Determinants of Exercise Capacity in Patients With Type 2 Diabetes

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OBJECTIVE — Type 2 diabetes is associated with reduced exercise capacity, but the cause of this association is unclear. We sought the associations of impaired exercise capacity in type 2 diabetes.

RESEARCH DESIGN AND METHODS — Subclinical left ventricular (LV) dysfunction was sought from myocardial strain rate and the basal segmental diastolic velocity (Em) of each wall in 170 patients with type 2 diabetes (aged 56 ± 10 years, 91 men), good quality echocardiographic images, and negative exercise echocardiograms. The same measurements were made in 56 control subjects (aged 53 ± 10 years, 29 men). Exercise capacity was calculated in metabolic equivalents, and heart rate recovery (HRR) was measured as the heart rate difference between peak and 1 min after exercise. In subjects with type 2 diabetes, exercise capacity was correlated with clinical, therapeutic, biochemical, and echocardiographic variables, and significant independent associations were sought using a multiple linear regression model.

RESULTS — Exercise capacity, strain rate, Em, and HRR were significantly reduced in type 2 diabetes. Exercise capacity was associated with age ($r = -0.37$, $P < 0.001$), male sex ($r = 0.26$, $P = 0.001$), BMI ($r = -0.19$, $P = 0.012$), HbA_{1c} (A1C; $r = -0.22$, $P = 0.009$), Em ($r = 0.43$, $P < 0.001$), HRR ($r = 0.42$, $P < 0.001$), diabetes duration ($r = -0.18$, $P = 0.021$), and hypertension history ($r = -0.28$, $P < 0.001$). Age ($P < 0.001$), male sex ($P = 0.007$), BMI ($P = 0.001$), Em ($P = 0.032$), HRR ($P = 0.013$), and A1C ($P = 0.0007$) were independent predictors of exercise capacity.

CONCLUSIONS — Reduced exercise capacity in patients with type 2 diabetes is associated with diabetes control, subclinical LV dysfunction, and impaired HRR.

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Clinical and observational studies have shown that exercise capacity is a strong predictor of cardiovascular and overall mortality (1). Patients with type 2 diabetes often complain of fatigue and reduced exercise capacity. Although these symptoms may be related to other disease conditions, such as hypertensive left ventricular (LV) hypertrophy or coronary artery disease, the presence of diabetes may independently contribute to the impaired exercise capacity (2).

The causes of reduced exercise capacity in type 2 diabetes are unknown. Overt LV diastolic dysfunction, evidenced by abnormal transmitral flow, has been associated with impaired functional capacity in uncomplicated well-controlled type 2 diabetes (2). However, primary myocardial disease may be present in many patients with type 2 diabetes, without overt systolic or diastolic dysfunction, independent of LV hypertrophy and coronary artery disease (3). Cardiac autonomic dysfunction may play an important role in the development of diabetic heart disease (3). Reduced heart rate recovery (HRR) immediately after exercise is an important indicator of cardiac autonomic dysfunction and contributes to cardiovascular morbidity and mortality in other diseases (4,5). In this study, we sought the extent to which diabetes control, impaired HRR, and subclinical LV dysfunction influence exercise capacity in patients with type 2 diabetes and without significant coronary artery disease.

RESEARCH DESIGN AND METHODS

— In addition to the 195 patients with type 2 diabetes, we also studied 56 normal control subjects, who lacked cardiac symptoms, had an ejection fraction >50%, and had no history of coronary artery disease. Patients with moderate to severe valvular disease, atrial fibrillation or other severe arrhythmias, congenital heart disease, respiratory disease, and leg problems were excluded. Medications including β-blockers, calcium channel antagonists, ACE inhibitors, and nitrates were discontinued at least 12 h before the exercise test. The ethics committee of Princess Alexandra Hospital approved this project, and informed consent was obtained from each subject.

Clinical and biochemical variables

Fasting body weight was measured with the same scale, and height was measured at the same time. BMI was calculated as weight in kilograms divided by height in meters squared (2). Seated resting heart rate and blood pressure were measured in each patient after at least a 15-min rest but before the echocardiogram or stress test. Heart rate and blood pressure were also monitored during the exercise test.

Blood for glucose, HbA_{1c} (A1C), insulin, urea, creatinine, and lipid profile was drawn from patients after fasting for at least 8 h and before oral antidiabetic drugs or insulin and treadmill exercise testing. Glucose was measured by the hexokinase method (Hitachi Modular Analyzer; Tokyo, Japan) and A1C by the high-performance liquid chromotography method (high-pressure liquid chromatography; Bio-Rad Variant). Insulin

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Abbreviations: HRR, heart rate recovery; LV, left ventricular.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

was assayed by two-site immunoenzymometric assay with fluorescence detection using a semiautomated immunoassay analyzer (Tosoh AIA-600; Edward Keller, Melbourne, Australia). Total cholesterol and triglycerides were determined enzymatically with the cholesterol oxidase-peroxidase amino phenazone phenol and the glycerol-3-phosphate oxidase-peroxidase amino phenazone phenol method (Hitachi Modular Analyzer). HDL cholesterol was measured using a homogeneous assay (Roche Diagnostics, Mannheim, Germany). Measurements were calibrated using secondary standards for automated analyzers (Roche Diagnostics). Low-density cholesterol was calculated using the Friedewald formula (6).

Conventional and tissue Doppler echocardiography

Subjects were examined in the left lateral decubitus position using a standard commercial ultrasound machine (Vivid 7; GE Vingmed, Horten, Norway) with a 3.5-MHz phased array probe. Both conventional echocardiographic data and color tissue Doppler data were acquired in the parasternal and three apical views (apical four-chamber, two-chamber, and long-axis views) using standard harmonic imaging and a high-frequency acquisition, respectively. The imaging angle was adjusted to ensure a parallel or perpendicular alignment of the beam with the myocardial segment of interest. Mitral inflow indexes were recorded. All images were saved digitally in raw-data format to a magneto optical disk for off-line analysis

LV diameters and wall thicknesses were measured from two-dimensional targeted M-mode echocardiography. LV mass was determined by Devereux's formula (7). Resting LV end-diastolic and end-systolic volumes and ejection fraction were computed using a modified Simpson's biplane method. Using standard commercial software (Echopac PC; GE-Vingmed, Horten, Norway), resting myocardial strain rate and basal segmental myocardial early diastolic velocity (Em) were measured in each of six walls (septal, lateral, anteroseptal, posterior, inferior, and anterior LV walls) in the three apical views using a 10×5–mm^2 sample volume, as previously described (8,9). Variability in the measurement of myocardial strain rate and Em has been previously reported from our laboratory (8,9).

Stress testing

Exercise stress testing by treadmill was performed in all patients and control subjects, with the goal of excluding those with coronary artery disease. Subjects were encouraged to achieve their maximal exercise capacity. Blood pressure and cardiac status (using a 12-lead electrocardiogram) were monitored and recorded during the exercise test. Exercise capacity was calculated in metabolic equivalents, and HRR was measured as the difference between maximal heart rate and 1-min heart rate immediately after peak exercise. Abnormal exercise capacity was defined by the following formula: METs = 18.0–0.15 × age (10), and abnormal HRR was defined as HRR ≤18 beats per minute (5).

Regional wall motion was analyzed by two observers blinded to the patient's clinical data; infarction was identified by resting wall motion abnormalities, and ischemia was identified by inducible wall motion abnormalities. Patients with LV ejection fraction <50% or infarction or ischemia were excluded.

Statistical analysis

Values were expressed as a means ± SD. Comparison between the groups was performed using Student's independent-sample *t* test for continuous variables and the χ^2 test for categorical variables. Univariate and multivariate analyses were used to examine correlations between exercise capacity and potential predictors. Data were analyzed using standard statistical software (SPSS, Chicago, IL). A *P* value <0.05 was considered statistically significant.

RESULTS

Clinical characteristics

Of 195 patients, 21 were excluded due to inducible wall motion abnormality and 4 due to poor images. Of the remaining 170 patients with type 2 diabetes (duration 10 ± 9 years), few had complications (30 had treated retinopathy, 27 had increased serum creatinine, and 9 had claudication or clinical signs of peripheral vascular disease). The treatment of diabetes included insulin ($n = 61$), metformin ($n = 104$), and sulfonylureas ($n = 55$). Insulin levels (mean value 17 ± 16 mU/l) were measured in 44 patients who were not taking exogenous insulin; in these patients, the homeostasis model assessment index was 5.9 ± 6.1, indicating significant insulin resistance.

Cardiovascular disturbances in type 2 diabetes

Table 1 summarizes the clinical, hemodynamic, and echocardiographic features of patients and control subjects. Abnormal HRR was present in 34 patients (20%) and 5 control subjects (9%). Exercise capacity, strain rate, Em, and HRR were significantly decreased in diabetic patients.

Predictors of maximal exercise capacity

Table 2 compares diabetic patients with normal and abnormal exercise capacity for age. Reduced exercise capacity was associated with increasing age ($r = -0.37$, $P < 0.001$), obesity ($r = -0.19$, $P = 0.012$), A1C ($r = -0.22$, $P = 0.009$), and longer duration of type 2 diabetes ($r = -0.18$, $P = 0.021$) and hypertension ($r = -0.28$, $P < 0.001$). Better exercise capacity was associated with male sex ($r = 0.26$, $P = 0.001$), preserved diastolic function (Em) ($r = 0.43$, $P < 0.001$), and preserved HRR ($r = 0.42$, $P < 0.001$). However, there was no correlation between exercise capacity and insulin levels or insulin resistance in the 44 patients who had no insulin treatment.

The independent predictors of exercise capacity (model $R^2 = 0.38$) were age ($\beta = -0.33$, $P < 0.001$), male sex ($\beta = 0.18$, $P = 0.007$), BMI ($\beta = -0.24$, $P = 0.001$), Em ($\beta = 0.16$, $P = 0.032$), HRR ($\beta = 0.18$, $P = 0.013$), and A1C ($\beta = -0.18$, $P = 0.0007$). Significant correlations were not found between exercise capacity and LV systolic function, although strain rate ($r = 0.142$, $P = 0.065$) had a trend to correlate with exercise capacity. Although Em was a correlate of exercise capacity in both women ($\beta = 0.16$, $P = 0.013$) and men ($\beta = 0.29$, $P = 0.004$), the other independent predictors of exercise capacity in women (age [$\beta = 0.32$, $P = 0.004$] and BMI [$\beta = -0.35$], $P = 0.013$) were different from men (HRR [$\beta = 0.31$, $P = 0.002$] and type 2 diabetes duration [$\beta = -0.28$, $P = 0.009$]).

Correlates of abnormal HRR in type 2 diabetes

Table 3 shows comparison of clinical and echocardiographic characteristics of diabetic patients with and without abnormal HRR. Reduced HRR is negatively associated with increasing age ($r = -0.30$, $P < 0.001$), higher resting heart rate ($r =$

Table 1—*Comparison of clinical and echocardiographic characteristics in patients with diabetes and control subjects*

	Diabetic patients	Control subjects	*P*
n	170	56	
Clinical features			
Age (years)	56 ± 10	53 ± 10	NS
Sex (male)	91	29	NS
BMI (kg/m^2)	31 ± 6	30 ± 7	NS
Heart rate (bpm)	83 ± 13	78 ± 17	0.016
Peak heart rate (bpm)	153 ± 18	162 ± 23	0.008
Systolic blood pressure (mmHg)	133 ± 16	130 ± 16	NS
Diastolic blood pressure (mmHg)	82 ± 9	80 ± 12	NS
Peak systolic blood pressure (mmHg)	191 ± 27	195 ± 20	NS
Peak diastolic blood pressure (mmHg)	88 ± 10	87 ± 13	NS
Exercise capacity (METS)	7.9 ± 2.8	10.9 ± 4.6	<0.001
HRR (beats/min)	26 ± 9	32 ± 12	0.002
Blood biochemistry			
A1C (%)	7.9 ± 1.6	5.6 ± 0.4	<0.001
Glucose (mmol/l)	8.9 ± 3.7	4.8 ± 0.5	<0.001
Total cholesterol (mmol/l)	4.8 ± 1.0	5.6 ± 0.9	<0.001
LDL choleserol (mmol/l)	2.7 ± 1.0	3.4 ± 0.7	<0.001
HDL cholesterol (mmol/l)	1.3 ± 0.4	1.6 ± 0.6	0.006
Triglycerides (mmol/l)	1.9 ± 1.3	1.4 ± 0.7	0.02
Creatinine (μmol/l)	0.08 ± 0.03	0.09 ± 0.02	NS
Urea (mmol/l)	6.2 ± 2.3	6.1 ± 1.7	NS
M-mode echocardiography			
LV end-diastolic dimension (cm)	4.5 ± 0.5	4.8 ± 0.5	0.008
Intraventricular septum diastolic dimension (cm)	1.1 ± 0.2	1.1 ± 0.2	NS
Posterior wall diastolic dimension (cm)	1.0 ± 0.3	1.0 ± 0.2	NS
Fractional shortening (%)	36 ± 6	36 ± 3	NS
Two-dimensional echocardiography			
LV end-diastolic volume (ml)	73 ± 23	79 ± 22	NS
LV end-systolic volume (ml)	28 ± 11	29 ± 10	NS
LV ejection fraction (%)	62 ± 6	64 ± 5	NS
LV mass index (g/m^2)	97 ± 36	93 ± 22	NS
Doppler			
Mitral early peak velocity (m/s)	0.8 ± 0.2	0.7 ± 0.1	<0.001
Mitral late peak velocity (m/s)	0.8 ± 0.2	0.7 ± 0.2	<0.001
Early-to-late peak diastolic transmitral flow velocity ratio	1.0 ± 0.3	1.0 ± 0.4	NS
Mitral valve deceleration time (ms)	240 ± 49	234 ± 38	NS
Isovolumic relaxation time (ms)	104 ± 17	109 ± 16	NS
Tissue characteristics			
Mean basal myocardial early diastolic velocity (cm/s)	5.4 ± 1.9	7.0 ± 2.0	<0.001
Strain rate (s-1)	1.3 ± 0.2	1.6 ± 0.3	<0.001

Data are means ± SD. NS, no significant difference.

-0.21, $P = 0.007$) and systolic blood pressure ($r = -0.19$, $P = 0.016$), longer duration of diabetes ($r = -0.15$, $P = 0.048$) or hypertension history ($r = -0.24$, $P = 0.002$), and A1C ($r = -0.22$, $P = 0.005$). Preserved HRR is associated with preserved diastolic function (Em) ($r = 0.37$, $P < 0.001$), systolic function (strain rate) ($r = 0.30$, $P < 0.001$), and exercise capacity ($r = 0.42$, $P < 0.001$). However, there was no correlation between HRR and insulin levels or insulin resistance in the 44 patients who had no insulin treatment.

All factors associated with HRR were entered into a forward stepwise multiple linear regression model ($R^2 = 0.30$). The independent predictors of HRR were age ($\beta = -0.21$, $P = 0.009$), resting heart rate ($\beta = -0.20$, $P = 0.005$), strain rate ($\beta = 0.22$, $P = 0.002$), exercise capacity ($\beta = 0.25$, $P = 0.002$), and A1C ($\beta = -0.15$, $P = 0.042$).

CONCLUSIONS — Exercise capacity is a powerful predictor of all-cause and cardiovascular mortality (1). The current study demonstrates that in addition to the expected associations with aging, female sex, and obesity, impaired exercise capacity in type 2 diabetes is associated with poor diabetes control, LV diastolic dysfunction, and reduced HRR.

Exercise capacity and diabetes control

Previous studies have shown that type 2 diabetes is associated with significant cardiopulmonary dysfunction. The association of poor glycemic control with worse exercise capacity in this study is consistent with a previous large study in asymptomatic type 2 diabetes (11). Other studies have shown that A1C has an inverse correlation with maximum oxygen uptake (12), work capacity (13), or exercise duration (14). Importantly, chronic maintenance of near normoglycemia is associated with improved cardiopulmonary function (15), and exercise capacity increased 24% after improved glycemic control was attained after initiating continuous subcutaneous insulin infusion (16).

The mechanism of the association between type 2 diabetes control and exercise capacity is unclear. Poor glycemic control has been associated with increased stiffness of large conduit vessels. The compliance of the aorta is believed to be of prime importance for modulating coronary artery blood flow, which has important consequences for myocardial work capacity and, therefore, exercise capacity (17). Poor diabetes control has been shown to be associated with subclinical LV dysfunction (18,19). Insulin resistance is associated with poor diabetes control, and previous studies demonstrated a negative correlation between insulin resistance and peak exercise capacity in diabetic patients (20). Unfortunately, insulin resistance did not correlate with exercise capacity in this study, perhaps due to the limited number of patients included in the subgroup. However, impaired exercise capacity may be observed in mild and even pre-diabetic states, where insulin resistance may be an important contributor. Glycosylation may impair the function of a number of proteins, and vascular or endothelial dysfunction may be a plausible connection between reduced exercise capacity and the metabolic disturbances associated with poor diabetes control, including abnormalities in glucose transport and usage, increased free fatty acids, carnitine deficiency, and changes in calcium homeostasis.

Table 2—*Significant differences in clinical and echocardiographic characteristics between patients with and without abnormal exercise capacity*

	Normal exercise capacity	Abnormal exercise capacity	*P*
n	52	118	
Clinical features			
Age (years)	55 ± 9	56 ± 11	NS
Sex (male)	34 (65)	57 (48)	0.04
BMI (kg/m^2)	29 ± 5	32 ± 6	0.002
Heart rate (beats/min)	82 ± 13	84 ± 14	NS
Peak heart rate (beats/min)	161 ± 15	150 ± 18	<0.001
Exercise capacity (mets)	10.8 ± 2.1	6.6 ± 2.1	<0.001
HRR (beats/min)	29 ± 8	25 ± 10	0.004
Clinical history			
Diabetes duration (years)	9 ± 9	11 ± 9	NS
Hypertension	21 (40)	71 (60)	0.023
Hypercholesterolemia history	22 (42)	78 (66)	0.006
Blood biochemistry			
A1C (%)	7.4 ± 1.2	8.1 ± 1.8	0.001
Glucose (mmol/l)	7.9 ± 2.7	9.4 ± 4.0	0.008
Triglycerides (mmol/l)	1.6 ± 1.1	2.0 ± 1.3	0.043
Treatment			
Insulin	15 (29)	46 (39)	NS
Metformin	27 (52)	77 (65)	NS
Sulphonylureas	12 (23)	43 (36)	NS
ACE inhibitors	15 (29)	53 (45)	NS
Calcium blockers	5 (10)	16 (14)	NS
β-Blockers	4 (8)	11 (9)	NS
Nitrates	0	2 (2)	NS
Lipid-lowering drugs	16 (31)	67 (57)	0.007
Doppler			
Mitral early peak velocity (m/s)	0.7 ± 0.2	0.8 ± 0.2	0.048
Mitral late peak velocity (m/s)	0.7 ± 0.1	0.8 ± 0.2	<0.001
Early-to-late peak diastolic transmitral flow velocity ratio	1.1 ± 0.3	1.0 ± 0.3	NS
Mitral valve deceleration time (ms)	242 ± 51	239 ± 48	NS
Isovolumic relaxation time (ms)	107 ± 16	103 ± 17	NS
Tissue characteristics			
Mean basal myocardial early diastolic velocity (cm/s)	6.3 ± 2.0	5.1 ± 1.7	<0.001
Strain rate (s-1)	1.3 ± 0.2	1.2 ± 0.2	NS

Data are means ± SD or *n* (%). No differences were observed for age, resting heart rate, resting or exercise systolic and diastolic blood pressure, clinical evidence of microvascular disease, smoking, duration of diabetes, renal function, cholesterol or its fractions, diabetic therapy (insulin, oral agents), cardiovascular medications other than statins, LV dimensions, mass, volume, or ejection fraction. NS, no significant difference.

Exercise capacity and LV function

In this study, the correlation between LV function and diabetes control in diabetic patients (3) may also suggest that lower exercise capacity is due to myocardial dysfunction. The association in this study between LV diastolic dysfunction and exercise performance in type 2 diabetes is consistent with results from previous studies in patients without (21) and with (2) type 2 diabetes. The lack of correlation between exercise capacity and LV systolic function in this study also confirms previous studies showing a poor correlation of exercise capacity with indexes of LV systolic function in patients with dilated cardiomyopathy (22) and hypertensive heart disease (23).

Patients with type 2 diabetes have an impaired cardiac output response to increasing workload, and this is further impaired by hypertension (24). LV diastolic dysfunction caused by diabetes is associated with decreased LV compliance, which results in an upward left shift of the LV end-diastolic pressure-volume relation, leading to the limited ability to increase cardiac output by means of the Frank-Starling mechanism during exercise (25). The relatively fixed stroke volume associated with type 2 diabetes may restrain cardiac output during maximal performance and limit exercise capacity (25).

Exercise capacity and autonomic cardiac function

Exercise results in prompt withdrawal of vagal tone and subsequent sympathetic activation, while recovery is associated with parasympathetic activation followed by sympathetic withdrawal. HRR correlates with vagal activity. Previous studies have shown that reduced HRR is associated with type 2 diabetes (26).

The development of reduced HRR is associated with type 2 diabetes only among subjects with both poor physical fitness and autonomic dysfunction (26). Exercise training improves both autonomic function and exercise capacity in type 2 diabetes (27). The results of the current study are consistent with previous studies (13) and suggest that abnormalities in HRR correlate with exercise performance in diabetes. The mechanism of this may reflect a role for autonomic dysfunction, although this requires further study.

Persistent hyperglycemia in diabetes may weaken parasympathetic control and enhance sympathetic activity (28), consistent with independent prediction of HRR by A1C levels in the current study. Indeed, increased resting heart rate itself may reflect autonomic dysfunction. Patients with high parasympathetic activation usually have low resting heart rate and baseline oxygen consumption and may achieve high workload for a certain level of oxygen consumption. Abnormal cardiac autonomic function has been associated with poor cardiac output responses to exercise in diabetes (29), probably due to abnormal hemodynamic regulation during exercise. In addition, an indirect link between cardiac autonomic dysfunction and impaired exercise capacity is demonstrated by associations of cardiac autonomic dysfunction with insulin resistance (30) or poor glycemic control (as in the current study) and impaired resting left ventricular diastolic filling (31).

Limitations

Although this study documents an association between exercise capacity and poor diabetes control, evidence of diabetic myocardial disease and probable autonomic dysfunction (reduced HRR),

Table 3—*Comparison of clinical and echocardiographic characteristics of diabetic patients with and without abnormal HRR*

	Normal HRR	Abnormal HRR	*P*
n	136	34	
Clinical features			
Age (years)	55 ± 10	61 ± 9	0.001
BMI (kg/m^2)	31 ± 5	34 ± 7	0.005
Heart rate (bpm)	82 ± 13	87 ± 15	0.044
Peak heart rate (bpm)	156 ± 17	142 ± 18	<0.001
Exercise capacity (METS)	8.4 ± 2.8	5.9 ± 2.0	<0.001
HRR (beats/min)	30 ± 7	13 ± 4	<0.001
Clinical history			
Hypertension	63 (46)	29 (85)	<0.001
Hypercholesterolemia history	75 (55)	25 (74)	NS
Current smoking	56 (41)	12 (35)	NS
Diabetes duration (years)	9 ± 9	14 ± 9	0.015
Peripheral vascular disease	4 (3)	5 (15)	0.007
Renal impairment	17 (13)	10 (29)	0.02
Retinopathy	20 (15)	10 (29)	0.046
Blood biochemistry			
A1C (%)	7.7 ± 1.5	8.7 ± 1.8	0.001
Glucose (mmol/l)	8.8 ± 3.5	9.4 ± 4.5	NS
Triglycerides (mmol/l)	1.8 ± 1.2	2.5 ± 1.4	0.005
Creatinine (μmol/l)	0.08 ± 0.04	0.08 ± 0.02	NS
Urea (mmol/l)	6.2 ± 2.0	6.7 ± 3.1	NS
Treatment			
Insulin	44 (32)	17 (50)	NS
Metformin	79 (58)	25 (74)	NS
Sulphonylureas	43 (32)	12 (35)	NS
ACE inhibitors	48 (35)	20 (59)	0.021
Calcium blockers	14 (10)	7 (21)	NS
β-Blockers	9 (7)	6 (18)	NS
Nitrates	2 (1)	0	NS
Lipid-lowering drugs	62 (46)	21 (62)	NS
Doppler			
Mitral early peak velocity (m/s)	0.8 ± 0.2	0.8 ± 0.2	NS
Mitral late peak velocity (m/s)	0.8 ± 0.2	0.8 ± 0.2	NS
Early-to-late peak diastolic transmitral flow velocity ratio	1.1 ± 0.3	1.0 ± 0.2	NS
Mitral valve deceleration time (ms)	235 ± 50	258 ± 42	0.016
Isovolumic relaxation time (ms)	106 ± 17	100 ± 18	NS
Tissue characteristics			
Mean basal myocardial early diastolic velocity (cm/s)	5.7 ± 1.9	4.6 ± 1.3	<0.001
Strain rate (s-1)	1.3 ± 0.2	1.2 ± 0.2	NS

Data are means ± SD or *n* (%). No differences were observed for sex, resting or exercise systolic and diastolic blood pressure, hypercholesterolemia and smoking, cholesterol or its fractions, diabetic therapy (insulin, oral agents), cardiovascular medications other than ACE inhibitors, LV dimensions, mass, volume, or ejection fraction. NS, no significant difference.

such a cross-sectional study cannot define a causal relationship. Identifying the causal relationships will require a number of intervention studies, and we have initiated this process with interventions to improve insulin resistance and glycemic control.

While tissue Doppler parameters appear to be less load dependent than conventional blood flow Doppler, they are certainly not load independent. Consequently, higher levels of blood pressure in the group with reduced exercise capacity may be a contributor to reduced myocardial function. Nonetheless, our data do show that the association of tissue velocity with exercise capacity is independent of blood pressure. Finally, the type and duration of comorbidity and medications may affect exercise capacity, even though we failed to show a correlation of therapy with exercise capacity in this study.

This study demonstrates that impaired exercise capacity in type 2 diabetes is not only associated with physical characteristics such as age, sex, and BMI but also with subclinical LV dysfunction and cardiac autonomic dysfunction. The mechanisms of this association will be clarified by subsequent intervention trials, but it seems likely that these effects are linked by diabetes control.

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