Cardiac Adaptations to Acute Hemodynamic Stress in Function, Perfusion, and Energetics in Type 2 Diabetes With Overweight and Obesity

Amrit Chowdhary,[1] Wasim Javed,[1] Sharmaine Thirunavukarasu,[1] Nicholas Jex,[1] Sindhoora Kotha,[1] Peter Kellman,[2] Peter Swoboda,[1] John P. Greenwood,[1] Sven Plein,[1] and Eylem Levelt[1]

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Heart failure (HF) is the most common initial presentation of cardiovascular disease in type 2 diabetes (T2D) (1). Coronary microvascular dysfunction and compromised cardiac energy production have been proposed as pivotal features underpinning diabetic cardiomyopathy (2). Although functional alterations are highly prevalent in asymptomatic T2D patients, the relative associations of impaired cardiac energetics and perfusion to systolic and diastolic subclinical functional changes at rest and in response to acute hemodynamic stress in T2D have not been reported. Better understanding these relationships may lead to new therapeutic targets to prevent HF development in T2D patients.

Using cardiovascular magnetic resonance (CMR) and ^{31}P magnetic resonance spectroscopy (^{31}P-MRS), we assessed changes in cardiac energetics, perfusion, global longitudinal shortening (GLS), and systolic and diastolic function in response to increases in cardiac workload with dobutamine stress in T2D patients with overweight or obesity (n = 36) and nonathletic healthy volunteers (n = 20). Additionally, we compared results against those for 12 veteran athletes. The nonathletic healthy control group was selected because trained veteran endurance athletes are known to be markedly insulin sensitive. As a result, they represent an excellent control group for patients with T2D.

Participants across the three groups showed similar age, sex, and ethnicity distribution. The BMI was significantly higher in the T2D group (with 10 being normal body weight, BMI 23 [22–24], and 26 being overweight, BMI 31 [29–32]). None of the participants had a documented history of cardiovascular disease (prior diagnosis of stroke, myocardial infarction, angina, moderate or severe valvular heart disease, atrial fibrillation, or any prior cardiovascular interventions), in line with the exclusion criteria. None of the participants reported exertional symptoms, and they were all considered class I based on New York Heart Association functional classification. Participants with T2D were free of diabetes complications as per exclusion criteria (retinopathy, nephropathy, or neuropathy) and were receiving only oral glucose-lowering treatments or diet control for the management of diabetes. Patients receiving insulin therapy were excluded from the study. Participants in the control groups were not receiving any medications.

This prospective case–control study complied with the Declaration of Helsinki and was approved by the National Research Ethics Committee (approval no. 19/WM/0365). Informed written consent was obtained from each participant. The data will be shared on reasonable request to the corresponding author.

For the stress protocol, intravenous dobutamine infusion up to 40 μg/kg/min was given to achieve a target heart rate of 65% of the age-predicted maximum. Mean rate pressure product (RPP) (RPP = systolic blood pressure × heart rate) was recorded at rest and under stress. Target heart rate was maintained for the duration of the ^{31}P-MRS and dobutamine stress CMR acquisitions. The triglyceride index was calculated as a surrogate marker of insulin resistance, and plasma N-terminal prohormone B-type natriuretic peptide (NT-proBNP) concentrations were measured.

Demographic, biochemical, and rest and stress CMR and ^{31}P-MRS data are shown in Table 1. T2D patients showed significant reductions in resting energetics compared with the control groups, which confirmed the findings of previous studies. Increases in RPP with dobutamine stress were similar across study groups. In response to acute stress, further reductions in myocardial phosphocreatine-to-ATP (PCr/ATP) ratios were seen in T2D patients but also to a similar relative extent in healthy volunteers and veteran athletes. The rest and stress left ventricular ejection fractions (LVEF) were similar across all groups, and all showed similar increments in LVEF with dobutamine stress. T2D patients showed significant reductions in GLS and mitral inflow E/A ratios at rest. During dobutamine stress, all groups showed similar increments in GLS and similar decrements in E/A ratio, but these parameters remained significantly higher in the two control groups. T2D patients showed lower stress

[1]Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, U.K.
[2]National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD

Corresponding author: Eylem Levelt, e.levelt@leeds.ac.uk

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Table 1—Demographics and biochemical and CMR characteristics

	HV (n = 20)	Veteran athletes (n = 12)	T2D (n = 36)	ANOVA
Age (years)	57 (51–62)	58 (52–64)	59 (57–62)	0.6
Male (n, %)	12 (60)	7 (58)	23 (64)	0.7
BMI (kg/m^2)	25 (23–26)	24 (23–26)†	28 (26–29)Ω	0.006
Fasting glucose (mmol/L)	4.9 (4.8–5.2)	4.9 (4.7–5.1)†	9.1 (8–12)Ω	**0.001**
Glycated hemoglobin (mmol/mol)	35 (34–38)	35 (33–37)†	66 (58–69)Ω	**<0.0001**
NT-proBNP (pg/mL)	59 (41–75)	50 (36–64)†	114 (58–171)Ω	**<0.0001**
Triglyceride index	3.7 (3.6–3.8)	3.6 (3.5–3.7)†	4.2 (4.1–4.3)Ω	**<0.0001**
Cardiac structural changes				
LV end diastolic volume (mL)	151 (134–167)	168 (150–186)†	128 (119–137)	**0.001**
LV end diastolic volume index (mL/m^2)	83 (75–92)	91 (84–98)†	66 (62–71)Ω	**<0.0001**
LV end systolic volume (mL)	57 (48–65)	66 (55–76)†	51 (46–56)	0.05
LV end systolic volume index (mL/m^2)	31 (27–35)	36 (32–40)†	26 (24–29)	**0.002**
LV stroke volume (mL)	94 (84–104)	102 (91–113)†	77 (71–83)Ω	**0.0003**
LV ejection fraction (%)	63 (61–65)	62 (60–65)	60 (59–62)	0.2
LV mass (g)	96 (83–109)	108 (89–127)	99 (92–106)	0.5
LV mass/LV end diastolic volume (mg/mL)	0.64 (0.59–0.70)	0.64 (0.57–0.70)†	0.79 (0.74–0.85)Ω	**0.0008**
Rest and stress strain, diastolic assessment, ejection fraction, and perfusion				
Stress RPP (bpm*mmHg)	16,196 (14,088–18,342)	15,121 (12,976–17,854)	16,907 (14,402–19,524)	0.07
Rest RPP (bpm*mmHg)	6,583 (4,877–8,421)	5,995 (2,439–7,996)	7,077 (5,142–8,913)	0.09
ΔRPP (bpm*mmHg)	8,972 (6,335–11,703)	9,566 (6,629–13,101)	8,824 (6,143–11,563)	0.7
Increase in RPP (%)	138	152	137	0.07
Rest GLS (%)	18 (17–19)	20 (18–21)†	17 (16–18)	0.008
Stress GLS (%)	25 (22–28)	24 (22–26)	20 (18–22)Ω	0.01
Rest E/A ratio	1.38 (1.13–1.62)	1.53 (1.35–1.98)†	1.02 (0.89–1.15)Ω	**0.0007**
Stress E/A ratio	1.22 (0.95–1.49)	1.25 (1.01–1.37)†	0.78 (0.70–0.87)Ω	**0.0003**
Rest LV EF (biplanar) (%)	65 (63–68)	63 (60–65)	63 (61–65)	0.4
Stress LV EF (biplanar) (%)	77 (74–80)	74 (70–78)	76 (74–78)	0.4
Stress MBF (mL/g/min)	1.89 (1.70–2.02)	1.97 (1.56–2.37)†	1.49 (1.34–1.63)Ω	**0.006**
Rest MBF (mL/g/min)	0.68 (0.64–0.74)	0.60 (0.50–0.70)	0.67 (0.62–0.71)	0.2
Myocardial perfusion reserve	2.70 (2.38–3.02)	3.44 (2.54–4.35)†	2.37 (2.11–2.62)	**0.01**
Rest and stress myocardial energetics				
Stress RPP (bpm*mmHg)	15,732 (13,786–18,213)	14,738 (12,770–17,214)	16,234 (13,979–18,531)	0.07
Rest RPP (bpm*mmHg)	6,397 (4,596–8,201)	5,846 (4,078–7,606)	6,983 (5,003–8,901)	0.09
ΔRPP (bpm*mmHg)	9,416 (6,532–12,059)	9,196 (6,335–11,836)	9,151 (6,500–11,721)	0.7
Increase in RPP (%)	145	148	135	0.2
Rest PCr/ATP	1.98 (1.80–2.16)	2.07(1.86–2.29)†	1.72 (1.46–1.70)Ω	**0.03**
Stress PCr/ATP	1.62 (1.40–1.84)	1.61 (1.37–1.85)	1.41 (1.35–1.57)	0.3
P value, rest and stress PCr/ATP ratio	0.004	0.03	**0.001**	

Values are means and 95% CI (lower limit of 95% CI – upper limit of 95% CI); §Statistical significance between HV and athletes; †$P < 0.05$ between athletes and T2D; Ω$P < 0.05$ between HV and T2D. The values in bold indicate statistical significance.

myocardial blood flow (MBF) than the control groups. The NT-proBNP concentrations and triglyceride index calculations were higher in the T2D group.

Rest LVEF correlated with rest MBF (r = 0.26, P = 0.03), and stress LVEF correlated with stress MBF (r = 0.44, P = 0.01). There was no significant correlation between perfusion parameters and diastolic function. While rest energetics correlated with rest E/A ratio (r = 0.39, P = 0.007) and stress energetics correlated with stress E/A ratio (r = 0.40, P = 0.01), there was no significant correlation between energetics and LVEF. Suggesting links between insulin resistance, myocardial energetics, diastolic function, and GLS, triglyceride index correlated with rest and stress PCr/ATP ratios (r = −0.33, P = 0.04 and r = −0.36, P = 0.03, respectively), E/A ratios (r = −0.49, P = 0.0001 and r = −0.45, P = 0.01, respectively), and GLS (r = 0.001, P = 0.49 and r = 0.46, P = 0.002, respectively).

To the best of our knowledge, this is the first study to explore not only the rest relationships but also the hemodynamic stress relationships between energetics, MBF, strain, LVEF, and diastolic function. In this study we confirmed that T2D patients with overweight or obesity show reductions in myocardial energetics, GLS, and diastolic function at rest. In response to dobutamine stress, T2D patients with overweight or obesity as well as healthy volunteers and age-matched veteran athletes show decrements in myocardial energetics and diastolic function. They show similar increments in GLS and LVEF but with a blunted increment in stress MBF in T2D patients with overweight or obesity. We showed that rest and stress MBF are associated with rest and stress LVEF, and rest and stress energetics are associated with rest and stress diastolic parameters, suggesting that diastolic function is a more energetically sensitive

process than global systolic function. This study gives important insights into the distinct associations between energetics, perfusion, and plasma metabolic parameters with diastolic and systolic function in diabetes with overweight or obesity and support development of patient-specific therapies and monitoring strategies.

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