Title:

One-year unsupervised individualized exercise training intervention enhances cardiorespiratory fitness but not muscle deoxygenation or glycemic control in adults with type 1 diabetes

Authors:

Antti-Pekka E. Rissanen, Heikki O. Tikkanen, Anne S. Koponen, Jyrki M. Aho, Juha E. Peltonen

Corresponding Author:

Antti-Pekka E. Rissanen
Department of Sports and Exercise Medicine
Clinicum, University of Helsinki
Alppikatu 2, 00530 Helsinki, Finland
Telephone: +358 9 434 2100
Fax: +358 9 490 809
E-mail: antti-pekka.rissanen@helsinki.fi

Institutional Affiliations:

A.-P.E. Rissanen. Department of Sports and Exercise Medicine, Clinicum, University of Helsinki, Alppikatu 2, 00530 Helsinki, Finland. E-mail: antti-pekka.rissanen@helsinki.fi

H.O. Tikkanen. Department of Sports and Exercise Medicine, Clinicum, University of Helsinki, Alppikatu 2, 00530 Helsinki, Finland; Clinic for Sports and Exercise Medicine, Foundation for Sports and Exercise Medicine, Helsinki, Finland; Institute of Biomedicine, School of Medicine, University of Eastern Finland, Kuopio, Finland. E-mail: heikki.tikkanen@uef.fi

A.S. Koponen. Department of Sports and Exercise Medicine, Clinicum, University of Helsinki, Alppikatu 2, 00530 Helsinki, Finland; Clinic for Sports and Exercise Medicine, Foundation for Sports and Exercise Medicine, Helsinki, Finland. E-mail: anne.s.koponen@helsinki.fi

J.M. Aho. Clinic for Sports and Exercise Medicine, Foundation for Sports and Exercise Medicine, Alppikatu 2, 00530 Helsinki, Finland. E-mail: jyrki.aho@hula.fi

J.E. Peltonen. Department of Sports and Exercise Medicine, Clinicum, University of Helsinki, Alppikatu 2, 00530 Helsinki, Finland; Clinic for Sports and Exercise Medicine, Foundation for Sports and Exercise Medicine, Helsinki, Finland. E-mail: juha.peltonen@helsinki.fi

Abstract

Adaptations to long-term exercise training in type 1 diabetes are sparsely studied. We examined the effects of a 1-year individualized training intervention on cardiorespiratory fitness, exercise-induced active muscle deoxygenation, and glycemic control in adults with and without type 1 diabetes. Eight men with type 1 diabetes (T1D) and eight healthy men (CON) matched for age, anthropometry, and peak pulmonary O_2 uptake ($\dot{V}O_{2peak}$), completed a 1-year individualized training intervention in an unsupervised real-world setting. Before and after the intervention, the subjects performed a maximal incremental cycling test, during which alveolar gas exchange (volume turbine and mass spectrometry) and relative concentration changes in active leg muscle deoxygenated ($\Delta[HHb]$) and total ($\Delta[tHb]$) hemoglobin (near-infrared spectroscopy) were monitored. Peak O_2 pulse, reflecting peak stroke volume, was calculated ($\dot{V}O_{2peak}$/peak heart rate). Glycemic control (glycosylated hemoglobin A_{1c} [HbA_{1c}]) was evaluated. Both T1D and CON averagely performed one resistance- and 3-4 endurance training sessions per week (~1 h/session at ~moderate intensity). Training increased $\dot{V}O_{2peak}$ in T1D ($p=0.004$) and CON ($p=0.045$) (Group×Time $p=0.677$). Peak O_2 pulse also rose in T1D ($p=0.032$) and CON ($p=0.018$) (Group×Time $p=0.880$). Training increased leg $\Delta[HHb]$ at peak exercise in CON ($p=0.039$) but not in T1D (Group×Time $p=0.052$), while no changes in leg $\Delta[tHb]$ at any work rate were observed in either group ($p>0.05$). HbA_{1c} retained unchanged in T1D (from 58±10 to 59±11 mmol/mol, $p=0.609$). In conclusion, one-year adherence to exercise training enhanced cardiorespiratory fitness similarly in T1D and CON but had no effect on active muscle deoxygenation or glycemic control in T1D.

Keywords: cardiorespiratory fitness, deoxygenation, diabetes, glycemic control, near-infrared spectroscopy

Introduction

Diabetes is associated with increased cardiovascular risk independent of atherosclerosis, dyslipidemia, and hypertension (Fang et al. 2004). Along with its several other health benefits, physical activity improves cardiovascular risk factors in type 1 diabetes (Chimen et al. 2012). Although a benefit of physical activity on microvascular complications has also been questioned (Makura et al. 2013), a favorable effect of physical activity on cardiovascular disease in type 1 diabetes has mainly been suggested (Wadén et al. 2008, Tielemans et al. 2013). Overall, regular physical activity and exercise training are recommended to type 1 diabetes patients (Chimen et al. 2012, Colberg et al. 2016).

The risk of cardiovascular complications is strongly predicted by peak pulmonary O_2 uptake ($\dot{V}O_{2peak}$), which reflects cardiorespiratory fitness (Kodama et al. 2009). In an integrated manner, $\dot{V}O_2$ response to acute exercise is determined by alveolar gas exchange, hemoglobin concentration [Hb], cardiac function, muscle blood flow, and muscle O_2 extraction and utilization (Wagner 1996). While exercise training has been shown to increase $\dot{V}O_{2peak}$ in type 1 diabetes by short-term studies (Wallberg-Henriksson et al. 1982, Wallberg-Henriksson et al. 1984, Laaksonen et al. 2000, Rigla et al. 2000, Fuchsjäger-Mayrl et al. 2002, Yardley et al. 2014), more specific integrated respiratory and cardiovascular adaptations to longer-term (>4 months) training have not been studied.

Cardiac dysfunction is characteristic of diabetes (Fang et al. 2004) and impairs systemic O_2 delivery during exercise (Gusso et al. 2012, Rissanen et al. 2015). Peak O_2 pulse is an estimate of peak left ventricular stroke volume (Whipp et al. 1996) and has been reported to rise after aerobic training in type 1 diabetes adults (Rigla et al. 2000). Other human studies of cardiac adjustments to exercise training in type 1 diabetes are sparse. Vascular dysfunction is also evident in type 1 diabetes (Kindig et al. 1998, Järvisalo et al. 2004, Kivelä et al. 2006,

Mason et al. 2006), probably having an independent limiting influence on muscle blood flow and therewith O_2 delivery also during exercise (Rissanen et al. 2015). Aerobic training enhances endothelial function (Fuchsjäger-Mayrl et al. 2002) and leads to muscle capillary neoformation (Wallberg-Henriksson et al. 1982) in type 1 diabetes patients, and has also been shown to increase the expression of pro-angiogenic genes in type 1 diabetes mice (Kivelä et al. 2006). However, animal (Kivelä et al. 2006), cross-sectional (Mason et al. 2006), and short-term training intervention (Wallberg-Henriksson et al. 1984) studies have suggested that these vascular effects would be deficient relative to individuals without diabetes. Instead, subjects with and without type 1 diabetes have displayed a similar training-induced rise in enzymatic capacity to utilize O_2 (Wallberg-Henriksson et al. 1984).

The main purpose of the present study was to explore whether a long-term 1-year exercise training intervention induces different integrated adaptations of cardiorespiratory fitness, peak O_2 pulse (indirectly reflecting cardiac pump function), and exercise-induced active muscle deoxygenation in adults with and without type 1 diabetes. This study also investigated the effect of the 1-year training intervention on glycosylated hemoglobin A_{1c} (HbA_{1c}) because, on the one hand, it is uncertain whether regular physical activity can provide a glycemic benefit (i.e., reduce HbA_{1c}) in type 1 diabetes (Chimen et al. 2012, Kennedy et al. 2013, Yardley et al. 2014), and on the other hand, no long-term training intervention studies have examined the issue although such studies would be needed (Kennedy et al. 2013). In addition, a suggested inverse association between $\dot{V}O_{2peak}$ and HbA_{1c} (Baldi and Hofman 2010) also justifies examining the effects of exercise training on both of the two key variables.

Based on cardiac impairments (Fang et al. 2004, Gusso et al. 2012, Rissanen et al. 2015) and suggested deficient exercise effects on vasculature (Wallberg-Henriksson et al. 1984, Kivelä et al. 2006, Mason et al. 2006) in type 1 diabetes, we hypothesized that training would overall elicit lesser improvements in $\dot{V}O_{2peak}$, peak O_2 pulse, and active muscle deoxygenation in

adults with type 1 diabetes than in well-matched adults with no diabetes. Furthermore, based on short-term training intervention studies (Chimen et al. 2012), we expected to observe no training-induced reduction of HbA_{1c} in adults with type 1 diabetes.

Materials and methods

The present study was a part of an ARTEMIS-Helsinki project, which belonged to a Canadian-Finnish collaboration entitled "ARTEMIS – Innovation to Reduce Cardiovascular Complications of Diabetes at the Intersection of Discovery, Prevention and Knowledge Exchange". The context, aims, and selected preliminary results of ARTEMIS-Helsinki and ARTEMIS have been described elsewhere (Noble et al. 2013).

Subjects and study design

Forty-two male volunteers were assessed for inclusion in this study: 15 type 1 diabetes patients recruited from the patient pool of the FinnDiane Study (Wadén et al. 2005) and 27 healthy subjects recruited mainly from the employees and the students of University of Helsinki, Helsinki, Finland. The exclusion criteria were an age of <18 or >45 years; a previous diagnosis or previous clinical evidence of any diabetes-related microvascular complication (i.e., nephropathy, neuropathy, retinopathy), hypertension, or any chronic disease other than diabetes of the diabetes patients; β-blocker medication; medication influencing glucose homeostasis apart from multiple daily insulin injections of the diabetes patients; physical disability; substance abuse; smoking; and elite athlete status. Every subject gave written informed consent prior to participating in this study, which conformed to the

Declaration of Helsinki and was approved by the Ethics Committee of Hospital District of Helsinki and Uusimaa, Helsinki, Finland.

The study flow chart presented in Fig. 1 details the design and flow of this study: After the enrollment, exclusions, nonrandomized allocation (i.e., training intervention or no intervention), and discontinuations, eight subjects with type 1 diabetes and 13 healthy subjects completed a 1-year individualized exercise training intervention. To completely match these two training groups for baseline age, anthropometry, and also $\dot{V}O_{2peak}$, five healthy subjects with the highest baseline $\dot{V}O_{2peak}$ values were excluded from further analyses. Consequently, eight type 1 diabetes patients (T1D; diabetes onset at the age of 22.9 ± 11.1 years) and eight healthy controls (CON) were included in between-group analyses (T1D vs. CON) evaluating the effects of the training intervention. *Post hoc* statistical power calculations proved the adequacy of these sample sizes (see Results).

In addition, five healthy subjects served as Reference group: At baseline and after a 1-year period, they went through same clinical measurements as T1D and CON but were only instructed to maintain their lifestyle (particularly diet and physical activity) during the period. Age and $\dot{V}O_{2peak}$ of Reference group were very different from those of T1D and CON (see Results), and the sample size of Reference group (n = 5) remained small. Hence, to avoid confounding the between-group analyses (T1D vs. CON) but to demonstrate the repeatability of clinical measurements, Reference group was analysed separately from T1D and CON.

Training intervention

T1D and CON completed a 1-year individualized exercise training intervention in an unsupervised real-world setting. Before the intervention, all subjects performed a maximal incremental cycling exercise test among other baseline clinical measurements (see below). The subjects allocated to training groups were also given a 30-min lecture containing

research-based justification for general effects and principles of endurance and resistance training, and general instructions on adjusting insulin and carbohydrate consumption according to physical activity. The lectures were given by exercise physiologists to 1-3 subjects at a time and also included face-to-face discussions aiming at individual goal setting: The overall goal of the intervention was to increase and improve exercise training in real-world circumstances according to individual's desires and goals, which were set based on the individual results of the baseline measurements.

During the intervention, the subjects used heart rate monitors (five T1D, six CON: Suunto t6c, Suunto Oy, Vantaa, Finland; three T1D, two CON: Polar RS800CX, Polar Electro Oy, Kempele, Finland) to collect data (duration, energy expenditure, mean heart rate [HR]) on every exercise session in their individual training diaries. The subjects monthly emailed the diaries, which included the collected data and information on exercise modes, to the researchers, who then emailed individual prescriptive feedback to the subjects. The monthly feedback focused on frequency, duration, modes, intensity, and progression of performed training. An exercise mode was regarded as 1) endurance training if it included various dynamic aerobic and/or anaerobic activities involving large muscle groups (e.g., walking, jogging, running, cycling, ball games), and 2) resistance training if it aimed at improving or maintaining muscular strength, power, and/or endurance (Howley 2001). Exercise intensity was interpreted as % of HR reserve (Howley 2001): % of HRR = (mean HR - resting HR) / (peak HR - resting HR) × 100%, where resting HR was the lowest nocturnal HR obtained by Firstbeat Bodyguard (Firstbeat Technologies Oy, Jyväskylä, Finland) at the night following the maximal incremental cycling exercise test at baseline, and peak HR was the peak HR during the baseline exercise test.

Clinical measurements

T1D visited the laboratory twice both before (baseline) and after (post) their 1-year training intervention. CON and Reference group visited the laboratory once at baseline and twice after their 1-year periods of training (CON) or no (Reference group) interventions. The visits were preceded by abstinence from physical exercise and alcohol for at least 24 h. At the first visit (paid only by T1D at baseline and by all groups after the 1-year periods), the subjects reported to the laboratory after overnight fast and their venous blood was drawn for measurement of HbA_{1c}. At the second visit, which consisted of pre-exercise measurements and a cardiorespiratory exercise test, the subjects reported to the laboratory 2-3 h after an unstandardized meal.

The pre-exercise measurements were preceded by completing a questionnaire on personal health and medical history (T1D also reported their daily insulin doses within a 3-day period around the second visit). A single question included in the questionnaire was used to enquire subjects' level of leisure-time physical activity (LTPA) at baseline: "*If you think about your past three months and physical activity sessions lasting more than 20 minutes in all settings (e.g., commutation, walking a dog, recreation, sport), how many times a week and how long at a time have you engaged in physical activity?*". This question meets the general recommendations (i.e., frequency, duration, all settings) for enquiring LTPA (van Poppel et al. 2010). The pre-exercise measurements then comprised measuring height, determining body composition by the bioimpedance method (InBody 720, Biospace Co., Ltd., Seoul, South Korea), measuring thickness of subcutaneous fat with skinfold calipers at the near-infrared spectroscopy (NIRS) recording site described (see below), obtaining resting 12-lead electrocardiography (ECG), measuring resting blood pressure, and performing flow-volume spirometry (Medikro Spiro 2000, Medikro Oy, Kuopio, Finland). Additionally, a physician examined the subjects to ensure suitability for exercise testing. Capillary blood was drawn from a fingertip to analyze glucose concentrations (Glucocard x-meter, Arkray Factor, Inc.,

Shiga, Japan) before the exercise test; T1D had pre-exercise glucose of 9.2 ± 2.6 mmol/L (highest 14.2 mmol/L) at baseline and 8.0 ± 2.1 mmol/L (highest 11.8 mmol/L) after the intervention with no ketosis, according to the guidelines at the time when the experiments were performed (i.e., between the years 2009-2013) (American Diabetes Association 2004). [Hb] was also analyzed (ABL725, Radiometer, Copenhagen, Denmark) from capillary blood.

The cardiorespiratory exercise test was performed on a cycling ergometer (Monark Ergomedic 839E, Monark Exercise AB, Vansbro, Sweden): The test was initiated by 5-min rest, while the subjects sat relaxed on the ergometer, and 5-min baseline unloaded cycling, after which step incremental exercise (40W / 3 min) was begun with a work rate of 40W. The subjects continued exercising until volitional exhaustion.

Breath-by-breath ventilation was measured by a low-resistance turbine (Triple V, Jaeger Mijnhardt, Bunnik, The Netherlands) to determine inspiratory and expiratory flow and volumes during the exercise test. Inspired and expired gases were continuously sampled at mouth and analyzed for concentrations of O_2, CO_2, N_2, and Ar by mass spectrometry (AMIS 2000, Innovision A/S, Odense, Denmark) after calibration with precision-analyzed gas mixtures. Breath-by-breath respiratory data were collected as raw data, which were transferred to a computer to determine gas delays for each breath. This way, the concentrations were aligned with volume data, and the profile of each breath was built. Breath-by-breath alveolar gas exchange was then calculated with the AMIS algorithms, and the data were interpolated to obtain second-by-second values. Pulmonary O_2 uptake ($\dot{V}O_2$) was analyzed as absolute (L/min) and anthropometry-adjusted (mL/min/kg body weight; mL/min/kg fat-free mass [FFM] [Batterham et al. 1999]) values. Respiratory exchange ratio (RER) was calculated as a ratio of CO_2 output and $\dot{V}O_2$; RER of ≥ 1.10 was reached in every test, suggesting the maximality of the tests performed (Edvardsen et al. 2014).

Fingertip pulse oximetry (Nonin 9600, Nonin Medical, Inc., Plymouth, MA) was used to monitor arterial O_2 saturation (SpO_2) during the exercise test, while HR and the electrical activity of the heart were monitored by ECG (PowerLab, ADInstruments, Oxford, United Kingdom). Systolic and diastolic arterial pressures were measured automatically (Tango+, SunTech Medical, Morrisville, NC) from the brachial artery at seated rest and at the end of each work rate. Mean arterial pressure (MAP) was calculated: MAP = (systolic blood pressure + 2 × diastolic blood pressure) / 3. Peak O_2 pulse was derived by dividing $\dot{V}O_{2peak}$ by peak HR (Whipp et al. 1996).

Active leg muscle deoxygenation, reflecting local imbalance between O_2 delivery and utilization, was examined during the exercise test using a continuous wave NIRS system (Oxymon Mk III Near-Infrared Spectrophotometer, Artinis Medical Systems, Zetten, The Netherlands). The NIRS optodes (i.e., one transmitting, one receiving) operated at wavelengths of 765 and 860 nm corresponding to the specific extinction coefficients of deoxygenated (HHb) and oxygenated hemoglobin (O_2Hb), respectively. The NIRS probe, housed in an optically dense plastic holder, was attached to the skin by double-sided adhesive tape and covered by elastic tape after placing it over the right vastus lateralis (VL) muscle at mid-thigh level and parallel to the long axis of the muscle. This anatomical location was measured to be the same during baseline- and post-measurements. The inter-optode distance was set between 35-45 mm to reach good signal quality before the measurements. The principles of NIRS and its applications in exercise physiology have been described elsewhere (Ferrari et al. 2004); briefly, the intensity of incident and transmitted light was recorded continuously and, along with the specific optical pathlength and extinction coefficients, used for on-line estimation and display of relative concentration changes of HHb (Δ[HHb]), O_2Hb (Δ[O_2Hb]), and total hemoglobin (Δ[tHb] = Δ[HHb] + Δ[O_2Hb]) from their resting concentration levels (i.e., the NIRS device was zeroed at rest). A differential pathlength factor

value of 5.51 (Duncan et al. 1995) and a sampling frequency of 10 Hz were used for collecting NIRS data. The NIRS data were averaged to give values in 1-s intervals and time-aligned with the cardiorespiratory data. The averaged Δ[HHb] responses were also normalized (%Δ[HHb]) so that 0% represents the lowest mean of the last 30 s of any work rate and 100% represents the highest mean of the last 30 s of any work rate.

Statistical analysis

Data are expressed as mean ± standard deviation (SD). The mean values of the last 30 s at seated rest, during unloaded cycling, at each work rate, and at peak exercise were included in further analyses. $\dot{V}O_{2peak}$ was determined as the highest value of a 60-s moving averaging interval. Shapiro-Wilk test was used to check normality and data were log transformed when appropriate. One-way ANOVA was used to compare descriptive characteristics and acute exercise responses at baseline as well as characteristics of exercise training between T1D and CON. One-way repeated-measures ANOVA was used to assess whether within-group changes from baseline to post occurred in T1D, CON, or Reference Group. Two-way repeated-measures ANOVA was used to evaluate whether there were between-group differences in changes from baseline to post between T1D and CON: Group×Time interactions were evaluated with Group (T1D vs. CON) as a between-subjects factor and with Time (Baseline, Post) as a within-subject factor. If a significant interaction was observed, the *t*-test with Bonferroni correction was used. In case of nonnormally distributed data despite log transformation, nonparametric tests were used for between-group (Mann-Whitney U) and within-group (Wilcoxon signed-rank) analyses. Associations between key variables were examined by Pearson's correlation coefficient. Standardized effect sizes (ES = mean intervention-induced difference / between-subjects SD) were calculated with threshold values of ≤0.2 trivial, >0.2 small, >0.6 moderate, and >1.2 large (Hopkins et al. 2009). The results

were computed with IBM SPSS Statistics 21 (IBM Corporation, Armonk, NY), while statistical significance was set at $p < 0.05$.

Results

Descriptive characteristics

At baseline, the descriptive characteristics presented in Table 1 were similar between T1D and CON. Training increased [Hb] in T1D, absolute forced vital capacity (FVC) in both T1D and CON, and FVC (% of reference value) in T1D with no Group×Time interactions. Other training effects were not observed in the descriptive characteristics.

In addition to the data in Table 1, thickness of subcutaneous fat of the VL muscle (9 ± 4 vs. 13 ± 7 mm, $p = 0.410$), resting nocturnal HR (51 ± 9 vs. 47 ± 5 bpm, $p = 0.251$), and resting systolic (133 ± 14 vs. 128 ± 11 mmHg, $p = 0.514$) and diastolic (86 ± 7 vs. 79 ± 16 mmHg, $p = 0.287$) blood pressures were similar for T1D and CON at baseline, respectively.

Moreover, training decreased basal (baseline: 0.35 ± 0.19 IU/kg/d; change: -0.06 ± 0.06 IU/kg/d, ES = 1.0, moderate, $p < 0.05$) but not rapid-acting (baseline: 0.30 ± 0.09 IU/kg/d; change: 0.06 ± 0.07 IU/kg/d, $p = 0.114$) nor total (baseline: 0.65 ± 0.26 IU/kg/d; change: -0.01 ± 0.09 IU/kg/d, $p = 0.867$) daily insulin doses of T1D.

Training intervention

Table 2 shows that: 1) exercise training was similar in T1D and CON in terms of frequency, duration, energy expenditure, modes, and intensity; 2) training on average consisted of 3-4 endurance training sessions and one resistance training session per week; 3) mean training

intensity was moderate (Howley 2001); and 4) no consistent progression in training was observed within either of the training groups.

Cardiorespiratory adaptations

At baseline, work rates and cardiorespiratory responses at peak exercise, including $\dot{V}O_{2peak}$ (L/min: $p = 0.451$; mL/min/kg: $p = 0.974$; mL/min/kg FFM: $p = 0.120$), were similar between T1D and CON ($p > 0.05$) (Table 3). Training increased peak work rates and $\dot{V}O_{2peak}$ in both groups. Specifically, $\dot{V}O_{2peak}$ (mL/min/kg FFM) increased 10% ± 7% in T1D (ES = 1.4, large, $p = 0.004$) and 8% ± 9% in CON (ES = 0.9, moderate, $p = 0.045$). Additionally, peak O_2 pulse (mL/beat/kg FFM) rose 10% ± 11% in T1D (ES = 0.9, moderate, $p = 0.032$) and 11% ± 10% in CON (ES = 1.1, moderate, $p = 0.018$). No significant Group×Time interactions were observed for any peak responses, whereas peak MAP was higher in T1D than in CON ($p = 0.016$ for the Group effect).

The magnitude of training-elicited changes in work rates and cardiorespiratory responses at peak exercise had no associations with the characteristics of exercise training in T1D ($p > 0.05$) (variables in Tables 2 and 3 were examined). On the contrary, consistent associations were observed in CON: Percentual change (Δ) in peak work rate (W) vs. frequency ($r = 0.77$, $p = 0.027$), Δpeak work rate (W) vs. duration ($r = 0.78$, $p = 0.022$), Δpeak work rate (W/kg FFM) vs. duration ($r = 0.71$, $p = 0.048$), Δpeak O_2 pulse (mL/beat) vs. endurance training frequency ($r = 0.83$, $p = 0.043$), and Δpeak O_2 pulse (mL/beat) vs. duration ($r = 0.72$, $p = 0.044$). The training-induced changes in work rates and cardiorespiratory responses were not significantly associated with baseline $\dot{V}O_{2peak}$ (T1D and CON), baseline HbA_{1c} (T1D), training-induced change in HbA_{1c} (T1D), nor diabetes duration (T1D) ($p > 0.05$).

Leg muscle deoxygenation adaptations

At baseline, leg muscle $\%\Delta[HHb]$, $\Delta[HHb]$, and $\Delta[tHb]$ at any work rate were similar between T1D and CON ($p > 0.05$) (Fig. 2 and Fig. 3). Training decreased $\%\Delta[HHb]$ at submaximal work rates in CON but not in T1D, while one significant Group×Time interaction was observed for $\%\Delta[HHb]$ at 80W (Fig. 2A-B). Within-group changes and Group×Time interaction for $\%\Delta[HHb]$ at peak exercise were not significant ($p > 0.05$). Training increased $\Delta[HHb]$ at peak exercise in CON (ES = 0.5, small, $p < 0.039$) but not in T1D, and significant as well as borderline significant Group×Time interactions were observed for $\Delta[HHb]$ at 160W and peak exercise, respectively (Fig. 2C-D). No within-group changes or Group×Time interactions for $\Delta[tHb]$ at any work rate were observed ($p > 0.05$) (Fig. 3).

Reference group

At baseline, Reference group aged 28.6 ± 1.0 yrs was younger than CON ($p = 0.017$) and had higher $\dot{V}O_{2peak}$ (54 ± 10 mL/min/kg FFM) than T1D ($p = 0.024$). Changes in anthropometry, hematology, or spirometry were not observed in Reference group after one year ($p > 0.05$). Furthermore, $\dot{V}O_{2peak}$ did not change ($+3\% \pm 6\%$, $p = 0.245$), there were no changes in peak work rates or cardiorespiratory responses, and no evident changes in leg muscle $\%\Delta[HHb]$, $\Delta[HHb]$, or $\Delta[tHb]$ at any work rate were seen in Reference group ($p > 0.05$). Based on the Reference group data, a typical percentage error for $\dot{V}O_{2peak}$ (mL/min/kg FFM) was $2.9\% \pm 3.1\%$ (Hopkins 2000). Overall, these data on Reference group reflect the repeatability of the methods used in this study.

Statistical power

Post hoc calculations demonstrated that at least six subjects per group were needed to obtain statistical power of 80% for the observed training-elicited change in the main outcome of this

study ($\Delta\dot{V}O_{2peak}$ [mL/min/kg FFM] = 9% ± 8% in a pooled population [T1D+CON], alpha <5 %).

Discussion

The present study demonstrates how the 1-year unsupervised individualized training intervention led to equivalent improvements in $\dot{V}O_{2peak}$ in type 1 diabetes patients (T1D) and healthy subjects (CON) matched for baseline age, sex, anthropometry, and $\dot{V}O_{2peak}$. Peak O_2 pulse also increased similarly in the groups, suggesting similar training-induced improvements in stroke volume and thus cardiac pump function. Instead, training elevated active leg muscle deoxygenation (Δ[HHb]) at peak exercise in CON but not in T1D, while no training-induced changes in active leg muscle Δ[tHb] at peak exercise or any other work rate were observed in either group. These findings together provide the following novel evidence: Despite the equivalent training-induced increases in $\dot{V}O_{2peak}$ in adult men with and without type 1 diabetes, even long-term training, at least at this volume and intensity, was unable to improve NIRS-derived local active muscle O_2 extraction in men with type 1 diabetes. Meanwhile, no reduction of HbA_{1c} was evident in T1D even after such a long-term training intervention. We also observed consistent associations between training dose and training-induced adaptations in CON but not in T1D.

Reduced $\dot{V}O_{2peak}$ strongly predicts increased cardiovascular risk (Kodama et al. 2009), which is independently pronounced in diabetes (Fang et al. 2004). Accordingly, several studies have reported reduced $\dot{V}O_{2peak}$ in both adolescents and adults with type 1 diabetes (Gusso et al. 2012, Rissanen et al. 2015). However, type 1 diabetes patients are likely capable of attaining similar $\dot{V}O_{2peak}$ to healthy subjects, but this may depend on them maintaining good glycemic

control (Baldi and Hofman 2010). Short-term aerobic training programs of 2-4 months have resulted in 6-14% (Wallberg-Henriksson et al. 1982, Wallberg-Henriksson et al. 1984, Laaksonen et al. 2000, Rigla et al. 2000) or even 27% (Fuchsjäger-Mayrl et al. 2002) increases in $\dot{V}O_{2peak}$ in type 1 diabetes. By contrast, it has remained uncertain whether regular physical activity can provide a glycemic benefit (i.e., reduce HbA_{1c}) in type 1 diabetes (Chimen et al. 2012, Kennedy et al. 2013, Yardley et al. 2014). The latter uncertainty has been supposed to be due to excessive energy consumption around the time of physical activity (to meet energetic requirements but particularly to avoid hypoglycemia) and to training-induced reduction of insulin requirements (Chimen et al. 2012). It has also been postulated that previously performed training interventions may have been too short-term to reduce HbA_{1c} in this patient group (Kennedy et al. 2013). In the present study, the long-term training intervention of one year increased $\dot{V}O_{2peak}$ similarly in T1D (10%) and CON (8%). Meanwhile, basal insulin dose decreased in T1D but no changes were observed in their total insulin dose or HbA_{1c}. These findings indicate that 1) long-term recreational-like training seems to have a similar effect on $\dot{V}O_{2peak}$ in adults with and without type 1 diabetes, 2) even long-term training does not reduce HbA_{1c} in adults with type 1 diabetes, and 3) a reduction of HbA_{1c} is not thus a prerequisite for nor a consequence of an improvement in $\dot{V}O_{2peak}$.

Cardiac dysfunction is characteristic of diabetes (Fang et al. 2004). Diabetes-specific defects in cardiac output may include systolic impairments but are primarily due to diastolic dysfunction (i.e., reduced ventricular relaxation, preload, and compliance) (Fang et al. 2004), the different components of which are manifested also during exercise (Gusso et al. 2012, Rissanen et al. 2015). While endurance training has been shown to improve cardiac pump function in animal models of type 1 diabetes (Loganathan et al. 2007), human studies examining effects of training on cardiac function in type 1 diabetes are sparse. A 10% increase in peak O_2 pulse, which is an estimate of peak left ventricular stroke volume (Whipp

et al. 1996), has been observed after three months of aerobic training in type 1 diabetes adults (Rigla et al. 2000). In addition, echocardiography studies in patients with type 2 diabetes have produced contradictory findings: Both training-induced improvements (Hollekim-Strand et al. 2014) and no improvements (Ofstad et al. 2014) in myocardial function have been observed with high training intensity possibly leading to more pronounced effects (Hollekim-Strand et al. 2014). In the current study, peak O_2 pulse rose in a similar manner in the training groups (T1D: 10%, CON: 11%) after the long-term one-year exposure to regular exercise, suggesting a similar improvement in cardiac pump function in the groups. In addition, no between-group differences (i.e., significant Group×Time interactions) in adaptations of peak SpO_2, peak HR, or [Hb] were present. Thus, accepting both the highly surrogate nature of peak O_2 pulse and its inability to separate diastolic and systolic components of cardiac function, we suggest that the net effect of the 1-year training intervention on the different components of peak systemic O_2 delivery was equivalent in T1D and CON. However, further human studies providing evidence of more detailed cardiac adaptations to exercise training in type 1 diabetes are required, particularly because Baldi et al. (2016) have recently reviewed that more vigorous exercise may be needed to improve cardiac function in individuals with diabetes.

In addition to cardiac defects, type 1 diabetes is also characterized by vascular dysfunction manifested as endothelial dysfunction (Järvisalo et al. 2004), reduced arterial compliance (Mason et al. 2006), decreased capillary-to-fiber ratio (Kivelä et al. 2006), and impaired microvascular blood flow (Kindig et al. 1998). These vascular defects are overall reflected by our finding of higher MAP at peak exercise in T1D (i.e., significant Group effect), while the components of cardiac output (HR and O_2 pulse [the surrogate for stroke volume]) were similar in T1D and CON. This suggests pronounced peak systemic vascular resistance in T1D, thus consistent with our recent study (Rissanen et al. 2015). We also observed that training decreased leg muscle %Δ[HHb] at submaximal work rates in CON but not in T1D,

whereas Δ[HHb] at peak exercise increased only in CON. In other words, maximal deoxygenation capacity (i.e., peak Δ[HHb]) of the leg muscle increased only in CON, which also led to the decreases in submaximal %Δ[HHb] only in CON.

While the training-induced increase in peak active muscle Δ[HHb] (or [HHb]) has recently been reported by cross-sectional studies (using either continuous wave [Rissanen et al. 2012], frequency-domain [Boone et al. 2016], or time-resolved [Okushima et al. 2016] NIRS) and a longitudinal study (using continuous wave NIRS [Takagi et al. 2016]), it is a novel finding that such improvement of local microvascular deoxygenation capacity was totally absent in T1D. To explain this we also analyzed the data on leg muscle Δ[tHb], which is a surrogate for microvascular blood volume (Ferrari et al. 2004) and reflects local O_2 diffusion capacity (Groebe and Thews 1990): No increases in Δ[tHb] were observed at peak exercise or any other work rate in T1D or CON. This agrees with recent cross-sectional (Okushima et al. 2016) and longitudinal (Takagi et al. 2016) studies examining the VL muscle and suggests that the capacity for diffusive O_2 conductance may not be as important for deoxygenation and aerobic performance in the VL muscle as it is in some other muscles such as the rectus femoris (Okushima et al. 2016). By contrast, another cross-sectional study (Boone et al. 2016) illustrated higher [tHb] levels in the VL muscle at peak exercise in individuals with higher $\dot{V}O_{2peak}$ compared to less fit individuals. However, the NIRS data of our present study indicate that increased local leg muscle O_2 extraction mainly explains the training-induced increase in peak leg muscle Δ[HHb] in CON. That is to say that training did not improve local leg muscle O_2 extraction in T1D, whose peak leg muscle Δ[HHb] thus retained unchanged.

The unaltered O_2 extraction in T1D may be explained by their unaltered HbA_{1c}: It has been hypothesized that pronounced affinity of glycosylated hemoglobin for O_2 is linked with blunted microvascular O_2 extraction and deoxygenation in the VL muscle at high exercise intensities (Tagougui et al. 2015). Theoretically, both deficient muscle fiber type

transformation (from type IIb to IIa or even from IIa to I) and/or unaltered enzymatic oxidative capacity of muscle mitochondria could also explain the remained level of O_2 extraction in T1D; however, at least the latter of these maladaptations is unlikely as even poorly controlled type 1 diabetes patients with HbA_{1c} ~10 % have displayed a normal training response in mitochondrial enzyme activities (Wallberg-Henriksson et al. 1984). After all, however, any maladaptations in the VL muscle in T1D were not sufficiently severe to prevent overall improvements in exercise capacity and cardiorespiratory fitness.

The main strength and novelty of this study reside in the 1-year duration of the training intervention: To our knowledge, no previous studies have examined training-induced adaptations of cardiorespiratory fitness or glycemic control after such a long training period in patients with type 1 diabetes. This was also the first longitudinal study to examine the effect of exercise training on active muscle deoxygenation in individuals with diabetes. Another strength of this study was the individual documenting of training that enabled exploring associations between the characteristics and the outcomes of training: While different characteristics of training had consistent associations with observed training-induced adaptations in CON (e.g., the higher the training volume, the greater the increase in peak work rate), no such dose-response associations were evident in T1D. This may highlight the need for greater individualization of exercise prescription in type 1 diabetes, although it is certainly of note that the intervention as such was beneficial also for T1D despite the lack of dose-response associations.

One limitation of the present study is that the allocation of T1D and CON subjects to training groups was performed in a nonrandom fashion. This was due to the substantial subject burden imposed by the relatively long-term intervention including intensive collecting of individual exercise data. While we acknowledge that a randomized design would have been necessary to preclude selection bias, the nonrandom allocation hardly affected comparisons between T1D

and CON. Regarding the maximality of the exercise tests performed, while our findings of RER (≥ 1.10 reached in every test) suggest the maximality of the tests (Edvardsen et al. 2014), a plateau in $\dot{V}O_2$ at high intensities was not observed in five subjects at baseline (three T1D, two CON) and four subjects after the intervention (three T1D, one CON), which slightly questions the maximality of the nine particular tests (Poole and Jones 2017). It can still be argued that as the $\dot{V}O_2$ plateau was absent in only a few subjects including those from both T1D and CON, this issue hardly had any effect on our between-group comparisons. Lack of consistent progression in training of T1D and CON may also be regarded as a limitation. However, more often than not, recreational-like training is certainly characterized by such lack of progression. Therewith, the completed training intervention likely reflected real-world circumstances, which was one purpose of this study. Furthermore, diet was not controlled during the intervention, which also reflects real-world circumstances but completely obviates drawing any conclusions regarding the dietary effects on the study outcomes.

The findings of this study are mainly applicable to nonathlete but already physically active adults with relatively well-controlled type 1 diabetes (HbA_{1c} ~7.5 % in T1D) and without clinically overt macro- or microvascular complications. In terms of baseline physical activity, while self-report and direct measures of physical activity (or exercise training) may differ substantially from each other (Prince et al. 2008), our data on self-reported baseline LTPA and directly measured exercise training during the intervention suggest that training duration (per any time unit) did not increase that much in T1D or CON during the intervention. If this was the case, any observed training-induced improvements had to result mainly from long-term adherence to regular exercising as well as from improvements and individualization of other exercise training characteristics (i.e., frequency, modes, intensity).

In summary, one-year adherence to exercise training, on average consisting of one resistance training session and 3-4 endurance training sessions performed per week at ~moderate

intensity and for ~one hour at a time, induced similar improvements in $\dot{V}O_{2peak}$ in T1D and CON matched for baseline age, sex, anthropometry, and $\dot{V}O_{2peak}$. This similarity was accompanied by equivalent increases in peak O_2 pulse. By contrast, training enhanced NIRS-derived active muscle microvascular O_2 extraction at peak exercise in CON but not at all in T1D. Meanwhile, no glycemic benefit was evident in T1D even after such a long-term training intervention. Furthermore, training was characterized by consistent dose-response associations in CON but not in T1D.

The above-summarized findings provide novel evidence of clinical importance: First, as $\dot{V}O_{2peak}$ is known to be a strong predictor of overall cardiovascular risk (Kodama et al. 2009) and peak O_2 pulse indirectly reflects cardiac pump function capacity (Whipp et al. 1996), it is important to observe significant and "normal" training-induced improvements in the two variables in individuals with type 1 diabetes given the major burden of cardiovascular morbidity in diabetes (Chaturvedi 2007). Second, however, the absence of improvements in active muscle microvascular O_2 extraction in T1D indicates that even long-term training, at least at this volume and intensity, does not induce significant adaptations regarding active muscle microvascular O_2 delivery and utilization in individuals with diabetes. Particularly in this context, it is notable that while improved glycemic control decreases the risk of microvascular complications (The Diabetes Control and Complications Trial Research Group 1993), even long-term training does not seem to reduce HbA_{1c} in adults with type 1 diabetes. Third, the lack of dose-response associations in T1D may highlight the need for more individualized exercise prescription in type 1 diabetes.

Conflict of interest statement

The authors declare no conflicts of interest

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Table 1. Descriptive characteristics of the training groups at baseline and after the intervention.

| | T1D (n = 8) | | CON (n = 8) | | *p* at |
	Baseline	Post	Baseline	Post	Baseline [a]
Age (yr)	33.4 ± 6.3	34.3 ± 6.4	37.9 ± 7.1	38.9 ± 7.0	0.205
Diabetes duration (yr)	10.5 ± 6.8 (range: 4.0-24.0)	11.4 ± 6.9	-	-	-
Anthropometry					
Weight (kg)	80 ± 11	80 ± 12	86 ± 13	86 ± 10	0.340
Height (cm)	180 ± 11	180 ± 11	181 ± 6	181 ± 6	0.713
BMI (kg/m^2) [b]	24.9 ± 2.8	24.7 ± 3.1	26.3 ± 3.8	26.2 ± 2.8	0.834
Body fat (%)	16 ± 5	16 ± 6	21 ± 9	20 ± 7	0.151
Fat-free mass (kg)	68 ± 10	67 ± 10	67 ± 7	68 ± 6	0.901
Hematology					
[Hb] (g/L)	144 ± 6	150 ± 8†	146 ± 3 [c]	149 ± 10 [c]	0.661
HbA$_{1c}$ (mmol/mol)	58 ± 10 [c]	59 ± 11 [c]‡	-	34 ± 2	-
HbA$_{1c}$ (%)	7.3 ± 0.9 [c]	7.5 ± 1.1 [c]‡	-	5.3 ± 0.2	-
Spirometry					
FVC (L)	5.5 ± 0.9	5.6 ± 0.9*	5.6 ± 0.7	5.8 ± 0.6*	0.825
FVC (% of reference value)	97 ± 12	99 ± 11*	98 ± 12	102 ± 10	0.773
FEV$_1$ (L)	4.5 ± 0.7	4.5 ± 0.7	4.6 ± 0.5	4.6 ± 0.4	0.626
FEV$_1$ (% of reference value)	96 ± 13	96 ± 13	101 ± 11	100 ± 8	0.411
Physical activity					
LTPA (h:min/wk)	3:28 ± 2:01	- §	4:01 ± 2:00	- §	0.590

Data are means ± SD.

[a] Between-group difference at baseline is evaluated with Group (T1D vs. CON) as a between-subjects factor.

[b] Non-normally distributed data: Non-parametric tests are used to compare the groups at Baseline (Mann-Whitney U) and Baseline vs. Post (Wilcoxon signed-rank).

[c] n = 7.

* Significantly ($p < 0.05$) different from Baseline.

† Significantly ($p < 0.01$) different from Baseline.

‡ Significantly ($p < 0.01$) different from CON.

§ See Table 2 for the details of exercise training during the intervention, please.

BMI, body mass index; [Hb], hemoglobin concentration; HbA$_{1c}$, glycosylated hemoglobin A$_{1c}$; FVC, forced vital capacity; FEV$_1$, forced expiratory volume in one second; LTPA, leisure-time physical activity.

Table 2. Exercise training performed *per month* by the training groups during the intervention.

	T1D (n = 8)	CON (n = 8)	*p* [a]
Total volume			
Frequency (training sessions/mo)	16 ± 4	18 ± 4	0.454
Duration (h:min/mo)	16:58 ± 6:07	16:52 ± 4:39	0.967
Energy expenditure (kcal/mo)	7759 ± 4540	7762 ± 3812	0.462
Mode			
Endurance training frequency (sessions/mo)	13 ± 4	15 ± 6 [b]	0.317
Resistance training frequency (sessions/mo)	3 ± 1	3 ± 3 [b]	0.927
Intensity			
Mean heart rate (bpm)	122 ± 12	122 ± 6	0.994
Mean heart rate (% of HRR)	57 ± 5	55 ± 8	0.553
Progression			
The 1st third of the intervention:			
Energy expenditure (kcal/mo) [c]	7749 ± 4583	7206 ± 2179	0.529
The 2nd third of the intervention:			
Energy expenditure (kcal/mo) [c]	6975 ± 3935	8592 ± 5396	0.401
The 3rd third of the intervention:			
Energy expenditure (kcal/mo) [c]	8610 ± 5637	7342 ± 4408	0.753

Data are means ± SD.

[a] Between-group difference is evaluated with Group (T1D vs. CON) as a between-subjects factor.

[b] n = 6 (two subjects in CON did not report their exercise modes).

[c] Non-normally distributed data: Non-parametric Mann-Whitney U test is used to compare the groups.

HRR, heart rate reserve.

Table 3. Effects of the training intervention on work rates and cardiorespiratory responses at peak exercise.

	T1D (n = 8)		CON (n = 8)		p for
	Baseline	Post	Baseline	Post	Group× Time [a]
Work rate (W) [b]	237 ± 34	254 ± 27*	255 ± 17	282 ± 36*	-
Work rate (W/kg FFM)	3.5 ± 0.4	3.9 ± 0.5†	3.8 ± 0.3	4.1 ± 0.4*	0.977
$\dot{V}O_2$ (L/min)	3.04 ± 0.60	3.27 ± 0.53*	3.22 ± 0.24	3.53 ± 0.46*	0.567
$\dot{V}O_2$ (mL/min/kg)	38 ± 4	41 ± 3†	38 ± 4	41 ± 5*	0.916
$\dot{V}O_2$ (mL/min/kg FFM)	45 ± 5	49 ± 6†	48 ± 3	52 ± 5*	0.677
Ventilation (L/min)	130 ± 33	131 ± 31	143 ± 26	146 ± 27	0.750
SpO_2 (%)	96 ± 1	97 ± 2	95 ± 2	95 ± 2	0.632
Heart rate (bpm)	175 ± 11	173 ± 9	184 ± 12	180 ± 13	0.634
O_2 pulse (mL/beat)	18 ± 4	19 ± 3	18 ± 1	20 ± 2†	0.361
O_2 pulse (mL/beat/kg FFM)	0.26 ± 0.03	0.28 ± 0.03*	0.26 ± 0.02	0.29 ± 0.03*	0.880
MAP (mmHg) §	147 ± 26 [c]	140 ± 10 [c]	131 ± 11 [d]	119 ± 16 [d] *	0.758

Data are means ± SD.

[a] Between-group difference in change from baseline to post is evaluated with Group (T1D vs. CON) as a between-subjects factor and Time (Baseline, Post) as a within-subject factor.

[b] Non-normally distributed data: Non-parametric tests are used to compare the groups (Mann-Whitney U) and Baseline vs. Post (Wilcoxon signed-rank), and use of repeated-measures ANOVA is inappropriate.

[c] n = 6.

[d] n = 7.

* Significantly ($p < 0.05$) different from Baseline.

† Significantly ($p < 0.01$) different from Baseline.

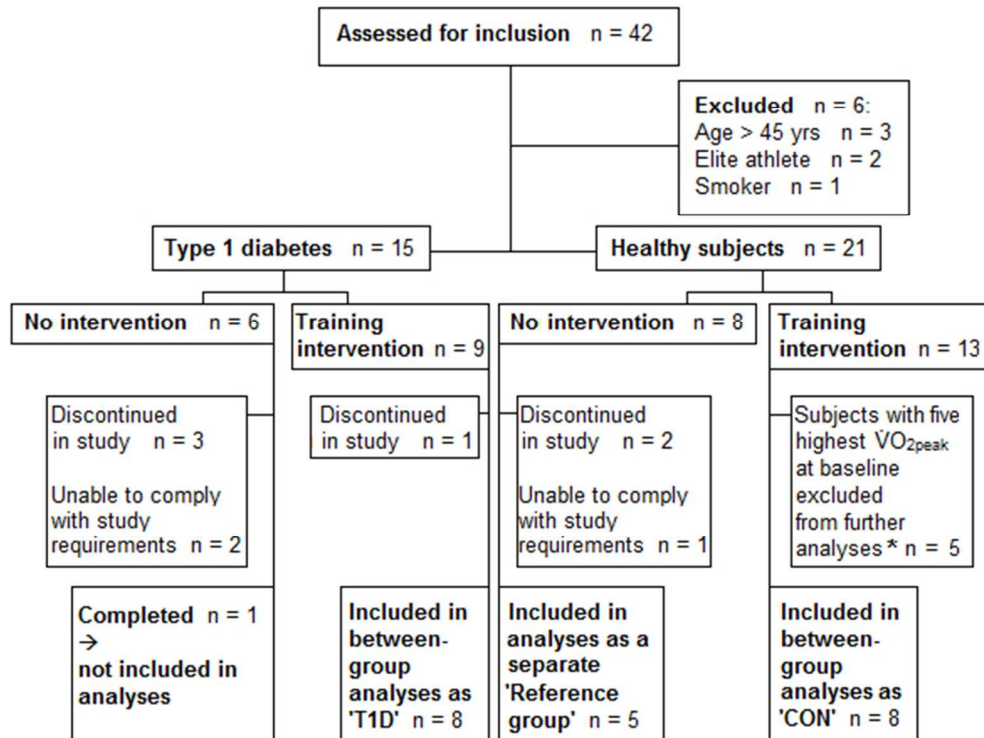§ Significant ($p < 0.05$) difference between T1D and CON.

FFM, fat-free mass; $\dot{V}O_2$, pulmonary O_2 uptake; SpO_2, arterial O_2 saturation; MAP, mean arterial pressure.

Figure captions

Fig. 1. Study flow chart. * Five trained healthy subjects with the highest peak pulmonary O_2 uptake ($\dot{V}O_{2peak}$) values at baseline were excluded from further between-group analyses to match the training groups (T1D and CON) also for baseline $\dot{V}O_{2peak}$.

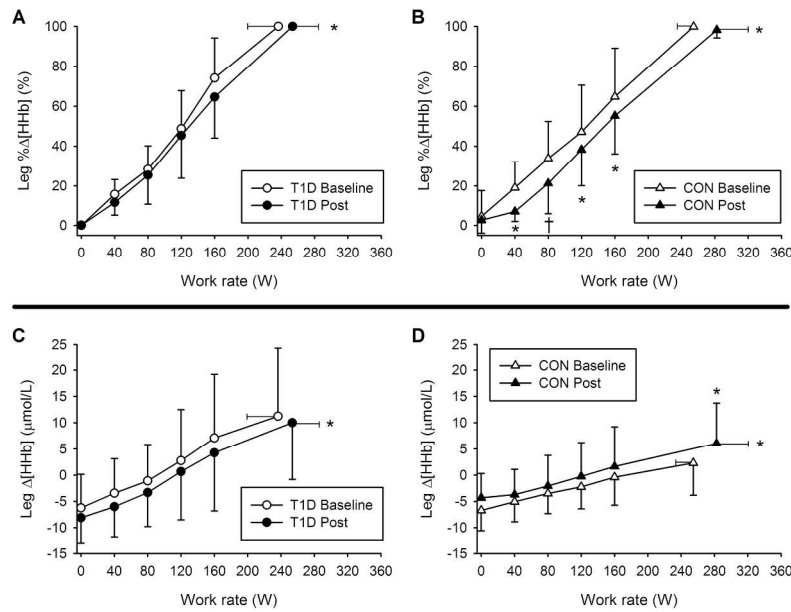**Fig. 2.** Normalized relative (%Δ[HHb]) and relative (Δ[HHb]) concentration changes in the vastus lateralis muscle deoxyhemoglobin as a function of work rate in T1D (A, C; *circles*) and CON (B, D; *triangles*) at baseline (white plots) and after the 1-year training intervention (= Post; black plots). Presented work rates on the x-axis include unloaded cycling (i.e., 0 W), work rates accomplished by every subject, and mean peak work rate. Significant within-group difference between Baseline and Post (* $p < 0.05$; † $p < 0.01$) (one-way repeated-measures ANOVA). Significant Group×Time interactions for Leg %Δ[HHb] at 80 W ($p = 0.047$) and Leg Δ[HHb] at 160 W ($p = 0.029$) as well as borderline significant Group×Time interaction for Leg Δ[HHb] at peak exercise ($p = 0.052$) were observed (two-way repeated-measures ANOVA).

Fig. 3. Relative concentration changes in the vastus lateralis muscle total hemoglobin (Δ[tHb]) as a function of work rate in T1D (A; *circles*) and CON (B; *triangles*) at baseline (white plots) and after the 1-year training intervention (= Post; black plots). Presented work rates on the x-axis include unloaded cycling (i.e., 0 W), work rates accomplished by every subject, and mean peak work rate. Significant within-group difference between Baseline and Post (* $p < 0.05$) (one-way repeated-measures ANOVA). No significant Group×Time interactions for Leg Δ[tHb] at any work rate ($p > 0.05$) were observed (two-way repeated-measures ANOVA).

Study flow chart. * Five trained healthy subjects with the highest peak pulmonary O2 uptake (VO2peak) values at baseline were excluded from further between-group analyses to match the training groups (T1D and CON) also for baseline VO2peak.

157x117mm (96 x 96 DPI)

Normalized relative (%Δ[HHb]) and relative (Δ[HHb]) concentration changes in the vastus lateralis muscle deoxyhemoglobin as a function of work rate in T1D (A, C; circles) and CON (B, D; triangles) at baseline (white plots) and after the 1-year training intervention (= Post; black plots). Presented work rates on the x-axis include unloaded cycling (i.e., 0 W), work rates accomplished by every subject, and mean peak work rate. Significant within-group difference between Baseline and Post (* $p < 0.05$; † $p < 0.01$) (one-way repeated-measures ANOVA). Significant Group×Time interactions for Leg %Δ[HHb] at 80 W ($p = 0.047$) and Leg Δ[HHb] at 160 W ($p = 0.029$) as well as borderline significant Group×Time interaction for Leg Δ[HHb] at peak exercise ($p = 0.052$) were observed (two-way repeated-measures ANOVA).

120x80mm (600 x 600 DPI)
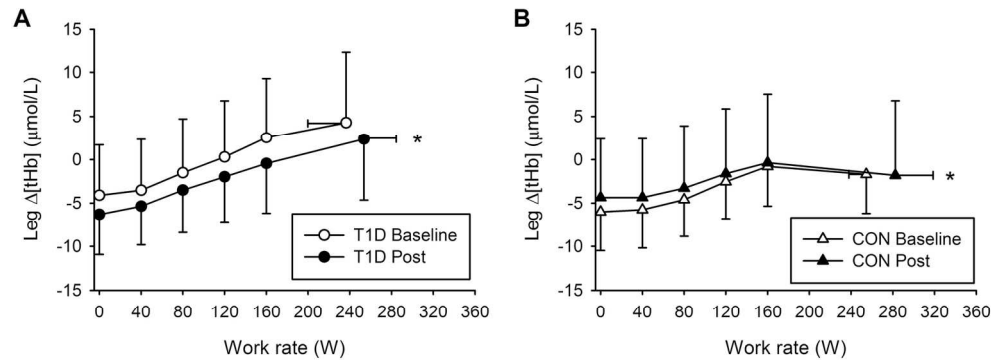
Relative concentration changes in the vastus lateralis muscle total hemoglobin (Δ[tHb]) as a function of work rate in T1D (A; circles) and CON (B; triangles) at baseline (white plots) and after the 1-year training intervention (= Post; black plots). Presented work rates on the x-axis include unloaded cycling (i.e., 0 W), work rates accomplished by every subject, and mean peak work rate. Significant within-group difference between Baseline and Post (* $p < 0.05$) (one-way repeated-measures ANOVA). No significant Group×Time interactions for Leg Δ[tHb] at any work rate ($p > 0.05$) were observed (two-way repeated-measures ANOVA).

78x34mm (600 x 600 DPI)