Impact of continuous vs. interval training on oxygen extraction and cardiac function during exercise in type 2 diabetes mellitus

Title page

Title: Impact of continuous vs. interval training on oxygen extraction and cardiac function during exercise in type 2 diabetes mellitus

Running title: Exercise and oxygen extraction in diabetes

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DECLARATIONS

Funding

This work was supported by internal resources (Hasselt University).

Conflict of interest

The authors declare that they have no conflict of interest.

Ethics approval

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). The study was part of a clinical trial and registered at Clinicaltrials.gov (NCT number: NCT03299790)

Consent to participate

All participants gave written informed consent, prior to the execution of the tests.

Consent to Publish

Full anonymity is guaranteed in this paper. No personal details such as date of birth, names and contact details are included in this paper.

Availability of data and material

Raw data is available upon request. Requests should be oriented towards the corresponding author or last author.

Code availability

Not applicable

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.).

L.V.R. performed the incremental exercise tests, assisted by J.D.B., K.V., E.V. and N.M.. C.K. analysed the data of the breath-by-breath gas exchange analyses.

W.M.A.F. assisted with blood sample collection and preparation of samples.

Exercise training sessions were supervised by L.V.R., J.D.B., E.V., K.V., N.M., W.M.A.F. and C.K..

L.V.R. and D.H. performed the statistical analyses. L.V.R. and D.H. wrote the manuscript. J.D.B., 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 of the manuscript to be submitted.

Acknowledgements

We would like to thank all the participants for their participation in this study, and the clinicians from the Department of Cardiology at Jessa hospital for the support in this study.

Abstract

Purpose Exercise training improves exercise capacity in type 2 diabetes mellitus (T2DM). It remains to be elucidated whether such improvements result from cardiac or peripheral muscular adaptations, and whether these are intensity-dependent.

Methods 27 patients with T2DM (without known cardiovascular disease (CVD)) were randomized to high-intensity interval training (HIIT, n=15) or moderate-intensity endurance training (MIT, n=12) for 24 weeks (3 sessions/week). Exercise echocardiography was applied to investigate cardiac output (CO) and oxygen (O_2) extraction during exercise, while exercise capacity (($\dot{V}O_{2peak}$ (mL/kg/min)) was examined via cardiopulmonary exercise testing at baseline and after 12 and 24 weeks of exercise training, respectively. Changes in glycaemic control (HbA1c and glucose tolerance), lipid profile and body composition were also evaluated.

Results 19 patients completed 24 weeks of HIIT (n=10, 66±11 years) or MIT (n=9, 61±5 years). HIIT and MIT similarly improved glucose tolerance (p_{Time}=0.001, $p_{Interaction}$>0.05), $\dot{V}O_{2peak}$ (mL/kg/min) (p_{Time}=0.001, $p_{Interaction}$>0.05), and exercise performance (W_{peak}) (p_{Time}<0.001, $p_{Interaction}$>0.05). O_2 extraction increased to a greater extent after 24 weeks of MIT (56.5%, p_1=0.009, p_{Time}=0.001, $p_{Interaction}$=0.007). CO and left ventricular longitudinal strain (LS) during exercise remained unchanged (p_{Time}>0.05). A reduction in HbA1c was correlated with absolute changes in LS after 12 weeks of MIT (r=-0.792, p=0.019, LS at rest) or HIIT (r=-0.782, p=0.038, LS at peak exercise).

Conclusion In patients with well-controlled T2DM, MIT and HIIT improved exercise capacity, mainly resulting from increments in O_2 extraction capacity, rather than changes in cardiac output. In particular, MIT seemed highly effective to generate these peripheral adaptations.

NCT03299790, initially released 09/12/2017

Keywords; stress echocardiography, left ventricular function, type 2 diabetes, exercise tolerance, exercise training

LIST OF ABBREVIATIONS

A	Late diastolic inflow
AGE's	Advanced glycation end products
ANOVA	Analysis of variance
APLAX	Apical long-axis
AP2C	Apical two chamber
AP4C	Apical four chamber
AP5C	Apical five chamber
AUC	Area under the curve
BMI	Body mass index
BPM	Beats per minute
BSA	Body surface area
CO	Cardiac output
CPET	Cardiopulmonary exercise test
CVD	Cardiovascular diseases
Dt	Deceleration time
E	Early diastolic inflow
e'$_s$	Early diastolic velocity at the septal annulus
E/e' ratio	LV filling pressure
ET	Ejection time
HbA1c	Glycated haemoglobin A1c
HC	Healthy control
HDL	High density lipoprotein
HIIT	High-intensity interval training
HR	Heart rate
IVCT	Isovolumic contraction time
IVRT	Isovolumic relaxation time
IVSd	Interventricular septum thickness end-diastole
LDL	Low density lipoprotein
LS	Longitudinal strain
LV	Left-ventricular
LVM	LV mass
LVMi	LV mass indexed for BSA
LVDd	LV diameter end-diastole
LVPWd	LV posterior wall thickness end-diastole
LVOT	LV outflow tract diameter
MIT	Moderate-intense training
NT-proBNP	N-terminal pro-B-type natriuretic peptide
O_2	Oxygen

OGTT	Oral glucose tolerance test
PLAX	Parasternal long axis
RER	Respiratory exchange ratio
SD	Standard deviation
SV	Stroke volume
T2DM	Type 2 diabetes mellitus
TDI	Tissue Doppler imaging
$\dot{V}O_2$	Oxygen uptake

INTRODUCTION

Type 2 diabetes mellitus (T2DM) accounts for approximately 90% of the total cases of diabetes (>460 million worldwide) (Saeedi et al., 2019). Treatment intensification is required, as many targets (e.g. tight glycaemic control) are not properly achieved, contributing to the high morbidity and mortality rates (Hansen et al., 2020). Patients suffering from diabetes have a 30% higher risk of developing heart failure, and cardiovascular diseases (CVD) are a major source of complications leading to extensive health care costs (Dal Canto et al., 2019; Rorth et al., 2018).

Exercise intolerance is known to be a significant predictor of all-cause mortality and is consistently reported among patients with T2DM (Kokkinos et al., 2009; Nadeau et al., 2009; Nesti et al., 2020). Cardiac dysfunction seems to be an important factor, as patients with T2DM have been reported to display a 23% lower cardiac output (CO), as opposed to healthy controls (Wilson et al., 2017). Fortunately, exercise training not only improves the clinical course of diabetes (improved physical fitness, enhanced glycaemic and lipid control and a lower blood pressure), but also resting cardiac function (especially diastolic function) (Hansen et al., 2019; Umpierre et al., 2013; Verboven et al., 2019). As a result, exercise training is a cornerstone in the management of T2DM (American Diabetes, 2020).

However, as oxygen uptake ($\dot{V}O_2$) is determined by CO and oxygen (O_2) extraction, both central and peripheral factors may underlie exercise intolerance and contribute to the improvements in $\dot{V}O_2$ after exercise training. Wilson *et al.* (Wilson et al., 2019) recently demonstrated, by the use of exercise echocardiography, the potential of exercise training to reverse cardiac dysfunction in patients with T2DM and thereby improving exercise tolerance. Though, such exercise training studies using stress (pharmacologically-induced/exercise) echocardiography are scarce. Though this is of major importance to resemble patients' functional status, as pathological symptoms (e.g. chest pain or dyspnoea) are often absent at rest and/or exaggerated during exercise (Ha et al., 2007). Indeed, up to 33% of the patients with T2DM report such symptoms during exercise, while resting echocardiographic findings are normal (Jorgensen et al., 2016).

Moreover, an impaired O_2 extraction has also been reported to limit exercise tolerance in patients with T2DM, which could be attributed to attenuated responses in muscular blood flow (Baldi et al., 2003; Bauer et al., 2007). By combining stress echocardiography and breath-by-breath analyses, our research group recently reported a limited O_2 extraction to underlie exercise intolerance in patients with T2DM (but without clinical signs of CVD) (Van Ryckeghem L, 2020). Of interest, O_2 extraction capacity is responsive to exercise training, as shown in patients suffering from peripheral artery disease (Baker et al., 2017).

Though, several aspects of exercise training such as the impact of exercise volume and intensity need to be elucidated. High-intensity interval training (HIIT) is gaining interest because of superior effects on glycaemic control and exercise capacity in patients with diabetes mellitus (Liu et al., 2019). Furthermore, Wilson *et al.* (Wilson et al., 2019) reported an improved stroke volume during submaximal exercise after HIIT. However, HIIT was compared to a non-exercising control group and stress echocardiography was not simultaneously combined with breath-by-breath analyses, impeding to investigate O_2 extraction capacity. It therefore remains to be established whether HIIT is indeed superior compared to traditional types of exercise training such as moderate-intense training (MIT) to improve cardiovascular health in T2DM population. The aim of our study was to investigate to which extent central (CO) or peripheral (O_2 extraction) factors underlie improvements in exercise capacity ($\dot{V}O_2$ peak), in patients with well-controlled T2DM but without established CVD by using exercise echocardiography with simultaneous breath-by-breath analyses. Based on the previous studies (Liu et al., 2019; Wilson et al., 2019), we hypothesized that supervised HIIT exerts superior effects, compared to supervised MIT.

METHODS

Study design and subjects

This randomised-controlled trial was executed at the REVAL Rehabilitation Research Centre (Hasselt University, Hasselt, Belgium) and the Department of Cardiology (Jessa hospital, Hasselt, Belgium). Twenty-nine asymptomatic (no dyspnoea or chest pain at rest or during exercise) patients with T2DM, aged between 18-81years and diagnosed according to the criteria of the American Diabetes Association (American Diabetes, 2020), were recruited using a convenience sampling method (informed by general practitioners and based on availability and/or willingness to participate). Stable pharmacological treatment (e.g. anti-hypertensive, glucose- and lipid-lowering drugs) for at least three months was requested, and patients had to be able to perform a maximal incremental exercise test. Patients were excluded if one of the following diseases or symptoms was reported: renal disease, retinopathy, neurological, orthopaedic, oncologic or pulmonary diseases prohibiting the performance of an exercise test, cardiovascular diseases (e.g. valve disease, coronary artery disease, congenital heart disease) and symptoms of dyspnoea or chest pain (during exercise)). The following parameters were evaluated: anthropometric measures and body composition, cardiopulmonary exercise testing (CPET), exercise echocardiography and blood samples analyses (glycaemic control, lipid profile). Body composition was evaluated at the start of the intervention and after 24 weeks of the intervention. All other assessments were performed at baseline and after respectively 12 and 24 weeks of exercise training.

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 their participation. The study was registered at Clinicaltrials.gov (NCT number: NCT03299790)

Anthropometry and body composition

Anthropometric measures (height and body weight) were assessed 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). Body mass index (BMI; kg/m²) and body surface area (BSA; m²) 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, Vilvoorde, Belgium) from which whole-body lean tissue mass, fat mass and body fat percentage were determined.

Blood parameters

Fasted blood samples (lithium heparin tubes, Greiner Bio-One, Vilvoorde, Belgium) were collected to evaluate lipid profile (total cholesterol, HDL- and LDL-cholesterol and triglycerides) and insulin levels. Thereafter, a 5-point oral glucose tolerance test (OGTT, sodium fluoride tubes, Greiner Bio-One, Vilvoorde, Belgium) was performed after ingestion of 75g of glucose (dextrose monohydrate) dissolved in 250mL of water. Blood samples were stored for 30min at room temperature and thereafter for 120min at 4°C. Afterwards, samples were centrifuged (1650g, for 15min) and plasma was stored at -80°C and analysed in badge for insulin (sandwich electrochemiluminescence immunoassay), total cholesterol, HDL- and LDL-cholesterol (enzymatic colorimetry), triglycerides (colorimetry) and glucose (colorimetry, Roche Cobas 8000, Roche Diagnostics International Ltd, Rotkreuz, Switzerland). Non-fasted blood samples were analysed for glycated haemoglobin A1c (HbA1c, Menarini HA-8180 HbA1c auto-analyser, Menarini Diagnostics, Diegem, Belgium) and N-terminal pro-B-type natriuretic peptide (NT-proBNP, electrochemiluminescence immunoassay, Cobas e 801 immunoassay analyser, Menarini Diagnostics, Diegem, Belgium). Insulin resistance was estimated using the homeostasis assessment of insulin resistance (HOMA-IR), calculated as fasting plasma glucose (mmol/L)*fasting serum insulin (mU/L))/22.5 (Matthews et al., 1985). From the glucose measurements of the OGTT, the total area under the curve (tAUC) was estimated using the trapezoidal rule. All measurements were performed by the clinical laboratory of the Jessa Hospital (Hasselt, Belgium).

Echocardiography with combined ergospirometry

The exercise echocardiographic assessment was performed as described elsewhere (Van Ryckeghem L, 2020). In brief, cardiac function was evaluated in the apical two-, four- and five chamber view (AP2C, AP4C, AP5C) and

in the apical long-axis view (APLAX) using a phased array probe (Vivid E90 and GE M5S 1.5-4.5 MHz, GE Health Medical, Milwaukee, Wisconsin, USA). Prior outcomes regarding cardiac function were CO, left ventricular longitudinal strain (LS, within the AP4C view) and parameters of diastolic function (early diastolic filling phase (E), early diastolic velocity at the septal annulus (e'_s) and left ventricular filling pressure (E/e')).

Breath-by-breath analyses were simultaneously applied (CS-200 Ergo-Spiro, Schiller AG, Switzerland) for the evaluation of respiratory exchange ratio (RER) and oxygen uptake ($\dot{V}O_2$). 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) and a pedal frequency of 60-65 revolutions per minute (rpm) was applied. The exercise echocardiographic assessment included 2 stages of evaluation; rest and at peak stress. The latter was performed when RER exceeded 1.03 after which the cycling workload (W) was remained constant during the assessments. Systolic and diastolic blood pressure were monitored during the entire 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). Images were digitally stored in a cine-loop format containing at least three cardiac cycles for each measure and analyses were performed via the EchoPAC software version 201 (General Electric Vingmed, Horten, Norway).

Cardiopulmonary exercise testing

A CPET was performed in the upright position to determine peak oxygen uptake ($\dot{V}O_{2peak}$) as the exercise echocardiographic assessments were executed during submaximal effort. An electronically braked cycle ergometer (eBike, GE Medical systems, Milwaukee, Wisconsin, USA) was used and combined with breath-by-breath analyses (Jaeger Oxycon Pro, Carefusion, Acertys group, Aartselaar, Belgium). Continuous 12-lead ECG monitoring (KISS™ Multilead, GE Medical systems, Freiburg, Germany) and pulse oximetry (WristOx$_2$ 3150, Nonin Medical, Plymouth, USA) were applied during the test.

A standardized (stepwise) protocol was applied including 3min of resting period, 3min of warming-up at 20W, followed by an incremental test period (starting at 20W, stepwise increase of 20W/min) and a recovery phase of 5min at 20W. A cycling speed of at least 60 rpm was requested and participants were encouraged to cycle until volitional exhaustion. The test was terminated in the presence of clinical indications (e.g. 2mm of ST depression) (Task Force of the Italian Working Group on Cardiac et al., 2006). Following parameters were assessed: $\dot{V}O_2$, workload (W), HR and RER at ventilatory thresholds and at peak exercise ($\dot{V}O_{2peak}$ (peak $\dot{V}O_2$ within the last 30 seconds of the test and W_{peak} (peak W tolerated for 1min), HR_{peak}, RER_{peak}). Before starting the CPET, capillary blood glucose levels were checked from the fingertip (Accu-Chek Aviva, Roche Diagnostics, Machelen, Belgium). Performance of the test was not allowed in case of hyperglycaemia (>300mg/dL). Carbohydrate supplementation was used in case of hypoglycaemia (<70mg/dL) and the test performed if glucose levels normalized (>100mg/dL).

Exercise training program

Participants were randomly allocated (using sealed envelopes, 1:1 ratio) to HIIT or MIT. The program was based on a previous exercise training study of Mitranun *et al.* (Mitranun et al., 2014) and was extended to 24 weeks of exercise training (3 sessions/week). The intervention consisted of 4 phases (phase 1: week 1-2, phase 2: week 3-6, phase 3: week 7-12, phase 4: week 13-24) and is represented in Supplementary table 1. A warming-up and cool-down of 5min was applied during each session. Training volumes (average % of HR_{peak}) were designed to be equal for both groups during each phase. The results of the CPET (W_{peak}, HR_{peak} and $\dot{V}O_{2peak}$) were used to personalize the exercise program and continuous HR monitoring was used (Polar H7, Polar Electro Oy, Finland) to monitor intensity. $\dot{V}O_{2peak}$ was converted to the corresponding HR zones (Hansen et al., 2017).

A standardized pedal frequency of 70 revolutions per minute was applied for each exercise training session. After 12 weeks of exercise training, a CPET was performed to adapt the individual program. Blood glucose values were checked via the use of a blood sample from the fingertip prior to, and following each training session (explained above).

Statistical analyses

All statistical analyses were performed in SPSS V.24 (IBM SPSS Statistics for Windows, Chicago, IL, USA). Data are expressed as mean ± standard deviation (SD). Normality was checked via the Shapiro-Wilk test. Independent sample T-tests, paired T-tests, Mann-Whitney U tests and Wilcoxon-signed rank tests (non-parametric alternative)

were applied whenever appropriate and Holm-Bonferroni correction was used to correct for multiple testing (α_1=0.05 (start vs 24 weeks of exercise training), α_2=0.025 (start vs 12 weeks of exercise training), α_3=0.017 (12 vs 24 weeks of exercise training)) and level of statistical significance set at p_1=0.05, p_2=0.025, p_3=0.017 (two-tailed). Differences in proportions between groups were evaluated using the Fisher's exact test. To investigate interaction effects (within factors: time (baseline, 12 and 24 weeks of exercise training, between factors: groups (HIIT vs. MIT)), two-way mixed analyses of variance (ANOVA's) were executed with a level of statistical significance set at p-value <0.05 (p_{Time}, $p_{Interaction}$, two-tailed).

RESULTS

General characteristics

Inclusion of participants was schematically presented in the flowchart (Figure 1). Groups were comparable regarding age, gender distribution, disease duration, body weight, BMI, BSA and body composition (p>0.05; Table 1).

Table 1 General characteristics

	MIT (*n*=9)		HIIT (*n*=10)	
Demographics				
Sex (male/female)	8/1		9/1	
Age (years)	66 ± 11		61 ± 5	
Disease duration (years)	12 ± 9		7 ± 4	
Smoking (n)	0		0	
Ex-smokers (n)	3		5	
Medication use				
Insulin (%)	0%		10	
Oral antidiabetics				
Metformin (%)	77.8		80	
Insulin secretion stimulation drugs (%)	33.3		30	
Incretin mimetics and DPP4-inhibitors (%)	11.1		20	
SGLT2-inhibitors(%)	0		30	
Statins (%)	44.4		60	
Fibrates (%)	11.1		10	
B-blocker (%)	11.1		30	
ACE-inhibitor (%)	11.1		40	
Diuretics (%)	0		30	
Sartans (%)	0		10	
Calcium antagonists (%)	22.2		20	
Anticoagulation/antithrombotics (%)	33.3		10	
	Pre	**Post**	**Pre**	**Post**
Body weight (Kg)	89 ± 20.9 [a]	87 ± 18.8 [a] ‡	96.6 ± 17.6	96.5 ± 17.8
Height (cm)	173 ± 6	-	179 ± 6 *	-
BMI (Kg/m²)	29.8 ± 7.1 [a]	29.2 ± 6.4 ‡	30.1 ± 5.1	30.1 ± 5.3
BSA (m²)	2.06 ± 0.23	2.03 ± 0.22 ‡	2.18 ± 0.2	2.18 ± 0.22
Body composition				
Fat mass (%)	30.1 ± 3.2	28.4 ± 3.9 ‡	29.2 ± 5	28.2 ± 4.9
Fat mass (Kg)	26.5 ± 8.2 [a]	24.7 ± 8 [a] ‡	28.1 ± 8.3	27.3 ± 8
Lean mass (Kg)	58.1 ± 10.6	58.6 ± 11.1	63.6 ± 9.4	64.8 ± 10.6

Population characteristics. Data are presented as means ± SD. BMI; body mass index, BSA; body surface area, DPP4; dipeptidylpeptidase-4, SGLT-2; sodium-glucose co-transporter-2, ACE; angiotensin converting enzyme. a: Data not normally distributed, non-parametric tests used. Significant differences between groups at *P < 0.05. Significant difference within groups at ‡ p<0.05.

Exercise intervention characteristics and tolerance of the exercise program

Exercise volume (average % of HR_{peak}) was similar between groups during all phases (p>0.05 between groups, Supplementary table 2). Absolute energy expenditure was significantly higher (p<0.05) in the HIIT group as opposed to the MIT group during phase 1 (295±54kcal vs 243±34kcal, p=0.024), phase 3 (335±53kcal vs 271±42kcal, p=0.011) and phase 4 (381±55kcal vs 287±48kcal, p=0.001). Such differences were not observed when energy expenditure was indexed for (baseline) body weight (p>0.05 between groups). Within the HIIT group, two events occurred in two participants during a training session (one hypoglycaemic event, one event of exercise-induced hyperventilation) for which the session was discontinued respectively.

Body composition

Within the MIT group, body weight (p=0.039), BMI (p=0.041), BSA (p=0.017) and fat mass and proportion in fat mass (kg and %, p=0.001 and p=0.007)) decreased significantly after 24 weeks of exercise training (Table 1). The HIIT group only displayed a significant decrease in body fat (%, p=0.028).

Blood sample analyses

Generally, exercise training significantly ($p_{Time}<0.05$) improved glycaemic control (HbA1c levels, fasting glucose and insulin levels, glucose tolerance (lower tAUC) and whole-body insulin resistance) and total cholesterol levels without interaction effects ($p_{Interaction}>0.05$, Table 2). However, different effects were found between MIT and HIIT. While glucose tolerance (tAUC) was improved after both 24 weeks of MIT ($p_1=0.019$) and HIIT ($p_1=0.012$), insulin resistance (HOMA-IR) was only improved by HIIT ($p_1=0.007$), driven by a decrease in fasting insulin levels ($p_1=0.011$). HIIT specifically improved total cholesterol levels after 12 weeks of exercise training ($p_2=0.008$) while significance was lost after 24 weeks of exercise training ($p_1>0.05$). In contrast, MIT only exerted a significant decrease in total cholesterol after 24 weeks of exercise training ($p_1=0.038$). NT-proBNP levels remained unchanged during the exercise intervention ($p_{Time}>0.05$).

Table 2 Blood profile changes following a 24-week exercise training intervention

	MIT (*n*=9)			HIIT (*n*=10)				
	Pre	Mid	Post	Pre	Mid	Post	P Time	P Time*Group
HbA1c (%)	6.8 ± 0.5	6.5 ± 0.5 ‡2	6.6 ± 0.6	6.6 ± 0.7	6.5 ± 0.7	6.5 ± 0.7	**0.031**	0.321
HDL cholesterol (mg/dL)	53 ± 18	50 ± 16	51 ± 16	47 ± 13	45 ± 14	44 ± 12	0.07	0.86
Non-HDL cholesterol (mg/dL)	106 ± 35	96 ± 31	94 ± 29 ‡1	118 ± 20	108 ± 16 ‡2	121 ± 28	**0.029**	0.064
Total cholesterol (mg/dL)	160 ± 40	147 ± 37	145 ± 33 ‡1	164 ± 19	153 ± 19 ‡2	165 ± 28	**0.009**	0.114
Triglycerides (mg/dL)	126 ± 74	122 ± 57	133 ± 88	142 ± 72	139 ± 66	159 ± 91	0.323	0.869
NT-proBNP (ng/L)	72 ± 27 a	90 ± 52 a	72 ± 33 a	60 ± 22 a	63 ± 31 a	65 ± 27 a	0.094	0.083
Fasting glucose (mg/dL)	148 ± 39	132 ± 27	131 ± 30 ‡1	134 ± 17	126 ± 13	128 ± 14	**0.002**	0.361
Fasting insulin (pmol/L)	94 ± 42	88 ± 38	79 ± 33	112 ± 95 a	87 ± 70 a	66 ± 62 a ‡1	**0.009**	0.266
$tAUC_{glucose}$ (mmol/L/0-120min)	1690 ± 373	1486 ± 324	1461 ± 249 ‡1	1609 ± 284	1510 ± 261	1385 ± 283 ‡1	**0.001**	0.549
HOMA-IR	5.2 ± 3.3	4.2 ± 2.0	3.7 ± 1.9	5.0 ± 3.8 a	3.8 ± 3.0 a	2.9 ± 2.7 a ‡1	**0.014**	0.789

Data are mean ± SD. HbA1c; blood glycated haemoglobin A1c, HDL; high-density lipoprotein, NT-proBNP; N-terminal pro-B-type natriuretic peptide, tAUC; total area under the curve, HOMA-IR; homeostasis assessment of insulin resistance. a: Data not normally distributed, non-parametric tests used. Within group differences; ‡1; Pre vs post (α_1=0.05), ‡2; Pre vs Mid (α_2=0.025), ‡3; Mid vs Post (α_3=0.017).

Exercise capacity

Prior to the intervention, exercise performance (W_{peak}) was higher in the HIIT group as opposed to the MIT group (p_1=0.014). Exercise capacity ($\dot{V}O_{2peak}$ (mL/kg/min)) improved significantly and to a similar extent after 24 weeks of HIIT (p_1=0.019) or MIT (p_1=0.017) ($p_{Interaction}$>0.05, Table 3). Within the MIT group, absolute $\dot{V}O_{2peak}$ (mL/min) did not significantly increase after 24 weeks of exercise training (p_1>0.05), in contrast to the HIIT group (p_1=0.02). Exercise performance (W_{peak}) increased significantly after 12 and 24 weeks of HIIT (p_2=0.001 and p_1=0.001) or MIT (p_2=0.015 and p_1=0.001), respectively. HIIT resulted in a shift of both VT1 and VT2 towards higher $\dot{V}O_2$ (p_1=0.002 and p_1=0.001) and W (p_1=0.001 and p_1<0.001) after 24 weeks of exercise. Effects were already significant after 12 weeks of HIIT for VT2 on $\dot{V}O_2$ (p_2=0.002) and W (p_2=0.001). MIT resulted in a shift of VT1 towards a higher W (p_1=0.021) and VT2 towards a higher $\dot{V}O_2$ (p_1=0.013) after 24 weeks of exercise. Maximal systolic blood pressure significantly decreased after 24 weeks of MIT (p_1=0.047).

Table 3: Exercise capacity following a 24-week exercise training intervention

	MIT (*n*=9)			HIIT (*n*=10)				
	Pre	Mid	Post	Pre	Mid	Post	P Time	P Time*Group
HR_{rest} (bpm)	75±20	74±12	71±14	70±9	69±9	67±8	0.146	0.453
Peak exercise performance								
$\dot{V}O_{2peak\ \%\ of\ predicted}$ (%)	106±13 [a]	112±23	118±17 ‡1	109±25	119±25	119±24 ‡1	**0.002**	0.744
$\dot{V}O_{2peak}$ (mL/min)	2079±520	2234±623	2291±489	2496±696	2734±682	2710±652 ‡1	**0.003**	0.648
$\dot{V}O_{2peak}$ (mL/kg/min)	23.4±3.1	-	26.6±4.3 ‡1	26.6±8.9	-	28.9±8.8 ‡1	**0.001**	0.713
HR_{peak} (bpm)	152±19	153±21	151±19	155±19	158±15	154±18	0.832	0.477
$Workload_{peak}$ (W)	156±26	183±36 [a] ‡2	191±43 ‡1	200±42 *1	224±50 ‡2	228±50 ‡1	**<0.001**	0.393
Blood pressure and saturation								
$BPsys_{rest}$ (mmHg)	137±16	135±8 [a]	125±10 ‡1, ‡3	132±10	124±10	127±9	**0.028**	0.123
$BPdia_{rest}$ (mmHg)	78±10 [a]	83±10	79±8	80±7	79±5	80±5	0.906	0.478
$BPsys_{max}$ (mmHg)	185±31	192±20	184±18 [a]	180±12 [a]	190±17 [a]	194±13 ‡1	0.21	0.087
$BPdia_{max}$ (mmHg)	86±11	85±10 [a]	81±7	86±5 [a]	87±6	84±5	**0.014**	0.461
$SaO2_{rest}$ (%)	97±1 [a]	97±1	97±1	96±2	97±1	97±1	0.837	0.188
$SaO2_{minimal}$ (%)	96±1	95±1	95±1[a]	96±1	96±2	95±1	0.451	0.166
First ventilatory threshold								
$\dot{V}O_2$ at VT1 (mL/min)	1340±305	1457±356	1494±252	1470±376	1641±311 [a]	1756±357 ‡1	**<0.001**	0.577
Workload at VT1 (W)	113±17	120±21	136±26 ‡1	126±25	134±28	152±29 ‡1	**<0.001**	0.995
HR at VT1 (bpm)	113±13	112±18	112±18	108±12	106±14	111±10	0.22	0.823
RER at VT1	0.91±0.07	0.87±0.06	0.92±0.03	0.87±0.06	0.87±0.06	0.88±0.05	0.073	0.291
Second ventilatory threshold								
$\dot{V}O_2$ at VT2 (mL/min)	1765±417	1992±480	2025±426 ‡1	2158±588	2454±577 ‡2	2543±588 ‡1	**<0.001**	0.666
Workload at VT2 (W)	162±25 [a]	185±38	180±37	190±32	218±42 ‡2	230±44 *2, ‡1	**<0.001**	0.094
HR at VT2 (bpm)	138±19	138±21	137±19	136±17	139±19	139±17	0.872	0.264
RER at VT2	1.13±0.07	1.06±0.06	1.11±0.07	1.06±0.1	1.06±0.09	1.04±0.07	0.174	0.058
RER_{peak}	1.21±0.09	1.19±0.09	1.20±0.1	1.15±0.11	1.16±0.08	1.16±0.1	0.929	0.507
Borg scores and blood glucose								
Borg score dyspnoea	5±2	6±2 [a]	6±3	6±2	7±2	6±3 [a]	0.406	0.538
Borg score fatigue	5±1	4±1[a]	5±2	6±2	6±1*3	6±3 [a]	0.764	0.573
$Blood\ glucose_{start}$ (mg/dL)	191±64 [a]	167±55	179±57	153±47 [a]	137±29	146±33	0.129	0.803
$Blood\ glucose_{end}$ (mg/dL)	172±55	132±35	148±39	157±51	131±24	117±10	**0.016**	0.716

Exercise capacity. Data are presented as means ± SD. HR; heart rate, $\dot{V}O_2$; oxygen uptake, BP; blood pressure, SaO_2; oxygen saturation, VT1; first ventilatory threshold, RER; respiratory exchange ratio, VT2; second ventilatory threshold. a: Data not normally distributed (non-parametric alternative used). Between group differences; *1; Pre (α_1=0.05), *2; Post (α_2=0.025), *3; Mid (α_3=0.017). Within group differences; ‡1; Pre vs post (α_1=0.05), ‡2; Pre vs Mid (α_2=0.025), ‡3; Mid vs Post (α_3=0.017).

Resting cardiac function

Resting cardiac function was similar between groups at the start of the study ($p>0.05$ between groups; Supplementary Table 3). Left ventricular mass was higher in the HIIT group compared to the MIT group ($p_1=0.039$), attributed to a higher LVDd in the HIIT group ($p_1=0.031$). MIT led to significant increases in E/A (0.77±0.24 vs 0.84±0.19, $p_2=0.017$) after 12 weeks of exercise training, whereas ejection time increased after 24 weeks of MIT (271±17ms vs 290±25ms, $p_1=0.015$ respectively).

Exercise echocardiography

Prior to the intervention, systolic (CO, LS) and diastolic (E, e'_s and E/e') function were similar in both groups during exercise ($p_1>0.05$; Table 4). O_2 extraction during exercise increased significantly after 24 weeks of exercise training in both the HIIT and MIT group (13±3mL/dL vs 16±3mL/dL, $p_1=0.04$ and 12±2mL/dL vs 19±5mL/dL, $p_1=0.009$) with a significant interaction effect in favour of MIT ($p_{Interaction}=0.007$). Other ergospirometry-related parameters significantly changed during exercise as a result of the intervention in both the MIT and HIIT group after 24 weeks of exercise training; $CO/\dot{V}O_2$ decreased (5.7±1.8 vs 3.9±1.5, $p_1=0.002$ and 6.5±1.5 vs 4.7±1.5, $p_1=0.02$) and O_2 pulse during exercise significantly increased in the MIT group (11±2mL/bpm vs 14±2mL/bpm, $p_1=0.018$). Parameters of systolic (CO, LS) and diastolic function (E, e'_s, E/e') remained unchanged after the intervention, both at rest and during exercise.

Table 4: Cardiac function during exercise echocardiography following the exercise intervention

	MIT (*n*=9)			HIIT (*n*=10)				
	Pre	Mid	Post	Pre	Mid	Post	P Time	P Time*Group
HR_{rest} (bpm)	71±8	67±14	67±14	74±8	64±8 ‡2	63±10 ‡1	**0.003**	0.221
Peak exercise performance								
$\dot{V}O_{2peak}$ (mL/min)	1400±205	1579±94	1916±461 a ‡1	1699±547	1930±427 *2	1927±428	**<0.001**	0.085
$\dot{V}O_{2peak\ \%\ of\ predicted}$ (%)	78±11	84±7	101±19 ‡1	80±21	89±13	89±11	**0.001**	0.061
HR_{peak} (bpm)	127±13	128±13	131±27	140±14	136±12	131±19	0.893	0.414
W_{peak} (W)	105±17	111±8	136±37 ‡1	134±42	151±40 *1	157±43	**0.001**	0.38
RER_{peak}	1.07±0.04	1.06±0.05	1.05±0.04	1.03±0.06	1.03±0.04	1.02±0.04	0.083	0.763
Peripheral parameters								
O_2 pulse $_{rest}$ (mL/bpm)	4±1 a	4±2	4±1	6±5 a	5±1	4±1	0.383	0.511
O_2 pulse $_{peak}$ (mL/bpm)	11±2 a	12±2	14±2 ‡1, ‡3	12±4	14±2	15±2	**0.001**	0.557
O_2 extraction $_{rest}$ (mL/dL)	5±2	5±2	6±2	6±3	7±2	6±2	0.96	0.456
O_2 extraction $_{peak}$ (mL/dL)	12±2	13±3	19±5 ‡1	13±3	17±5	16±3 ‡1	**0.001**	**0.007**
Systolic function								
CO_{rest} (L/min)	4.7±0.9	5.3±1.2 ‡2	4.2±1	5±1.1	4.5±1.3	4.8±1.1	0.391	0.123
CO_{peak} (L/min)	11.4±2.3	12±1.8	10.2±2.3	13.7±2.3	11.5±3.3	12.6±3.3	0.483	0.071
CI $_{rest}$ (L/min/m²)	2.38±0.4	-	2.14±0.44	2.35±0.52	-	2.3±0.48	0.308	0.688
CI $_{peak}$ (L/min/m²)	5.7±1.06	-	5.14±1.11	6.44±1.35	-	5.93±1.44	0.148	0.889
Longitudinal $strain_{rest}$ (%)	-17.3±1.6	-18.6±1.7	-18.7±2.1	-16.6±2.8	-18±2.5	-18.2±1.8	0.193	0.776
Longitudinal $strain_{peak}$ (%)	-21.1±3.3	-24±2.2	-22.1±1.8	-20.2±3.6	-22.5±3.5	-22.5±3	0.17	0.531
Absolute change in $LS_{peak\text{-}rest}$ (%)	4.6 ± 3.1	5.3 ± 2.1	4.8 ± 2.3	4.4 ± 3	4.8 ± 1.3	4.3 ± 3.1	0.885	0.987
Diastolic function								
E_{rest} (m/sec)	0.62±0.14	0.62±0.13	0.59±0.1	0.57±0.18	0.56±0.14	0.52±0.14	0.433	0.78
E_{peak} (m/sec)	1.06±0.24	1.15±0.17	1.09±0.13	1.23±0.1	1.13±0.14	1.14±0.14	0.694	0.068
e'$_{s\ rest}$ (m/sec)	0.06±0.01	0.06±0.02	0.06±0.01	0.06±0.01	0.06±0.02	0.05±0.02[a]	0.144	0.886
e'$_{s\ peak}$ (m/sec)	0.11±0.05	0.13±0.03	0.13±0.04	0.14±0.05	0.13±0.04	0.13±0.03	0.286	0.365
E/e' $_{rest}$	11.4±3.9	11.1±3.4	11.1±3.3	9.8±2.7 a	9.4±1.3	10.6±2.7	0.784	0.511
E/e' $_{peak}$	10.9±5	9.4±2.1	9.4±3.1	10.3±5.9 a	9.7±4	8.8±1.9 ‡1	0.095	0.917
Other								
CO/W (L/min/W)	3.6±1.2 a	4.3±1.2	3.8±0.8	3.4±1.4	3.1±0.8 *2	3.7±1.3	0.841	0.375
$CO/\dot{V}O_2$	5.7±1.8	5.3±0.9	3.9±1.5 ‡1	6.5±1.5	4.6±1.3	4.7±1.5 ‡1	**0.001**	0.176

Exercise echocardiography. Data are presented as means ± SD. HR; heart rate, $\dot{V}O_2$; oxygen uptake, W; workload, CO; cardiac output, CI; cardiac index, LS; longitudinal strain, E; peak velocity of early diastolic filling phase, e'$_s$; early diastolic velocity at the septal annulus, E/e'; left ventricular filling pressure. a: Data abnormally distributed (non-parametric alternative used). Between group differences; *1; Pre (α_1=0.05), *2; Post (α_2=0.025), *3; Mid (α_3=0.017). Within group differences; ‡1; Pre vs post (α_1=0.05), ‡2; Pre vs Mid (α_2=0.025), ‡3; Mid vs Post (α_3=0.017).

Correlations

Changes in HbA1c levels were negatively correlated with (absolute) changes in LS during exercise in the HIIT group after 12 and 24 weeks of intervention (r=0.-809, p=0.028 and r=-0.782, p=0.038; Supplementary table 4). Within the MIT group, HbA1c was negatively correlated with resting LS after 12 and 24 weeks of intervention (r=-0.824, p=0.023 and r=-0.792, p=0.019).

Observed power

Given the explorative nature of the study, a post-hoc power was calculated for effects of the different exercise training programs on O_2 extraction during exercise (paired T-test, start vs. 24 weeks of exercise training). Observed power was 0.849 for HIIT and 0.95 for MIT (effect size 1.1591 and 1.391, α error probability 0.05, total sample size 10 and 9). Observed power for the repeated measures ANOVA was 0.954 (repeated measures; start of the intervention, 12 and 24 weeks of exercise training) and 0.85 (interaction effects; MIT vs. HIIT).

DISCUSSION

This study compares the effects of 24 weeks of supervised exercise training (HIIT vs. MIT) on cardiac function and O_2 extraction capacity in patients with T2DM and without known CVD. For the first time within this population, exercise echocardiography was combined with simultaneous breath-by-breath analyses, allowing to (indirectly) investigate O_2 extraction by applying the Fick principle (Tibby et al., 1997). As such evaluations were lacking in previous studies, it remained to be elucidated whether improvements in exercise capacity are related to central and/or peripheral adaptations. Both exercise programs were safe and well tolerated by the participants and resulted in an improved exercise performance ($\dot{V}O_{2peak}$ and peak workload) and improved glycaemic control (lower tAUC). Improvements in exercise capacity, especially in the MIT group, were related to peripheral adaptations (increased O_2 extraction capacity) rather than central adaptations (cardiac output remained unchanged).

The intervention effects are in accordance with the expectations in patients with T2DM. Indeed, exercise capacity ($\dot{V}O_{2peak}$ (mL/kg/min) improved with an expected magnitude, respectively 13.6% and 10.5% after MIT and HIIT (Boule et al., 2003; Liu et al., 2019). In addition, body composition (body weight, body fat percentage, BMI), glycaemic control (fasting blood glucose, peripheral insulin resistance) and lipid profile (total cholesterol levels) improved to a similar extent as reported by other studies (Liu et al., 2019; Pan et al., 2018). Nevertheless, this was not the case for triglyceride levels and some aspects (e.g. body weight) mainly applied to MIT only, which is in contrast to the reported effectiveness of HIIT interventions (Liu et al., 2019). The tight glycaemic control at baseline could have contributed to the relatively small improvements in HbA1c levels (Snowling & Hopkins, 2006). HIIT exerted improvements in exercise capacity earlier in the intervention as opposed to MIT and therefore seemed to be more effective on the short term (12 weeks of exercise training) (De Nardi et al., 2018). Though, high-intensity training seemed to exert a strong initial boost in exercise capacity which flattens afterwards, while moderate-intense training exerted a slower but modest progression, which is in line with a previous study of our research group (Hansen et al., 2009).

The exercise intervention was highly effective to improve O_2 extraction capacity during exercise. O_2 extraction is determined by the O_2 delivery (muscle blood flow) and O_2 flux (flux towards the myocytes), implicating that an impaired muscle blood flow can underlie an impaired O_2 extraction in patients with T2DM (Poitras et al., 2018). Indeed, Sacre *et al.* (Sacre et al., 2015) reported a relation between exercise intolerance and blood flow reserve in patients with T2DM. However, it remains doubtful whether adaptations in muscle blood flow contributed to an improved O_2 extraction capacity, as Bauer *et al.* (Bauer et al., 2007) demonstrated that abnormal responses in muscle blood flow mainly affect $\dot{V}O_2$ kinetics at onset of exercise (without affecting $\dot{V}O_{2peak}$) in patients with T2DM. Nevertheless, exercise training is known to improve endothelial function in T2DM patients (Lee et al., 2018). Second, a decrease in HbA1c levels could contribute to an increased O_2 extraction by improving O_2 flux (high HbA1c levels impede O_2 flux because of increased affinity for O_2) (Poitras et al., 2018). However, changes in HbA1c and O_2 extraction were not correlated and therefore other factors are more likely to have contributed to the increased O_2 extraction capacity.

Indeed, mitochondrial dysfunction is supposed to underlie impairments in O_2 extraction and concomitantly exercise capacity in T2DM (McCoy et al., 2017). An increased O_2 extraction could relate to an increased mitochondrial content resulting from exercise-induced mitochondrial biogenesis, which is however not consistently reported and not mandatory as increments in oxidative capacity have been reported in patients with T2DM without changes in mitochondrial content (Larsen et al., 2014; Sparks et al., 2013). Furthermore, the role of exercise intensity remains to be elucidated, as previous work of our research group reported similar improvements in mitochondrial oxidative capacity after moderate vs high-intensity training in patients with T2DM (Hansen et al., 2009). Lastly, an increased O_2 extraction capacity might result from an increased skeletal muscle capillary density by exercise training, which has been reported in obese persons displaying glucose intolerance (Prior et al., 2014). Of interest, improvements in O_2 extraction in our study were observed earlier by HIIT as opposed to MIT (after respectively 12 and 24 weeks of exercise training). A previous exercise intervention in sedentary non-diabetic persons reported an increased muscle capillary density after both MIT and HIIT for eight weeks, whereas mitochondrial oxidative capacity was only improved by HIIT (Daussin et al., 2008). Although this might indicate a more potent effect of HIIT on the skeletal muscle oxidative capacity, it remains unclear whether our results were driven by similar mechanisms.

Intriguingly, our data could not confirm the potential of exercise training to improve cardiac function, which is widely reported in previous studies (Verboven et al., 2019) at rest and recently by Wilson *et al.* (Wilson et al., 2019) during exercise. Prior to the intervention, 11 out of the 27 (40.7%) patients with T2DM displayed some form of diastolic dysfunction at rest and only one patient displayed a positive diastolic stress test. Wilson *et al.* (Wilson et al., 2017) already demonstrated an impaired ventricular filling to be associated with limited cardiac reserve and exercise capacity in patients with T2DM. The association between positive diastolic stress tests and exercise intolerance was recently confirmed by Nishi *et al.* (Nishi et al., 2020) in a large cohort of patients with T2DM (n=161). However, our study could not confirm the results of Hollekim-Strand *et al.* (Hollekim-Strand et al., 2014) who reported superior effects of HIIT on resting parameters of diastolic function and LS.

The absolute changes in LS were negatively associated with decreases in HbA1c levels, stipulating the importance of glycaemic control. Indeed, optimizing glycaemic control in patients with poorly controlled T2DM is associated with improved strain (Leung et al., 2016). Hyperglycaemia and the concomitant collagen deposition closely relate to the development of myocardial fibrosis, a major determinant affecting myocardial deformation (and therefore strain), in the diabetic heart (Jia et al., 2018). From diabetic animal models, exercise training seems to reverse cardiac fibrosis by reducing collagen deposition, being an important factor determining deformation parameters *in vivo* (Novoa et al., 2017; Verboven et al., 2019). Therefore, a reduced collagen deposition as result of improved glycaemic control could underlie adaptations in myocardial deformation. Of interest, the correlations were significant after 24 weeks of exercise training, but were dominated by the first 12 weeks of the exercise program, emphasizing the effectiveness of exercise training on the short term (Verboven et al., 2019).

Collectively, our data, combined with the study of Wilson *et al.* (Wilson et al., 2019), stipulate the potential of exercise training to improve cardiovascular health and exercise capacity in the T2DM population. Both limitations at central level (cardiac output) and peripheral level (O_2 extraction) can be reversed (or at least partially) by exercise training, at least in patients with T2DM but without a known diagnosis of CVD. Determining the underlying cause of exercise intolerance in T2DM population is of clinical interest, especially in terms of exercise training therapy, in order to optimize the latter according to the individual's phenotype (e.g. effects warranted on the short term or not, whether exercise capacity is dominated at the central level). Stress echocardiography with simultaneous breath-by-breath analyses could be useful in this setting. However, larger studies including patients with poorly controlled diabetes and/or diabetic complications are warranted to have a better understanding of the effects of diabetes on cardiovascular health and the opportunities for exercise training therapy.

Limitations

Several limitations need to be addressed in this randomised controlled trial. To start with, the limited sample size impedes to compare subgroups according to the patient characteristics (e.g. age and gender) and investigate the effects of the latter. The age range of inclusion was very broad (18 – 81 years of age), which could have affected the results. However, as age was not significantly different between both groups, the effect of the latter was minimal. Second, a methodological and conceptual limitation in the study regarding gender distribution should be addressed. All but one of the participants in each of the groups was a male, so that there is no potential to extrapolate findings towards female patients. Such a disbalanced proportion is an imminent risk when recruiting using a convenience sampling method (based on availability and willingness to participate) without applying prespecified quota. In addition, previous intervention studies investigating cardiac function after exercise training have mainly included male patients and so female patients are understudied. Therefore, future studies should include prespecified quota, in order to increase the external validity. Third, patients displayed an adequate glycaemic control. It therefore remains to be elucidated to what extent the degree of glycaemic control can influence the effect of the intervention impeding to extrapolate our results towards the entire diabetes population.

Eventually, some methodological limitations need to be addressed. O_2 extraction was measured indirectly. The latter can be measured directly using arterial blood gas analyses but requires arterial punctures. The procedure to obtain arterial blood gasses is difficult to execute during high-intensity exercise, and therefore this technique was not applied in our study.

Conclusion

In patients with well-controlled T2DM and without a diagnosis of CVD or signs of cardiac dysfunction (during exercise), an improved exercise capacity was related to adaptations at the peripheral level (oxygen extraction capacity) rather than at the central level (cardiac output). Adaptations were more rapidly exerted by HIIT, although MIT was equally effective on the long term.

Figure captions

Figure 1: Flowchart of the study. T2DM: Type 2 Diabetes Mellitus, CAD; Coronary artery disease, MIT; moderate-intense training, HIIT; high-intensity interval training.

Supplementary Table 1: Design of the exercise training program

Program	*Time frame*	*Intensity*	*Duration (excluding warm-up and cool-down) and frequency*
MIT	Week 1 – 24	35min at 70-80% of HR_{peak}	35min, 3x/week
HIIT	Week 1 – 2	35min at 70-80% of HR_{peak}	35min, 3x/week
	Week 3 – 6	6 x 1min at 90-100% of Wpeak, 6 x 4min at 70% of HR_{peak}	30min, 3x/week
	Week 7 – 12	7 x 1min at 90-100% of Wpeak, 7 x 4min at 70% of HR_{peak}	35min, 3x/week
	Week 13 – 24	8 x 1min at 90-100% of Wpeak, 8 x 4min at 70% of HR_{peak}	40min, 3x/week

Design of the exercise training program. HR_{peak}; peak heart rate achieved during cardiopulmonary exercise testing, Wpeak; maximal achieved workload during cardiopulmonary exercise testing

Supplementary Table 2: Details of the exercise training program

	MIT (*n*=9)				**HIIT (*n*=10)**			
	Week 1-2	**Week 3-6**	**Week 7-12**	**Week 13-24**	**Week 1-2**	**Week 3-6**	**Week 7-12**	**Week 13-24**
Heart rate								
$HR_{average}$ (bpm)	115±13	114±13	114±13	115±13	117±8	120±11	121±12	123±11
$HR_{average}$ (%)	74±2	73±1	73±2	74±2	72±2	75±4	75±4 [a]	77±3 [a]
HR_{peak} (%)	81±2	81±3[a]	82±2	82±2	82±2	91±6 [a] *	91±8 [a] *	93±7 [a] *
Energy expenditure								
Caloric $expenditure_{average}$ (kcal)	243±34	257±40	271±42	287±48	295±54*	286±49	335±53*	381±55*
Caloric expenditure indexed for body $weight_{average}$ (kcal/Kg)	2.83±0.63	2.98±0.65	3.16±0.72	3.33±0.73	3.17±0.95[a]	3.08±0.86	3.59±0.95	4.09±1.04
Blood glucose								
Blood glucose at $start_{average}$ (mg/dL)	182±44	175±29	163±24	161±22	153±26	152±24	153±26	156±31
Blood glucose at $end_{average}$ (mg/dL)	115±29[a]	112±23 [a]	110±17	104±13	112±20	119±22	120±20	131±23*

Details of the exercise training program. HR; heart rate. a; data not normally distributed (non-parametric alternative used). Significant differences at between groups at * $p < 0.05$

Supplementary Table 3: Resting cardiac function following the exercise intervention

	MIT (*n*=9)			HIIT (*n*=10)		
	Pre	Mid	Post	Pre	Mid	Post
Cardiac structure and dimensions						
IVSd (mm)	11±1	11±1	11±1	12±1	12±1	12±1
LVPWd (mm)	11±2	11±1	11±1	12±2	12±2	12±1
LVDd (mm)	40±3	43±3	41±7	45±4 *1	46±5	42±6
LVM (g)	142±34	165±39	162±56	190±48 *1	205±62	180±41
LVMi (g/m²)	71±14	-	81±25	88±16 *1	-	72±31 a
LVOT (mm)	21±1	21±1	20±1 ‡3	22±1	21±2	22±1 a *2
Systolic function						
s'_s (m/sec)	0.07±0.01	0.06±0.02	0.07±0.01a	0.07±0.02	0.07±0.01	0.07±0.02a
IVCT (ms)	70±15	72±10 a	70±11	80±27 a	87±20	86±37a
ET (ms)	271±17	285±27	290±25 ‡1	279±31	283±19	285±29
Diastolic function						
E (m/sec)	0.63±0.15	0.7±0.1	0.68±0.12	0.54±0.1	0.62±0.16a	0.58±0.15
A (m/sec)	0.86±0.17	0.9±0.33	0.8±0.2	0.65±0.1 *1	0.7±0.13	0.62±0.15 a
E/A	0.77±0.24	0.84±0.19 ‡2	0.88±0.24	0.84±0.17 a	0.9±0.25	0.94±0.22
Dt (ms)	194±56	175±32	213±38	208±24	190±45	230±30
e'_s (m/sec)	0.06±0.02	0.06±0.01 a	0.06±0.02	0.05±0.01 a	0.06±0.02	0.06±0.03 a
a'_s (m/sec)	0.1±0.02	0.09±0.01	0.09±0.01	0.09±0.02	0.1±0.02	0.09±0.02 ‡3
E/e'	12±2.3	12.4±3.2	11.6±3	10.1±1.8	10.4±2.5	11.1±4
IVRT (ms)	89±32	97±18	85±18	102±25	96±22	103±42 a

Resting echocardiography. Data are presented as means ± SD. HR; heart rate, 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, LVOT; left ventricular outflow tract diameter, LVEDV; left ventricular end-diastolic volume, LVESV; left ventricular end-systolic volume, 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, a'_s; late diastolic velocity at the septal annulus, E/e'; left ventricular filling pressure, IVRT: isovolumic relaxation time (ms), LVEF; left ventricular ejection fraction, SV; stroke volume, CO; cardiac output, s'_s: peak systolic velocity at the septal annulus, IVCT; isovolumic contraction time, ET; ejection time. a: Data not normally distributed (non-parametric alternative used). Between group differences; *1; Pre (α_1=0.05), *2; Post (α_2=0.025), *3; Mid (α_3=0.017). Within group differences; ‡1; Pre vs post (α_1=0.05), ‡2; Pre vs Mid (α_2=0.025), ‡3; Mid vs Post (α_3=0.017).

Supplementary Table 4: correlations between changes in cardiac function and changes in glycaemic control

	MIT (*n*=9)						HIIT (*n*=10)					
	Pre to Post		Pre to Mid		Mid to Post		Pre to Post		Pre to Mid		Mid to Post	
HbA1c	r	p	r	p	r	p	r	p	r	p	r	p
LS at rest	-0.824	**0.023***	-0.792	**0.019***	0.498	0.256	-0.3	0.469	-0.234	0.577	-0.297	0.475
LS during exercise	0.478	0.338	-0.314	0.449	-0.419	0.408	-0.809	**0.028***	-0.782	**0.038***	-0.513	0.194
$\dot{V}O_{2peak}$	-0.007	0.986	-0.096	0.821	0.194	0.645	0.229	0.525	0.517	0.126	0.162	0.654
CO at rest	-0.037	0.93	0.624	0.098	0.199	0.636	0.506	0.2	0.474	0.236	0.162	0.677
CO during exercise	0.008	0.986	-0.3	0.513	-0.253	0.546	0.147	0.706	0.412	0.31	-0.191	0.651
O_2 extraction at rest	0.286	0.534	-0.327	0.474	-0.068	0.899	-0.544	0.164	-0.24	0.566	0.001	0.999
O_2 extraction during exercise	-0.202	0.7	-0.113	0.81	0.249	0.591	-0.188	0.628	-0.457	0.255	0.255	0.542

Pearson correlations between changes in HbA1c (absolute changes) and changes in exercise echocardiographic parameters (expressed as percentages). LS; left ventricular longitudinal strain (and percentages expressed as absolute changes), $\dot{V}O_{2peak}$; peak oxygen uptake, CO; cardiac output. Significant at * $p<0.05$

References

American Diabetes, A. (2020). Standards of Medical Care in Diabetes-2020 Abridged for Primary Care Providers. *Clin Diabetes*, *38*(1), 10-38. https://doi.org/10.2337/cd20-as01

Baker, W. B., Li, Z., Schenkel, S. S., Chandra, M., Busch, D. R., Englund, E. K., Schmitz, K. H., Yodh, A. G., Floyd, T. F., & Mohler, E. R., 3rd. (2017). Effects of exercise training on calf muscle oxygen extraction and blood flow in patients with peripheral artery disease. *J Appl Physiol (1985)*, *123*(6), 1599-1609. https://doi.org/10.1152/japplphysiol.00585.2017

Baldi, J. C., Aoina, J. L., Oxenham, H. C., Bagg, W., & Doughty, R. N. (2003). Reduced exercise arteriovenous O2 difference in Type 2 diabetes. *J Appl Physiol (1985)*, *94*(3), 1033-1038. https://doi.org/10.1152/japplphysiol.00879.2002

Bauer, T. A., Reusch, J. E., Levi, M., & Regensteiner, J. G. (2007). Skeletal muscle deoxygenation after the onset of moderate exercise suggests slowed microvascular blood flow kinetics in type 2 diabetes. *Diabetes Care*, *30*(11), 2880-2885. https://doi.org/10.2337/dc07-0843

Boule, N. G., Kenny, G. P., Haddad, E., Wells, G. A., & Sigal, R. J. (2003). Meta-analysis of the effect of structured exercise training on cardiorespiratory fitness in Type 2 diabetes mellitus. *Diabetologia*, *46*(8), 1071-1081. https://doi.org/10.1007/s00125-003-1160-2

Dal Canto, E., Ceriello, A., Ryden, L., Ferrini, M., Hansen, T. B., Schnell, O., Standl, E., & Beulens, J. W. (2019). Diabetes as a cardiovascular risk factor: An overview of global trends of macro and micro vascular complications. *Eur J Prev Cardiol*, *26*(2_suppl), 25-32. https://doi.org/10.1177/2047487319878371

Daussin, F. N., Zoll, J., Dufour, S. P., Ponsot, E., Lonsdorfer-Wolf, E., Doutreleau, S., Mettauer, B., Piquard, F., Geny, B., & Richard, R. (2008). Effect of interval versus continuous training on cardiorespiratory and mitochondrial functions: relationship to aerobic performance improvements in sedentary subjects. *Am J Physiol Regul Integr Comp Physiol*, *295*(1), R264-272. https://doi.org/10.1152/ajpregu.00875.2007

De Nardi, A. T., Tolves, T., Lenzi, T. L., Signori, L. U., & Silva, A. (2018). High-intensity interval training versus continuous training on physiological and metabolic variables in prediabetes and type 2 diabetes: A meta-analysis. *Diabetes Res Clin Pract*, *137*, 149-159. https://doi.org/10.1016/j.diabres.2017.12.017

Ha, J. W., Lee, H. C., Kang, E. S., Ahn, C. M., Kim, J. M., Ahn, J. A., Lee, S. W., Choi, E. Y., Rim, S. J., Oh, J. K., & Chung, N. (2007). Abnormal left ventricular longitudinal functional reserve in patients with diabetes mellitus: implication for detecting subclinical myocardial dysfunction using exercise tissue Doppler echocardiography. *Heart*, *93*(12), 1571-1576. https://doi.org/10.1136/hrt.2006.101667

Hansen, D., Dendale, P., Coninx, K., Vanhees, L., Piepoli, M. F., Niebauer, J., Cornelissen, V., Pedretti, R., Geurts, E., Ruiz, G. R., Corra, U., Schmid, J. P., Greco, E., Davos, C. H., Edelmann, F., Abreu, A., Rauch, B., Ambrosetti, M., Braga, S. S., Barna, O., Beckers, P., Bussotti, M., Fagard, R., Faggiano, P., Garcia-Porrero, E., Kouidi, E., Lamotte, M., Neunhauserer, D., Reibis, R., Spruit, M. A., Stettler, C., Takken, T., Tonoli, C., Vigorito, C., Voller, H., & Doherty, P. (2017). The European Association of Preventive Cardiology Exercise Prescription in Everyday Practice and Rehabilitative Training (EXPERT) tool: A digital training and decision support system for optimized exercise prescription in cardiovascular disease. Concept, definitions and construction methodology. *Eur J Prev Cardiol*, *24*(10), 1017-1031. https://doi.org/10.1177/2047487317702042

Hansen, D., Dendale, P., Jonkers, R. A., Beelen, M., Manders, R. J., Corluy, L., Mullens, A., Berger, J., Meeusen, R., & van Loon, L. J. (2009). Continuous low- to moderate-intensity exercise training is as effective as moderate- to high-intensity exercise training at lowering blood HbA(1c) in obese type 2 diabetes patients. *Diabetologia*, *52*(9), 1789-1797. https://doi.org/10.1007/s00125-009-1354-3

Hansen, D., Kraenkel, N., Kemps, H., Wilhelm, M., Abreu, A., Pfeiffer, A. F., Jordao, A., Cornelissen, V., & Voller, H. (2019). Management of patients with type 2 diabetes in cardiovascular rehabilitation. *Eur J Prev Cardiol*, *26*(2_suppl), 133-144. https://doi.org/10.1177/2047487319882820

Hansen, D., Mellbin, L., Cosentino, F., De Bacquer, D., Grobbee, D., Van Ryckeghem, L., Standl, E., & Beulens, J. W. (2020). High awareness of diabetes as a key cardiovascular risk factor among healthcare professionals but suboptimal treatment: Results from a survey of the European Association of Preventive Cardiology. *Eur J Prev Cardiol*, 2047487320911845. https://doi.org/10.1177/2047487320911845

Hollekim-Strand, S. M., Bjorgaas, M. R., Albrektsen, G., Tjonna, A. E., Wisloff, U., & Ingul, C. B. (2014). High-intensity interval exercise effectively improves cardiac function in patients with type 2 diabetes mellitus and diastolic dysfunction: a randomized controlled trial. *J Am Coll Cardiol*, *64*(16), 1758-1760. https://doi.org/10.1016/j.jacc.2014.07.971

Jia, G., Hill, M. A., & Sowers, J. R. (2018). Diabetic Cardiomyopathy: An Update of Mechanisms Contributing to This Clinical Entity. *Circ Res*, *122*(4), 624-638. https://doi.org/10.1161/CIRCRESAHA.117.311586

Jorgensen, P. G., Jensen, M. T., Mogelvang, R., von Scholten, B. J., Bech, J., Fritz-Hansen, T., Galatius, S., Biering-Sorensen, T., Andersen, H. U., Vilsboll, T., Rossing, P., & Jensen, J. S. (2016). Abnormal echocardiography in patients with type 2 diabetes and relation to symptoms and clinical characteristics. *Diab Vasc Dis Res*, *13*(5), 321-330. https://doi.org/10.1177/1479164116645583

Kokkinos, P., Myers, J., Nylen, E., Panagiotakos, D. B., Manolis, A., Pittaras, A., Blackman, M. R., Jacob-Issac, R., Faselis, C., Abella, J., & Singh, S. (2009). Exercise capacity and all-cause mortality in African American and Caucasian men with type 2 diabetes. *Diabetes Care*, *32*(4), 623-628. https://doi.org/10.2337/dc08-1876

Larsen, S., Skaaby, S., Helge, J. W., & Dela, F. (2014). Effects of exercise training on mitochondrial function in patients with type 2 diabetes. *World J Diabetes*, *5*(4), 482-492. https://doi.org/10.4239/wjd.v5.i4.482

Lee, J. H., Lee, R., Hwang, M. H., Hamilton, M. T., & Park, Y. (2018). The effects of exercise on vascular endothelial function in type 2 diabetes: a systematic review and meta-analysis. *Diabetol Metab Syndr*, *10*, 15. https://doi.org/10.1186/s13098-018-0316-7

Leung, M., Wong, V. W., Hudson, M., & Leung, D. Y. (2016). Impact of Improved Glycemic Control on Cardiac Function in Type 2 Diabetes Mellitus. *Circ Cardiovasc Imaging*, *9*(3), e003643. https://doi.org/10.1161/CIRCIMAGING.115.003643

Liu, J. X., Zhu, L., Li, P. J., Li, N., & Xu, Y. B. (2019). Effectiveness of high-intensity interval training on glycemic control and cardiorespiratory fitness in patients with type 2 diabetes: a systematic review and meta-analysis. *Aging Clin Exp Res*, *31*(5), 575-593. https://doi.org/10.1007/s40520-018-1012-z

Matthews, D. R., Hosker, J. P., Rudenski, A. S., Naylor, B. A., Treacher, D. F., & Turner, R. C. (1985). Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*, *28*(7), 412-419. https://doi.org/10.1007/bf00280883

McCoy, J., Bates, M., Eggett, C., Siervo, M., Cassidy, S., Newman, J., Moore, S. A., Gorman, G., Trenell, M. I., Velicki, L., Seferovic, P. M., Cleland, J. G. F., MacGowan, G. A., Turnbull, D. M., & Jakovljevic, D. G. (2017). Pathophysiology of exercise intolerance in chronic diseases: the role of diminished cardiac performance in mitochondrial and heart failure patients. *Open Heart*, *4*(2), e000632. https://doi.org/10.1136/openhrt-2017-000632

Mitranun, W., Deerochanawong, C., Tanaka, H., & Suksom, D. (2014). Continuous vs interval training on glycemic control and macro- and microvascular reactivity in type 2 diabetic patients. *Scand J Med Sci Sports*, *24*(2), e69-76. https://doi.org/10.1111/sms.12112

Nadeau, K. J., Zeitler, P. S., Bauer, T. A., Brown, M. S., Dorosz, J. L., Draznin, B., Reusch, J. E., & Regensteiner, J. G. (2009). Insulin resistance in adolescents with type 2 diabetes is associated with impaired exercise capacity. *J Clin Endocrinol Metab*, *94*(10), 3687-3695. https://doi.org/10.1210/jc.2008-2844

Nesti, L., Pugliese, N. R., Sciuto, P., & Natali, A. (2020). Type 2 diabetes and reduced exercise tolerance: a review of the literature through an integrated physiology approach. *Cardiovascular Diabetology*, *19*(1), 134. https://doi.org/10.1186/s12933-020-01109-1

Nishi, T., Kobayashi, Y., Christle, J. W., Cauwenberghs, N., Boralkar, K., Moneghetti, K., Amsallem, M., Hedman, K., Contrepois, K., Myers, J., Mahaffey, K. W., Schnittger, I., Kuznetsova, T., Palaniappan, L., & Haddad, F. (2020). Incremental value of diastolic stress test in identifying subclinical heart failure in patients with diabetes mellitus. *Eur Heart J Cardiovasc Imaging*, *21*(8), 876-884. https://doi.org/10.1093/ehjci/jeaa070

Novoa, U., Arauna, D., Moran, M., Nunez, M., Zagmutt, S., Saldivia, S., Valdes, C., Villasenor, J., Zambrano, C. G., & Gonzalez, D. R. (2017). High-Intensity Exercise Reduces Cardiac Fibrosis and Hypertrophy but Does Not Restore the Nitroso-Redox Imbalance in Diabetic Cardiomyopathy. *Oxid Med Cell Longev*, *2017*, 7921363. https://doi.org/10.1155/2017/7921363

Pan, B., Ge, L., Xun, Y. Q., Chen, Y. J., Gao, C. Y., Han, X., Zuo, L. Q., Shan, H. Q., Yang, K. H., Ding, G. W., & Tian, J. H. (2018). Exercise training modalities in patients with type 2 diabetes mellitus: a systematic review and network meta-analysis. *Int J Behav Nutr Phys Act*, *15*(1), 72. https://doi.org/10.1186/s12966-018-0703-3

Poitras, V. J., Hudson, R. W., & Tschakovsky, M. E. (2018). Exercise intolerance in Type 2 diabetes: is there a cardiovascular contribution? *J Appl Physiol (1985)*, *124*(5), 1117-1139. https://doi.org/10.1152/japplphysiol.00070.2017

Prior, S. J., Blumenthal, J. B., Katzel, L. I., Goldberg, A. P., & Ryan, A. S. (2014). Increased skeletal muscle capillarization after aerobic exercise training and weight loss improves insulin sensitivity in adults with IGT. *Diabetes Care*, *37*(5), 1469-1475. https://doi.org/10.2337/dc13-2358

Rorth, R., Jhund, P. S., Mogensen, U. M., Kristensen, S. L., Petrie, M. C., Kober, L., & McMurray, J. J. V. (2018). Risk of Incident Heart Failure in Patients With Diabetes and Asymptomatic Left Ventricular Systolic Dysfunction. *Diabetes Care*, *41*(6), 1285-1291. https://doi.org/10.2337/dc17-2583

Sacre, J. W., Jellis, C. L., Haluska, B. A., Jenkins, C., Coombes, J. S., Marwick, T. H., & Keske, M. A. (2015). Association of Exercise Intolerance in Type 2 Diabetes With Skeletal Muscle Blood Flow Reserve. *JACC Cardiovasc Imaging*, *8*(8), 913-921. https://doi.org/10.1016/j.jcmg.2014.12.033

Saeedi, P., Petersohn, I., Salpea, P., Malanda, B., Karuranga, S., Unwin, N., Colagiuri, S., Guariguata, L., Motala, A. A., Ogurtsova, K., Shaw, J. E., Bright, D., Williams, R., & Committee, I. D. F. D. A. (2019). Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. *Diabetes Res Clin Pract*, *157*, 107843. https://doi.org/10.1016/j.diabres.2019.107843

Snowling, N. J., & Hopkins, W. G. (2006). Effects of different modes of exercise training on glucose control and risk factors for complications in type 2 diabetic patients: a meta-analysis. *Diabetes Care*, *29*(11), 2518-2527. https://doi.org/10.2337/dc06-1317

Sparks, L. M., Johannsen, N. M., Church, T. S., Earnest, C. P., Moonen-Kornips, E., Moro, C., Hesselink, M. K., Smith, S. R., & Schrauwen, P. (2013). Nine months of combined training improves ex vivo skeletal muscle metabolism in individuals with type 2 diabetes. *J Clin Endocrinol Metab*, *98*(4), 1694-1702. https://doi.org/10.1210/jc.2012-3874

Task Force of the Italian Working Group on Cardiac, R., Prevention, Piepoli, M. F., Corra, U., Agostoni, P. G., Belardinelli, R., Cohen-Solal, A., Hambrecht, R., & Vanhees, L. (2006). Statement on cardiopulmonary exercise testing in chronic heart failure due to left ventricular dysfunction. Recommendations for performance and interpretation. *Eur J Cardiovasc Prev Rehabil*, *13*(1), 10-12. https://doi.org/10.1097/00149831-200602000-00003

Tibby, S. M., Hatherill, M., Marsh, M. J., Morrison, G., Anderson, D., & Murdoch, I. A. (1997). Clinical validation of cardiac output measurements using femoral artery thermodilution with direct Fick in ventilated children and infants. *Intensive Care Med*, *23*(9), 987-991. https://doi.org/10.1007/s001340050443

Umpierre, D., Ribeiro, P. A., Schaan, B. D., & Ribeiro, J. P. (2013). Volume of supervised exercise training impacts glycaemic control in patients with type 2 diabetes: a systematic review with meta-regression analysis. *Diabetologia*, *56*(2), 242-251. https://doi.org/10.1007/s00125-012-2774-z

Van Ryckeghem L, K. C., Verboven K, Verbaanderd E, Frederix I, Bakelants E, Petit T, Jogani S, Stroobants S, Dendale P, Bito V, Verwerft J, Hansen D. (2020). Exercise capacity is related to attenuated responses in oxygen extraction and left ventricular longitudinal strain in asymptomatic type 2 diabetes patients. *European Journal of Preventive Cardiology*, *e-pub ahead of print*.

Verboven, M., Van Ryckeghem, L., Belkhouribchia, J., Dendale, P., Eijnde, B. O., Hansen, D., & Bito, V. (2019). Effect of Exercise Intervention on Cardiac Function in Type 2 Diabetes Mellitus: A Systematic Review. *Sports Med*, *49*(2), 255-268. https://doi.org/10.1007/s40279-018-1003-4

Wilson, G. A., Wilkins, G. T., Cotter, J. D., Lamberts, R. R., Lal, S., & Baldi, J. C. (2017). Impaired ventricular filling limits cardiac reserve during submaximal exercise in people with type 2 diabetes. *Cardiovasc Diabetol*, *16*(1), 160. https://doi.org/10.1186/s12933-017-0644-1

Wilson, G. A., Wilkins, G. T., Cotter, J. D., Lamberts, R. R., Lal, S., & Baldi, J. C. (2019). HIIT Improves Left Ventricular Exercise Response in Adults with Type 2 Diabetes. *Med Sci Sports Exerc*, *51*(6), 1099-1105. https://doi.org/10.1249/MSS.0000000000001897

Figure legends and supplementary data

Figure 1: Figure 1: Flowchart of the study. T2DM: Type 2 Diabetes Mellitus, CAD; Coronary artery disease, MIT; moderate-intense training, HIIT; high-intensity interval training.

Supplementary Table 1: Design of the exercise training program

Supplementary Table 2: Details of the exercise training program

Supplementary Table 3: Resting cardiac function following the exercise intervention

Supplementary Table 4: correlations between changes in cardiac function and changes in glycaemic control