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# Cardiac adaptations to acute hemodynamic stress in function, perfusion and energetics in type 2 diabetes with overweight/obesity

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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 haemodynamic 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 $^{31}$phosphorus MR spectroscopy ($^{31}$P-MRS) we assessed changes in cardiac energetics, perfusion, global longitudinal shortening (GLS), systolic and diastolic function in response to increases in cardiac workload with dobutamine stress in T2D patients with overweight/obesity (n=36) and non-athletic healthy volunteers(n=20). Additionally, we compared results against 20 veteran athletes. The non-athletic healthy control group were 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 3 groups showed similar age, sex and ethnicity distribution. The body mass index (BMI) was significantly higher in the T2D group (with 10 normal body weight BMI 23[22-24] and 26 overweight 31[29-32]). None of the participants had a documented history of cardiovascular disease (prior diagnosis of stroke, myocardial infarction, angina, moderate or above 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 approved by the National Research Ethics Committee (Ref: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 40µg/kg/min was given to achieve a target heart rate of 65% of the age-predicted maximum. Mean rate pressure product (RPP= systolic blood pressure × heart rate) was recorded at rest and stress. Target heart rate was maintained for the duration of the $^{31}$P-MRS and dobutamine stress CMR acquisitions. Triglyceride-index was calculated as a surrogate marker of insulin resistance and plasma N-terminal pro hormone 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. Confirming the findings of previous studies, T2D patients showed significant reductions in resting energetics compared to the control groups. Increases in RPP with dobutamine stress were similar across study groups. In response to acute stress, further reductions in myocardial PCr/ATP were seen in T2D patients, but also to a similar relative extent in healthy volunteers and veteran athletes (Figure-1). 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 in-flow E/A ratios at rest. During dobutamine stress, all groups showed similar increments in GLS and similar decrements in E/A ratio (Figure-1), but these parameters remained significantly higher in the two control groups. T2D patients showed lower stress MBF than the control groups (Figure-1). The NTproBNP 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 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 (r=-0.33, p=0.04 and r=-0.36, p=0.03), E/A (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 but also the haemodynamic stress relationships between energetics, myocardial blood flow, strain, LVEF and diastolic function. In this study we confirmed that T2D patients with overweight/obesity show reductions in myocardial energetics, GLS and diastolic function at rest. In response to dobutamine stress, T2D patients with overweight/obesity as well as healthy volunteers and age-matched veteran athletes show decrements in myocardial energetics and diastolic function, and similar increments in GLS and LVEF, but with a blunted increment in stress MBF in T2D patients with overweight/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/obesity and support development of patient-specific therapies and monitoring strategies.

**References**

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## Table 1: Demographics, biochemical and CMR characteristics

| | **HV** (n=20) | **Veteran athletes** (n=12) | **T2D** (n=36) | **ANOVA** |
|---|---|---|---|---|
| Age (yrs) | 57 [51-62] | 58 [52-64] | 59 [57-62] | 0.6 |
| Male (n,%) | 12 (60) | 7 (58) | 23(64) | 0.7 |
| Body mass index (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 haemoglobin (mmol/mol) | 35 [34-38] | 35 [33-37]† | 66 [58-69]Ω | **<0.0001** |
| NTproBNP (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 |
| Delta RPP (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 | 1.38 [1.13-1.62] | 1.53 [1.35-1.98] † | 1.02 [0.89-1.15] Ω | **0.0007** |
| Stress E/A | 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 myocardial blood flow (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 myocardial blood flow (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 |
| Delta RPP (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 | 0.004 | 0.03 | **0.001** | |

Values are mean [LL of 95% confidence interval – UL of 95% confidence interval]; § indicates statistical significance between HV and athletes; †indicates p<0.05 between athletes and T2D; Ω indicates p<0.05 between HV and T2D

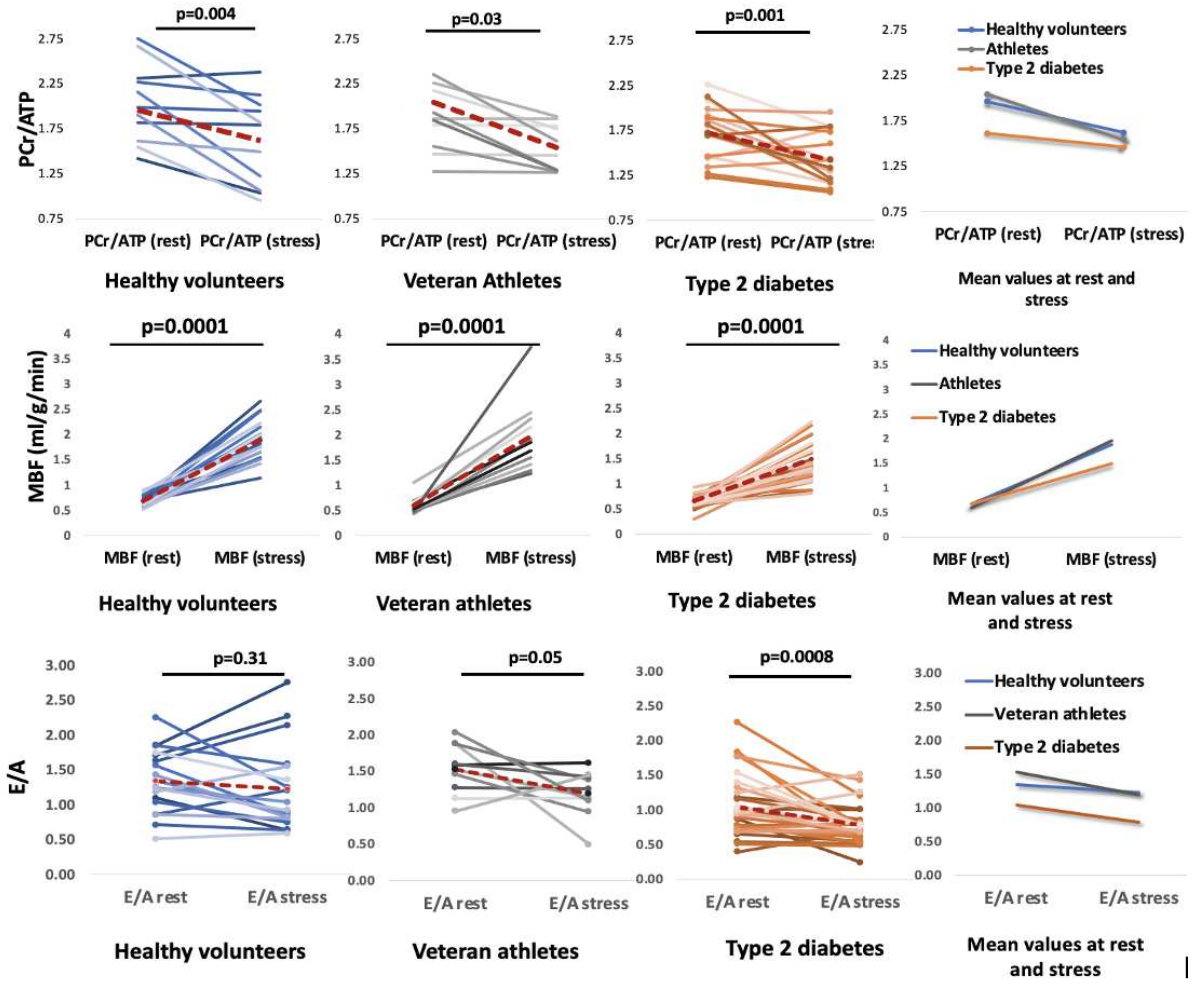


**Figure-** Representative graphs of cardiac energetics (top panel), stress myocardial blood flow (second panel) and diastolic function (third panel) changes in response to acute hemodynamic stress achieved by dobutamine infusion in healthy volunteers, veteran athletes and patients with T2D.