Diabetologia (2005) 48: 394–402
DOI 10.1007/s00125-004-1632-z

ARTICLE

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Determinants of subclinical diabetic heart disease

Received: 6 April 2004 / Accepted: 9 August 2004 / Published online: 8 January 2005

Abstract *Aims/hypothesis:* Subclinical left ventricular (LV) dysfunction has been shown by tissue Doppler and strain imaging in diabetic patients in the absence of coronary disease or LV hypertrophy, but the prevalence and aetiology of this finding remain unclear. This study sought to identify the prevalence and the determinants of subclinical diabetic heart disease. *Methods:* A group of 219 unselected patients with type 2 diabetes without known cardiac disease underwent resting and stress echocardiography. After exclusion of coronary artery disease or LV hypertrophy, the remaining 120 patients (age 57±10 years, 73 male) were studied with tissue Doppler imaging. Peak systolic strain of each wall and systolic (Sm) and diastolic (Em) velocity of each basal segment were measured from the three apical views and averaged for each patient. Significant subclinical LV dysfunction was identified according to Sm and Em normal ranges adjusted by age and sex. Strain and Em were correlated with clinical, therapeutic, echocardiographic and biochemical variables, and significant independent associations were sought using a multiple linear regression model. *Results:* Significant subclinical LV dysfunction was present in 27% diabetic patients. Myocardial systolic dysfunction by peak strain was independently associated with glycosylated haemoglobin level ($p<0.001$) and lack of angiotensin-converting enzyme inhibitor treatment ($p=0.003$). Myocardial diastolic function (Em) was independently predicted by age ($p=0.013$), hypertension ($p=0.001$), insulin ($p=0.008$) and metformin ($p=0.01$) treatment. *Conclusions/interpretation:* In patients with diabetes mellitus, subclinical LV dysfunction is common and associated with poor diabetic control, advancing age, hypertension and metformin treatment; ACE inhibitor and insulin therapies appear to be protective.

Keywords Myocardial early diastolic velocity · Strain · Subclinical diabetes heart disease

Abbreviations ACE: angiotensin-converting enzyme · BP: blood pressure · DT: mitral valve deceleration time · E/A: ratio of the early to the late peak diastolic transmitral flow velocity · HbA_1c: haemoglobin A1c · LV: left ventricular · LVEF: left ventricular ejection fraction · PVD: peripheral vascular disease

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Introduction

Cardiovascular disease is the most common cause of death in patients with diabetes mellitus. These patients have an increased incidence of heart failure, and diabetes mellitus has an adverse impact on the prognosis of patients with heart failure-findings that may be attributable to the presence of a clinically inapparent diabetic cardiomyopath. This is characterised by defects in both diastolic and systolic function, in patients among whom coronary artery disease and left ventricular (LV) hypertrophy have been excluded.

The spectrum of diabetic heart disease involves a progression from the normal heart, to preclinical LV diastolic and systolic dysfunction (detectable only with sophisticated imaging techniques), followed by overt echocardiographic evidence of LV dysfunction (still clinically silent) and finally symptomatic heart failure. In subjects without evidence of clinical cardiovascular disease at baseline, the presence of subclinical disease is associated with a significantly increased risk of coronary heart disease, with the increased risk of total mortality being 2.9 for men and 1.7 for women [1]. Moreover, in uncomplicated well-controlled type 2 diabetes, LV dysfunction detected by echocardiography has been associated with impaired functional capacity observed in these patients [2]. A follow-up study

over 6.4 years demonstrated that diabetic subjects had a higher prevalence of clinical and subclinical cardiovascular disease at baseline, and the presence of subclinical cardiovascular disease and diabetes was associated with significantly increased adjusted relative risk of death, relative risk of incident coronary heart disease, and incident myocardial infarction [3]. Thus, subclinical cardiovascular disease is an important determinant of clinical cardiovascular disease among diabetic patients, and the detection of subclinical cardiovascular disease in these patients may provide an approach for identifying high-risk individuals who may benefit from earlier and more active intervention to prevent clinical disease.

Although overt diastolic and systolic dysfunction may be identified by conventional approaches such as mitral inflow patterns and left ventricular ejection fraction (LVEF), the initial stage of this process may be concealed by various compensatory mechanisms [4]. By using new echocardiographic techniques that are sensitive to minor dysfunction, such as tissue Doppler to measure myocardial velocity [5] and more sophisticated measures of local deformation, such as strain and strain rate [6], previous studies [7, 8] have shown abnormal myocardial function in patients with diabetes mellitus but without overt heart disease. While these results have been shown to be abnormal across populations, the prevalence of abnormal findings has remained undefined. Moreover, the aetiology of diabetic heart muscle disease remains unclear. Age, hypertension, diabetic control and medical therapy are all plausible contributors. In this study, we sought to screen patients likely to have abnormal myocardial function in the general population after exclusion of LV hypertrophy and coronary artery disease, and to evaluate the contribution of factors to its severity.

Subjects and methods

Patient selection We studied 219 unselected asymptomatic diabetic patients without a history of either coronary artery disease, moderate to severe valvular disease, atrial fibrillation or other severe arrhythmias and congenital heart disease. Most of these patients were recruited from hospital diabetic clinics (n=116), with some from community general practices (n=45) and the remainder from a cardiology referral service for cardiac disease screening. The diagnosis of diabetes was made in the presence of a random plasma glucose ≥11.1 mmol/l or fasting plasma glucose ≥7.0 mmol/l. The Ethics Committee of Princess Alexandra Hospital approved this project and informed consent was obtained from every subject.

Biochemical analysis Blood for biochemical analysis was obtained from fasting venous samples. Glucose, HbA_1c, insulin, total cholesterol, high density lipoprotein and triglycerides were determined by standard methods. Glucose was measured by the hexokinase method (Hitachi Modular Analyser, Japan) and HbA_1c by high pressure liquid chromatography (Bio-Rad Variant, Hercules, CA). High density lipoprotein cholesterol (HDL-C) was measured as a homogeneous assay in liquid phase (Boehringer Mannheim, Mannheim, Germany) on a Hitachi 747 autoanalyser. The Friedewald equation was used to calculate LDL-C levels if TG was <400 mg/dl (4.5 mmol/l).

Resting echocardiography Using a standard commercial ultrasound machine (Vivid 7, GE Vingmed, Horten, Norway) with a 2.5-MHz phased array probe, we acquired three apical views (apical four-chamber, two-chamber, and long-axis views) using standard harmonic imaging. Mitral inflow velocities were recorded by using conventional pulsed-wave Doppler echocardiography. All images were saved digitally in raw-data format to magneto optical disk for offline analysis.

Left ventricular diameters and wall thicknesses were measured from two-dimensional targeted M-mode echocardiography. LV mass was determined by Devereux's formula [9]. LV hypertrophy was defined as LV mass index (LVMI, g/m^2) greater than 131 g/m^2 in men and greater than 100 g/m^2 in women [10]. Resting LV end-diastolic, end-systolic volumes and ejection fraction were computed using a modified Simpson's biplane method.

Stress testing Stress testing was performed in all patients, with the goal of excluding those with evidence of coronary disease. Exercise echocardiography was performed in patients who were able to exercise maximally, using a standard symptom-limited exercise protocol, selected in accordance with the age and fitness of the subject. The remaining 47 patients underwent a standard dobutamine–atropine echocardiography protocol.

Regional wall motion analysis was scored as normal, mildly hypokinetic, severely hypokinetic and akinetic by two observers blinded to the patients' clinical data. Infarction was identified by resting wall motion abnormalities, and ischaemia was identified by inducible wall motion abnormalities. Patients with LV hypertrophy, LV ejection fraction <50% or infarction or ischaemia were excluded.

Tissue Doppler acquisition and analysis The same echocardiograph machine was used to acquire colour tissue Doppler data using a high frequency acquisition. The imaging angle was adjusted to ensure a parallel alignment of the beam with the myocardial segment of interest.

Tissue velocity curves were obtained from colour tissue Doppler images using standard commercial software (Echopac PC, GE-Vingmed, Horten, Norway). Resting tissue Doppler velocity profiles within a 5×10-mm^2 sample volume were derived from the basal segment of the septal, lateral, anteroseptal, posterior, inferior and anterior LV walls. Myocardial peak systolic (Sm) and early diastolic filling (Em) velocity were measured and averaged for each patient. Myocardial strain curves were extracted from tissue Doppler imaging data by placing a sample volume (5×10 mm^2) in the mid-myocardial layer of each of the six walls in the three apical views. Peak strain was defined as the greatest value on the strain curve. Segments where the signal was of insufficient quality, or the insonation angle >20° were excluded.

Age- and gender-specific normal ranges of Sm or Em have been reported in healthy controls [11], and significant subclinical diabetic heart disease was defined as greater than one standard deviation less than the mean normal value adjusted by age and sex. Strain currently lacks normal ranges based on large numbers of patients and was therefore not used as the cut-off for subclinical dysfunction. However, because of its sensitivity as a systolic marker, it was analysed as a continuous variable in the regression analyses.

Interobserver and intraobserver variability Variability in the measurement of peak strain and myocardial velocities using the same acquired imaging data was re-evaluated in 15 randomly selected patients by two independent observers. To determine reproducibility, the same observer who was blinded to the former results measured peak strain and myocardial velocities for each of the selected patients again at a separate time (at least 2 weeks). To test inter-observer variability, another observer, who was unaware of patient identity and the first observer's results, analysed the same patients' data in the same way.

Statistical analysis Values were expressed as a mean ± standard deviation. Univariate and multiunivariate analyses were used to examine correlations between peak strain or myocardial early diastolic velocity and potential predictors of myocardial disease. Data were analysed using standard statistical software (SPSS, Chicago, IL). A p value <0.05 was considered statistically significant.

Table 1 Clinical characteristics of the diabetic patients with and without significant subclinical left ventricular dysfunction

	LVD (n=32)	Normal (n=88)	p Value
Clinical features			
Age (years)	54±12	58±10	NS
Sex (m)	17 (53%)	56 (64%)	NS
Diabetic duration (years)	9±8	11±8	NS
BMI (kg/m^2)	34±7	30±6	0.001
Heart rate (beats/min)	72±9	72±13	NS
Systolic BP (mmHg)	137±17	136±22	NS
Diastolic BP (mmHg)	77±9	76±13	NS
Hypertension	20 (63%)	46 (52%)	NS
Diabetic complications			
Peripheral vascular disease	3 (9%)	10 (11%)	NS
Renal impairment	7 (22%)	21 (24%)	NS
Retinopathy	9 (28%)	21 (24%)	NS
Neuropathy	5 (16%)	22 (25%)	NS
Blood biochemistry			
HbA_1c (%)	8.2±1.8	7.9±1.8	NS
Glucose (mmol/l)	9.7±3.8	9.8±4.5	NS
Total chol (mmol/l)	4.3±0.8 (29)	4.8±1.1 (83)	0.018
LDL chol (mmol/l)	2.2±0.8 (26)	2.6±0.7 (58)	0.019
HDL chol (mmol/l)	1.2±0.3 (28)	1.3±0.4 (60)	0.037
TG (mmol/l)	2.1±1.2 (29)	1.9±1.3 (83)	NS
Creatinine (μmol/l)	0.08±0.02	0.09±0.05	NS
Urea (mmol/l)	6.0±2.4	7.1±3.3	NS
Diabetic treatment			
Insulin	9 (28%)	35 (40%)	NS
Diet therapy	3 (9%)	7 (8%)	NS
Metformin	23 (77%)	38 (43%)	0.006
Sulphonylureas	15 (47%)	45 (51%)	NS
Other treatment			
ACE inhibitors	12 (38%)	49 (56%)	NS
Calcium blockers	7 (22%)	18 (20%)	NS
Beta blockers	1 (3%)	19 (22%)	0.017
Statin	14 (44%)	27 (31%)	NS

ACE Angiotensin-converting enzyme, *BMI* body mass index, *BP* blood pressure, *HbA_1C* haemoglobin A1c, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *LVD* subclinical left ventricular dysfunction, *NS* no significant difference, *TG* triglycerides

Results

Clinical and echocardiographic characteristics Of 219 patients, 26 were excluded due to coronary artery disease and 51 due to LV hypertrophy and 22 due to a non-diagnostic stress test for ischaemia. In the remaining 120 patients (age 57 ±10 years, 73 male), 12 segments (from 11 patients) where the signal was of insufficient quality, or the insonation angle >20° were excluded. Subclinical LV dysfunction was present in 27% of these 120 patients, with identification of subclinical LV systolic dysfunction in 16%, LV diastolic dysfunction in 21% and both LV systolic and diastolic dysfunction in 10%. Only seven patients had systolic dysfunction alone. The clinical and echocardiographic characteristics of these patients are summarised in Tables 1 and 2. Other than the new

Table 2 Echocardiographic characteristics of the diabetic patients with and without significant subclinical left ventricular dysfunction

	LVD (n=32)	Normal (n=88)	p Value
Echocardiography			
LV EDV (ml)	77±24	81±22	NS
LV ESV (ml)	30±9	32±12	NS
LV EF (%)	61±5	62±5	NS
LVMI (g/m^2)	87±19	92±20	NS
Doppler			
E (m/s)	0.8±0.2	0.8±0.2	NS
A (m/s)	0.8±0.2	0.8±0.2	NS
E/A	1.1±0.3	1.0±0.3	NS
DT (ms)	244±46	252±51	NS
IVRT (ms)	108±37	102±21	NS
Tissue Doppler imaging			
Sm (cm/s)	4.1±0.9	5.8±1.1	<0.001
Em (cm/s)	3.9±1.2	6.4±1.8	<0.001
Strain (%)	20±3	22±3	<0.001

A Mitral late peak velocity, *DT* mitral valve deceleration time, *E* mitral early peak velocity, *E/A* ratio of the early to the late peak diastolic transmitral flow velocity, *Em* basal myocardial early diastolic velocity, *LV* left ventricular, *LVD* subclinical LV dysfunction, *LVEDV* LV end-diastolic volume, *LVEF* LV ejection fraction, *LVESV* LV end-systolic volume, *LVMI* LV mass index, *NS* no significant difference, *Sm* basal myocardial systolic velocity.

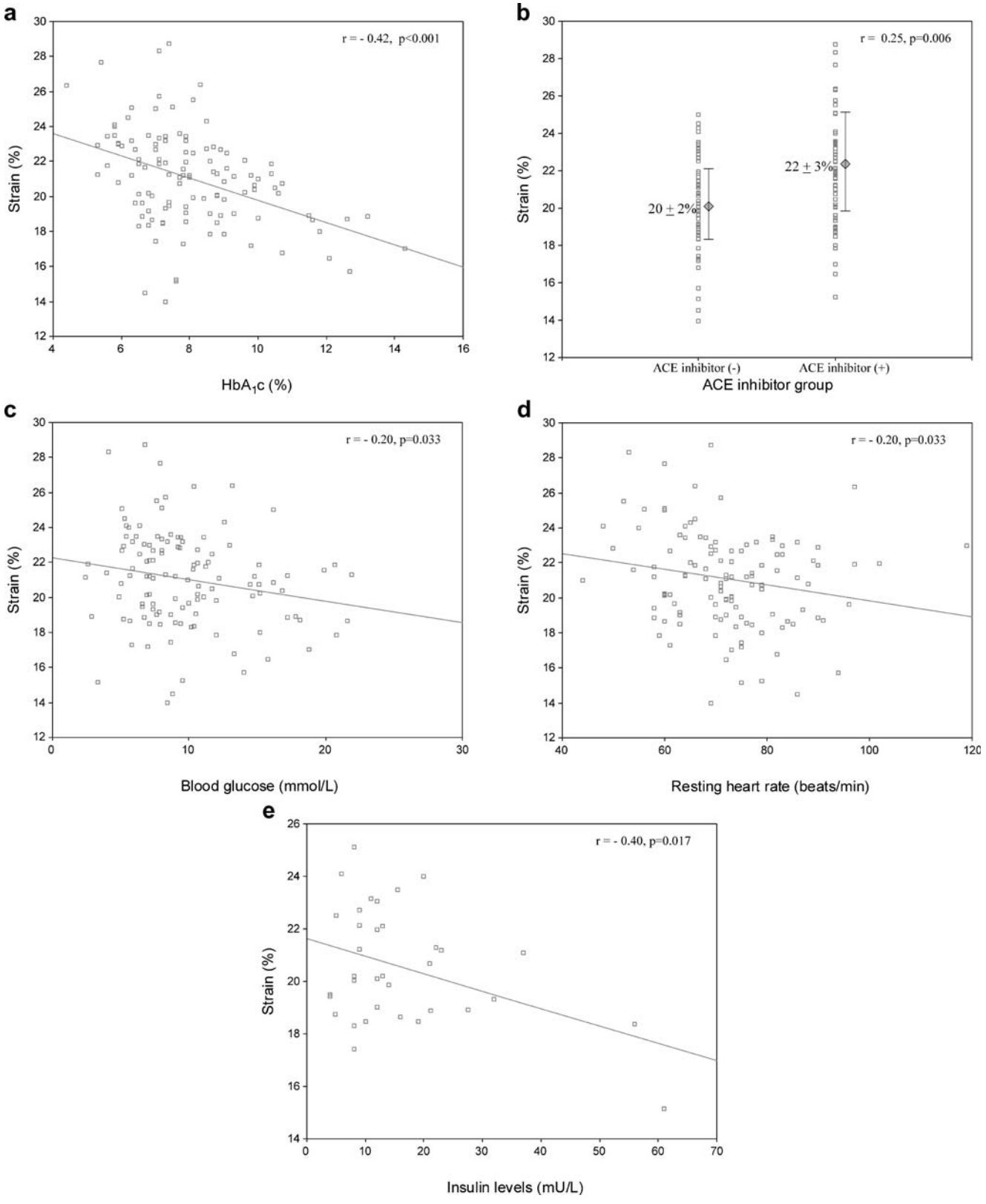

Fig. 1 Association of peak myocardial systolic strain with: HbA_1c (**a**), angiotensin-converting enzyme (ACE) inhibitor therapy (**b**), blood glucose levels (**c**), resting heart rate (**d**), insulin levels in patients not taking exogenous insulin (**e**)

parameters, no standard clinical or echo criteria could be used to diagnose subclinical diabetic heart disease.

Correlates of systolic dysfunction Figure 1 illustrates the significant univariate associations with peak strain, which was positively correlated with ACE inhibitor treatment (r=0.25, p=0.006), and negatively associated with heart rate (r=−0.20, p=0.033), glucose (r=−0.20, p=0.03) and HbA_1c (r=−0.420, p<0.001). When all these associated factors were entered into a forward stepwise regression model, the results showed only the association with HbA_1c (r=−0.42, p<0.001) and ACE inhibitor treatment (r=0.24, p=0.003) to be independent predictors of peak strain (r^2=0.24) (Table 3). In a subgroup of 35 patients who were not taking exogenous insulin, who had insulin measurements (mean insulin 16±13 mIU/l), strain was also significantly associated with insulin levels (r=−0.400, p=0.017).

Further analysis of patients with and without subclinical LV systolic dysfunction showed strain (19±2 vs 21±3%, p=0.005), Em (4.3+1.2 vs 6.0±2.0 cm/s, p<0.001) and age (51±13 vs 58±10 years, p=0.036) were significantly less, but body mass index (36±7 vs 30±6, p=0.002) and the percentage of patients on metformin (89 vs 46%, p=0.008) were significantly greater in patients with subclinical systolic dysfunction compared with the remainder.

Factors associated with diastolic dysfunction Figure 2 illustrates the significant univariate associations with Em. This was negatively associated with age (r=−0.285, p=0.002), hypertension history (r=−0.303, p=0.001), body mass index (r=−0.204, p=0.026) and metformin treatment (r=−0.295, p=0.001), and positively associated with insulin treatment (r=0.287, p=0.001). When all these associated factors were entered a forward stepwise regression

Table 3 Factors associated with left ventricular systolic and diastolic function in diabetes

	Systolic function strain (%)				Diastolic function Em (cm/s)			
	Univariate (r)	p Value	Multivariate (β)	p Value	Univariate (r)	p Value	Multivariate (β)	p Value
General information								
Age	0.093	0.311			−0.285	0.002	−0.206	0.013
Heart rate	−0.195	0.033			−0.077	0.404		
BMI (kg/m^2)	−0.014	0.880			−0.204	0.026		
Systolic BP	0.034	0.710			−0.064	0.484		
Diastolic BP	−0.073	0.427			−0.006	0.944		
Hypertension	0.020	0.827			−0.303	0.001	−0.273	0.001
Complications								
PVD	−0.065	0.481			−0.017	0.850		
Renal impairment	0.003	0.975			−0.065	0.481		
Retinopathy	0.074	0.421			−0.033	0.722		
Neuropathy	−0.038	0.682			−0.143	0.119		
Diabetic control								
HbA_1C (%)	−0.420	<0.001	−0.415	<0.001	−0.104	0.258		
Glucose (mmol/l)	−0.195	0.038			0.076	0.410		
Diabetic treatment								
Insulin	0.170	0.063			0.287	0.001	0.226	0.008
Diet therapy	−0.090	0.327			−0.003	0.978		
Metformin	−0.158	0.085			−0.295	0.001	−0.215	0.01
Sulphonylureas	−0.026	0.775			−0.165	0.072		
Other treatment								
ACE inhibitors	0.251	0.006	0.243	0.003	0.043	0.644		
Calcium blockers	0.068	0.462			−0.086	0.350		
Beta-blockers	0.157	0.087			0.02	0.829		
Statin	−0.154	0.093			−0.089	0.332		
Echocardiography								
LV EF (%)	0.159	0.083			0.097	0.292		
E (m/s)	0.129	0.177			0.180	0.058		
A (m/s)	−0.013	0.889			−0.427	<0.001		
E/A	0.106	0.270			0.637	<0.001		
DT (ms)	0.160	0.094			−0.08	0.403		

A Mitral late peak velocity, *ACE* angiotensin-converting enzyme, *BP* blood pressure, *DT* mitral valve deceleration time, *E* mitral early peak velocity, *E/A* ratio of the early to the late peak diastolic transmitral flow velocity, *HbA_1c* haemoglobin A1c; *LV* left ventricular, *LVEF* LV ejection fraction, *PVD* peripheral vascular disease, *NS* no significant difference

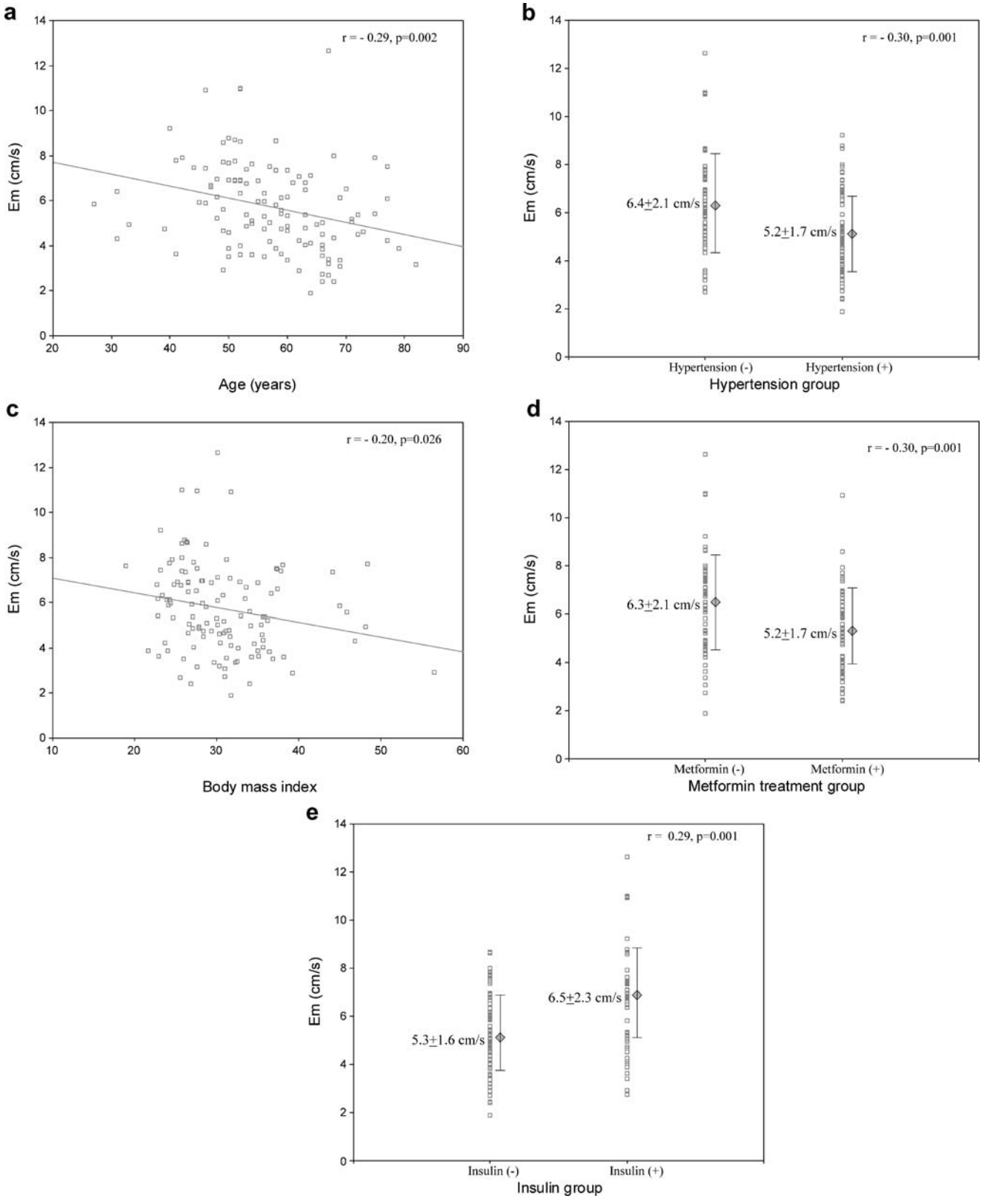

Fig. 2 Association of peak early diastolic myocardial velocity (Em) with: age (**a**), hypertension history (**b**), body mass index (**c**), metformin treatment (**d**), insulin treatment (**e**)

model, the results showed only the associations of age (r=−0.21, p=0.013), hypertension (r=−0.27, p=0.001), insulin treatment (r=0.23, p=0.008) and metformin treatment (r=−0.22, p=0.01) to be independent predictors of Em (r^2=0.27) (Table 3).

Analysis of patients with and without significant subclinical LV diastolic dysfunction demonstrated strain (19±3 vs 22±33%, p<0.001) and Em (3.6±0.9 vs 6.3±1.8 cm/s, p<0.001) were significantly less but body mass index (34±8 vs 30±6, p=0.007) was significantly higher in patients with subclinical diastolic dysfunction compared with those without subclinical LV diastolic dysfunction.

Although β-blocker use was significantly greater in patients without LV dysfunction, this was not an independent correlate of either systolic or diastolic dysfunction.

Interobserver and intraobserver variability There were no significant differences in peak strain and Em between the observer (22±2%, 6.1±1.8 cm/s) and another observer (22±2%, 6.0±2.0 cm/s) or repeat measurement by the same observer (21±2%, 6.0±1.9 cm/s) after a 2-week interval. Mean absolute differences in peak strain and Em were 2±1% (range from 1 to 3%), 0.4±0.4 cm/s (range from 0.0 to 1.4 cm/s) between the two observers and were 1±1% (range from 0 to 3%), 0.3±0.3 cm/s (range from 0.0 to 1.0 cm/s) between the two measurements by the same observer, respectively.

Discussion

The recent use of sensitive and less load-dependent techniques such as strain, strain rate and myocardial velocity by tissue Doppler imaging has demonstrated the occurrence of both systolic and diastolic abnormalities as a marker of "preclinical" heart disease in diabetic patients [7, 8]. Based on recently described age- and gender-adjusted normal ranges, we identified subclinical diabetic heart disease in 27% of patients without known heart disease, with the incidence of LV diastolic dysfunction exceeding that of isolated systolic dysfunction. Poor diabetic control appears to be associated with worse systolic function and this may be avoided by ACE inhibitor treatment, while advancing age and hypertension are associated with worse diastolic dysfunction, which appears less frequent in patients treated with insulin.

Determinants of LV systolic function The correlation between HbA_1c and myocardial systolic function suggests that systolic dysfunction in diabetic subjects may be a result of cardiac changes directly triggered by hyperglycaemia. These clinical findings are consistent with previous studies with diabetes in animals [12] and humans [13]. Failure to identify this in previous studies in type 2 diabetes [14] probably reflects the use of less sensitive markers of LV function. Myocardial dysfunction in diabetes may be functional—resulting from alterations in substrate supply and utilisation, elevated NEFA levels and abnormalities in regulation of calcium homeostasis. However, it may also be structural—both apoptosis and necrosis have been identified in diabetic heart disease and myocyte cell death caused by either apoptosis or necrosis or both may be a major reason for the reduced myocardial contractility. Evidence in vivo has shown that hyperglycaemia directly induces apoptotic cell death and myocyte necrosis in the myocardium, triggered by reactive oxygen species derived from high levels of glucose [15]. Myocyte apoptosis and necrosis initiated by hyperglycaemia result in myocardial cell loss, which may impair the ability of the myocardium to develop force, accounting for reduced contractility.

ACE inhibitors are beneficial in nondiabetic patients with asymptomatic LV systolic dysfunction. This study suggests a protective effect of ACE inhibitors on myocardial function in diabetic patients, and is congruous with a previous study demonstrating prevention of systolic dysfunction in diabetes by chronic ACE inhibitor treatment [16]. This effect may be mediated by reduction of LV afterload due to the anti-hypertensive effects of ACE inhibitors. It may also be due to a number of other beneficial humoral effects caused by ACE inhibitors, including increases in kinin levels (which stimulate production of endothelium-derived nitric oxide, prostacyclin and hyperpolarising factor) and reduction of endothelin-1 levels. These effects may increase the number of perfused capillaries in diabetic subjects [17] and improve endothelial dysfunction and coronary blood flow. Finally, improved insulin sensitivity and glycaemic control with ACE inhibitors may also contribute to improved LV systolic function.

Determinants of LV diastolic function As expected, both age and hypertension were associated with LV diastolic function. The more important finding of this study is that insulin treatment has a positive effect on LV diastolic function, confirmed directly by animal data [18] and indirectly by kidney–pancreas transplantation in humans [19]. The beneficial effect of insulin treatment on diastolic function is possibly related to maintaining a more normal metabolic milieu and prevention of further myocardial structural change or fibrosis. Altered myocardial energy metabolism has been shown to contribute to LV diastolic functional changes in patients with type 2 diabetes [20]. Both islet transplantation and insulin therapy lead to a complete reversal of the haemodynamic and metabolic alterations in diabetes [21], and insulin improves energy metabolism in diabetic hearts during hypoperfusion and significantly reduced the elevated diastolic tension [22]. The formation of collagen advanced glycation endproducts (AGE) due to hyperglycaemia is associated with LV chamber stiffness [23], and exposure to AGE or overexpression of the AGE receptor is associated with abnormal intracellular calcium handling [24] and thus abnormal myocardial relaxation. Insulin therapy has been shown to reverse passive-elastic changes in diabetic rats [18] and to normalise sarcoplasmic reticulum protein expression and function [25]. Furthermore, progressive structural changes in the myocardium caused by diabetes might be prevented by early insulin treatment and selectively reversed by delayed insulin treatment [26]. Finally, some indirect evidence also supports a beneficial effect of insulin therapy on diastolic dysfunction.

An insulin sensitiser (troglitazone) has been shown to protect against relaxation abnormalities caused by hyperglycaemia [27] and pioglitazone decreased LV collagen accumulation and improved LV diastolic function of prediabetic rat hearts [28]. Similarly, regular insulin treatment in type I diabetics is associated with normal or nearly normal diastolic function in young patients with diabetes of short duration [29] or less severe diastolic dysfunction in type 1 diabetic patients with a relatively higher HbA_1c value or longer duration of the known disease compared with type 2 diabetic patients [30].

The interesting finding of this study is that metformin appears to have a weak adverse effect on LV diastolic function. A previous animal study demonstrated that metformin provided cardio-protection against hyperglycaemia-induced abnormalities in myocyte relaxation [31], possibly due to its effect on insulin resistance, which may prevent the increment of diastolic chamber stiffness but have no effect on elevated collagen concentration in diabetes [32]. However, other studies have shown that metformin treatment did not increase glucose oxidation or glucose disposal under conditions of physiological hyperinsulinaemia [33] and even had no significant effect on insulin sensitivity [34]. Although metformin treatment may produce a mild effect on insulin resistance at the initial stage of treatment, metformin resistance might develop after a period of treatment. Another possible explanation is that most patients in this study on metformin were obese and obesity has an adverse effect on LV diastolic function.

Limitations The use of stress echo to identify ischaemia may not completely exclude the presence of coronary artery disease. However, in the absence of resting wall motion abnormalities and significant ischaemia, it seems improbable that coronary disease accounted for abnormal function. Albuminuria is associated with LV diastolic and systolic dysfunction, but unfortunately, these data were not obtained.

Conclusions The findings of this study demonstrate that subclinical LV dysfunction is common in diabetic patients without known cardiac disease and the severity of diabetic heart disease is affected by many factors. Diabetic control is a determinant of systolic dysfunction, which may be spared by ACE inhibitor treatment. Although increasing age and metformin treatment potentiate diastolic dysfunction, control of hypertension and insulin therapy appear to attenuate these diastolic changes. These associations may yield clues to potential interventions for early diabetic heart disease.

Acknowledgements Supported in part by a Clinical Centres of Research Excellence Award from the National Health and Medical Research Council of Australia. None of the authors have conflicts of interest relevant to this work.

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