Usefulness of At Rest and Exercise Hemodynamics to Detect Subclinical Myocardial Disease in Type 2 Diabetes Mellitus

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Patients with type 2 diabetes mellitus (T2DM) might have subclinical myocardial dysfunction identified at rest or unmasked during exercise. We examined the correlates of the myocardial exercise response in patients with T2DM. Myocardial dysfunction was sought during at rest and exercise echocardiography in 167 healthy patients with T2DM (97 men, 55 ± 10 years). Myocardial ischemia was excluded using stress echocardiography. Standard echocardiography and color tissue Doppler imaging measures (early diastolic tissue velocity [Em], strain, and strain rate) were acquired at baseline and peak stress. The calibrated integrated backscatter was calculated from the at rest parasternal long-axis view. The longitudinal diastolic functional reserve index after exercise was defined as ΔEm [1 − (1/Em_{base})]. The clinical, anthropometric, and metabolic data were collected at rest and stress. Subclinical myocardial dysfunction at baseline (n = 24) was independently associated with weight (odds ratio [OR] 1.02, p = 0.04) and hemoglobin A1c (OR 1.36, p = 0.03). This group displayed an impaired exercise response that was independently associated with a reduced exercise capacity (OR 0.84, p = 0.034) and longitudinal diastolic functional reserve index (OR 0.69, p = 0.001). Inducible myocardial dysfunction (stress Em <−9.9 cm/s) was identified after exercise in 70 of the remaining 143 subjects. This finding was associated with calibrated integrated backscatter (OR 1.08, p = 0.04) and lower peak heart rate (OR 0.97, p = 0.002) but not metabolic control. The intensity of the metabolic derangement in patients with T2DM was associated with subclinical at rest myocardial dysfunction, but not with the myocardial exercise response. In conclusion, the association of an abnormal stress response with nonmetabolic factors, including backscatter and blunted peak heart rate, suggests potential roles for myocardial fibrosis and cardiac autonomic neuropathy in patients with nonischemic diabetic heart disease. **(Am J Cardiol 2011;107:615–621)**

In addition to hastening atherosclerosis, type 2 diabetes mellitus (T2DM) and the metabolic syndrome[1] have been linked to myocardial disease in the absence of ischemic heart disease and hypertension.[2] This is likely multifactorial, secondary to the accumulation of advanced glycated end products, myocardial fibrosis, microvascular disease, and autonomic neuropathy. Diabetic heart disease is initially asymptomatic; however, nonspecific symptoms of fatigue, dyspnea, or reduced exercise tolerance will gradually develop. Early detection might facilitate measures to prevent disease progression. Tissue velocity and deformation imaging can detect myocardial dysfunction when the conventional 2-dimensional echocardiographic parameters are normal.[3] In early diabetic heart disease, myocardial function might be preserved at rest, with exercise unmasking a blunting of contraction and relaxation, indicative of an abnormal functional reserve.[4] Longitudinal function is typically reduced initially, reflective of the early involvement of the subendocardial fibers.[5] Impairment in the at rest and peak exercise systolic tissue velocity has been associated with common metabolic risk factors in asymptomatic patients.[6] We sought to identify whether early diastolic tissue velocity (Em), deformation imaging, and tissue characterization could identify diabetic heart disease not apparent at rest and examined the correlates of myocardial dysfunction with exercise.

Methods

A total of 167 apparently healthy subjects with T2DM (97 men, 55 ± 10 years) and no macro- or microvascular complications of T2DM or history of hypertension or valvular, congenital, or ischemic heart disease were recruited from the hospital clinics of the Princess Alexandra Hospital and its local community. Sinus rhythm and normal renal function were required for inclusion. Antihypertensive medications were withheld for ≥12 hours before testing. The human research ethics committees of Princess Alexandra Hospital and the University of Queensland (Brisbane, Australia) approved the present study.

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Table 1
Characteristics of myocardial dysfunction at rest and unmasked by exercise

Variable	At Rest Em			Stress Em		
	Normal (n = 143)	Abnormal (n = 24)	p Value	Normal (n = 73)	Abnormal (n = 70)	p Value
Age (years)	55 ± 10	53 ± 11	0.389	53 ± 9	58 ± 10	0.007
Type 2 diabetes mellitus duration (years)	5.3 ± 5.5	9.7 ± 8.9	0.024	5.1 ± 5.4	6.1 ± 6.3	0.310
Weight (kg)	89.5 ± 17.0	98.5 ± 28.5	0.035	89.7 ± 17.4	90.2 ± 16.9	0.848
Body mass index (kg/m^2)	31.3 ± 5.4	33.7 ± 7.2	0.054	31.5 ± 5.6	31.2 ± 5.3	0.768
Fasting glucose (mmol/L)	8.1 ± 2.8	9.6 ± 3.8	0.030	8.2 ± 3.0	8.2 ± 2.8	0.873
Hemoglobin A1c (%)	7.4 ± 1.4	8.1 ± 1.6	0.024	7.5 ± 1.4	7.4 ± 1.4	0.458
Total cholesterol			0.105			0.019
mmol/L	4.8 ± 0.9	4.5 ± 0.8		5.0 ± 0.8	4.7 ± 1.0	
mg/dl	186 ± 35	174 ± 31		193 ± 31	182 ± 39	
Low-density lipoprotein cholesterol			0.035			0.084
mmol/L	2.7 ± 0.8	2.3 ± 0.8		2.8 ± 0.8	2.6 ± 0.9	
mg/dl	104 ± 31	89 ± 31		108 ± 31	101 ± 35	
Creatinine (mmol/L)	79 ± 18	77 ± 24	0.624	78 ± 17	80 ± 19	0.459
Microalbuminuria (%) [albumin/creatinine (g/mol)]	16 (11%); 0.7*; IQR 0.9	6 (25%); 1.1*; IQR 2.2	0.064	7 (10%); 0.8*; IQR 0.7	8 (11%); 0.7*; IQR 0.9	0.720
Statin therapy	55 (38%)	16 (67%)	0.010	24 (33%)	32 (46%)	0.116
Angiotensin-converting enzyme inhibitors and/or angiotensin-receptor blockers	58 (41%)	18 (75%)	0.005	28 (39%)	30 (43%)	0.474
β Blockers	9 (6%)	1 (4%)	0.684	1 (1%)	8 (11%)	0.013
At rest heart rate (beats/min)	85 ± 13	88 ± 16	0.330	88 ± 12	81 ± 13	0.001
At rest systolic blood pressure (mm Hg)	133 ± 17	138 ± 17	0.259	132 ± 16	134 ± 17	0.572
At rest diastolic blood pressure (mm Hg)	81 ± 10	86 ± 8	0.033	81 ± 10	81 ± 9	0.949
Peak heart rate (beats/min)	163 ± 20	159 ± 19	0.363	170 ± 17	155 ± 20	<0.001
Exercise capacity (METs)	9.2 ± 3.2	7.5 ± 2.5	0.013	9.4 ± 3.3	9.0 ± 3.0	0.439
At rest end-systolic volume (ml)	25 ± 10	29 ± 12	0.137	26 ± 10	25 ± 10	0.314
At rest end-diastolic volume (ml)	73 ± 19	78 ± 26	0.210	72 ± 20	73 ± 19	0.753
At rest ejection fraction (%)	65 ± 7	64 ± 8	0.241	64 ± 6	67 ± 7	0.017
Stress end-systolic volume (ml)	18 ± 7	10 ± 8	0.224	18 ± 7	18 ± 7	0.906
Stress end-diastolic volume (ml)	69 ± 19	71 ± 23	0.590	69 ± 18	70 ± 21	0.718
Stress ejection fraction (%)	74 ± 5	73 ± 6	0.553	74 ± 5	74 ± 6	0.852
Change in ejection fraction (%)	9 ± 6	9 ± 7	0.825	10 ± 6	7 ± 7	0.014
At rest early diastolic tissue velocity (cm/s)	−5.7 ± 1.5	−3.1 ± 1.0	<0.001	−5.8 ± 1.4	−5.5 ± 1.6	0.365
At rest systolic tissue velocity (cm/s)	4.9 ± 1.1	2.9 ± 1.4	<0.001	4.9 ± 1.1	4.8 ± 1.2	0.614
Stress early diastolic tissue velocity (cm/s)	−9.9 ± 2.5	−6.3 ± 4.5	<0.001	−11.5 ± 1.9	−8.1 ± 1.7	<0.001
Stress systolic tissue velocity (cm/s)	8.0 ± 2.0	5.4 ± 2.6	<0.001	8.3 ± 1.9	7.5 ± 2.2	0.012
Change in systolic tissue velocity (cm/s)	3.1 ± 1.9	2.5 ± 1.6	0.184	3.5 ± 1.8	2.6 ± 1.9	0.006
Left ventricular longitudinal functional reserve index	3.5 ± 2.5	1.3 ± 2.2	<0.001	5.3 ± 1.7	1.6 ± 1.7	<0.001
At rest strain (%)	−20.8 ± 3.1	−19.6 ± 3.7	0.09	−20.6 ± 3.0	−20.8 ± 3.2	0.605
Stress strain (%)	−21.2 ± 3.5	−21.2 ± 3.6	0.978	−20.6 ± 3.7	−22.0 ± 3.2	0.020
At rest strain rate (s^{-1})	−1.3 ± 0.3	−1.4 ± 0.3	0.160	−1.3 ± 0.3	−1.3 ± 0.3	0.728
Stress strain rate (s^{-1})	−1.9 ± 0.5	−2.0 ± 0.5	0.181	−1.9 ± 0.5	−1.9 ± 0.4	0.692
Calibrated integrated backscatter (dB)	−17.1 ± 5.4	−16.3 ± 5.7	0.539	−18.0 ± 4.9	−15.9 ± 5.8	0.019
Height-indexed left ventricular mass (g/m$^{2.7}$)	51.0 ± 16.7	45.2 ± 16.6	0.125	52.4 ± 18.1	49.6 ± 15.0	0.360

No statistically significant difference noted between at rest or Stress Em groups for gender, smoking status, height, waist/hip ratio, triglycerides, high-density lipoprotein cholesterol, hypoglycemic therapy, or peak systolic or diastolic blood pressure.

* Median value given as nonparametric distribution.

IQR = interquartile range.

Clinical data were collected regarding subject age, gender, weight, height, waist and hip circumference, smoking status, and duration of T2DM. Venesection was performed before exercise after the subjects had fasted for ≥8 hours. The tested parameters included fasting glucose, hemoglobin A1c (HbA1c), creatinine, and lipid profile. Microalbuminuria, a marker of microvascular disease, was quantified using a random urinary albumin/creatinine ratio and defined as ≥2.5 g/mol for men and ≥3.5 g/mol for women. The heart rate and blood pressure were measured at baseline, throughout exercise, and during recovery. The peak exercise capacity was estimated in METs according to the duration of exercise using the equation: METs = [speed × (0.1 + [grade × 1.8]) + 3.5]/3.5.

Standard commercially available cardiac ultrasound machines (Vivid 7, General Electric Medical Systems, Milwaukee, WI) were used to perform M-mode and 2-dimensional echocardiography to assess the chamber wall thickness, valvular morphology, and chamber volumes. Baseline parasternal and apical images were acquired in