Exercise capacity is related to attenuated responses in oxygen extraction and left ventricular longitudinal strain in asymptomatic type 2 diabetes patients

Peer-reviewed author version

VAN RYCKEGHEM, Lisa; KEYTSMAN, Charly; VERBOVEN, Kenneth; Verbaanderd, Elvire; FREDERIX, Ines; Bakelants , Elise; Petit, Thibault; Jogani, Siddharth; Stroobants , Sarah; DENDALE, Paul; BITO, Virginie; VERWERFT, Jan & HANSEN, Dominique (2021) Exercise capacity is related to attenuated responses in oxygen extraction and left ventricular longitudinal strain in asymptomatic type 2 diabetes patients. In: European Journal of Preventive Cardiology, 28 (16) , p. 1756 -1766.

DOI: 10.1093/eurjpc/zwaa007
Handle: http://hdl.handle.net/1942/36617

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Running title: Cardiac performance during exercise and exercise capacity in type 2 diabetes

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Word count: 3702 (main body of text)

Abstract

Background Type 2 diabetes mellitus (T2DM) is associated with reduced exercise capacity and cardiovascular diseases, both increasing morbidity and risk for premature death. As exercise intolerance often relates to cardiac dysfunction, it remains to be elucidated to what extent such an interplay occurs in T2DM patients without overt cardiovascular diseases.

Design Cross-sectional study, NCT03299790

Methods Fifty-three T2DM patients underwent exercise echocardiography (semi-supine bicycle) with combined ergospirometry. Cardiac output (CO), left ventricular longitudinal strain (LS), oxygen uptake ($\dot{V}O_2$) and oxygen (O_2) extraction were assessed simultaneously at rest, low- and high-intensity exercise. Glycemic control and lipid profile were assessed in the fasted state. Participants were assigned according to their exercise capacity being adequate or impaired ($EX_{adequate}$; $\dot{V}O_{2peak}$ <80% and $EX_{impaired}$; $\dot{V}O_{2peak}$ ≥80% of predicted $\dot{V}O_{2peak}$) to compare O_2 extraction, CO and LS at all stages.

Results Thirty-eight participants ($EX_{impaired}$; n=20 and $EX_{adequate}$; n=18) were included in the analyses. Groups were similar regarding HbA1c, age and sex (p>0.05). At rest, CO was similar in the $EX_{impaired}$ group vs. $EX_{adequate}$ group (5.1±1L/min vs. 4.6±1.4L/min, p>0.05) and increased equally during exercise. $EX_{impaired}$ patients displayed a 30.7% smaller increase in O_2 extraction during exercise compared to the $EX_{adequate}$ group (p=0.016) which resulted in a lower O_2 extraction at high-intensity exercise (12.5±2.8mL/dL vs. 15.3±3.9mL/dL, p=0.012). LS was similar at rest but increased significantly less in the $EX_{impaired}$ vs. $EX_{adequate}$ patients (1.9±2.5% vs 5.9±4.1%, p=0.004).

Conclusions In asymptomatic T2DM patients, an impaired exercise capacity is associated with an impaired response in oxygen extraction and myocardial deformation (LS).

Word count: 249 words

Trial registry: Effect of High-intensity Interval Training on Cardiac Function and Regulation of Glycemic Control in Diabetic Cardiomyopathy (https://clinicaltrials.gov/ct2/show/NCT03299790)

Keywords; stress echocardiography, left ventricular function, type 2 diabetes, exercise capacity, diabetic complications

Introduction

Type 2 Diabetes Mellitus (T2DM) is often associated with a lower exercise capacity, consequently elevating the risk for premature death. (1, 2) Despite the awareness of cardiovascular disease (CVD) being a major cause of morbidity and mortality in diabetes patients, these complications still account for extensive health care costs. (3, 4) In healthy individuals, the cardiac output (CO) can be estimated during a cardiopulmonary exercise test (CPET), as maximal oxygen uptake ($\dot{V}O_{2peak}$) is mostly dominated by the CO and therefore linearly related to the latter. (5) In T2DM patients (without a history of CVD) displaying a reduced exercise capacity, CO is up to 23% lower compared to healthy controls during submaximal exercise, and differences in CO only start to appear during exercise. (6) Therefore, silent cardiac dysfunction might causally relate to an impaired exercise capacity, in clinically asymptomatic T2DM patients. This stipulates the importance of examining cardiac function during exercise. Indeed, up to 33% of T2DM patients report symptoms of dyspnoea or chest pain but have a normal echocardiography at rest. Of interest, less than 50% of T2DM patients presenting with abnormal echocardiographic findings report such symptoms. (7) Hence, an impaired exercise capacity could indeed be related to exercise-induced cardiac dysfunction.

However, $\dot{V}O_2$ is the product of CO and oxygen (O_2) extraction, the latter also being affected in T2DM patients during exercise. (8) Accordingly, it remains to be examined whether an impaired exercise capacity in T2DM would be primarily associated to cardiac dysfunction or limited O_2 extraction, or the combination of both.

Notwithstanding the clinical relevance of these associations, especially with respect to targeted (cardiac or peripheral muscle oriented) patient treatment, previous studies (6, 8, 9) display some methodological limitations. First, exercise capacity ($\dot{V}O2$) and cardiac function were evaluated separately on different timeframes and/or in different positions (upright vs. semi-supine position). Indeed, exercise testing was performed using upright cycle ergometers, while cardiac function was examined after this exercise test in the semi-supine position. (6, 9) However, CO is higher in the supine position compared to the upright position, mainly attributed to elevated end-diastolic volumes (10), potentially resulting in an overestimation of the CO during exercise testing. (6, 8, 9) Hence, the simultaneous assessment of CO and $\dot{V}O2$ during exercise remains to be investigated in T2DM patients. Second, $\dot{V}O_2$ was not reported during exercise echocardiography in other studies (6, 9) although it becomes highly dependent on CO when exceeding the anaerobic threshold. (11, 12) Lastly, CO was measured using different methods; bioreactance methods (8) vs. transthoracic echocardiography (6, 9), the latter being preferred for evaluating cardiac function. (13)

The aim of this study was therefore to simultaneously evaluate CO and O_2 extraction by combining exercise echocardiography with ergospirometry in order to clarify whether impaired exercise capacity is related to cardiac dysfunction (assessed CO) or rather an impaired O_2 extraction in asymptomatic T2DM patients.

Methods

Study design and subjects

This cross-sectional study was performed at REVAL (Rehabilitation Research Centre), Faculty of Rehabilitation Sciences, Hasselt University, Belgium and the Department of Cardiology, Jessa hospital (Hasselt, Belgium). We included 53 asymptomatic (no history or symptoms of cardiovascular disease) T2DM patients (aged 18-81 years) using following inclusion criteria; diagnosed according to the criteria of the American Diabetes Association (14), stable pharmacologic treatment for at least three months (e.g. anti-hypertensive, glucose- and lipid-lowering drugs) and able to perform a maximal incremental exercise test. Patients were excluded if renal disease, retinopathy, neurological, orthopaedic, oncologic or pulmonary diseases prohibiting the performance of an exercise test, and/or evidence of cardiovascular diseases (e.g. valve disease, coronary artery disease, congenital heart disease, symptoms of dyspnoea or chest pain (during exercise)) was present. Blood samples were collected for the evaluation of glycemic control, lipid profile and N-terminal pro-B-type natriuretic peptide (NT-proBNP). Exercise echocardiography was performed to evaluate exercise-related cardiac performance. Based on the exercise capacity, patients were divided into two groups ($EX_{impaired}$; $\dot{V}O_{2peak}$ <80% and $EX_{adequate}$; $\dot{V}O_{2peak}$ ≥80% of the predicted oxygen uptake respectively), according to the standardized criteria. (15) The study protocol was approved by the medical ethical committee of Jessa hospital (Hasselt, Belgium) and Hasselt University (Hasselt, Belgium) and was performed according to the Declaration of Helsinki (2013). All participants gave written informed consent, prior to the execution of the tests. The study was part of a clinical trial and registered at Clinicaltrials.gov (NCT number: NCT03299790)

Body composition

Anthropometric measures (body height and weight) were assessed in the fasted state, using a wall-mounted Harpenden stadiometer (ICD 250DW, De Grood Metaaltechniek, Nijmegem, The Netherlands) and a digital-balanced weighing scale (Seca 770, Seca Hamburg, Germany). BMI (kg/m^2) and body surface area (BSA, m^2)) were calculated. Body composition was analysed by using a Dual Energy X-ray Absorptiometry scan (Hologic Series Delphi-A Fan Beam X-ray Bone Densitometer) from which whole-body lean tissue mass, fat mass and fat percentage were determined.

Blood parameters

On the first evaluation day, fasted blood samples (lithium heparin tubes) were collected to evaluate lipid profile (total cholesterol, HDL- and LDL-cholesterol and triglycerides) and insulin levels. A 5-point oral glucose tolerance test (OGTT, sodium fluoride tubes) was performed after ingestion of 75g glucose (dextrose monohydrate) dissolved in 250mL of water. Blood samples were stored for 30 min at room temperature and thereafter for 120 min at 4°C. Afterwards, samples were centrifuged (1650g, for 15 min) and plasma stored at -80°C until analyses for insulin, total cholesterol, HDL- and LDL-cholesterol,

triglycerides and glucose (Roche Cobas 8000, Roche Diagnostics International Ltd, Rotkreuz, Switzerland). On the second evaluation day, non-fasted blood samples were analysed for glycated haemoglobin A1c (HbA1c, Menarini HA-8180 HbA1c auto-analyser, Menarini Diagnostics, Diegem, Belgium) and NT-proBNP (electrochemiluminescence immunoassay, Cobas e 801 immunoassay analyser, Menarini Diagnostics, Diegem, Belgium). Whole body insulin resistance was estimated using the homeostasis assessment of insulin resistance (HOMA-IR). (16) From the glucose measurements of the OGTT, total area under the curve (tAUC) for plasma glucose was estimated using the trapezoidal rule. All blood sample analyses were performed at the clinical laboratory (Jessa Hospital, Hasselt, Belgium).

Echocardiography with combined ergospirometry

Echocardiography using a phased array probe (Vivid E90 and GE M5S 1.5-4.5 MHz, GE Health Medical, Milwaukee, Wisconsin, USA) was performed by a trained cardiologist in exercise imaging. Images were digitally stored in a cine-loop format containing at least three cardiac cycles for each measure and analysed offline via the EchoPAC software version 201 (General Electric Vingmed, Horten, Norway).

Resting echocardiography (supine position) included following measurements: left ventricular (LV) outflow tract diameter (LVOT) determined as the cross-sectional area of the aortic valve in the parasternal long axis view in mid-systole, dimensions of the LV ((interventricular septum thickness end-diastole (IVSd), LV posterior wall thickness end-diastole (LVPWd), LV diameter end-diastole (LVDd) and relative wall thickness (RWT)) and estimation of the LV mass (LVM) via the formula of Devereux and indexed for BSA (LVMi). (17) Diastolic function was evaluated according to the latest guidelines (18) and included: mitral inflow pattern (early (E) and late (A) diastolic flow, deceleration time (Dt)) using pulsed wave Doppler at the tips of the mitral leaflets. Pulsed wave tissue Doppler imaging (TDI) was used for early diastolic velocity (e'_s) at the septal annulus. The E/e'_s ratio was measured as an indicator for LV filling pressures.

Exercise echocardiography (semi-recumbent position) included following measurements; diastolic function as previously described (18) and end-systolic and end-diastolic LV volumes (LVESV, LVEDV) were assessed in combination with LV ejection fraction (LVEF) using the Simpson's biplane method in the apical four chamber view (AP4C). (19) Cardiac output (CO) was measured using the velocity time integral of the flow through the aortic valve in the apical five chamber view via pulsed wave Doppler, LVOT and heart rate (HR). 2D Speckle tracking analyses were performed in the AP4C view for left ventricular longitudinal strain (LS) and defined in accordance with consensus on strain measurements and reported as absolute values. (20) Contractile reserve in LS was expressed as the absolute increase from rest to high-intensity exercise. Systolic pulmonary artery pressure was estimated by measuring the peak tricuspid regurgitatant velocities with colloid contrast enhancement. (18) Mean pulmonary artery pressure (mPAP) was calculated using the Chemla formula. (21)

The exercise echocardiographic assessment included 3 stages of evaluation; rest, low- and high-intensity exercise. Breath-by-breath gas exchange analyses (CS-200 Ergo-Spiro, Schiller AG, Switzerland) were simultaneously performed for evaluation of respiratory exchange ratio (RER) and oxygen uptake ($\dot{V}O_2$). Oxygen pulse (O_2 pulse) and O_2 extraction were defined as $\dot{V}O_2$/HR and $\dot{V}O_2$/CO, respectively. Relative O_2 extraction ($O_{2\text{-}FFM}$ extraction) was defined as ($\dot{V}O_2$/CO)/FFM_{legs}.

Prior to every test, a volume and gas calibration was executed according to the manufacturer's recommendations. A standardized ramp-stage protocol (initial workload of 20W, gradually increased by 10W/min) was applied on a semi-supine bicycle (Ergocouch erg 911 LS, Ergosana, Rotterdam, The Netherlands). A cycling frequency of 60-65 revolutions per minute was applied during the test and participants were encouraged to achieve maximal effort. Low-intensity exercise (steady state cycling workload according with 80-100 beats per minute (bpm)) was used for the diastolic stress test, eliminating fusion of the E and A wave. (22) High-intensity exercise evaluation was performed when RER exceeded 1.03 (steady state cycling workload). Systolic and diastolic blood pressure were measured prior to the echocardiographic evaluation and monitored during the exercise echocardiographic assessment, using an electronic sphygmomanometer (Omron®, Omron Healthcare, IL, USA). Continuous 12-lead ECG monitoring was applied during the test (CardioSoft v6.7, Acertys, Aartselaar, Belgium).

Statistical analyses

Statistical analyses were performed in SPSS V.24 (IBM SPSS Statistics for Windows, Chicago, IL, USA). Data were expressed as mean ± standard deviation (SD) and only included if the prior outcome (CO during exercise echocardiography) was successfully examined. Normality was checked via the Shapiro-Wilk test. Homogeneity was assessed via the Box's M test and Levene's test. Sphericity was checked via Mauchly's test. Descriptive statistics included independent sample T-tests and Mann-Whitney U tests (non-parametric alternative). Pearson correlations were calculated for cardiac function and blood parameters and indicators for physical fitness ($\dot{V}O_{2peak}$ and W_{peak}) and linear regression was performed to explain variances. Two-way mixed ANOVA's were executed to investigate mean differences for cardiac function and exercise physiology. Level of statistical significance was set at $p<0.05$ (two-tailed). Holm-Bonferroni correction was used to correct for multiple testing of independent sample T-tests and Mann-Whitney U tests ($\alpha_1=0.05$, $\alpha_2=0.025$, $\alpha_3=0.017$) and level of statistical significance set at $p_1=0.05$, $p_2=0.025$, $p_3=0.017$ (two-tailed).

Results

General characteristics

Out of the 53 asymptomatic T2DM patients recruited in the study, 38 patients were included in the analyses (Figure 1). Use of medication was similar in both groups and nearly 50% were on lipid managing treatment (Supplementary table 1). Groups were comparable for age, sex and disease duration (Table 2). Body weight, BMI, BSA, fat mass, whole body lean mass and fat free mass in the legs were higher in the $EX_{impaired}$ vs. $EX_{adequate}$ group ($p<0.05$, Table 2). Whole body fat percentage was similar between groups ($p>0.05$). Fasted insulin levels and HOMA-IR were significantly higher ($p=0.006$ and $p=0.004$ respectively) and HDL-cholesterol levels lower in the $EX_{impaired}$ group compared to the $EX_{adequate}$ group ($p=0.013$, Table 2). Other parameters for glycemic control (HbA1c, fasting plasma glucose, tAUC glucose) and lipid profile (LDL-cholesterol, total cholesterol, triglycerides) were comparable between groups ($p>0.05$, Table 2).

Resting Cardiac function (supine position)

LVPWd and RWT were significantly elevated in the $EX_{impaired}$ group compared to the $EX_{adequate}$ group ($p=0.031$ and $p=0.019$ respectively, Table 3). Other measures of left ventricular morphology and dimensions and diastolic function were similar between groups (Table 3). There was no difference in NT-proBNP levels (Table 2).

Cardiac function during exercise

Blood pressure (semi-supine position) and HR were similar at all stages between both groups (Table 5). The main effect of different stages of evaluation (intensity effect) for CO was significant ($F(2,70)=253.987$, $p<0.001$, Figure 4). There was no significant main effect of group nor interaction for CO ($p>0.05$). At high-intensity exercise, LS was significantly lower in the $EX_{impaired}$ vs. $EX_{adequate}$ group ($p_3=0.004$). The main effect of different stages of evaluation (intensity effect) for LS was significant ($F(2,62)=20.966$, $p<0.001$). The same applied for the main effect for group ($F(1,31)=4.701$, $p=0.038$) and for interaction effects ($F(2,62)=5.229$, $p=0.008$). As a result, CO and responses in CO during exercise were similar between groups while responses in LS were smaller in the $EX_{impaired}$ group compared to the $EX_{adequate}$ group which resulted in a reduced LS at high intensity exercise (Figure 4 and Table 5). Except for LVEDVi and SVi which were lower at low-intensity exercise in the $EX_{impaired}$ group compared to the $EX_{adequate}$ group (43 ± 10mL/m² vs 53 ± 11mL/m² and 31 ± 8mL/m² vs 39 ± 7mL/m², $p_2=0.004$ and $p_2<0.001$) all other parameters of cardiac function were comparable between both groups (Table 5). Details on duration of the exercise protocol are reported in Supplementary table 2.

Ergospirometry related parameters during exercise

By design, absolute (mL/min) and relative (mL/Kg/min) $\dot{V}O_{2peak}$ were significantly lower in the $EX_{impaired}$ vs. $EX_{adequate}$ group ($p=0.002$ and $p<0.001$, Figure 4 and Table 5). Workload (W) and exercise intensity (RER) were similar in both groups at all stages ($p_2>0.025$ and $p_3>0.017$ respectively). $\dot{V}O_2$ was

significantly lower in the $EX_{impaired}$ group at the first ventilatory threshold (VT1) compared to the $EX_{adequate}$ group ($p<0.05$) and the same applied for VEpeak ($p=0.003$) and $\Delta\dot{V}O2/\Delta W$ ($p=0.035$).

O_2 pulse was similar at rest and during low-intensity exercise between groups ($p>0.05$), but was lower in the $EX_{impaired}$ group at high-intensity exercise ($p_3=0.015$). The main effect of the different stages of evaluation (intensity effect) for O_2 pulse was significant ($F(2,70)=359.998$, $p<0.001$). The same applied for the main effect for group ($F(1,35)=6.429$, $p=0.016$) and for interaction effects ($F(2,70)=4.78$, $p=0.011$).

O_2 extraction was significantly lower at both low- and high-intensity exercise in the $EX_{impaired}$ vs. $EX_{adequate}$ group ($p_2=0.012$ and $p_3=0.012$ respectively). The main effect of different stages of evaluation (intensity effect) was significant ($F(2,70)=223.875$, $p<0.001$). The same applied for the main effect for group ($F(1,35)=6.658$, $p=0.014$) and for interaction effects ($F(2,70)=4.072$, $p=0.021$). $O_{2\text{-}FFM}$ extraction was significantly lower at rest and during exercise in the $EX_{impaired}$ vs. $EX_{adequate}$ group ($p_1=0.044$, $p_2=0.003$ and $p_3<0.001$ respectively). Similar results were observed in the two-way mixed ANOVA (effect of stages of evaluation: $F(2,70)=183.862$, $p<0.001$; interaction effect; $F(2,70)=7.558$, $p=0.001$; effect of group: $F(1,35)=12.928$, $p=0.001$). As a result, O_2 pulse and O_2 extraction increased significantly different between groups during exercise testing (Figure 4 and Table 5).

Correlations and regression

Significant correlations for blood parameters and cardiac function or exercise capacity are presented in Supplementary table 3. O_2 extraction was significantly correlated with glycemic control (HbA1c and tAUCglucose, $p=0.02$ and $p=0.03$, respectively) which explained 12.4% and 15.9% of the variance in O_2 extraction at high-intensity exercise, respectively. Similar relations were observed for $O_{2\text{-}FFM}$ extraction. LS was significantly correlated with fasted serum insulin levels and HDL-cholesterol levels ($p=0.012$ and $p=0.005$) which explained respectively 16.1% and 19.8% of the variance in LS at high-intensity exercise. In addition, LS at high intensity exercise was significantly correlated with $\dot{V}O2peak$-predicted ($r=0.538$, $p=0.001$) and relative $\dot{V}O2peak$ ($r=0.562$, $p=0.001$) and explained 26.7% and 29.3% of their variance respectively.

Discussion

This study investigated the underlying mechanism for impaired exercise capacity in asymptomatic T2DM patients. By simultaneously measuring cardiac output (CO) and oxygen uptake ($\dot{V}O_2$), we could determine whether impaired cardiac function and/or oxygen extraction was responsible for impaired exercise capacity in asymptomatic T2DM patients. Our study shows that an impaired exercise capacity in asymptomatic T2DM patients is primarily attributed to limitations at the peripheral level (oxygen extraction) rather that at the cardiovascular level (cardiac output). Moreover, it was also observed that

left ventricular longitudinal strain increased significantly less in T2DM patients with impaired exercise capacity during exercise.

CO was similar at rest and exercise between exercise tolerant vs. intolerant patients, and the difference in response was only minor (9.2% smaller in intolerant patients, $p>0.05$). In contrast, Wilson *et al.* compared responses in CO during submaximal exercise in T2DM patients with healthy individuals, demonstrating a 55% smaller response in CO, attributed to impaired ventricular filling rates. (6) Noteworthy, CO was estimated differently (use of stroke volume) in the study of Wilson *et al.* and the greater CO in our study might (partly) be attributed to the applied exercise intensity, as HR was approximately 14% higher in our study, while CO greatly relies on HR. (23) This confirms the methodological concerns raised in the introduction; an adequate exercise intensity (above the anaerobic threshold) is essential to properly evaluate CO and responses in CO. (11, 12) Therefore, the results from previous studies should be reconsidered.

Previous studies (6, 9) demonstrated that exercise capacity is related to end-diastolic volumes in T1DM and T2DM patients. However, in our study, end-diastolic volumes and CO were only positively correlated with $\dot{V}O_{2peak}$ in the tolerant patients ($r=0.591$ and $r=0.509$, $p<0.05$) and not in the intolerant patients. Therefore, our study could not confirm the predictive role of end-diastolic volumes and CO. Considering that up to 25% of T2DM patients display symptoms of dyspnoea during exercise even though cardiac function is normal (at least in rest), the role of CO is not fully clear.(7)

Left ventricular longitudinal strain (LS) is increasingly used as a non-invasive marker of subclinical LV dysfunction and estimates myocardial deformation, enabling the detection of subtle wall abnormalities or ischemia in a reproducible manner. (24, 25) Up to 32% of well-controlled T2DM patients without a history of cardiovascular diseases display reductions in LS, and aberrations relate to adverse outcomes (mortality and hospitalisation). (26, 27)

Surprisingly, despite a similar response of all the classical parameters (CO, LVEF, E/e',..), intolerant patients displayed an inferior response (1.9% vs. 5.6% increase, $p<0.05$) in myocardial deformation (LS) during exercise. Importantly, aberrations only occurred during exercise, and even worsened with increasing exercise intensity. Peak myocardial deformation was associated with $\dot{V}O_{2peak}$, however this relation was driven by the tolerant patients, as such relation was not observed in the intolerant patients. In addition, resting myocardial deformation was not associated with $\dot{V}O_{2peak}$. Therefore, interpreting resting LS without information on exercise capacity would likely result in a significant amount of patients displaying these exercise-related aberrations in LS to be left undetected. Our results suggest that left-ventricular LS, measured during exercise, could be an indicator of early left-ventricular dysfunction, preceding deterioration in classical parameters such as LVEF. Aberrations in resting strain have been found to precede changes in LVEF in patients receiving chemotherapy, supporting this hypothesis. (28)

However, limitations at the peripheral level seemed to underlie impaired exercise capacity. Indeed, intolerant patients displayed an inferior response in O_2 extraction (30.7% smaller) in comparison to exercise tolerant patients. Importantly, just like LS, aberrations only occurred during exercise and

worsened with increasing exercise intensity. Due to physiological limitations (e.g. haemoglobin concentrations), O_2 extraction from the arterial blood reaches a maximum during exercise. In order to increase the $\dot{V}O_2$ and maintain O_2 extraction, an increased O_2 delivery (e.g. elevated blood flow) and/or O_2 flux towards the myocytes (e.g. increased capillary density) is required. (29-31) Bauer *et al.* (32) and MacAnaney *et al.*(33) showed attenuated responses in muscle blood flow during the onset of exercise in T2DM patients, probably attributed to impaired vasodilation. Bauer *et al.* (32) did not report differences in $\dot{V}O_{2peak}$, which is in contrast to the study of Lalande *et al*.(34) However, in the latter, $\dot{V}O_{2peak}$ was limited at the cardiovascular level, as CO was lower in the T2DM patients. Therefore, impairments regarding O_2 flux should be considered. The latter can be affected by HbA1c, due to an increased affinity for O_2, impeding the flux. (29) However, although HbA1c levels explained 19% of the variance in O_2 extraction in the tolerant patients ($r=-0.491$, $p<0.05$), HbA1c levels did not underlie impairments in exercise capacity as such a relation was not observed in patients with an impaired exercise capacity.

Further, the capillary surface area seems to limit O_2 flux, as animal models for T2DM display impairments in muscle capillary haemodynamics during exercise. (35) Additionally, O_2 is extracted in a concentration gradient driven manner, and mitochondrial dysfunction, which is reported in diabetes patients, could result in a reduced O_2 flux towards the myocyte. (8) Indeed, decreased mitochondrial activity has been reported in muscle tissue of diabetes patients although alterations in gene expression (e.g. cytochrome oxidase) are not consistently reported in literature. (36) Impairments at the mitochondrial level can prematurely result in the switch towards the (oxygen-independent) anaerobic metabolism. Within sedentary T2DM patients, this switch is accelerated and accompanied by greater lactate production, potentially related to muscle morphology. (32, 37) Indeed, in our study, $\dot{V}O_2$ was 17% lower ($p<0.05$) at VT1 in the intolerant patient group compared to the tolerant patient group, indicating an impaired balance between the aerobic and anaerobic system. However, via the applied methods in our study, we could not elucidate to what extent a limited capillary density or mitochondrial dysfunction (or a combination) would be responsible for an impaired O_2 flux and therefore limited O_2 extraction. (36)

These results have significant clinical implications on the patients' prognosis. First, to remediate impaired exercise capacity in T2DM patients, it seems mandatory to target the skeletal muscles to optimise O_2 extraction. In order to achieve this goal, it may be suggested that greater endurance exercise intensities should be applied. (38) Second, a significantly reduced change in LS during exercise in exercise intolerant T2DM patients could be of great prognostic importance. In asymptomatic T2DM patients with no history of cardiovascular disease, an impaired global longitudinal strain is a predictor of future adverse left ventricular remodelling and adverse cardiovascular events, thus providing incremental prognostic value beyond clinical data, HbA1c and diastolic function. (39, 40) As a result, exercise intolerant T2DM patients should deserve investigation of LS (preferably during exercise) and, in case of abnormalities, greater primary prevention of adverse cardiac events or remodelling. In this

regard, applying exercise echocardiography with combined ergospirometry is helpful in these T2DM patients.

Limitations

Eleven of the 51 exercise echocardiographic assessments needed to be excluded because of insufficient image quality. External validity is limited due to the disproportion in participating males and females. Physical activity levels were not objectively assessed in this population, impeding to control for this factor.

Conclusion

In asymptomatic T2DM patients, exercise capacity seems to be dominated at the muscular level (oxygen extraction) rather than the cardiovascular level (cardiac output). Importantly, these aberrations only start to appear during exercise. These results stipulate the need for exercise echocardiography with simultaneous ergospirometry in T2DM patients with impaired exercise capacity to properly evaluate cardiac function and exercise capacity in a comprehensive manner.

Acknowledgements

We would like to thank all the participants for their participation in this study. Furthermore, we thank the clinicians from the Department of Cardiology at the Jessa hospital for all the support in this study. Blood samples were collected and analysed in cooperation with the University Biobank of Limburg (UBiLim).

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. This work was supported by internal resources (Hasselt University).

Compliance with ethical standards (Conflict of interest)

The authors declare that they have no conflict of interest.

Author contributions

L.V.R. and D.H. conceived and designed the study. L.V.R. included the participants. The cardiologists (I.F., T.P., E.B., S.J., S.S.) executed the echocardiographic assessments and L.V.R assisted (execution of electrocardiogram, ergospirometry). L.V.R. performed the offline measurements of the echocardiographic assessments (assisted by J.V.) and C.K. analysed the data of the breath-by-breath gas exchange analyses. E.V. assisted in the conduction of the study as part of her internship. L.V.R. and D.H. performed the statistical analyses. L.V.R. and D.H. wrote the manuscript. K.V., C.K., J.V., I.F., E.V., E.B.,T.B., S.J., S.S., P.D. and V.B. critically reviewed the manuscript. All authors gave their final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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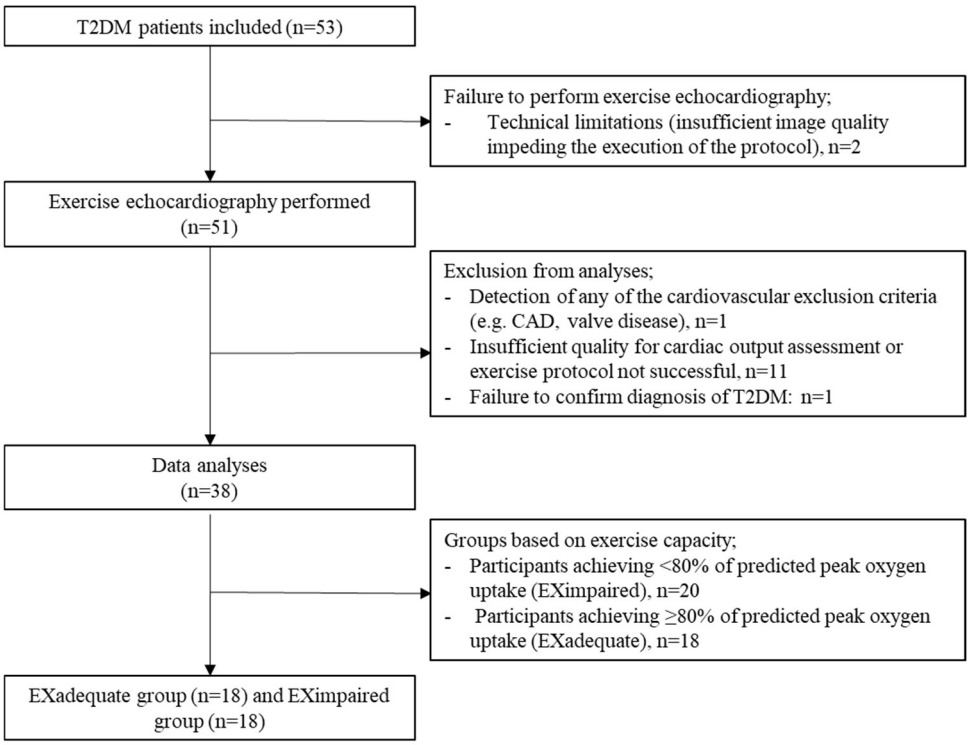
Figure 1: Flowchart of the study



Flowchart of the study. T2DM; type 2 diabetes mellitus, CAD; coronary artery disease, EXadequate; adequate exercise capacity, EXimpaired; impaired exercise capacity.

Table 2: General characteristics

	$EX_{adequate}$ (n=18)	**$EX_{impaired}$ (n=20)**	**P value**
Demographics			
Sex (male/female)	15/3	17/3	
Age (years)	62±7	61±9	0.676
Disease duration (years)	10±6	8±7 [a]	0.228
Smoking (n)	0	4	
Body weight (kg)	81±14	94±13	**0.006**
Body length (cm)	173±7	176±7	0.114
BMI (kg/m²)	27.2±4	30.3±4	**0.024**
BSA (m²)	1.97±0.19	2.12±0.16	**0.015**

Body composition			
Fat mass (%)	27.8±7	30.7±4.3	0.126
Fat mass (kg)	22.5±7.9	28.6±5.9	**0.011**
Lean mass (kg)	55±9.1	61.1±8.2	**0.035**
Fat free mass legs (kg)	15.7±2.7	17.8±2.2	**0.016**
Blood sample analyses			
HbA1c (%)	6.8±0.8	7.2±0.9 [a]	0.217
NT-proBNP (ng/µL)	66±32 [a]	63±23 [a]	0.463
Blood sample analyses – fasted state			
Glucose (mg/dL)	137±31	151±38 [a]	0.21
Insulin (pmol/L)	67±45 [a]	106±50 [a]	**0.006**
HDL-cholesterol (mg/dL)	55±18	43±8	**0.013**
LDL-cholesterol (mg/dL)	88±31	86±37	0.868
Total cholesterol (mg/dL)	165±37	157±41	0.541
Triglycerides (mg/dL)	109±56 [a]	139±64	0.159
tAUCglucose (mmol/L/0-120 min)	1697±390	1767±380	0.583
HOMA-IR	3.35±2.66 [a]	5.94±3.55 [a]	**0.004**

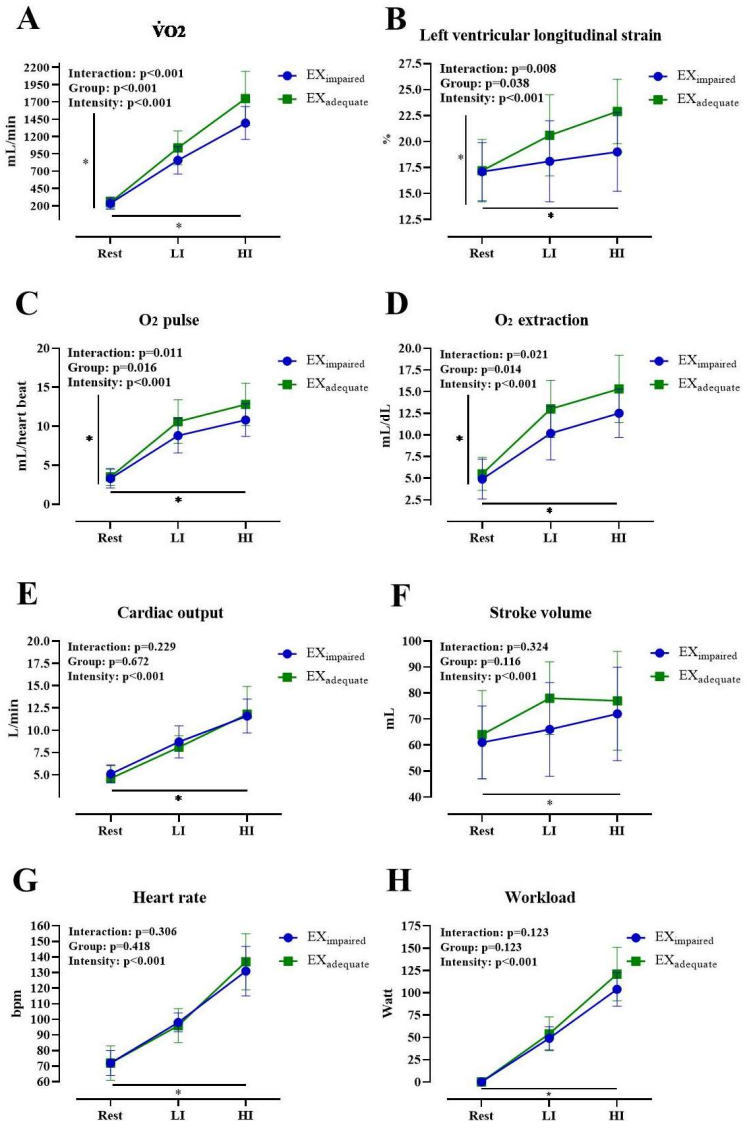
Group characteristics. Data are presented as means ± SD. BMI; body mass index, BSA; body surface area, HbA1c; blood glycated haemoglobin A1c, NT-proBNP; N-terminal pro-B-type natriuretic peptide, HDL; high-density lipoprotein, LDL; low-density lipoprotein, tAUCglucose; total area under the curve, HOMA-IR; homeostasis model assessment of insulin resistance. a: Data not normally distributed, Mann-Whitney U test used. Significant differences between two groups at *P < 0.05.

Table 3: Resting cardiac function in the supine position

	$EX_{adequate}$ (n=18)	**$EX_{impaired}$ (n=20)**	**P value**
Cardiac structure and dimensions			
IVSd (mm)	11±1 [a]	12±2	0.077
LVPWd (mm)	11±2	12±2 [a]	**0.031 ***
LVDd (mm)	42±3	41±5	0.332
LVM (g)	155±36	169±45	0.253
LVMi (g/m²)	78±13	80±17	0.726
RWT	0.52±0.11	0.6±0.12	**0.019 ***
LVOT (cm)	2.1±0.16	2.1±0.13	0.071
Diastolic function			
E (m/sec)	0.54±0.16	0.59±0.14 [a]	0.176
A (m/sec)	0.70±0.15	0.75±0.17	0.307
E/A	0.79±0.19	0.92±0.43 [a]	0.675
Dt (ms)	187±30	187±37	0.57
e'_s (m/sec)	0.6±0.1 [a]	0.6±0.1	0.851
E/e'_s	9.9±1.8 [a]	10±3.7 [a]	0.798

Resting echocardiography. Data are presented as means ± SD. IVSd; interventricular septum thickness end-diastole, LVPWd; left ventricular posterior wall thickness end-diastole, LVDd; left ventricular diameter end-diastole, LVM; left ventricular mass, LVMi; left ventricular mass indexed for BSA, RWT; relative wall thickness, LVOT; left ventricular outflow tract diameter, E; peak velocity of early diastolic filling phase, A; peak velocity of late diastolic filling phase, Dt; deceleration time, e'_s; early diastolic velocity at the septal annulus, E/e'_s; left ventricular filling pressure. a: Data not normally distributed, Mann-Whitney U test used. Significant differences between two groups at *P < 0.05.

Figure 4: Responses in cardiac function and exercise physiology during exercise



Two-way mixed ANOVA repeated measures. Data are presented as means ± SD. LI; low-intensity exercise, HI; high-intensity exercise. Blue circles; $EX_{impaired}$ group, green squares; $EX_{adequate}$ group. Panel A; analyses for oxygen uptake (V̇O2), panel B; analyses for left ventricular longitudinal strain, panel C; analyses for O_2 pulse, panel D; analyses for O_2 extraction, panel E; analyses for cardiac output (CO), panel F; analyses for stroke volume, panel G; analyses for heart rate, panel H; analyses for workload.

Table 5: Cardiac performance during exercise and exercise parameters

	$EX_{adequate}$ (n=18)	**$EX_{impaired}$ (n=20)**	**P value**
$\dot{V}O_{2\ peak\text{-}predicted}$ (%)	90.4±6.9	65.8±8.7	**<0.001 ***
$\dot{V}O_{2\ peak}$ (mL/kg/min)	21.8±4.7 [a]	15±2.7	**<0.001 ***
Responses (from rest to high-intensity exercise)			
$CO_{response}$ (L/min)	7.1±2.4	6.5±1.6	0.22
O_2 extraction $_{response}$ (mL/dL)	9.8±2.9	7.5±2.7	**0.016 ***
$LS_{response}$ (%)	5.6±4.1	1.9±2.5	**0.004***
$\Delta\dot{V}O2/\Delta W$	12.5±1.7	11.3±1.7	**0.035 ***
Evaluation at rest			
Blood pressure BPsys (mmHg) BPdia (mmHg)	 147±16 85±12	 151±16 87±9	 0.438 0.46
HR (bpm)	72±11	72±8	0.987
Diastolic function			
E (cm/s)	54±12	57±17	0.522
e'_s (cm/s)	5.4±1.1 [a]	6±1.6	0.196
E/e'_s	10±3 [a]	10±3	0.654
LVEDV (mL)	94±19	93±19	0.797
LVEDVi (mL/m²)	48±9	44±8	0.152
mPAP (mmHg)	11±4 [a]	10±5	0.782
Systolic function			
CO (L/min)	4.6±1.4 [a]	5.1±1	0.099
CI (L/min/m²)	2.36±0.77 [a]	2.36±0.43	0.593
SV (mL)	64±17	61±14 [a]	0.426
SVi (mL/m²)	33±9	29±6 [a]	0.067
LVEF (%)	67±10	66±9	0.611
LVESV (mL)	31±11	32±11	0.707
LS (%)	17.2±3	17.1±2.8	0.738
Ergospirometry related parameters			
RER	0.85±0.07	0.88±0.07	0.118
$\dot{V}O_2$ (mL/min)	247±82	234±84	0.08
O_2 pulse (mL/beat)	3.5±1.1	3.3±1.2	0.636
O_2 extraction (mL/dL)	5.6±1.9	5±2.3 [a]	0.239
O_2 extraction fat free mass legs (mL/dL/kg)	0.35±0.1	0.29±0.14 [a]	**0.044 *[1]**
Evaluation at low intensity exercise			
Blood pressure BPsys (mmHg) BPdia (mmHg)	 179±19 87±15	 179±18 84±12	 0.961 0.63
HR (bpm)	99±11	98±6	0.718
Diastolic function			
E (cm/s)	85±11	87±15	0.536
e'_s (cm/s)	9±2	8.8±1.5	0.73
E/e'_s	10±2 [a]	10±3 [a]	0.718
LVEDV (mL)	105±21	91±22	0.055
LVEDVi (mL/m²)	53±11	43±10 [a]	**0.004 *[2]**
mPAP (mmHg)	15±7	18±8	0.252
Systolic function			
CO (L/min)	8.1±1.3	8.7±1.8	0.241
CI (L/min/m²)	4.12±0.74	4.08±0.77	0.88
SV (mL)	78±14	66±18	0.029

SVi (mL/m²)	39±7	31±8 [a]	**<0.001 *[2]**
LVEF (%)	76±11 [a]	73±13	0.633
LVESV (mL)	27±15	25±13	0.658
LS (%)	20.6±3.9	18.1±3.9	0.037
Ergospirometry related parameters			
Workload (watts)	54±19 [a]	49±13	0.613
RER	0.9±0.09	0.9±0.07	0.876
$\dot{V}O_2$ (mL/min)	1037±247	857±199 [a]	0.08
O_2 pulse (mL/beat)	10.6±2.8	8.8±2.2 [a]	0.08
O_2 extraction (mL/dL)	13±3.3	10.2±3.1	**0.012 *[2]**
O_2 extraction fat free mass legs (mL/dL/kg)	0.84±0.25	0.58±0.2	**0.003 *[2]**
Evaluation at high intensity exercise			
Blood pressure BPsys (mmHg) BPdia (mmHg)	 213±19 85±16	 198±22 89±11	 0.131 0.615
HR (bpm)	137±18	131±16	0.25
Diastolic function			
E (cm/s)	105±19	108±22 [a]	0.424
e'_s (cm/s)	12.8±3.3	12.2±3	0.521
E/e'_s	9±2 [a]	9±3	0.937
LVEDV (mL)	97±23	96±20	0.831
LVEDVi (mL/m²)	48±9	43±8 [a]	0.29
mPAP (mmHg)	21±10	21±9	0.888
Systolic function			
CO (L/min)	11.8±3.1	11.6±1.9	0.836
CI (L/min/m²)	6.08±1.6	5.42±0.83	0.163
SV (mL)	77±19	72±18	0.405
SVi (mL/m²)	39±8	34±8	0.069
LVEF (%)	80±6	76±13 [a]	0.593
LVESV (mL)	20±8	23±13 [a]	0.654
LS (%)	22.9±3.1	19±3.8	**0.004 *[3]**
Ergospirometry related parameters			
Workload (watts)	121±30	104±19	0.032
RER	1.06±0.05	1.06±0.04	0.799
$\dot{V}O_2$ (mL/min)	1749±392	1395±237	**0.002 *[3]**
O_2 pulse (mL/beat)	12.8±2.7	10.8±2.1	**0.015 *[3]**
O_2 extraction (mL/dL)	15.3±3.9 [a]	12.5±2.8	**0.012 *[3]**
O_2 extraction fat free mass legs (mL/dL/kg)	0.99±0.27 [a]	0.71±0.17	**<0.001 *[3]**
VEpeak (L/min)	55.6±10.3	46.1±8	**0.003 *[3]**
Exercise performance at VT1			
HR (bpm) at VT1	96±12 [a]	95±8	0.942
$\dot{V}O_2$ (mL/min) at VT1	875±199	747±136	**0.025 ***

Cardiac performance during exercise and exercise parameters. Data are presented as means ± SD. $\dot{V}O_{2\ peak\text{-}predicted}$; achieved percentage of predicted oxygen uptake, $\dot{V}O_{2\ peak}$; peak oxygen uptake, $CO_{response}$; response in cardiac output from rest to high-intensity exercise, O_2 extraction $_{response}$; response in oxygen extraction from rest to high-intensity exercise, LS $_{response}$; response in longitudinal strain from rest to high-intensity exercise, $\Delta\dot{V}O2/\Delta W$; response in oxygen uptake from rest to high-intensity exercise divided by response in workload, BPsys; systolic blood pressure, BPdia; diastolic blood pressure, HR; heart rate, E; peak velocity of early diastolic filling phase, e'_s; early diastolic velocity at the septal annulus, E/e'_s; left ventricular filling pressure, LVEDV; left ventricular end-diastolic volume, LVEDVi; left ventricular end-diastolic volume indexed for BSA, mPAP: mean pulmonary artery pressure, CO; cardiac output, CI; cardiac output indexed for BSA, SV; stroke volume, SVi; stroke volume indexed for

BSA, LVEF; left ventricular ejection fraction, LVESV; left ventricular end-systolic volume, LS; left ventricular longitudinal strain, RER; respiratory exchange ratio, V̇O2; oxygen uptake, O_2 pulse; oxygen pulse (V̇O2/HR), O_2 extraction; oxygen extraction (V̇O2/CO), VEpeak; peak ventilation, VT1; ventilatory threshold. a: Data not normally distributed, Mann-Whitney U test used. Significant differences between two groups at $^{*1}P_1 < 0.05$ (α_1), $^{*2}P_2<0.025$ (α_2), $^{*3}P_3<0.017$ (α_3).

Supplementary table 1: Medication use

	$EX_{adequate}$ (n=18)	**$EX_{impaired}$ (n=20)**
Medication use		
Insulin	5	4
Oral antidiabetics		
- Metformin	14	18
- Insulin secretion stimulation drugs	4	6
- Incretin mimetics and DPP4-inhibitors	7	5
- SGLT2-inhibitors	5	3
Statins	10	9
Fibrates	1	1
B-blocker	4	5
ACE-inhibitor	3	3
Diuretics	3	2
Sartans	2	3
Calcium antagonists	3	4
Anticoagulation/antithrombotics	2	6

DPP4; dipeptidylpeptidase-4, SGLT-2; sodium-glucose co-transporter-2, ACE; angiotensin converting enzyme.

Supplementary table 2: Details of the exercise protocol

	$EX_{adequate}$ (n=18)	**$EX_{impaired}$ (n=20)**	**P value ($EX_{adequate}$ vs $EX_{impaired}$)**
Total duration exercise protocol	16'16"±3'26"	15'15"±5'18"	0.503
Duration low-intensity stage	3'26"±0'47"	3'34"±1'50"	0.771
Duration high-intensity stage	3'16±1'15"	4'00"±2'49"	0.323
HR at start low-intensity stage (bpm)	93±8	95±6	0.481
HR at end low-intensity stage (bpm)	99±10	98±6 [a]	0.837
HR at start high-intensity stage (bpm)	127±15	121±13	0.215
HR at end high-intensity stage (bpm)	138±17 *	133±19 *	0.424
Increase in HR during high-intensity stage (%)	9±4.6	10.3±13.9	0.71

Details of the exercise protocol. Data are represented as mean ± SD. HR; heart rate. a: data not normally distributed, non-parametric alternative used. * p<0.005 for paired T-test (HR at start high-intensity stage vs HR at end high-intensity stage).

Supplementary table 3: Pearson correlations and regression analyses

	Pearson correlation		Linear regression	
	r	P value	Adjusted R^2	Regression coefficient
Correlation with HbA1c				

O_2 extraction at high intensity exercise (mL/dL)	-0.384	0.02	0.124	-1.637
$O_{2\text{-FFM}}$ extraction at high intensity exercise (mL/dL/kg)	-0.346	0.03	0.095	0.049
Correlation with tAUC				
CO at high intensity exercise	0.352	0.03	0.099	0.001
O_2 extraction at high intensity exercise (mL/dL)	-0.427	0.008	0.159	0.001
$O_{2\text{-FFM}}$ extraction at high intensity exercise (mL/dL/kg)	-0.403	0.01	0.139	<0.001
Correlation with insulin				
LS at high intensity exercise (%)	-0.433	0.012	0.161	0.012
Correlation with HDL-cholesterol				
LS at high intensity exercise (%)	0.472	0.005	0.198	0.04
Correlations of LS with exercise capacity				
$\dot{V}O_{2peak\text{-predicted}}$ (%)	0.538	0.001	0.267	0.02
$\dot{V}O_{2peak}$ (mL/kg/min)	0.562	0.001	0.293	0.697

Pearson correlations and regression analyses. HbA1c; blood glycated haemoglobin A1c, tAUCglucose; total area under the curve, CO; cardiac output, O_2 extraction; oxygen extraction, $O_{2\text{-FFM}}$ extraction; oxygen extraction in proportion to fat free mass in the legs, LS; longitudinal strain, HDL; high density lipoprotein, $\dot{V}O_{2peak\text{-predicted}}$; achieved percentage of predicted oxygen uptake, $\dot{V}O_{2\ peak}$; peak oxygen uptake.