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Gulsin, GS, Henson, J, Brady, EM et al. (12 more authors) (2020) Cardiovascular Determinants of Aerobic Exercise Capacity in Adults With Type 2 Diabetes. Diabetes Care, 43 (9). dc200706. pp. 2248-2256. ISSN 0149-5992

https://doi.org/10.2337/dc20-0706

Cardiovascular determinants of aerobic exercise capacity in adults with type 2 diabetes

Brief title: Determinants of exercise capacity in type 2 diabetes

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Word count: 3,727

Number of tables: 2

Number of figures: 2

Abstract

Objective

To assess the relationship between subclinical cardiac dysfunction and aerobic exercise capacity (peak V_{O_2}) in adults with type 2 diabetes (T2D), a group at high risk of developing heart failure.

Research design and methods

Cross-sectional study. We prospectively enrolled a multi-ethnic cohort of asymptomatic adults with T2D and no history, signs or symptoms of cardiovascular disease. Age-, sex-, and ethnicity-matched controls were recruited for comparison. Participants underwent bio-anthropometric profiling, cardiopulmonary exercise testing and cardiovascular magnetic resonance with adenosine stress perfusion imaging. Multivariable linear regression analysis was undertaken to identify independent associations between measures of cardiovascular structure and function and peak V_{O_2}.

Results

Two hundred and forty seven adults with T2D (age 51.8±11.9 years, 55% males, 37% black or south Asian ethnicity, HbA1c 7.4±1.1% (57±12 mmol/mol), duration of diabetes 61 (32 – 120) months and 78 controls were included. Subjects with T2D had increased concentric left ventricular (LV) remodelling, reduced myocardial perfusion reserve, and markedly lower aerobic exercise capacity (peak V_{O_2} 18.0±6.6 vs. 27.8±9.0mL/kg/min, $p<0.001$) compared with controls. In a multivariable linear regression model containing age, sex, ethnicity, smoking status and systolic blood pressure, only myocardial perfusion reserve (β=0.822,

p=0.006) and E/e' (β= -0.388, p=0.001) were independently associated with peak VO_2 in subjects with T2D.

Conclusions

In a multi-ethnic cohort of asymptomatic people with T2D, myocardial perfusion reserve and diastolic function are key determinants of aerobic exercise capacity, independent of age, sex, ethnicity, smoking status, or blood pressure.

Abbreviations

CMR=cardiovascular magnetic resonance

CPET=cardiopulmonary exercise testing

EF=ejection fraction

GLS=global longitudinal strain

HF=heart failure

HFpEF=heart failure with preserved ejection fraction

HFrEF=heart failure with reduced ejection fraction

LA=left atrium

LGE=late gadolinium enhancement

LV=left ventricle

MPR=myocardial perfusion reserve

NIHR=National Institute for Health Research

PEDSR=peak early diastolic strain rate

RER=respiratory exchange ratio

T2D=type 2 diabetes mellitus

Heart failure (HF) has emerged as one of the commonest and deadliest complications of type 2 diabetes (T2D)(1). Even in asymptomatic individuals with T2D there is a high prevalence of left ventricular (LV) systolic and diastolic dysfunction or cardiac remodelling(2,3). The American Heart Association has classified such individuals as having stage B HF(4) and this group are at high risk of developing clinical symptoms. Earlier identification of the cardiovascular manifestations of stage B HF may permit earlier diagnosis and treatment of those patients most at risk(5).

Individuals with T2D are recognised to have limitations in aerobic exercise capacity, even in the absence of overt cardiovascular disease(6,7), and this may be the first manifestation of stage B HF. Peak oxygen consumption (V_{O_2}) is the gold standard method of assessing maximal aerobic capacity(8) and reduced peak V_{O_2} is a strong risk factor for the development of cardiovascular disease and mortality(9), including HF(10). However, the relationship between cardiovascular structure, function, and aerobic exercise capacity in asymptomatic people with T2D is not fully understood.

Cardiovascular magnetic resonance imaging (CMR) is the gold standard imaging modality for assessment of cardiac volumes, mass and ejection fraction, and with the addition of stress perfusion imaging has the ability to provide accurate quantification of myocardial blood flow. No studies to date have used this technique to assess the associations of cardiovascular structure and function with aerobic exercise capacity in people with T2D.

The aims of this study were: (1) to determine the presence and nature of subclinical cardiovascular dysfunction in adults with T2D using multiparametric

CMR, and (2) to evaluate whether markers of subclinical cardiovascular dysfunction are independently associated with peak VO_2.

Research design and methods

Participants

This was a pooled analysis of individual baseline patient data from participants recruited to one of four studies evaluating the impact of T2D on cardiovascular structure and function(11-14). Adults with T2D were prospectively enrolled into these studies from primary and specialist care services in Leicestershire, UK, with support from the National Institute for Health Research (NIHR) East Midlands Clinical Research Network. Participants included in the current analyses were aged 18 to 75 years, with no prior history, clinical signs or symptoms of cardiovascular disease and no contraindications to CMR imaging or cardiopulmonary exercise testing (CPET). Exclusion criteria were: type 1 diabetes, stage 4 or 5 chronic kidney disease (estimated glomerular filtration rate <30mL/min/1.73m^2), known macrovascular disease (including myocardial infarction, transient ischemic attack, stroke, peripheral artery disease), presence of arrhythmia, history of HF, moderate or worse valvular heart disease, and cardiovascular symptoms (such as angina or limiting dyspnea during normal physical activity). Age-, sex- and ethnicity-matched controls without dysglycemia and free of prevalent cardiovascular disease were recruited for comparison. Ethical approval for each study was granted by the National Research Ethics Service, conducted according to the Declaration of Helsinki, and all participants provided written informed consent prior to any testing.

Assessments

Demographics, medical history and anthropometric measures were collected at the assessment visits. Smoking status was categorized as “never smoked”, “ex-

smoker", or "current smoker". A fasting blood sample was collected for biochemical profile for diabetes control, lipids, liver and kidney function.

Cardiovascular magnetic resonance imaging

CMR scanning was performed using a standardised protocol on Siemens scanners (Erlangen, Germany) at either 1.5T (Siemens Aera) or 3T (Siemens Skyra). In brief, after localisers, steady-state free precession cine images were acquired in four-, three- and two-chamber views. Perfusion images were then acquired after vasodilatory stress with adenosine (140μg/kg/min, infused intravenously for three minutes). At peak stress, a gadolinium-based contrast agent was injected followed by a 20mL bolus of normal saline, at a rate of 5mL/s, and perfusion images were acquired at three short-axis slices (basal, mid and apical). Rest imaging was performed approximately 10 minutes after stress. In between rest and stress imaging, a stack of short-axis slices was obtained using cine images to obtain coverage of the entire LV. Late gadolinium enhancement (LGE) images were acquired approximately 10 minutes after the rest perfusion contrast dose for assessment of focal myocardial fibrosis.

CMR images were analysed offline blinded to all patient details. Cardiac chamber volumes, function and strain were assessed by a single experienced observer (G.S.G) using cmr42 version 5 (Circle Cardiovascular Imaging, Calgary, Alberta, Canada). Myocardial strain measurement was performed using cmr42 Tissue Tracking from balanced steady-state free-precession short axis cine images (to calculate peak early diastolic strain rate, PEDSR) and from long axis cine images (to calculate GLS). Perfusion images were qualitatively assessed for focal and subendocardial perfusion defects, and individuals with reversible perfusion defects indicative of ischemia due to epicardial coronary artery disease were

excluded from further analyses. Quantitative myocardial perfusion analysis was performed using a saturation recovery gradient echo pulse sequence (at 1.5T)(13), with signal intensity versus time curves converted to concentration curves using a linear signal response to contrast agent with Fermi-constrained deconvolution(15) or using a dual sequence gradient echo method with inline automated reconstruction and post-processing for myocardial blood flow quantification (at 3T)(16) at base, mid and apical slice positions. LGE images were assessed for focal fibrosis, categorized as present or absent, and individuals with a subendocardial pattern of late enhancement indicative of previous myocardial infarction were excluded from further analyses.

Transthoracic echocardiography

Transthoracic echocardiography was performed in a subset of participants (175 T2Ds and 72 controls) by two accredited operators (A-MM and MSS) using an iE33 system with S5-1 transducer (Philips Medical Systems, Best, The Netherlands). Images were acquired and reported as per American Society of Echocardiography guidelines(17). Early diastolic transmitral flow velocities (E) and early diastolic mitral annular velocities (e') to estimate LV filling pressures were assessed by Doppler echocardiography per current recommendations(18).

Cardiopulmonary exercise testing

A symptom-limited incremental CPET was performed on a stationary electromagnetically braked cycle ergometer with expired gas analysis to determine peak V_{O_2}(19). One-minute workload increments were based on participant age, sex, height and weight(19). Each test was physician supervised with continuous ECG monitoring and blood pressure recording at two-minute intervals. Indications for medical termination were as previously described(20).

Subjects with ST-segment ECG changes indicative of myocardial ischemia during exercise testing were excluded from subsequent analyses. Breath-by-breath data were smoothed using a 30-second rolling mean and peak VO_2 was determined as the highest value.

Statistical analysis

Normality was assessed using histograms the Shapiro-Wilk test, and Q-Q plots. Continuous data are expressed as mean (± standard deviation), if normally distributed or median (interquartile range) if not. At baseline, patients and control groups were compared by independent *t*-tests or Mann-Whitney tests as appropriate. Categorical variables are presented as absolute and relative frequency, and were compared using the Chi-squared test or Fisher's exact test as appropriate. Biochemical, CMR, echocardiography and CPET variable between-group comparisons were undertaken using a general linear univariate analysis of variance, with adjustments for variables age, sex and ethnic group. Multiple imputation was used to impute missing CMR and echocardiography data. Correlations with peak VO_2 were assessed using Pearson correlation coefficient separately in participants with and without T2D. Generalised linear modelling was performed to identify independent associations of aerobic exercise capacity separately in patients with and without T2D. The dependent variable was peak VO_2 corrected for body weight. Only patients who achieved a respiratory exchange ratio (RER) ≥1 on CPET were included in correlation and regression analyses (total n=23 T2Ds excluded), to mitigate the confounding effects of tests where reaching of peak VO_2 was highly unlikely. A base model was adjusted for age, sex, ethnicity, smoking status, and systolic blood pressure, factors that are recognised for their associations with aerobic exercise capacity(21). CMR and

echocardiographic variables that significantly correlated with peak VO_2 were first analysed individually in the base model. Those CMR or echocardiographic variables found to be individually associated with peak VO_2 in the base model were then further selected and simultaneously entered into the base model to provide an assessment of whether these were associated with peak VO_2 independently of one another. A correlation matrix of included factors was assessed for potential multicolinearity; variables correlated with a magnitude ≥0.5 or ≤-0.5 were not included in the same regression model. Regression coefficients (β) are presented as point estimate and 95% confidence intervals. Statistical analysis was performed by G.S.G., E.B. and T.Y. using SPSS version 25.0 (Statistical Package for Social Sciences, Chicago, IL). A p value <0.05 was considered statistically significant.

Sponsor

The study sponsor of each study included was the University of Leicester, UK. Study funders (Novo Nordisk, the Medical Research Council, National Institute for Health Research and British Heart Foundation) provided financial support but had no role in study design (other than the external review process), data collection, data analysis, data interpretation or in the writing of reports (including the current manuscript).

Results

The study profile is displayed in figure 1. At baseline 259 subjects with T2D and 85 controls were recruited. Twelve subjects with T2D were found to be ineligible after consent. Reasons for ineligibility are shown in figure 1. A total of 247 subjects with T2D were therefore included in this analysis. Eighty-five healthy volunteers were enrolled for case-control comparison. Seven of these were subsequently excluded (three after blood sampling revealed a glycated hemoglobin level ≥6.0% and <6.5% indicating the presence of pre-diabetes, three who were unable to undergo CMR scanning due to claustrophobia, and one who developed arrhythmia during CPET). A total of 78 healthy volunteers were therefore included in case-control comparisons.

Case-control comparisons

Bio-anthropometric characteristics

The baseline demographic characteristics of subjects with T2D and controls are shown in table 1. Mean age of participants with T2D was 51.8±11.9 years, mean body mass index was 34.2±6.0 kg/m^2, median duration of diabetes was 61 (32 – 120) months, 45% were women, and 37% were from a black or minority ethnic group. The control group were similar for age, sex and ethnicity, but had lower overall body weight and body mass index. Those with T2D had a higher proportion of individuals with a history of smoking, hypertension and dyslipidemia compared with controls. Antihypertensive and lipid-lowering medication use was therefore higher in those with T2D compared to controls.

Fasting blood test results, adjusted for age, sex and ethnicity, are displayed in table 1. Both groups had similar renal function. Subjects with T2D had higher

overall glycated hemoglobin, lower total cholesterol and LDL cholesterol than controls.

Cardiovascular structure, function and fitness

Baseline CMR imaging, echocardiography and CPET, and echocardiography data comparing T2Ds and controls with adjustment for age, sex and ethnicity are displayed in supplemental table 1. Patients with T2D had similar absolute LV volumes but smaller indexed LV volumes and higher LV mass, with increased concentric LV remodelling (LV mass:volume 0.84±0.14 vs. 0.76±0.11g/mL, $p<0.001$) compared to controls. Similarly, there was no difference in absolute left atrial (LA) volumes but indexed LA volumes were smaller in T2Ds versus controls.

Overall there was no difference in LV ejection fraction (EF) between groups, however LV global longitudinal strain (GLS) was lower in T2Ds versus controls (-16.2±2.4 vs. -17.4±1.9%, $p<0.001$). LA ejection fraction was similar in both groups ($p=0.278$). With regards to diastolic function, there was no significant difference in LV peak early diastolic strain rate (1.02±0.23 vs. 1.05±0.22, $p=0.206$) or average E/e' (7.1 (3.1 – 9.4) vs. 7.1 (5.2 – 8.3), $p=0.438$) between groups, but E/A ratio was significantly lower in T2Ds (0.84 (0.66 – 1.05) vs. 1.10 (0.83 – 1.23), $p=0.006$).

Aortic distensibility was significantly lower in those with diabetes compared with controls (2.75 (1.74 – 4.03) vs. 4.92 (2.65 – 7.13) $mmHg^{-1}x10^{-3}$, $p<0.001$). Stress and rest perfusion imaging was performed in 208 T2Ds and 77 controls, and overall MPR was lower in subjects with T2D (2.60±1.24 vs. 3.54±1.15, respectively, $p<0.001$). Prevalence of non-ischemic LGE was low and there was no significant difference in the presence of LGE between T2Ds and controls (14 vs. 15%, $p=0.740$).

After adjustment for age, sex and ethnicity, both absolute and body-weight corrected peak VO_2 were significantly lower in the T2Ds versus controls (18.0±6.6 vs. 27.8±9.0mL/kg/min, p<0.001).

Correlations with aerobic exercise capacity

Correlations of participant characteristics and CMR measures of cardiac structure and function, with peak VO_2 separately in subjects with and without T2D are displayed in supplemental table 2.

In subjects with T2D, significant correlations were observed between peak VO_2 and age, T2D duration, systolic blood pressure, absolute and indexed LV volumes, LV EF, LV mass, LV GLS, average E/e' and MPR. In controls, significant correlations were observed between peak VO_2 and absolute and indexed LV volumes, LV EF, LV mass, absolute and indexed LA volumes, LV PEDSR, E/e', MPR, aortic distensibility.

Multivariable associations with aerobic exercise capacity

Participant characteristics

Multivariable associations between participant characteristics and peak VO_2 in subjects with and without T2D are displayed in supplemental table 3. In both groups with and without T2D, variables significantly associated with peak VO_2 were age (T2Ds: β= -0.195, p<0.001; controls: β= -0.448, p<0.001), male sex (T2Ds: β= 3.5437, p<0.001; controls: β=3.310, p=0.029), and white ethnicity (T2Ds: β=1.878, p=0.011; controls: β=4.915, p=0.003). Smoking status and resting systolic blood pressure were not significantly associated with peak VO_2 in either T2Ds or controls.

CMR and echocardiographic measures of cardiovascular structure and function

Associations of CMR measures of cardiovascular structure and function with peak VO_2, tested individually against the base model of bio-anthropometric characteristics, in participants with T2D and controls are shown in supplementary table 3. In patients with T2D, LV EF (β= -0.108, p=0.037), LV GLS (β=0.265, p=0.046), MPR (β=0.798, p=0.005), and E/e' (β= -0.385, p<0.001) had significant individual associations with peak VO_2. In controls, only LV EDV (β=0.082, p<0.001), LV EF (β= -0.297, p=0.012) and LV mass (β=0.129, p<0.001) were significantly associated with peak VO_2.

Multivariable associations between CMR measures of cardiovascular structure and function with significant individual associations with peak VO_2, simultaneously added to the base model of bio-anthropometric characteristics, are shown in table 2. In subjects with T2D, only E/e' (β= -0.388, p<0.001) and MPR (β=0.0822, p=0.006) were significantly associated with peak VO_2 independent of age, sex, ethnicity, smoking status and systolic blood pressure. Addition of HbA1c to the model did not significantly affect these associations (supplemental table 4). In controls, only LV mass was significantly associated with peak VO_2 (β=0.116, p=0.012).

Discussion

This is the first study to comprehensively describe the associations of aerobic exercise capacity with cardiac structure and function in asymptomatic people with T2D, using a combination of multiparametric CMR and echocardiography. Compared to controls, we have confirmed several markers of LV dysfunction in those with T2D and of these, LV diastolic filling pressure (E/e') and MPR were independently associated with peak VO_2. By contrast, only LV mass was associated with peak VO_2 in controls. Moreover, those with T2D displayed markedly lower levels of exercise capacity compared to controls, in the presence of overall normal LV ejection fraction.

To our knowledge only one other (smaller, n=170) study published over 15 years ago has assessed the cardiac determinants of exercise capacity in people with T2D(22). In a model containing age, male sex, body mass index and HbA1c, the only independent cardiac determinant of exercise capacity was basal early diastolic velocity. However, no measures of myocardial perfusion were performed. Exercise capacity was measured during treadmill stress testing performed for assessment of coronary artery disease and was estimated in metabolic equivalents and not peak VO_2. Furthermore, we assessed cardiovascular structure and function by multiparametric CMR, which is not limited by poor acoustic windows and operator dependency as in echocardiography.

Although there is a high prevalence of diabetes in both common forms of HF: HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF), emerging evidence suggests that people with T2D are particularly prone to developing HFpEF(23,24). Recent secondary analyses of the Look AHEAD trial have shown that baseline cardiorespiratory fitness is an

independent predictor of incident HFpEF (but not HFrEF) in T2D, after adjustment for traditional cardiovascular risk factors and interval myocardial infarction. Even though our T2D group overall had normal resting LV filling pressures (E/e'), these were associated with peak VO_2. It is well recognised that even in patients with HFpEF, where resting E/e' may be within the normal range, but exercise leads to abnormal elevations in LV filling pressures coupled with a diminished cardiac output reserve(25). A similar pattern has recently been observed in a cohort of asymptomatic people with T2D, in whom exercise echocardiography unmasked subclinical diastolic dysfunction and early HF even though resting filling pressures were within normal limits(26). We speculate that, because people with diabetes have less compliant ventricles, ventricular filling pressure rises faster on exercise than controls. Resting E/e' may therefore encompass the milieu of preclinical myocardial perturbations contributing to the pathogenesis of stage B HF, which are exacerbated during exercise.

While diastolic dysfunction has long been considered a central mechanism driving HFpEF, the role of microvascular inflammation and endothelial dysfunction are now increasingly being recognised(27). Subclinical alterations in myocardial perfusion could therefore be key drivers for the development of HFpEF in T2D(27), although studies evaluating the relationship between myocardial perfusion and diastolic function have to date yielded inconsistent findings(28,29), possibly due to different selection criteria and methods of assessment. Nevertheless, impaired MPR has been associated with increased cardiovascular mortality(30) and it is possible that targeting even subclinical impairments in myocardial perfusion may lower the risk of incident HF development in people with T2D. A striking finding in our cohort is that, even after

excluding subjects with reversible perfusion defects, previous myocardial infarction on CMR, and myocardial ischemia on exercise ECG, subjects with T2D had lower overall MPR than controls, as has been shown in several other cohorts(31,32), and this was independently associated with exercise capacity. This finding is also physiologically plausible as myocardial perfusion must increase during incremental exercise to meet myocardial oxygen demands, driven by increased heart rate and blood pressure. We have shown a similar relationship in pressure-overload hypertrophy in patients with aortic stenosis(33,34). It is possible that targeting even subclinical impairments in myocardial perfusion reserve may lower the risk of incident HF development in people with T2D.

Interventions to improve diastolic function and myocardial blood flow in asymptomatic people with T2D could therefore attenuate progression from stage B HF to overt HFpEF. For example, we have recently shown in a randomised trial that improvements in diastolic function occurred with exercise but not dietary weight loss(35). Limited and conflicting data exist regarding the impact of newer glucose-lowering therapies (sodium glucose co-transporter 2 inhibitors and glucagon-like peptide 1 receptor agonists) on diastolic function(36-38) in people with T2D, and these warrant further investigation. By contrast, few studies have evaluated treatment options for coronary microvascular dysfunction in T2D. In general, optimisation of traditional cardiovascular risk factors is advocated in the first instance(39), although good glycemic control is not itself convincingly associated with improved coronary microvascular function(40). Little to no data exist to demonstrate the efficacy of angiotensin converting enzyme inhibition, beta-blockade, calcium-channel inhibition, ranolazine and nitrates on improving coronary microvascular function in T2D(39), although mineralocorticoid receptor

antagonists may be beneficial(41). In a recent randomised, open label, active comparator trial of 26 weeks treatment with liraglutide or sitagliptin in young obese adults with T2D, we found no improvement in MPR with either study drug, suggesting that targeting the incretin pathway may not improve microvascular dysfunction in the medium term(36). However, MPR was a secondary outcome measure and the study was not therefore powered for this endpoint. Further studies are needed in people with T2D and stage B HF targeting both lifestyle and pharmacological interventions that improve diastolic function and/or MPR.

Strengths and limitations

The major strengths of the study are the detailed cardiac phenotyping (including absolute quantification of myocardial perfusion), the large sample size, use of CPET for absolute quantification of exercise capacity, and close matching of patient and control groups, In addition, we rigorously excluded those with established cardiovascular disease or low RER, which may have confounded the results. Lastly, there was a high proportion of both females and ethnic minorities which make the results more generalizable.

Our study also has several limitations. This was a pooled cohort of baseline CPET and CMR data from participants of studies in our unit, with minor differences in recruitment criteria. However, we used pre-specified inclusion and exclusion criteria for the present analyses to unify the study cohort, and all imaging was performed with standardised protocols and analysis techniques. We acknowledge that invasive angiography remains the gold standard modality for assessment of coronary artery disease, and subjects with diffuse, three-vessel coronary disease may not have regional perfusion defects detectable by CMR. Different perfusion acquisition and analysis methods were used between the

different pooled studies, which may have introduced systematic differences in MPR values(42). Each sub-study had its own T2D cases and controls, which were analysed with a common method, so differences in MPR between groups were not affected by analysis method.

As with any multiple regression model, there is a risk that omitted variables (which influence peak VO_2) may have sloped the estimates for those variables that were included in model. To minimise this risk, we exercised a rigorous approach for selection of variables to be included in our final regression models. We first tested for correlations with both the dependent variable and assessed for potential multicollinearity, then individually tested correlated imaging variables against the base model before selecting the final model. We did not have data on markers of insulin resistance (such as the Homeostatic Model Assessment of Insulin Resistance), dietary intake, physical activity levels etc., which may influence aerobic exercise capacity, and acknowledge this may have led to omitted variable bias and exaggerated the effect size of diastolic function and MPR. There is also the risk of measurement errors occurring in both our dependent variable (peak VO_2) and imaging variables, which may have been a source of imprecision. Every effort was made to minimise this risk. All CPET studies were performed according to a standardised protocol and a quality control CPET is undertaken every six weeks using a biological control in our unit. Image analysis was performed using standard protocols by experienced observers blinded to patient details (to minimise observer bias), with excellent test-retest reproducibility in our lab(43-46).

Conclusions

In asymptomatic people with T2D diastolic function and reduced MPR are key determinants of aerobic exercise capacity, independent of age, sex, ethnicity, smoking status, blood pressure, or glycemic control, and may drive the progression of stage B HF. Further studies are needed to determine whether strategies to reverse subclinical abnormalities in cardiovascular function lead to improvements in exercise capacity and prevent HF development in T2D.

Acknowledgements

Author contributions

GPM, EMB, MJD, TY, KK, and DW contributed to the design of the study. GSG, EGW, ZZH, LA, JH and JA recruited study participants, supervised assessment visits and clinical reviews. AMM performed the echocardiograms and cardiopulmonary exercise testing. GSG, PK and JDB analysed the data. GSG, EMB and TY performed the statistical analyses. GSG drafted the report, which was critically revised by GPM, EMB, MJD, TY and KK. All authors have read and approved the final version.

Statements of assistance

We thank Susan Mackness (NIHR Leicester Biomedical Research Centre) for research nurse support; Joanne Wormleighton and Kelly Parke (University Hospitals of Leicester NHS Trust) for support with CMR protocol design and scanning; and the study participants. We acknowledge support from the NIHR Leicester Biomedical Research Centre, NIHR Leicester Clinical Research Facility and the NIHR Collaboration in Leadership Applied Health Research and Care East Midlands.

Funding

This study was funded by the NIHR through a career development fellowship (G McCann, CDF 2014-07-045), the British Heart Foundation (BHF) through a Clinical Research Training Fellowship (G Gulsin, CRTF 32190), the Medical Research Council (MRC) through an Interdisciplinary Bridging Award, and Novo Nordisk.

Conflicts of interest

None.

Guarantor statement

Professor Gerry McCann is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Tables

Table 1. Demographic, clinical and bio-anthropometric characteristics of subjects with type 2 diabetes and controls.

	T2D (n=247)	**CONTROLS (n=78)**	***P*-value**
DEMOGRAPHICS			
Age, years	51.8±11.9	51.5±12.3	0.898
Sex, n (%)			
Male	136 (55)	42 (54)	0.851
Female	112 (45)	36 (46)	
Ethnic origin, n (%)			
Caucasian	155 (63)	53 (68)	0.405
Black or other minority ethnicity	92 (37)	25 (32)	
ANTHROPOMETRICS			
Height, cm	168±10	170±10	0.111
Weight, kg	96.9±19.1	72.0±13.6	**<0.001**
Body mass index, kg/m^2	34.2±6.0	24.8±3.1	**<0.001**
Systolic blood pressure, mmHg	138±16	129±18	**<0.001**
Diastolic blood pressure, mmHg	87±8	81±9	**<0.001**
Heart rate, beats/min	76±12	63±11	**<0.001**
MEDICAL HISTORY			
Diabetes duration, months	61 (32 - 120)	N/A	N/A
Smoking history, n (%)			
Never smoked	140 (56)	50 (64)	**0.023**
Ex-smoker	68 (28)	25 (32)	
Current smoker	39 (16)	3 (4)	
Hypertension, n (%)	121 (49)	5 (6)	**<0.001**
Dyslipidemia, n (%)	148 (60)	7 (9)	**<0.001**
MEDICATIONS			
ACE inhibitor, n (%)	67 (27)	4 (5)	**<0.001**
ARB, n (%)	28 (11)	0 (0)	**0.002**
Beta blocker, n (%)	16 (6)	0 (0)	**0.024**
Calcium channel blocker, n (%)	50 (20)	1 (1)	**0.001**
Statin, n (%)	144 (58)	7 (9)	**<0.001**
Metformin, n (%)	214 (87)	N/A	N/A
Sulfonylurea, n (%)	50 (20)	N/A	N/A
DPP-IV inhibitor, n (%)	16 (6)	N/A	N/A
SGLT2 inhibitor, n (%)	36 (15)	N/A	N/A
GLP-1 receptor agonist, n (%)	17 (7)	N/A	N/A
Insulin, n (%)	20 (8)		
FASTING BLOOD TESTS			
Urea, mmol/L	5.3±1.3	5.4±1.4	0.656
Creatinine, mmol/L	74±16	76±15	0.147
Estimated GFR, mL/min	84±10	83±9	0.811
Glucose, mmol/L	7.7 (6.7 - 9.5)	5.0 (4.8 - 5.3)	**<0.001**
HbA1c, %	7.4±1.1	5.4±0.3	**<0.001**

HbA1c, mmol/mol	57±12	36±3	**<0.001**
Total cholesterol, mmol/L	4.5±1.0	5.5±1.0	**<0.001**
Triglycerides, mmol/L	1.8 (1.2 - 2.6)	1.0 (0.7 - 1.4)	**<0.001**
LDL, mmol/L	2.4±0.8	3.2±0.9	**<0.001**
Hemoglobin, g/L	144±15	144±13	0.985

Data are n (%), mean±SD, or median (IQR). Abbreviations: ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker; GFR=glomerular filtration rate; GLP-1=glucagon-like peptide-1; DPP-IV=dipeptidyl peptidase-IV; LDL=low-density lipoprotein; SGLT2=sodium glucose cotransporter-2. Bold typeface indicates $p<0.05$.

Table 2. Multivariable associations between measures of cardiovascular structure and function with peak VO_2 in people with type 2 diabetes and controls.

T2Ds (n=224)				Controls (n=78)			
Variable	**B**	**95% CI**	**P-value**	**Variable**	**B**	**95% CI**	**P-value**
Age	−0.104	−0.172 to −0.036	**0.003**	Age	−0.446	−0.563 to −0.329	**<0.001**
Male sex	2.345	0.909 to 3.781	**0.001**	Male sex	−0.461	−3.596 to 2.675	0.773
White ethnicity	1.415	−0.041 to 2.871	0.057	White ethnicity	2.929	−0.220 to 6.078	0.068
Never smoked	2.034	0.193 to 3.874	**0.030**	Never smoked	−5.636	−12.185 to 0.914	0.092
Systolic blood pressure	−0.017	−0.062 to 0.027	0.443	Systolic blood pressure	−0.037	−0.125 to 0.052	0.417
LV ejection fraction	−0.041	−0.150 to 0.067	0.453	LV EDV	<0.001	−0.072 to 0.072	0.998
LV GLS	0.214	−0.072 to 0.499	0.142	LV ejection fraction	−0.143	−0.375 to 0.089	0.227
Myocardial perfusion reserve	0.822	0.235 to 1.409	**0.006**	LV mass	0.116	0.026 to 0.206	**0.012**
Average E/e’	-0.388	−0.595 to −0.180	**<0.001**				

*Excluding subjects with peak RER<1 on CPET. Abbreviations: CI=confidence interval; EDV=end-diastolic volume; GLS=global longitudinal strain; LV=left ventricle; T2D=type 2 diabetes. Bold typeface indicates p<0.05.

Figure legends

Figure 1. Study profile. Abbreviations: CMR=cardiovascular magnetic resonance imaging; CPET=cardiopulmonary exercise testing; MI=myocardial infarction; RER=respiratory exchange ratio; T2D=type 2 diabetes.

Figure 2. Scatterplots displaying the correlations of peak VO_2 in subjects with type 2 diabetes with A) myocardial perfusion reserve, and B) E/e'.