, Hanneksenrinne 7, 60220 Seinäjoki, Finland*
[b] *Department of Medicine, Central Hospital of Kymenlaakso, Kotka, Finland*
[c] *Appleton Heart Institute, Appleton, Wisconsin, USA*
[d] *Reumasäätiön sairaala, Heinola, Finland*

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Abstract *Aim:* The aim of this study was to evaluate myocardial function using pulsed and color-coded tissue Doppler imaging (TDI) and vascular wall elasticity using whole-body impedance cardiography (ICG) in patients with newly diagnosed Type 2 diabetes mellitus (DM2), and to compare the measurements with those of healthy controls.
Methods: Systolic (SBP) and diastolic (DBP) blood pressure and glycocylated hemoglobin (HbA1c) were measured in 49 men (mean age 52.3 ± 5.6 years, duration of DM2 1.8 years), and 15 healthy male control subjects (48.3 ± 7.4 years). Mitral annular peak systolic (Svm), early (Evm), and late (Avm) diastolic velocities as well as myocardial peak systolic (Sv), early (Ev) and late diastolic (Av) velocity from middle segments of the anterior, inferior and lateral wall and the inferior septum were measured by TDI. ICG at rest was used to measure cardiac index (CI) and pulse wave velocity (PWV).
Results: The patients had higher body mass index (BMI 29.1 ± 3.7 vs. 25.2 ± 2.4 kg/m^2, $p = 0.000$) and SBP (142 ± 15 vs. 120 ± 7 mmHg, $p = 0.005$) than the controls, CI was comparable (2.8 ± 0.5 vs. 2.8 ± 0.6 l/min/m^2). The patients had lower age adjusted myocardial Sv (3.8 ± 1.1 vs. 4.8 ± 1.1 cm/s, $p = 0.002$) and Ev (4.6 ± 1.6 vs. 6.2 ± 1.7 cm/s, $p = 0.011$), and also mitral annulus peak early diastolic velocity (Evm 7.8 ± 1.9 vs. 10.4 ± 2.6 cm/s, $p = 0.001$). In diabetic patients PWV (14.2 ± 2.7 vs. 10.0 ± 1.7 m/s, $p = 0.002$) was higher. Age ($r = -0.39$, $p = 0.001$), BMI ($r = -0.44$, $p = 0.000$) and PWV ($r = -0.52$, $p = 0.000$) correlated

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* Corresponding author. Tel.: +358 6 415 4586; fax: +358 6 415 4994.
E-mail addresses: seanlo@uta.fi, antti.loimaala@epshp.fi (A. Loimaala).

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significantly with Evm. PWV correlated with age ($r = 0.50$, $p = 0.000$), SBP ($r = 0.67$, $p = 0.000$), and HBA1c ($r = 0.36$, $p = 0.010$). In stepwise regression analysis, PWV ($\beta = -0.39$, $p = 0.000$) was the major determinant of Evm.
Conclusion: Myocardial function is impaired in asymptomatic patients with newly detected DM2 consistent with diabetic heart muscle disease. Arterial stiffness is strongly related to myocardial dynamics, and both may have the same pathophysiologic background.

Introduction

Type 2 diabetes mellitus (DM2) is a strong risk factor for heart disease.[1–3] Poor glycemic control and hypertension imply worse prognosis,[4] which may at least partially be attributable to myocardial disease.[5] Accumulating evidence suggests that abnormal LV contraction and filling are early features of the disease. Diabetic patients without coronary heart disease have myocardial perfusion defects during stress,[6] and myocardial acoustic properties are altered in diabetes, suggesting increased connective tissue.[7,8] Diabetes can lead to left ventricular (LV) dysfunction,[5] as found in patients with micro-vascular complications.[9] Additionally, long duration of Type 1 or 2 diabetes decreases myocardial tissue velocities and affects deformation.[10,11] We hypothesized that myocardial contractile function is already reduced and arterial stiffening may be present at the time of diagnosis. Tissue Doppler imaging (TDI) allows regional assessment of myocardial systolic and diastolic velocities,[12] and our aim was to evaluate myocardial function by TDI and vascular wall elasticity by whole-body impedance cardiography (ICG) in patients with newly diagnosed DM2, and to compare the measurements with healthy controls.

Methods

The study group consisted of 49 diabetic men out of 65 volunteers from the Tampere region recruited by a newspaper advertisement. Fifteen healthy doctors and normotensive middle-aged men served as controls. The study was approved by the local ethics committee, and all subjects gave written informed consent. Exclusion criteria were diagnosis of DM2 more than three years previously, history or ECG signs of myocardial infarction, a conduction disturbance on ECG, history of arrhythmias, symptoms or ECG signs of ischemia on exercise stress test, wall motion abnormalities on resting echocardiogram, significant valvular disease, insulin treatment, or any other chronic disease. Sixteen patients had diet-controlled diabetes, 33 patients were treated with oral hypoglycemic drugs, and 20 patients with anti-hypertensive medication (ACE-inhibitors 10, β-blockers 2, Ca-antagonist 3, and ACE-inhibitor combined with a diuretic or Ca-antagonist 5 patients). All patients had normal cutaneous and peripheral vibration sensitivity test and normal retina on ophthalmoscopy. There were 10 smokers and 22 ex-smokers in the diabetic group, but none in the control group.

Resting heart rate was measured from a 12-lead ECG after 5 min of supine rest. The subjects performed a maximal treadmill exercise stress test according to a standard protocol. Fasting blood samples (12 h) were taken from an antecubital vein. Blood glucose was assessed by the glucose dehydrogenase method (Roche Diagnostic System). Cobas Mira Plus automatic analyser (Roche Ltd., Basel, Switzerland) was used for the analyses. HbA1c was assessed by the immunochemical method (Cobas Integra, Hoffmann-La Roche Ltd., Basel, Switzerland) which is a quantitative determination based on immunoturbidimetric testing of inhibition in hemolysed whole blood.

Whole-body impedance cardiography

ICG measurements were performed at rest using a commercially available circulation-monitoring device for impedance-derived measurements (CircMon™ B 202, JR Medical Ltd.). Cardiac index (CI, l/min/m^2), stroke index (SI, ml/m^2), and pulse wave velocity (PWV, m/s) were determined as described previously.[13] Arterial PWV was measured between the aortic arch and the popliteal artery using the time delay between the sharp upstroke of simultaneously recorded whole-body impedance cardiogram and calf impedance plethysmogram. Recordings were made with voltage sensing channels of the monitor and automatically analyzed by the same device. Its operator independent repeatability is 0.54 m/s, reproducibility value is 2.98, and the corresponding value for Doppler is 2.17.[14]

Echocardiographic and tissue Doppler myocardial imaging measurements

Echocardiographic imaging was performed according to the recommendations of the American Society of Echocardiography.[15] M-mode, Doppler, and TDI images were stored on a magneto optic disc using a commercially available echocardiograph (VingMed System V, Horten, Norway), and all measurements were performed off-line. Transmitral flow velocities were obtained from the apical 4-chamber view by positioning the pulsed Doppler sample volume between the tips of the mitral leaflets. Means of at least three cardiac cycles were used for statistical analyses.

Color-coded TDI cine loops obtained with >100 frames/s from the apical 4- and 2-chamber views were used for TDI measurements. Myocardial peak systolic (Sv, cm/s), early (Ev, cm/s) and late (Av, cm/s) diastolic velocities, time to peak Sv (QS, ms), and Ev (QE, ms) were measured from the middle segments of the anterior, lateral and inferior wall, and from the inferior septum, and from the lateral mitral annulus velocity curves (Svm (cm/s), Evm (cm/s), and Avm (cm/s), respectively). An average of at least 12 measurements from the four myocardial segments, and of three measurements from the lateral mitral annulus were used in statistical analyses. Corresponding measurements (Spw, Epw, Apw) using pulsed TDI from the middle segment of the inferior septum were also obtained.

Statistical analysis

Clinical characteristics of the patients and controls are presented as means and standard deviations (SD). Associations between clinical and other study variables were investigated by Pearson's product moment correlation coefficients. In order to compare the possible differences in systolic and diastolic velocities between the diabetics and the controls, an analysis of covariance with age, heart rate during TDI measurements, blood pressure and medication were used as a covariate where appropriate and the results are presented as means, standard errors of estimation and 95% confidence intervals (CI) for the difference between the study groups. Determinants of the TDI velocities were assessed using a stepwise linear regression analysis and a commercial software package (SPSS 10.0.3).

Results

The mean duration of DM2 was 1.8 years from the initial diagnosis. Clinical, standard echocardiographic and hemodynamic characteristics are presented in Tables 1 and 2. The DM2 patients were slightly older, more obese, and had significantly higher resting systolic blood pressure. Smokers were not older compared to non-smokers ($p = 0.62$) unlike past-smokers (56 vs 52 years, $p = 0.014$ vs. non-smokers). Past-smokers had higher BMI compared to smokers (30.9 vs. 28.6 kg/m^2, $p = 0.058$) but no difference was observed between current and non-smokers ($p = 0.84$). The patients had higher mitral inflow *A* velocity. All control subjects had normal resting blood pressure. Pulse wave velocity was significantly higher in the patients indicating stiffer large arteries.

The systolic blood pressure was slightly lower in smokers (139 vs. 144 mmHg, $p = 0.31$, adjusted for age) vs. past or non-smokers, and also the PWV was lower in current and past-smokers (smokers and past-smokers 13.3 vs. 14.9 m/s non-smokers, $p = 0.085$ adjusted for age and BMI, $p =$ ANOVA). In addition, glucose balance was better in current smokers compared to non-smokers (7.2 vs. 8.6%, $p = 0.04$, ANOVA). Use of sulphonylureas was slightly but non-significantly higher in non-smokers compared to smokers ($p = 0.077$).

Tissue Doppler measurements are presented in Table 3. The average 4-wall myocardial peak systolic and early diastolic wall velocity was

Table 1 Clinical characteristics and echocardiographic measurements of the study subjects

Group	Control ($n = 15$)	DM2 ($n = 49$)	*p*-Value
Variable			
Age (years)	48.3 (7.4)	52.3 (5.6)	0.014
BMI (kg/m^2)	25.2 (2.4)	29.1 (3.7)	0.000
SBP (mmHg)	122 (6)	144 (16)	0.005
DBP (mmHg)	81 (8)	87 (8)	0.11
HR (bpm)	62 (8)	71 (12)	0.01
fBGluc (mmol/l)	4.8 (0.6)	8.5 (2.5)	0.000
EF (%)	73.9 (6)	69.6 (8)	0.11
IVSD (mm)	10.6 (1.2)	9.9 (1.8)	0.20
LVEDD (mm)	53 (3.8)	52 (6.9)	0.41
PWD (mm)	9.4 (1.3)	10.6 (1.7)	0.18
E (m/s)	0.66 (0.12)	0.66 (0.12)	0.76
A (m/s)	0.46 (0.06)	0.69 (0.17)	0.005

Values are means (SD). BMI = Body mass index (kg/m^2); SBP = systolic blood pressure (mmHg); DBP = diastolic blood pressure (mmHg); Hr = resting heart rate, beats per minute (bpm); fBGluc = fasting blood glucose (mmol/l); EF = left ventricular ejection fraction (%); IVSD = interventricular septal thickness in diastole (mm); LVEDD = left ventricular internal diameter in diastole (mm); PWD = posterior wall thickness in diastole (mm); *E* = mitral inflow early velocity (m/s); *A* = mitral inflow late velocity (m/s).

Table 2 Body hemodynamic data on the study groups

Group	Control ($n = 15$)	DM2 ($n = 49$)	p-Value
Variable			
CI	2.8 (0.6)	2.8 (0.5)	
	95% CI	−0.47 to 0.39	0.86
SI	46.2 (6.8)	41.5 (7.0)	
	95% CI	−8.4 to 1.4	0.16
PWV	10.0 (1.7)	14.2 (2.7)	
	95% CI	1.0 to 4.2	0.002

Values are means (SD). CI = Cardiac index (ml/min/m^2); 95% CI = 95% confidence interval for the difference between control and DM2 (analysis of covariance, adjusted for age); SI = stroke index (ml/m^2); PWV = pulse wave velocity (m/s).

significantly lower in patients compared to controls (adjustment for age and heart rate, ANOVA). Peak mitral annular early diastolic velocity was lower in the patients. After additional adjustment for resting systolic blood pressure, patients had lower mitral annular Evm (95% confidence interval for the difference −3.10 to −0.12 cm/s, $p = 0.034$) and average myocardial Sv in the four walls (95% confidence interval for the difference −1.81 to −0.16 cm/s, $p = 0.019$). In agreement with color TDI measurement, the pulsed tissue Doppler systolic peak velocities in the septum were similar, but the early diastolic velocity was significantly lower in the patients compared to the controls (Table 3, ANOVA). Mitral annular tissue Doppler *E*-velocities in patients with either ACE-inhibitor (8.0 cm/s) or a combination treatment with either ACE-inhibitor plus diuretic or Ca-antagonist (6.7 cm/s) were not significantly different from patients without medication (8.1 cm/s, $p = 0.96$ and $p = 0.11$ treatment vs. no anti-hypertensive medication, respectively, ANOVA). Since only few patients were on Ca-antagonists or β-blockers, comparison with other groups was not appropriate.

Interrelationships between clinical, echocardiographic, and hemodynamic variables were studied by correlation coefficients. Average peak myocardial Sv correlated with PWV ($r = -0.33$, $p = 0.012$), myocardial Ev most significantly with PWV ($r = -0.59$, $p = 0.000$), BMI ($r = -0.44$, $p = 0.000$) and SBP ($r = -0.42$, $p = 0.000$). Mitral annular Evm associated with PWV ($r = -0.52$, $p = 0.000$), BMI ($r = -0.44$, $p = 0.000$), and age ($r = 0.39$, $p = 0.001$). BMI correlated with SBP ($r = 0.36$, $p = 0.004$), a positive correlation was mostly marked with PWV ($r = 0.44$, $p = 0.000$). HBA1c correlated significantly only with PWV ($r = 0.36$, $p = 0.01$). According to stepwise regression analysis, which included only variables with a significant

Table 3 Tissue Doppler measurements in DM2 patients and healthy controls

Group	Control ($n = 15$)	DM2 ($n = 49$)	p-Value
Variable			
Sv (cm/s)	4.8 (1.1)	3.8 (1.1)	
	95% CI	0.4 to 1.8	0.002
Ev (cm/s)	6.2 (1.7)	4.6 (1.6)	
	95% CI	0.3 to 2.4	0.011
Av (cm/s)	4.8 (1.2)	4.8 (1.8)	
	95% CI	−0.4 to 1.6	0.23
QS (ms)	129 (38)	112 (30)	
	95% CI	−18 to 34	0.533
QE (ms)	512 (35)	480 (49)	
	95% CI	−15 to 31	0.521
Svm (cm/s)	7.8 (2.6)	7.1 (2.0)	
	95% CI	−0.3 to 2.3	0.135
Evm (cm/s)	10.4 (2.6)	7.8 (1.9)	
	95% CI	0.9 to 3.4	0.001
Avm (cm/s)	6.2 (1.8)	8.0 (2.1)	
	95% CI	−2.2 to 0.1	0.07
QSm (ms)	127 (55)	109 (25)	
	95% CI	−10 to 35	0.28
Qem (ms)	477 (36)	465 (45)	
	95% CI	−28 to 14	0.49
Acc (ms)	125 (29)	119 (34)	
	95% CI	−17 to 24	0.74
Dec (ms)	103 (15)	110 (29)	
	95% CI	−23 to 11	0.48
Spw (cm/s)	7.4 (1.9)	6.9 (1.1)	
	95% CI	−0.6 to 1.5	0.43
Epw (cm/s)	11.0 (1.7)	7.3 (2.3)	
	95% CI	1.2 to 4.9	0.002
Apw (cm/s)	8.2 (2.1)	8.5 (1.7)	
	95% CI	−1.5 to 1.5	0.99

Values are covariance corrected means (SD). Sv = Average peak systolic myocardial velocity of the anterior, inferior, lateral and septal middle segments (cm/s); Ev = average peak early diastolic myocardial velocity of the anterior, inferior, lateral and septal middle segments (cm/s); Av = average peak late diastolic myocardial velocity of the anterior, inferior, lateral and septal middle segments (cm/s); QS = time from q-wave to peak systolic myocardial velocity; QE = time from q-wave to peak early diastolic myocardial velocity; Svm = peak systolic mitral annular velocity (cm/s); Evm = peak early diastolic mitral annular velocity (cm/s); Avm = peak late diastolic mitral annular velocity (cm/s); QSm = time from q-wave to peak mitral annular systolic velocity; Qem = time from q-wave to peak mitral annular diastolic velocity; Acc = time from onset of the early diastolic Evm to peak Evm; Dec = time from peak Evm to baseline velocity; Spw = peak systolic velocity in the middle segment of the inferior septum by pulsed tissue Doppler (cm/s); Epw = peak early diastolic velocity in the middle segment of the inferior septum by pulsed tissue Doppler (cm/s); Apw = peak late diastolic velocity in the middle segment of the inferior septum by pulsed tissue Doppler (cm/s); 95% CI = 95% confidence interval for the difference between control and DM2 subjects (analysis of covariance, adjusted for age).

association with either systolic or early diastolic myocardial or mitral annular velocity, PWV was the only significant determinant of myocardial Ev ($\beta = -0.285$, $p = 0.001$) and of Evm ($\beta = -0.39$, $p = 0.000$), whereas age and CI were major determinants of myocardial (Sv) and mitral annular systolic velocity (Svm).

Discussion

To our knowledge, our finding that diabetic myocardial disease can be found very soon after the diagnosis of DM2 has not been reported previously. Patients with Type 2 diabetes have a higher cardiovascular morbidity due to several associated abnormalities.[16] Diabetic heart muscle disease may be one cause for excessive mortality.[17] Compared to previous reports the time from diagnosis of the disease was short (mean 1.8 years). None of the patients had evidence of micro-vascular complications (retinopathy, neuropathy) or signs of coronary artery disease (wall motion abnormality), and none was on insulin treatment. Standard echocardiographic parameters did not differ from the controls except for higher mitral inflow *A* velocity in the patients (Table 1). Systolic and diastolic myocardial velocities were reduced in the patients suggesting impaired myocardial function. Fang et al. reported that myocardial peak early diastolic velocity was on average 2 cm/s lower compared to healthy controls,[10] and that systolic strain and strain rate were lower. However, duration of diabetes was on average 11 years and end-organ damage was observed: peripheral vascular disease was present in 21%, renal impairment in 19%, neuropathy in 27% and subjects had wall motion abnormalities.[10] Likewise, Hansen et al.[11] found in eight Type 1 diabetic patients lower systolic and diastolic velocities compared to controls but duration of diabetes was 10–25 years. Since only a minority of DM2 patients have good disease control, multiple end-organ damage including diabetic heart is more likely to develop with time.[10,11]

Few studies have assessed myocardial contractility using TDI and compared it with arterial stiffness.[18,19] Our patients had significantly higher age adjusted PWV compared to controls (Table 2). After adjustment for BMI and heart rate there still remains a significant difference in PWV between patients and controls (13.8 m/s vs. 11.6 m/s, $p = 0.014$) indicating mediasclerosis in newly diagnosed DM2.[20] The patients had similar stroke index and cardiac index as the controls. However, in TDI measurements both the systolic and diastolic myocardial velocities were lower (Table 3). The mitral annular Evm was 25% lower which equals roughly 10 years of ageing in long axis function.[21] The myocardial pulsed tissue Doppler early diastolic velocity in the inferior septum was lower in patients (Table 3), as were the mean systolic and diastolic velocities in predefined myocardial segments. This finding agrees with Vinereanu et al.,[18] but their patients had wall motion abnormalities and valve regurgitations.

Because our patients were asymptomatic on stress testing, and did not show evidence of ischemic heart disease and had normal contraction on resting echocardiogram, it is unlikely that the lower myocardial velocities are due to epicardial coronary artery stenosis. Compared with the average peak systolic velocity of the middle segments of 4.7 cm/s in the MYDISE population,[21] our patients had 19% lower values (3.8 ± 1.1 cm/s) on average, whereas the Sv of our controls was comparable to that observed in the multi-center study (4.8 ± 1.1 vs. 4.7 ± 1.7 cm/s). This difference might be related to diabetes per se.

Although the causal relationship between arterial stiffening and myocardial velocities cannot be established in this study, epidemiologic and experimental studies in diabetic patients support our results.[16,17] Sv was significantly associated with PWV and myocardial and mitral annular early diastolic velocity correlated strongest with PWV, which correlated significantly with HBA1c, SBP, and age. Fig. 1 describes the association of PWV and mitral annular early diastolic velocity in diabetics. Two parallel processes may be involved in the arterial wall (increase of fibronectin/collagen and glycoprotein content, and vasoconstriction) and in the myocardium (decreased capillary density, fibrosis and muscle cell hypertrophy)[10,16] or arterial stiffness. Our findings concur with earlier reports,[7,8,10,19] and add to the current knowledge that myocardial function is reduced concomitantly with arterial stiffening in early onset diabetes.[16]

The major limitation of the study is that a matched control group was not available. However, myocardial tissue velocities in our control subjects are similar to those observed in a comparable age group of healthy subjects in the multicenter MYDISE study.[21] We used only age-, heart rate- and blood pressure-adjusted values for statistical comparisons. Our study was not powered to detect treatment effect of blood pressure medication, but statistical analyses show that the results are not biased by e.g. ACE-inhibitor treatment. We did not adjust the velocities for BMI because over-weight is a clinical feature of middle-aged subjects with DM2 in the Finnish population.

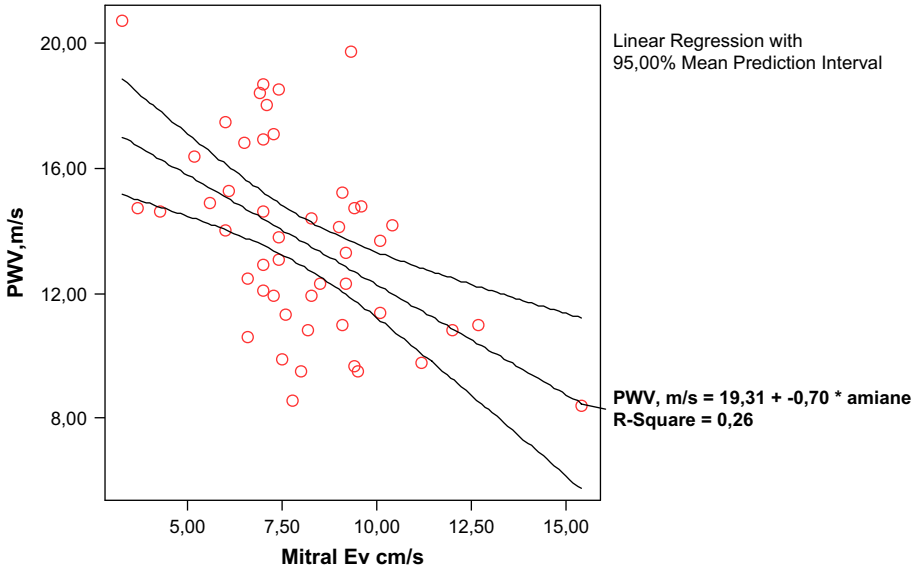

Figure 1 Correlation of arterial pulse wave velocity (PWV, m/s) with mitral annular peak early diastolic velocity in diabetics (Evm = amiane, cm/s).

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References

1. Burchfiel CM, Reed DM, Marcus EB, Strong JP, Hayashi T. Association of diabetes mellitus with coronary arteriosclerosis and myocardial lesions: an autopsy study from the Honolulu Heart Program. *Am J Epidemiol* 1993;**137**:1328–40.
2. Uusitupa M, Mustonen JN, Airaksinen KE. Diabetic heart muscle disease. *Ann Med* 1990;**22**:377–86.
3. Fein FS. Diabetic cardiomyopathy. *Diabetes Care* 1990;**13**:1169–79.
4. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus. *N Engl J Med* 1993;**329**:977–86.
5. Rubler S, Dlugash J, Yeceoglu YZ, Kumral T, Branwood AW, Grishman A. New type of cardiomyopathy associated with diabetic glomerulosclerosis. *Am J Cardiol* 1972;**30**:595–602.
6. Genda A, Mizuno S, Nunoda S, Nakayama A, Igarashi Y, Sugihara N, et al. Clinical studies on diabetic myocardial disease using exercise testing with myocardial scintigraphy and endomyocardial biopsy. *Clin Cardiol* 1986;**9**:375–82.
7. Perez JE, McGill JB, Santiago JV, Schechtman KB, Wagoner AD, Miller JG, et al. Abnormal myocardial acoustic properties in diabetic patients and their correlation with the severity of disease. *J Am Coll Cardiol* 1992;**19**:1154–62.
8. Di Bello V, Talarico L, Picano E, Di Muro C, Landini L, Paterni M, et al. Increased echo density of myocardial wall in the diabetic heart: an ultrasound tissue characterization study. *J Am Coll Cardiol* 1995;**25**:1408–15.
9. Kahn JK, Zola B, Juni JE, Vinik AI. Radionuclide assessment of left ventricular diastolic filling in diabetes mellitus with and without cardiac autonomic neuropathy. *J Am Coll Cardiol* 1986;**7**:114–20.
10. Fang ZY, Yuda S, Anderson V, Short L, Case C, Marwick TH. Echocardiographic detection of early diabetic myocardial disease. *J Am Coll Cardiol* 2003;**41**:611–7.
11. Hansen A, Johansson B-L, Wahren J, von Bibra H. C-peptide exerts beneficial effects on myocardial blood flow and function in patients with type 1 diabetes. *Diabetes* 2002;**51**:3077–82.
12. Sutherland GR, Stewart MJ, Groundstroem KW, Moran CM, Fleming A, Guell-Peris FJ, et al. Color Doppler myocardial imaging: a new technique for the assessment of myocardial function. *J Am Soc Echocardiogr* 1994;**7**:441–58.
13. Loimaala A, Huikuri HV, Kööbi T, Rinne M, Nenonen A, Vuori I. Exercise training improves baroreflex sensitivity in Type II diabetic men. *Diabetes* 2003;**52**:1837–42.
14. Kööbi T, Kähönen M, Iivainen T, Turjanmaa V. Simultaneous non-invasive assessment of arterial stiffness and haemodynamics – a validation study. *Clin Physiol Funct Imag* 2003;**23**(1):31–6.
15. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. *J Am Soc Echocardiogr* 1989;**2**:358–68.
16. Laakso M, Lehto S. Epidemiology of macrovascular disease in diabetes. *Diabetes Rev* 1997;**5**:294–315.
17. McGee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure. The Framingham Study. *N Engl J Med* 1971;**285**:1441–6.
18. Vinereanu D, Nicolaides E, Boden L, Payne N, Jones CJH, Fraser AG. Conduit arterial stiffness is associated with impaired left ventricular subendocardial function. *Heart* 2003;**89**:449–51.
19. Sohn DW, Chai IH, Lee DJ, Kim HC, Kim HS, Oh BH, et al. Assessment of mitral annulus velocity by Doppler tissue

imaging in the evaluation of left ventricular diastolic function. *J Am Coll Cardiol* 1997;**30**:474—80.
20. Asmar R, Topouchian J, Pannier B, Benetos A, Safar M. Pulse wave velocity as endpoint in large-scale intervention trial. The Complior Study. *J Hypertens* 2001;**19**(4): 813—8.
21. Mädler CF, Payne N, Wilkenshof O, Cohen A, Derumeaux GA, Pierard LA, et al. Myocardial Doppler in stress echocardiography (MYDISE) study investigators: Non-invasive diagnosis of coronary artery disease by quantitative stress echocardiography: optimal diagnostic models using off-line tissue Doppler in the MYDISE study. *Eur Heart J* 2003;**24**(17):1541—2.