Acute effects of high intensity training on cardiac function - A pilot study comparing subjects with type 2 diabetes to healthy controls.

Henning O Ness
1Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway.
Kristine Ljones
1Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway.
Randi H Gjelsvik
1Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway.
Arnt Erik Tjønna
1Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway.
Vegard Malmo
1Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway.
Hans Olav Nilsen
2Clinic of cardiology, St. Olavs University hospital, Trondheim, Norway.
Siri Marte Hollekim-Strand
4Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, Trondheim, Norway.
Håvard Dalen
1Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway.
Morten A Høydal (morten.hoydal@ntnu.no)
1Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway.

Research Article

Keywords: Exercise, echocardiography, right ventricle, left ventricle, heart, diabetes

Posted Date: February 3rd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1225196/v1

Abstract

Purpose. The purpose of this study was to evaluate the acute stress on the heart following one session of high intensity interval training in patients with type 2 diabetes (T2D) versus healthy controls.

Methods. High intensity aerobic exercise was performed by 4x4 minutes intervals (90-95% of maximal heart rate), followed by a ramp protocol to peak oxygen uptake (VO_{2peak}). Echocardiography was performed before, and 30 minutes after exercise. Heart rhythm was monitored 24h pre-exercise, during and 24h post exercise by Holter electrocardiogram.

Results. After exercise we report a reduction in in both groups in the early diastolic peak mitral annular velocity, the ratio of mitral peak early to late diastolic inflow. Further, left atrial end-systolic volume was reduced after exercise. The LV end-diastolic wall thickness increased in CG. T2D had significant more supraventricular extrasystoles per hour before and after exercise.

Conclusion. One single session of exhaustive exercise induced acute cardiac alterations in both left- and right-sided cardiac chambers with reduction in volumes and indices of systolic and diastolic dysfunction in both T2D patients and controls. There was no indication of different stress response in T2D compared to controls.

ClinicalTrials.gov Identifier: NCT02998008

Introduction

Type 2 diabetes (T2D) has become an increasingly prevalent condition worldwide and is likely to reach pandemic levels within the coming decades [1]. The condition is characterized by high blood glucose and altered insulin regulation and is strongly linked to obesity and inactivity. A number of complications are associated with the disease, such as kidney disease, retinopathy, cardiovascular diseases and development of diabetic cardiomyopathy [2]. Low cardiorespiratory fitness (maximal oxygen uptake; VO_{2max}), one of the strongest predictors for cardiovascular death, is also commonly observed in patients with T2D [3]. Diabetes patients are also more prone to arrhythmias and complications of those, like an increased risk of stroke in diabetes patients with atrial fibrillation [4]

Clinical studies confirm that diabetes is associated with left ventricular dysfunction independent of other heart disease [1]. During physical exercise, the myocardial metabolism depends on sufficient energy substrate provided by fatty acids and glucose. In healthy individuals there is a finetuned balance with a dynamic variation of the source of energy that depends on the workload of the heart and exercise intensity [5]. This substrate flexibility is, however, significantly impaired in diabetic patients because of insulin deficiency. Thus, the metabolism is more dependent on oxidation of fatty acids with consequences of reduced cardiac efficiency [6-8]. In addition, several studies report that diabetic hearts have a further reduction in efficiency which cannot be explained only by the reduced substrate flexibility [7,9]. This reduction is to some extent explained by increased oxygen consumption by non-contractile processes such as increased mitochondrial uncoupling, production of reactive oxygen species [10,11], impaired excitation-contraction coupling and Ca^{2+} handling [12,13]. Several studies show that these changes can be prevented by exercise training [14,15].

Despite numbers of studies showing beneficial effects by exercise, there are also studies showing impairment of the myocardium after vigorous prolonged exercise. A study from the North See Race showed elevations of troponin after prolonged vigorous exercise among well trained athletes [16]. Cardiac troponin (cTn) I and T (TnT) reflect myocardial cell damage [17] and is increasingly reported following exercise interventions. Studies have reported a reduction in contractility, increase in cardiac injury biomarkers and reduced right ventricular (RV) and left ventricular (LV) ejection fraction (EF) after long periods training at high intensity [18-24]. The effects are in most cases transient, but persistent changes such as development of fibrosis have been observed in cases where the patient have been exposed to extreme amounts of training in combination with having a predisposition for cardiac dysfunction [20].

Aim of the study

There is still a lot unknown regarding cardiac response to exercise, both in individuals with T2D and other individuals with predisposition for ischemic heart disease. The present study aimed to investigate the response on cardiac function and volume, biomarkers of cardiac stress as well as arrhythmias following one session of high intensity exhaustive exercise in patients with T2D compared to healthy individuals. Our hypothesis was that acute exercise training could provoke greater cardiac stress in patients with T2D compared to healthy individuals. For both groups we expected to find elevated levels of TnT as well as indications of impaired cardiac function following exhaustive exercise, with potentially more prominent findings in the RV.

Results

Physical characteristics and baseline blood parameters

The mean age was 56 years in both groups. Except from HbA1c, blood glucose and insulin C peptide, there was no difference between T2D and healthy controls in physical characteristics or in blood parameters at baseline (Table 1). HbA1c was significantly higher in diabetics (33%). The glucose levels were 57% higher amongst the diabetics, and the insulin C peptide was also 50% higher. No other baseline parameters were different between the groups at baseline.

Response to cardiopulmonary exercise test

VO_{2peak} was significantly higher in controls than the T2D group (Figure 1A), similar to minute ventilation (VE) (Figure 1B) and the ventilatory CO_2 per minute (VCO2) (Figure 1C), corresponding to reduced fitness level in the diabetes group compared to the controls. The average VO_{2peak} in the diabetes group and controls was 33.1±5.8 ml kg^{-1} min^{-1} and 44.0±6.6 ml min^{-1} kg^{-1} (difference $p < 0.01$), respectively. The peak heart rate was similar in the two groups with 181±12 beats min^{-1} in the T2D group and 175±10 beats min^{-1} in the control group (Figure 1D).

The response to acute exercise and group differences

We did not find any difference in the response to acute exercise between the two groups. However, when comparing the response to acute exercise within each group independently we observed a significant change from pre- to post-test on several parameter.

Change in blood samples after exercise

Despite that we observed individual changes on several of the measured blood parameters, we did, however, not detect any significant differences between the groups.

Glucose

Glucose levels were expected to decrease in diabetics during workout, but remained constant (8.6 mmol/L pre exercise, 8.2 mmol/L post exercise and 8.6 mmol/L 24h after exercise). In the control group, the glucose levels were significantly lower, but unchanged during the different time points (5.4 mmol/L pre-exercise, 5.3 mmol/L post-exercise and 6.2 mmol/L 24 hours after exercise (Figure 2 A-B).

Troponin T

All participants in the control group had TnT values <10 ng/L before the exercise training. In the T2D group, two participants had higher values, 13 ng/L and 11 ng/L respectively, whereas the remaining participants in the group had values <10 ng/L.

Three subjects in the T2D group had TnT ≥10 ng/L after workout. In two T2D subjects the serum levels of TnT remained elevated after 24 hours. In the control group two subjects had TnT elevation exceeding 10 ng/L post workout, where the subject with the highest measured TnT level (20ng/L) remained above 10 ng/L 24 hours post workout (Figure 2 C-D).

Cardiac function before and after exercise

Baseline echocardiographic examination revealed that the T2D group had smaller LV end-diastolic volume and smaller RV basal diameter, and lower peak tricuspid annular early diastolic velocity, while LV EF was similar between the two groups (Figure 3). No other differences were found between the two groups at baseline.

We did not observe any significant difference in cardiac measurements between the groups as a response to exercise. However, each group displayed several significant changes in measurements of systolic and diastolic function, both in the right and left ventricle, as well as in the left atrium (Table 2) when analyzing the response within each group independently. Heart rate during echocardiography was not significantly different between groups before or after exercise (CG; 65±13 and 83±14 beats min^{-1} and T2D; 69±12 and 79±8 beats min^{-1}, respectively. Differences not significant between groups, but significant within CG (p=0.03).

Alterations in LV following exercise

We found a significant reduction in the early diastolic peak mitral annular velocities, reaching 1.4 cm/s in the control group (p <0.001), and 0.8 cm/s in the T2D group (p <0.03). In patients with elevated TnT the corresponding reduction was 1.0 cm/s (p <0.001). The peak mitral annular systolic velocity was not significant different. However, the mitral inflow peak early diastolic velocity was reduced after exercise in both groups corresponding to 14 cm/s in the control group (p <0.02) and 12 cm/s in the T2D group (p <0.06, though not statistically significant). The pulsed-wave tissue Doppler measurements of the mitral annular velocities were in line with the presented (Table A.1).

The LV end-diastolic wall thickness increased in the control group after exercise ($p < 0.05$) with no significant change in the T2D group. Interestingly, the post exercise LV end-diastolic wall thickness was larger than before exercise measurements in all controls and 4/7 T2D patients in the blinded analyses. Also, we observed a non-significant reduced end-diastolic volume post exercise compared to baseline levels in both the control (-11 ml, $p = 0.109$ and T2D group (-10 ml, $p = 0.13$). The same was found when analysing three-dimensional recordings (Table A. 2 and A.3). Correspondingly, the internal dimension also displayed a small reduction in both groups. In patients with elevated TnT, we found a reduction of 20 ml ($p < 0.001$) in end-diastolic volume (Table A.4).

We did not observe any differences in any of the groups in systolic fractional shortening after exercise. LV EF was numerical >3 %-points lower in both groups after exercise, but the differences were not statistically significant. However, in patients with elevated TnT LV EF was reduced by 6.7 %-points after exercise ($p < 0.01$). The ratio of the mitral inflow peak early to late diastolic velocity was significantly reduced by 0.4 in both groups after exercise (both $p < 0.03$). In patients with elevated TnT the ratio was reduced by 0.5 ($p < 0.02$).

Alterations in RV following exercise

RV end-diastolic diameter (both basal and mid-ventricular) decreased after exercise. The measurements of the RV outflow tract at end-diastole and the RV outflow tract proximal diameter showed similar findings (online supplements). Tricuspid annular plane systolic excursion was reduced in both groups after workout. In patients with elevated TnT the reduction was at 4.5 mm ($p < 0.05$) (Table A.4).

Tricuspid early diastolic inflow decreased by 8 cm/s after exercise in the T2D group ($p < 0.04$), with a non-significant reduction (3.7 cm/s) in the control group ($p=0.92$). No other significant blood stream measurements across the tricuspid valve were found. The peak tricuspid annular early diastolic velocity was reduced by 1.3 cm/s ($p < 0.04$) in the control group and 1.8 cm/s ($p < 0.001$) in the T2D group. The pulsed-wave tissue Doppler measurements of the tricuspid annular velocities were in line with the presented (Table A.1). In patients with elevated TnT the reduction was 1.8 cm/s ($p < 0.001$, Table A.4).

Alterations in LA following exercise

LA volume was reduced after exercise. The results were consistent independently of the underlying measurements (4-chamber, 2-chamber or biplane views). In biplane measurements we found a 12 ml reduction in the control group ($p < 0.04$) and a non-significant 10.2 ml reduction in the T2D group ($p < 0.06$). In patients with elevated TnT the average volume reduction was 15.5 ml after exercise ($p < 0.01$, Table A.4).

Alterations in RA following exercise

Echocardiography revealed no clear change in RA volume or function in the two groups, nor in patients with elevated TnT, after exercise. Additional echocardiographic data are provided in appendix (Table A.1-5).

Holter electrocardiogram

We found significantly more premature supraventricular extrasystoles (SVES) and ventricular extrasystoles (VES) in the T2D group at baseline (Figure 4). The T2D group also displayed more premature ventricular beats after exercise. There was no effect of exercise on number of premature beats.

Discussion

This study aimed to investigate the acute stress response in the heart following high intensity exercise in T2D patients and healthy controls. The present study demonstrated significant differences in cardiorespiratory fitness level between T2D and the control group, but we did not observe any consistent differences in the cardiac response to exercise training compared to healthy controls. Interestingly, we showed that maximal LA and LV volume, LV ejection fraction, mitral- and tricuspid annular early diastolic velocities tricuspid inflow early velocity, were significantly altered after exhaustive exercise in both groups. These findings indicate that one single session of exhaustive high intensity exercise training influences the heart of both subjects with T2D and healthy controls causing, at least intermittent, impaired function.

Several studies have reported increased cardiac troponins after exercise training of short and long durations [25–27]. There is a broad agreement that cardiac impairment following exercise training is greatest in the least trained [22,28]. The VO_{2peak} in T2D corresponded to previous reported values of cardiorespiratory fitness in this patient group [29]. We found a significant 25% lower fitness level compared to the age-matched control group and this manifests the reported two times higher risk of cardiovascular mortality among subjects with T2D [30]. Myers et al have shown a 12% increase of survival with 1 metabolic equivalent (MET) (~3,5 ml kg^{-1} min^{-1}) improvement in VO_{2peak} [3]. The present study found a substantial ~3 MET (11 ml kg^{-1} min^{-1}) difference. The difference in cardiorespiratory fitness was further supported by the echocardiographic findings displaying smaller left- and right ventricles in T2D patients. With this taken into consideration, one could expect a greater increase of TnT in the T2D group since their VO_{2peak} was significantly lower than in the control group, demonstrating that T2D subjects had a significant lower fitness level. In the North Sea study TnT increase was also associated with a higher load of occult obstructive coronary artery disease [31]. Given that the T2D group displayed lower aerobic capacity, reduced cardiac function as well as a higher load of cardiovascular risk factors compared to the control group, we wanted to determine if the T2D group had a more severe increase in TnT post exercise. In contrast to our assumption, we found that only a few of the included subjects presented with elevated TnT post exercise and we did not observe any differences between subjects with T2D versus healthy controls. The former mentioned studies have detected increments far above 14 ng/L, which is the cut-off for myocardial infarction [17]. It should, however, be noted that it is currently no certain method of distinguishing a physiological response induced by exercise from pathology. One explanation for the discrepancy in our results compared to others may be the differences in exercise duration and total workload over time, where previous studies have performed relatively high intensity over hours. A recent study has shown that troponin is likely closer linked to intensity than duration [32]. A plausible explanation in our finding is that both groups were exposed to the same relatively high-intensity exercise. Notwithstanding, we did observe a rise in TnT in five subjects, whereof three were in the T2D group. Interestingly, those with elevated TnT (independent of group) had indications of more severely impaired cardiac function. Meanwhile, some have suggested that increased troponin levels after exercise could be caused by a physiological response that causes leakage of the unbound free form of troponins from the cytosol during exercise due to membrane damage, and not by necrosis that includes destruction of the contractile apparatus commonly observed after myocardial infarction [33].

LV end-diastolic volume, which has been reported as the most suited echocardiographic parameter to predict exercise capacity [34], was significantly lower among T2D than healthy controls. Before exercise, we found a 15% difference which confirms the major difference in aerobic capacity between the groups. LA end-systolic volume is another parameter highly associated with a physiological adaptation to exercise [35,36]. We did not find a difference between groups in our study, but we observed that both LV and LA end-systolic volumes was reduced after exercise in both groups. This observation of reduced LV and LA end-systolic volumes could in theory be explained partly by reduced blood volume. However, we also observed that both groups had a non-significant reduction of LV EF after exercise corresponding to >3%-points. In the subjects with elevated TnT post exercise the reduction in LV EF was significantly reduced after exercise (>6%-points). Even though LV EF is depending on preload, it is a relative measure (%) that will increase as the volume is reduced. Furthermore, we also observed that mitral- and tricuspid annular early diastolic velocities, and tricuspid annular plane systolic excursion were reduced after exercise. Thus, these changes indicate some degree of LV and RV dysfunction that was present after exercise which could not be explained by hypovolemia (dehydration) alone. Thus, the finding of reduced LV and RV function seem to partly be explained by some fatigue induced by the exhaustive exercise. This is further supported by the finding of increased myocardial wall thickness measured in all controls and in 4/7 T2D patients. This may be due to swelling/edema or increased blood volume in the myocardium. Exercised-induced muscle damage in other muscles have shown an inflammation-like response acutely after exercise, and we wonder if there is a similar mechanism in the myocardium [37]. However, this remains unclear and needs further investigation.

Furthermore, based on previous studies that have reported greater impairment of the RV compared to LV, after the exercise training [18,19,38,39] we also assumed that we would observe more profound changes in the RV in both groups. However, our results did not indicate more severe changers in the RV. This finding may also be explained by the relatively short duration of the exercise training. Although conducted at high intensity, the duration is short compared to earlier reports [18,19,39]. In fact, duration of the exercise training has been linked to degree of impairment of the RV, where longer durations seem to cause greater impairment [39]. The same study discovered RV dysfunction in endurance athletes, suggesting that long term processes like fibrosis might play a central part in the development of the dysfunction.

The acute changes observed after exercise training at high intensity are normally transient. La Gerche found a transient increase in RV volume and decline in RV function after three to 11 hours of exercise duration, which mainly recovered within a week [20,39]. Unfortunately, we did not follow up our population with echocardiographic recordings 24 hours after exercise. However, our data showing a decline of TnT 24 hours after could be an indication that the modest systolic and diastolic dysfunction is restored within a relatively short time.

There were significantly more premature atrial and ventricular beats in the T2D group at baseline. This is in accordance with previous studies on the topic and might be result of changes caused by both T2D itself, and the effects of common comorbidities like hypertension on the heart and autonomic nervous system [40,41]. There was no further effect of exercise on number of premature beats.

In skeletal muscle, mechanical stimuli induce stress responses that stimulates regeneration and improved function, as an adaption to the muscular work. It is still unknown if the same mechanisms relate to cardiac

adaption to exhaustive exercise, but our study indicate that similar adaptions may also take place in the myocardium.

Conclusion

Patients with T2D and healthy controls have similar cardiac responses to acute exhaustive exercise with an acute reduction in cardiac function following exercise training. Our data do not support that T2D patients have an increased risk for elevated troponins or cardiac dysfunction following high intensity exercise training compared to healthy controls. The impaired cardiac function was, however, more pronounced among those with a rise in cardiac troponins. Although a limitation in the study is a small sample size, the comprehensive and blinded echocardiographic- and electrophysiological analyses give valuable information regarding the acute cardiac responses of high intensity training in patients with T2D diabetes versus healthy controls and provides hypotheses to be followed in future research.

Methods

Subjects

Age-matched subjects with T2D (n=7) and healthy controls (n=7) were included. In total, fifteen men volunteered for the study. One person was excluded in the T2D group due to lack of parameters confirming T2D. Written informed consent was obtained prior to data collection. The study was approved by the Regional Comittee for Medical Research Ethics Central Norway, REK Central (REC ID 2016/1596) and is in conformance with the statement of ethical principles for medical research outlined in the Declaration of Helsinki. All methods were performed in accordance with the relevant guidelines and in agreement with the approval from the ethical committee. The study is registered in ClinicalTrials.gov Identifier: NCT02998008 (First posted: 20/12/2016).

Test procedure and protocols

Participant registration and timeline

Day 1. All participants completed a questionnaire from a medical doctor evaluating the health status and medical consent for training and cardiopulmonary exercise testing. Blood pressure was measured following 10 minutes of rest in a chair. Three tests were performed and the average of the latter two was used. Thereafter, height was measured in cm, followed by an Inbody scan (Inbody, AU). Subsequently, a Holter electrocardiogram (ECG) monitored the cardiac electrical activity 24 hours prior to, during and 24 hours after exercise. Lastly, a blood sample was collected from the participants at the end of day 1.

Day 2. Echocardiography was first performed immediately before the single bout of exhaustive exercise consisting of 4x4 minutes interval exercise and one last bout performed as a ramp protocol to assess peak oxygen uptake (VO_{2peak}). After the exercise all participants rested for 30 minutes before a second echocardiography was done. At the end of day 2, 30 minutes after the second echocardiography, a second blood sample was collected.

Day 3. Participants ended Holter ECG monitoring and one last blood sample was collected 24 hours after the exercise test.

Interval training and maximal oxygen uptake

The exercise was performed as a 4x4 minutes high intensity interval training. The intervals were conducted at about 90% of VO_{2peak} and were followed by 2-minute breaks with active recovery at 60%. We then added a fifth interval performed as a ramp protocol with increments in speed and/or inclination to measure VO_{2peak}. The cardiopulmonary exercise testing (CPET) to measure VO_{2peak} was performed at the NeXt Move core facility at NTNU - Norwegian University of Science and Technology. All participants were regularly offered water during and after exercise to avoid hypovolemia. As diabetic patients sometimes exhibit physical limitations, experienced personnel determined the best in dividual CPET regimen during a 6-minute warm-up on the treadmill (Woodway PPS55, USA Inc., Waukesha, WI, USA), by detecting functional walking or running speed and inclination, as well as subjective moderate aerobic intensity based on rated perceived exertion (RPE Borg scale 6-20). Subjects were then fitted with a heart rate monitor (H7, Polar Electro, Kempele, Finland) and facemask (7450 Series V2 CPET mask, Hans Rudolph Inc., Shawnee, KS, USA). During an initial period of 4 minutes at fixed submaximal workload serving as an extended warm-up, work economy measurements were made.

Maximal oxygen uptake (VO_{2max}) was defined using the following criteria: 1) VO_2 levelling off (<2 ml min^{-1} kg^{-1}) despite increase in workload and 2) Respiratory exchange ratio ≥1.05. If these criteria were not met, the term VO_{2peak} was used. A subject's $VO_{2peak}$was defined as the mean of the three successive highest VO_2 registrations achieved during the CPET. For simplicity, the term VO_{2peak} is used for all patients.

An individualized ramp protocol was used, until either exhaustion or fulfilment of the criteria for VO_{2max} or VO_{2peak} Workload was gradually increased, and gas measurements were recorded every tenth second using a mixing chamber ergospirometry system (Metalyzer II, Cortex Biophysik Gmbh, Leipzig, Germany).

Echocardiography

Echocardiographic recordings and analyses of the different chambers followed the recommendation by the American and European societies of Echocardiography [42]. Transthoracic echocardiography (TTE) was performed by one experienced cardiologist. All participants were examined in the left-lateral decubitus position. A Vivid E95 scanner with a phased-array transducer (M5S) (GE Ultrasound, Horten, Norway) was used. Echocardiographic data were stored digitally and analyzed after end of study inclusion by the same cardiologist. All echocardiograms were acquired with the operator blinded to group assignment to avoid any bias in the analyses. All analyses were performed by the same operator blinded to group assignment and whether the echocardiogram was recorded before or after the exhaustive exercise session. All measurements reflect the average of three cardiac cycles, as recommended for patients in sinus rhythm. The measurements are reported as absolute values and not indexed to body surface area.

Grey-scale two-dimensional (2D) views were recorded from the parasternal border in short- and long-axis, and the apical position in 4-chamber, 2-chamber, and long-axis views. Separate recordings were made to optimize

the volumetric measurements of the specific chambers, and similarly care was taken to avoid foreshortening and misalignment. Linear measurements of the LV myocardium and dimensions were done in parasternal long-axis recordings at end-diastole and end-systole immediately below the level of the mitral valve leaflet tips. The fractional shortening was calculated by the change in LV dimension divided by the end-diastolic dimension. Left atrial (LA) and LV volumes were measured by the summation of discs method in 4- and 2-chamber views by tracing of the endocardial border. LV EF was calculated as the percentage ejected blood volume during systole using biplane method of disc summation (Simpson's method). Right atrial (RA) and RV volumes were estimated from RV focused 4-chamber views by the area-length method. The dimension of the RV was measured in RV focused 4-chamber views at the basal and mid-ventricular level. Tricuspid annular plane systolic excursion was measured by reconstructed motion mode aligned to the movement of the basal right ventricular free wall.

Color coded Doppler mode was recorded through all valvular orifices and vessels to identify pathology as regurgitations and stenoses.

Blood flow was recorded by spectral Doppler with sample volume; a) at tip of the mitral leaflet and in the presence of mitral regurgitation aligned to the regurgitant jet, b) in the distal LV outflow tract, c) through the aortic valve, d) at tip of the tricuspid valve and in presence of tricuspid regurgitation aligned to the regurgitant jet, e) in the RV outflow tract. For all measurements care was taken to align the ultrasound beam to the blood flow direction. The mitral inflow peak early (E) and late (A) diastolic velocities and the early diastolic deceleration time was measured, and the E/A ratio was calculated.

Color tissue Doppler cine-loops were recorded in the apical 4-chamber, 2-chamber and long-axis views, and RV focused view. Target frame-rate for the color tissue Doppler recordings was 100 fps. Care was taken to align the ultrasound beam to the myocardial wall. Peak systolic (S') and early diastolic (e') mitral annular velocities were measured at the base of the six myocardial walls by color tissue Doppler, and the average values are used as measurements of the LV myocardial velocities. Pulsed-wave tissue Doppler velocity curves were recorded from the basal part of the left and right ventricle, at the septal and lateral points (near the insertion of the mitral valve) and from the RV free wall (near the insertion of the tricuspid valve). e' was measured at the base of the septal and anterolateral wall by pulsed-wave tissue Doppler and the average was used for calculation of the E/e' ratio. The tricuspid annular peak systolic and early diastolic velocities were measured by color tissue Doppler, as well as pulsed-wave Doppler, in the basal part of the right ventricular free wall.

Biochemical analysis

Blood samples were analyzed following standard operating procedures at St. Olavs Hospital. Glucose, hemoglobin A1c (HbA1c), total cholesterol, low density lipoprotein (LDL) cholesterol, TnT and insulin C peptide were all obtained before the training. Glucose and TnT were also obtained 1 hour and 24 hours post workout.

Body composition and weight:

Body composition was measured using the validated bioelectrical impedance unit, Inbody 720 (Biospace, Seoul, Korea) [43]. In this machine, four pairs of electrodes are implanted into the handles and floor scale of the analyzer. Before testing, subjects had fasted for minimum two hours. They were encouraged to go to the toilet

right before entering the scale. The subjects stood five minutes in upright position before entering the scale. They were barefoot. Due to the electrical impulse, people with pacemaker were not tested. Height, age, and gender were plotted om the scale-display. After two minutes, weight (kg), body mass index (BMI), muscle mass (kg), bodyfat % and visceral fat (cm^2) was measured by the scale. The device was auto-calibrated once a week when the machine was turned off.

Heart rhythm

A 48-hour ambulatory, continuous ECG recording (DigiTrak XT, Phillips Healthcare, Andover, MA) was used the 24 hours before and the 24 hours after the exercise session. Supraventricular and ventricular premature beats and arrhythmias were counted by the vendor specific software, but manually controlled by a trained physician.

Statistical analysis

Student's *t*-test (independent samples) was applied to compare different parameters between groups. Paired *t*-tests were used to compare changes within each group before and after exercise. Heart rhythm was not normally distributed, and thus, group differences were analyzed by Mann-Whitney two-tailed test (exact p-values) at pre- and post-exercise. Differences in TnT and glucose in blodsamples between T2D and control at baseline, 1 hour- and 24 hours post exercise was performed using a mixed-effect model for repeated measures corrected with Šídák's multiple comparisons test. With TnT as a markers cardiac stress we performed separate post hoc analyses to determine if individuals with rise in TnT following exercise also had more severe alterations in cardiac function than individuals with no elevation in TnT. Data from individuals with increased TnT (i.e., TnT >10 ng/L) was therefore additionally analyzed as a separate population and compared to all individuals with no rise inn TnT. Analyses was performed using GraphPad Prism (version 9.2.0)

Declarations

Ethics approval: Regional Comittee for Medical Research Ethics Central Norway, REK Central (REC ID 2016/1596) and is in conformance with the statement of ethical principles for medical research outlined in the Declaration of Helsinki. All methods were performed in accordance with the relevant guidelines and in agreement with the approval from the ethical committee. The study is registered in ClinicalTrials.gov Identifier: NCT02998008 (First posted: 20/12/2016).

Availability of data and materials: The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Author Contributions: Conceptualization, M.A.H.; methodology: HON, KL, RHG, AET, VM, HONI, SMH-S, HD, MAH; formal analysis, HON, KL, RHG, AET, VM, HONI, HD, MAH; investigation: HON, KL, RHG, AET, VM, HONI, SMH-S, HD, MAH; resources: MAH; writing—original draft preparation: HON, RHG; writing—review and editing: HON, KL, RHG, AET, VM, HONI, SMH-S, HD, MAH; supervision: HD,MAH. project administration, MAH.; funding acquisition, MAH. All authors have read and agreed to the published version of the manuscript.

Acknowledgment: The performance of 4x4 min interval training and testing of VO_{2max} was provided by NeXt Move, Norwegian University of Science and Technology (NTNU). *NeXt Move* is funded by the Faculty of

Medicine at NTNU and Central Norway Regional Health Authority."

Funding: The Liaison Committee between the Central Norway Regional Health Authority (RHA) and the Norwegian University of Science and Technology (NTNU). No relation to the industry exists. The funding source had no role in design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

References

1. Fang, Z. Y., Prins, J. B. & Marwick, T. H. Diabetic cardiomyopathy: evidence, mechanisms, and therapeutic implications. *Endocrine reviews* **25**, 543-567, doi:10.1210/er.2003-0012 (2004).
2. Zhuo, X., Zhang, P. & Hoerger, T. J. Lifetime direct medical costs of treating type 2 diabetes and diabetic complications. *Am J Prev Med* **45**, 253-261, doi:10.1016/j.amepre.2013.04.017 (2013).
3. Myers, J. *et al.* Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* **346**, 793-801, doi:10.1056/NEJMoa011858 (2002).
4. Cosentino, F. *et al.* 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). *European Heart Journal* **41**, 255-323, doi:10.1093/eurheartj/ehz486 (2019).
5. Stanley, W. C. & Chandler, M. P. Energy metabolism in the normal and failing heart: potential for therapeutic interventions. *Heart failure reviews* **7**, 115-130 (2002).
6. van den Brom, C. E. *et al.* Altered myocardial substrate metabolism is associated with myocardial dysfunction in early diabetic cardiomyopathy in rats: studies using positron emission tomography. *Cardiovascular diabetology* **8**, 39, doi:10.1186/1475-2840-8-39 (2009).
7. Mather, K. J. *et al.* Assessment of myocardial metabolic flexibility and work efficiency in human type 2 diabetes using 16-[18F]fluoro-4-thiapalmitate, a novel PET fatty acid tracer. *American journal of physiology. Endocrinology and metabolism* **310**, E452-460, doi:10.1152/ajpendo.00437.2015 (2016).
8. Anderson, E. J. *et al.* Substrate-specific derangements in mitochondrial metabolism and redox balance in the atrium of the type 2 diabetic human heart. *Journal of the American College of Cardiology* **54**, 1891-1898, doi:10.1016/j.jacc.2009.07.031 (2009).
9. Buchanan, J. *et al.* Reduced cardiac efficiency and altered substrate metabolism precedes the onset of hyperglycemia and contractile dysfunction in two mouse models of insulin resistance and obesity. *Endocrinology* **146**, 5341-5349, doi:10.1210/en.2005-0938 (2005).
10. Boudina, S. *et al.* Reduced mitochondrial oxidative capacity and increased mitochondrial uncoupling impair myocardial energetics in obesity. *Circulation* **112**, 2686-2695, doi:10.1161/circulationaha.105.554360 (2005).
11. Boudina, S. *et al.* Mitochondrial energetics in the heart in obesity-related diabetes: direct evidence for increased uncoupled respiration and activation of uncoupling proteins. *Diabetes* **56**, 2457-2466, doi:10.2337/db07-0481 (2007).
12. Stølen, T. O. *et al.* Interval training normalizes cardiomyocyte function, diastolic Ca2+ control, and SR Ca2+ release synchronicity in a mouse model of diabetic cardiomyopathy. *Circ Res* **105**, 527-536,

doi:10.1161/circresaha.109.199810 (2009).

13. Pereira, L. *et al.* Calcium signaling in diabetic cardiomyocytes. *Cell calcium* **56**, 372-380, doi:10.1016/j.ceca.2014.08.004 (2014).
14. Hafstad, A. D., Boardman, N. & Aasum, E. How exercise may amend metabolic disturbances in diabetic cardiomyopathy. *Antioxid Redox Signal* **22**, 1587-1605, doi:10.1089/ars.2015.6304 (2015).
15. Baekkerud, F. H. *et al.* High Intensity Interval Training Ameliorates Mitochondrial Dysfunction in the Left Ventricle of Mice with Type 2 Diabetes. *Cardiovascular toxicology*, doi:10.1007/s12012-019-09514-z (2019).
16. Kleiven, O. *et al.* Occult obstructive coronary artery disease is associated with prolonged cardiac troponin elevation following strenuous exercise. *Eur J Prev Cardiol*, 2047487319852808, doi:10.1177/2047487319852808 (2019).
17. Thygesen, K. *et al.* Third universal definition of myocardial infarction. *J Am Coll Cardiol* **60**, 1581-1598, doi:10.1016/j.jacc.2012.08.001 (2012).
18. Claessen, G. *et al.* Right ventricular fatigue developing during endurance exercise: an exercise cardiac magnetic resonance study. *Medicine and science in sports and exercise* **46**, 1717-1726, doi:10.1249/mss.0000000000000282 (2014).
19. Elliott, A. D. & La Gerche, A. The right ventricle following prolonged endurance exercise: are we overlooking the more important side of the heart? A meta-analysis. *Br J Sports Med* **49**, 724-729, doi:10.1136/bjsports-2014-093895 (2015).
20. La Gerche, A., Connelly, K. A., Mooney, D. J., MacIsaac, A. I. & Prior, D. L. Biochemical and functional abnormalities of left and right ventricular function after ultra-endurance exercise. *Heart* **94**, 860-866, doi:10.1136/hrt.2006.101063 (2008).
21. Mousavi, N. *et al.* Relation of biomarkers and cardiac magnetic resonance imaging after marathon running. *The American journal of cardiology* **103**, 1467-1472, doi:10.1016/j.amjcard.2009.01.294 (2009).
22. Neilan, T. G. *et al.* Myocardial injury and ventricular dysfunction related to training levels among nonelite participants in the Boston marathon. *Circulation* **114**, 2325-2333, doi:10.1161/circulationaha.106.647461 (2006).
23. Oxborough, D. *et al.* Dilatation and dysfunction of the right ventricle immediately after ultraendurance exercise: exploratory insights from conventional two-dimensional and speckle tracking echocardiography. *Circulation. Cardiovascular imaging* **4**, 253-263, doi:10.1161/circimaging.110.961938 (2011).
24. Trivax, J. E. *et al.* Acute cardiac effects of marathon running. *Journal of applied physiology (Bethesda, Md. : 1985)* **108**, 1148-1153, doi:10.1152/japplphysiol.01151.2009 (2010).
25. Airaksinen, K. E. J. Cardiac Troponin Release After Endurance Exercise: Still Much to Learn. *J Am Heart Assoc* **9**, e015912, doi:10.1161/jaha.120.015912 (2020).
26. Bjørkavoll-Bergseth, M. *et al.* Duration of Elevated Heart Rate Is an Important Predictor of Exercise-Induced Troponin Elevation. *J Am Heart Assoc* **9**, e014408, doi:10.1161/jaha.119.014408 (2020).
27. Aakre, K. M. & Omland, T. Physical activity, exercise and cardiac troponins: Clinical implications. *Prog Cardiovasc Dis* **62**, 108-115, doi:10.1016/j.pcad.2019.02.005 (2019).

28. Shave, R. *et al.* Exercise-induced cardiac troponin T release: a meta-analysis. *Med Sci Sports Exerc* **39**, 2099-2106, doi:10.1249/mss.0b013e318153ff78 (2007).
29. Hollekim-Strand, S. M. *et al.* 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**, 1758-1760, doi:10.1016/j.jacc.2014.07.971 (2014).
30. Go, A. S. *et al.* Heart disease and stroke statistics–2014 update: a report from the American Heart Association. *Circulation* **129**, e28-e292, doi:10.1161/01.cir.0000441139.02102.80 (2014).
31. Skadberg, O. *et al.* The cardiac troponin response following physical exercise in relation to biomarker criteria for acute myocardial infarction; the North Sea Race Endurance Exercise Study (NEEDED) 2013. *Clin Chim Acta* **479**, 155-159, doi:10.1016/j.cca.2018.01.033 (2018).
32. Marshall, L. *et al.* Effect of Exercise Intensity and Duration on Cardiac Troponin Release. *Circulation* **141**, 83-85, doi:10.1161/circulationaha.119.041874 (2020).
33. Gresslien, T. & Agewall, S. Troponin and exercise. *Int J Cardiol* **221**, 609-621, doi:10.1016/j.ijcard.2016.06.243 (2016).
34. Nambiar, L., Li, A., Howard, A., LeWinter, M. & Meyer, M. Left ventricular end-diastolic volume predicts exercise capacity in patients with a normal ejection fraction. *Clin Cardiol* **41**, 628-633, doi:10.1002/clc.22928 (2018).
35. Schnell, F. *et al.* Atrial volume and function during exercise in health and disease. *J Cardiovasc Magn Reson* **19**, 104, doi:10.1186/s12968-017-0416-9 (2017).
36. D'Andrea, A. *et al.* Left atrial volume index in highly trained athletes. *Am Heart J* **159**, 1155-1161, doi:10.1016/j.ahj.2010.03.036 (2010).
37. Peake, J. M., Neubauer, O., Della Gatta, P. A. & Nosaka, K. Muscle damage and inflammation during recovery from exercise. *J Appl Physiol (1985)* **122**, 559-570, doi:10.1152/japplphysiol.00971.2016 (2017).
38. La Gerche, A. *et al.* Disproportionate exercise load and remodeling of the athlete's right ventricle. *Medicine and science in sports and exercise* **43**, 974-981, doi:10.1249/MSS.0b013e31820607a3 (2011).
39. La Gerche, A. *et al.* Exercise-induced right ventricular dysfunction and structural remodelling in endurance athletes. *Eur Heart J* **33**, 998-1006, doi:10.1093/eurheartj/ehr397 (2012).
40. Huang, S. H. *et al.* The presence of ectopic atrial rhythm predicts adverse cardiovascular outcomes in a large hospital-based population. *Heart Rhythm* **17**, 967-974, doi:10.1016/j.hrthm.2020.01.024 (2020).
41. Sajeev, J. K. *et al.* Association between excessive premature atrial complexes and cryptogenic stroke: results of a case–control study. *BMJ Open* **9**, e029164, doi:10.1136/bmjopen-2019-029164 (2019).
42. Lang, R. M. *et al.* Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* **28**, 1-39.e14, doi:10.1016/j.echo.2014.10.003 (2015).
43. McLester, C. N., Nickerson, B. S., Kliszczewicz, B. M. & McLester, J. R. Reliability and Agreement of Various InBody Body Composition Analyzers as Compared to Dual-Energy X-Ray Absorptiometry in Healthy Men and Women. *J Clin Densitom* **23**, 443-450, doi:10.1016/j.jocd.2018.10.008 (2020).

Tables

Table 1. Physical characteristics and baseline blood samples presented as mean ± standard deviation.

Variable	T2D group (n=7)	Control group (n=7)	p-value
Age (years)	55.9±10.9	56.1±10.9	0.96
Height (cm)	177.7±8.2	183.1±6.0	0.18
Body weight (kg)	87.9±19.3	90.7±9.5	0.74
Skeletal muscle mass (kg)	37.7±7.3	38.8±4.6	0.72
Body fat (%)	25.2±5.3	22.9±8.2	0.55
Body fat (kg)	22.1±7.9	21.9±8.7	0.96
Visceral fat area	103.3±29.6	101.3±38.3	0.92
In body health score	77.1±5.6	76.4±10.7	0.88
BMI	28.0±5.0	27.0±2.8	0.67
HbA1c (%)	6.9±1.1	5.2±0.2	0.001
Glucose (mmol/L)	8.6±2.9	5.4±0.3	0.01
Insulin C peptide (pmol/L)	0.9±0.2	0.6±0.2	0.05
LDL cholesterol (mmol/L)	2.9±0.9	3.7±0.5	0.07
Total cholesterol (mmol/L)	4.7±1.0	5.5±0.7	0.13

Table 2. Echocardiography alterations by exercise training

T2D group (n=7)	Control group (n=7)				T2D group (n=7)			
Variable	Pre	Post	Change	P	Pre	Post	Change	P
Left ventricle (LV)								
Intraventricular septum thickness, end-diastolic (mm)	8.8±1.0	10.2±0.9	1.5	0.05	10.3±2.1	10.0±1.5	-0.3	0.64
LV internal dimension, end-diastolic (mm)	49.1±4.1	48.4±4.1	-0.7	0.48	45.7±4.7	43.7±4.4	-1.9	0.27
LV posterior wall thickness, end-diastolic (mm)	9.2±1.3	10.1±0.9	0.9	0.01	9.7±1.7	9.5±2.0	-0.2	0.81
LV fractional shortening (%)	27.1±4.0	29.6±5.5	2.6	0.41	26.1±4.4	27.1±5.1	1.0	0.71
LV ejection fraction, (%)	59.6±5.3	56.2±3.9	-3.4	0.22	61.7±5.7	58.2±6.7	-3.4	0.18
LV end-diastolic volume, (ml)	125±14	114±19	-11.4	0.10	106±17	96±16	-10.1	0.13
Peak systolic mitral annular velocity, mean six walls (cm/s)	7.4±1.0	7.1±1.2	-0.3	0.29	7.2±1.8	7.5±1.5	0.2	0.55
Peak early diastolic mitral annular velocity, mean six walls (cm/s)	7.7±2.0	6.3±1.9	-1.4	.004	6.8±1.4	6.0±1.7	-0.8	0.03
Mitral inflow peak early diastolic (E) velocity (cm/s)	66.2±13.6	52.6±12.7	-13.6	0.02	69.0±11.8	56.8±6.8	-12.2	0.06
Mitral inflow early diastolic deceleration time (ms)	217±38	338±129	120	0.09	232±55	281±108	50	0.20
E/A ratio	1.4±0.3	1.0±0.2	-0.4	0.03	1.2±0.5	0.8±0.2	-0.4	0.03
E/e' ratio	7.5±2.6	7.0±3.0	-0.5	0.46	8.4±2.3	8.7±3.4	0.3	0.75
Right ventricle (RV)								
RV basal end-	45.9±4.2	43.5±3.4	-2.4	0.10	36.4±5.9	34.9±6.5	-1.5	0.46

diastolic diameter (mm)								
RV mid-ventricular end-diastolic (mm)	30.1±3.4	28.2±3.0	-1.9	0.25	30.9±1.3	26.5±4.0	-4.4	0.04
Tricuspid annular plane systolic excursion (mm)	28.0±4.2	24.7±3.0	-3.3	0.14	23.4±4.3	21.3±1.8	-2.2	0.07
Tricuspid annular peak early diastolic velocity (cm/s)	9.9±2.3	8.6±1.3	-1.3	0.04	8.3±1.9	6.5±1.9	-1.8	0.001
Left atrium (LA)								
LA end-systolic volume (ml)	67±13	55±16	-12.0	0.04	60±20	50±18	-10.2	0.06
Right atrium (RA)								
RA end-systolic volume (ml)	58±19	62±18	3.4	0.66	42±17	37±15	-4.5	0.12

Data are mean±SD. All presented tissue Doppler velocities are recorded by color tissue Doppler, except for E/e' ratio which includes the average of septal and lateral e' measured in pulsed-wave tissue Doppler recordings.

Figures

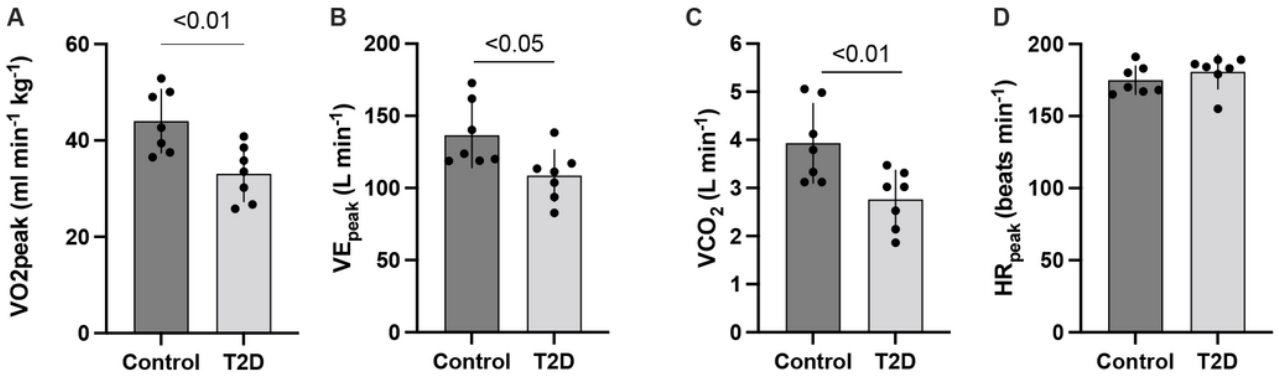

Figure 1

Baseline data from cardiopulmonary exercise tests between controls and individuals with type 2 diabetes (T2D). A, peak oxygen uptake (VO_{2peak}) displayed in ml min^{-1} kg^{-1}; B, Minute ventilation peak (VE_{peak}) displayed in L min^{-1}; C, ventilatory CO_2 per minute (VCO_2) displayed in L min^{-1}; D, peak heart rate (HR_{peak}) displayed in beats min^{-1}. Data presented as mean and SD. P values indicated in figure. Control: n=7, T2D: n=7.

Figure 2

Blood sample data from pre-, 1 hour- and 24 hours post-exercise. A, glucose in the control group; B, glucose in the T2D group; C, Troponin T (TnT) in the control group; D, TnT in the T2D group. Presented with individual data at each time-point. Detection limit (DL) for TnT was 10 ng/L. P values between T2D and control indicated. Control: n=7, T2D: n=7.

Figure 3

Selection of baseline echocardiographic. A, left ventricle (LV) end-diastolic volume (ml); B, LV ejection fraction (LV EF) (%); C, Tricuspid annular peak early diastolic velocity (cm/s, measured by pulsed-wave tissue Doppler); D, right ventricular (RV) basal diameter (mm). Data presented as mean and SD. P values indicated in figure. Control: n=7, T2D: n=7.

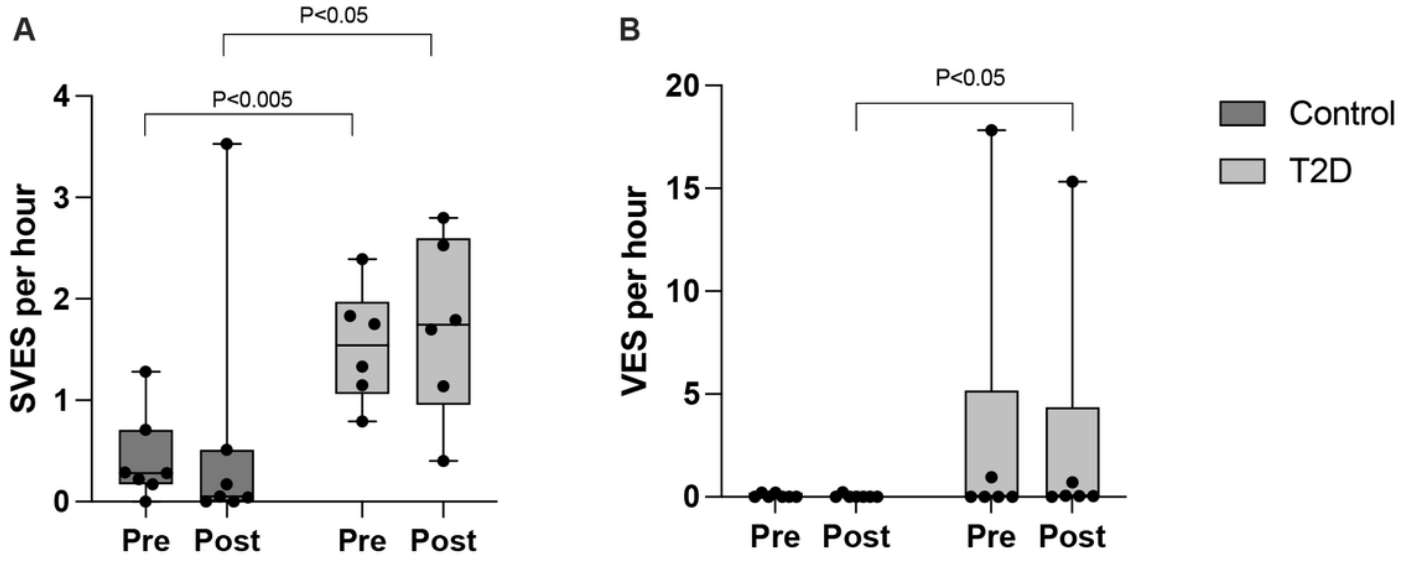

Figure 4

Holter electrocardiography. A; Supraventricular extrasystoles (SVES) per hour (Control: n=7, T2D: n=7) and B; ventricular extrasystoles (VES) per hour Control: n=7, T2D: n=6). Data presented with box and whiskers with minimum to maximum values. Pre represents the complete period 24 hours before exercise and Post

represents the complete period 24 hours after termination of exercise. No statistical differences within groups from pre- to post exercise was observed. P values indicated.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- corrected190122Supplementarydata.docx