HIIT Improves Left Ventricular Exercise Response in Adults with Type 2 Diabetes

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ABSTRACT

WILSON, G. A., G. T. WILKINS, J. D. COTTER, R. R. LAMBERTS, S. LAL, and J. C. BALDI. HIIT Improves Left Ventricular Exercise Response in Adults with Type 2 Diabetes. *Med. Sci. Sports Exerc.*, Vol. 51, No. 6, pp. 1099–1105, 2019. Type 2 diabetes is associated with reduced left ventricular reserve. It is unclear whether exercise training improves left ventricular function in people with type 2 diabetes. **Purpose**: This study aimed to determine whether 3 months of high-intensity interval training (HIIT) improves left ventricular function during exercise in adults with type 2 diabetes. **Methods**: Participants performed a $\dot{V}O_{2peak}$ test and received a DXA scan and total blood volume measurement at baseline. Left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and left ventricular stroke volume (LVSV) were then measured at rest and during low- and moderate-intensity semirecumbent exercise in adults with type 2 diabetes before and after 3 months of HIIT ($n = 11$) or no training (control) ($n = 5$). The effects of HIIT were determined using repeated-measures ANOVA. **Results**: HIIT increased $\dot{V}O_{2peak}$ by approximately 15% ($P < 0.002$) but did not change body composition or total blood volume. LVESV decreased and LVEDV and LVSV increased from rest to moderate-intensity exercise in both groups at baseline (all $P < 0.01$). Three months of HIIT increased LVEDV ($P = 0.008$) and LVSV ($P = 0.02$) at all conditions, but there was no difference in controls (all $P > 0.05$). HIIT augmented the reduction in LVESV from rest to moderate-intensity exercise ($P < 0.04$), but LVESV was unchanged in controls. Increased LVEDV explained 51% of the change in LVSV after HIIT intervention. Mitral inflow parameters and mitral annular velocities were unaffected by HIIT (all $P > 0.05$). **Conclusions**: HIIT training increased the LVSV response to exercise in adults with type 2 diabetes. These data suggest that HIIT can improve LV filling and emptying during exercise and reverse early cardiac consequences of type 2 diabetes. **Key Words:** DIASTOLE, SYSTOLE, SUBMAXIMAL EXERCISE, TRAINING, TYPE 2 DIABETES, CARDIAC FUNCTION

Reductions in aerobic capacity and associated reductions in cardiac reserve are well documented in diabetes (1–3). Aerobic capacity ($\dot{V}O_{2peak}$) is a strong predictor of subsequent cardiac events (4), and exercise training reduces rates of cardiovascular mortality in nondiabetic adults (5). Exercise training also improves $\dot{V}O_{2peak}$ and cardiac output in people with diabetes, but only to levels comparable with their untrained nondiabetic peers (6). Therefore, it is unclear whether people with diabetes receive the same cardiovascular benefit from training as nondiabetics (7). It is also unclear how diabetes reduces left ventricular cardiac reserve, and whether these functional limitations can be reversed by exercise training.

Left ventricular diastolic dysfunction, quantified by reduced peak velocities of early mitral inflow (E) and early mitral annular displacement (E′) measured at rest, is an early clinical finding in people with diabetes (8,9),which has been associated with reduced $\dot{V}O_{2peak}$ (10). During exercise, adults with well-controlled type 2 diabetes (T2D) have a greater increase in left ventricular end-diastolic pressure (11) and attenuated increases in left ventricular end-diastolic volume (LVEDV) (1,2), suggesting that impaired left ventricular filling reduces cardiac reserve in this cohort. However, it is not known whether exercise training, which improves left ventricular stroke volume (LVSV) in nondiabetic participants (12), also improves left ventricular diastolic function or increases left ventricular volumes during exercise in people with T2D.

Our poor understanding of the left ventricular exercise response in T2D results from a lack of data collected during exercise. Resting indices of diastolic function improve after exercise training in adults with well-controlled T2D (13,14), but there are no data during exercise. Moreover, the effects of training on resting left ventricular filling volumes are conflicting (13,14). Twenty weeks of exercise training augmented the stroke volume response during moderate-intensity exercise by approximately 6% in adolescents with type 1 diabetes (6). This was achieved by increased exercising LVEDV and

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reduced exercising left ventricular end-systolic volume (LVESV). However, no study has determined whether similar improvements are possible in adults with T2D, who have a different pathophysiology and longer exposure to diabetes. This study aimed to determine whether high-intensity interval training (HIIT) improved left ventricular performance during exercise in people with T2D. HIIT was chosen because it safely induces equal increases in $\dot{V}O_{2peak}$ in less time with greater exercise adherence (3,15). We hypothesized that 3 months of HIIT would improve $\dot{V}O_{2peak}$ and increase LVEDV and LVSV responses during semirecumbent submaximal exercise.

METHODS

Participants. Sixteen people with T2D between the ages of 34 and 62 yr were randomized to a HIIT (T2Dt $n = 11$) or control (T2Dc $n = 5$) group using a 2:1 randomization design. Participants were NZ European (13), Indian (2), and NZ Māori (1). One participant was a current smoker (one T2Dc), and four participants were ex-smokers (one T2Cc and three T2Dt). No participants had cardiovascular or respiratory disease, and all participants performed a negative exercise stress ECG test before being randomized into the protocol. Two people randomized to the training group (T2Dt) had mildly abnormal albumin/creatinine ratios; however, no participants had evidence of microvascular disease or complications. Participants with diabetes were treated with metformin (12), gliclazide (5), and insulin (3). This study was approved by the Northern B Health and Disability Ethics Committee 15/NTB/1/AM09, and informed consent was obtained from all participants before any testing was undertaken.

Overview of protocol. At baseline, each participant underwent a cardiac autonomic screening protocol to identify evidence of severe cardiac autonomic neuropathy, a peak exercise test to determine $\dot{V}O_{2peak}$, a body composition assessment (DEXA scan), an exercise echocardiogram, and a blood volume assessment. Baseline tests were repeated after the 3-month intervention (HIIT vs nontraining control) period.

Cardiac autonomic screening. To assure that no participant had severe cardiac autonomic dysfunction, autonomic function was tested in accordance with established clinical recommendations (16). Participants lay supine and were instrumented with standard lead-II ECG (FE132; ADInstruments, Dunedin, NZ), respiratory belt (MTL1132, ADInstruments), and finger photoplethysmography (Finometer® MIDI, FMS; Finapres Medical Systems BV, the Netherlands) verified against manual sphygmomanometer to measure heart rate (HR), breathing frequency, and beat-to-beat blood pressure, respectively. These measures were continuously sampled using an analog-to-digital converter at 1 kHz (Powerlab/3508, ADInstruments) and stored for offline analysis. HR and blood pressure responses to a battery of tests were quantified and compared with age-adjusted normative values to determine any evidence of severe autonomic dysfunction (16).

Peak exercise test. Peak oxygen consumption ($\dot{V}O_{2peak}$) with ECG was performed with a metabolic/ECG cart (COSMED Quark CPET, Italy) during incremental cycle ergometry to voluntary exhaustion. The exercise protocol began at 25 or 50 W and progressed with increments of 25 or 50 W (depending on the ability on the participants) every 2 min until the termination of the test. Workloads were adjusted using the Borg scale of perceived exertion to assure test duration did not exceed 12 min. Arm blood pressure (by auscultation) and HR (by 12-lead ECG) were recorded at rest and at the end (last 20 s) of each stage of exercise and during recovery. Breath-by-breath data were collected and analyzed using O_2 and CO_2 analyzers, which were calibrated before each test. The two highest consecutive 10-s recordings were averaged to determine $\dot{V}O_{2peak}$. At the termination of the test, the participant lay immediately in the supine position, and HR at 1 and 2 min into recovery was used for analysis of HR recovery. The protocol was repeated after the intervention in both groups using an HR monitor rather than an exercising ECG (the posttest was not diagnostic).

Exercise stress protocol. At least 24 h after the $\dot{V}O_{2peak}$ test, cardiac output ($\dot{Q}$), LVEDV, LVESV, and LVSV were determined with echocardiography at rest (supine and semirecumbent) and while participants pedaled a semirecumbent (30°) cycle ergometer at workloads equal to 40% and 60% of their previously determined $\dot{V}O_{2peak}$. Target HR values were calculated by regressing HR values to $\dot{V}O_{2peak}$ as a percentage of maximum. These workloads were then adjusted as the participant pedaled to assure participants achieved and maintained an HR within 5 bpm of target for the duration of measurements. HR values were recorded continuously, and the average HR during echocardiographic imaging was reported. Blood pressure was obtained at the end of every stage.

Echocardiography. Echocardiographic images were obtained using a Vivid E9 (GE Medical systems, Milwaukee, WI) ultrasound system by a research sonographer who had received additional training in exercise echocardiography. Resting supine LV dimensions were obtained in the parasternal long axis view (17) from which LV mass calculated in accordance with the American Society of Echocardiography (ASE) guidelines (17). LV volumes (LVEDV and LVESV) were obtained in the apical four-chamber view using a two-dimensional echocardiography in accordance with the ASE guidelines (17). Peak mitral inflow velocities (E and A) were obtained at rest in the apical four-chamber view using pulsed-wave Doppler with the sample volume placed between the mitral valve leaflets (18), and the E/A ratio was calculated. In the same view, pulsed-wave Doppler was used to obtain peak mitral annulus velocities (E′, A′, and S′) (tissue Doppler imaging) (19) with the sample volume placed on the mitral valve annulus at the junction with the interventricular septum. LV volumes (LVEDV and LVESV) and mitral annular velocities (E′, A′, and S′) were then obtained in the semirecumbent position at rest and during 40% and 60% $\dot{V}O_{2peak}$. Three consecutive beats were stored digitally for all variables measured during all conditions and analyzed with customized dedicated research software (EchoPAC version 112.0.0, Advanced Analysis Technologies, GE Medical Systems).

TABLE 1. Participant baseline characteristics.

Variable	T2Dc	T2Dt
n (% female)	5 (40)	11 (36)
Age (yr)	51 ± 5	52 ± 2
Weight (kg)	89.9 ± 10.4	96.6 ± 6.6
BMI ($kg \cdot m^{-2}$)	32.1 ± 3.3	33.5 ± 1.7
FFM (kg)	54.2 ± 5.3	60.7 ± 3.6
Total fat (kg)	34.5 ± 5.6	35.2 ± 3.6
Self-reported fitness history ($h \cdot wk^{-1}$)	3.8 ± 1.8	3.1 ± 0.6
Diabetes duration (yr)	6.0 ± 1.8	7.8 ± 1.3
HbA1c ($mmol \cdot mol^{-1}$)	61.2 ± 10.7	61.9 ± 12.1
Blood volume ($mL \cdot kg^{-1}$)	54.3 ± 5.1	58.0 ± 3.5

Values are expressed as means ± SE.

All analysis was performed on anonymized (participant identifiers removed) files by a blinded sonographer after completion of the entire study. LVEDV and LVESV were visually traced with papillary muscles excluded in accordance with ASE guidelines (17) from which LVSV (LVEDV–LVESV) and ejection fraction (EF; LVSV/LVEDV) were derived. Apical two-chamber views could not be obtained in all individuals during exercise. Therefore, apical four-chamber views were used to estimate volumes. In our laboratory, apical four-chamber images during supine rest showed good agreement ($R^2 = 0.92$) when regressed to biplane images; therefore, we believe that the apical four-chamber images provide a valid volume measurement. Volumes were indexed to participants' fat-free mass (FFM) (obtained through a DEXA scan) because this has been identified as an appropriate scaling method to control for differences in adiposity (20). $\dot{Q}$ was calculated as the average HR during the image acquisition × corresponding LVSV. Stroke work (SW) was calculated as LVSV × mean arterial blood pressure (MABP) × 0.0136 (21).

Blood volume assessment. Total hemoglobin mass was measured using carbon monoxide (CO) rebreathing (22). In brief, the participant rested for 20 min, after which mixed-venous concentrations of hemoglobin ([tHb]) and carboxyhemoglobin ([HbCO]) were measured in triplicate (OSMS, Radiometer, Denmark). Any CO in the participant's system before the protocol was determined by the participant exhaling till residual volume onto a CO meter while wearing nose pegs and was factored into the final estimate. CO dosage was calculated as body mass × 0.7 $mL \cdot kg^{-1}$ (females) and 0.8 $mL \cdot kg^{-1}$ (males). However, in cases where body mass index (BMI) >25 $kg \cdot m^{-2}$, excessive dosage was avoided by applying a hypothetical body mass to attain a BMI of 25, and dosing at hypothetical body mass × 1 $mL \cdot kg^{-1}$.

HIIT and adherence record. Participants randomized into the 3-month HIIT training program were asked to complete 3 × 20-min supervised interval sessions per week for 3 months. Each session was designed so that participants spent at least 10 min exercising at an intensity that increased their HR to at least 90% of their peak HR. Each participant was issued with an HR monitor (POLAR RC3GPS, M400 and A300) to record HR during the session and for later collection of adherence data. Participants adopted an incremental program as follows: month 1, 1-min intervals interspaced by 1-min rest periods; month 2, 2-min intervals interspaced by 2-min rest periods; and month 3, 3-min intervals with 2-min moderate-intensity periods. Adherence was quantified in two ways: total adherence (% session adherence) and intensity adherence (completed sessions attending that met the HR target, at least 1 interval with an HR ≥ 90% at age-predicted maximal HR). Participants were included in training group data analysis if they achieved a total adherence of ≥50%. The number of completed sessions that met the target intensity (≥1 interval reached ≥90%) was then calculated to determine the intensity adherence. Control participants were instructed to maintain their usual lifestyle for the duration of the intervention period.

Statistical analysis. Statistical analysis was performed using SPSS (SPSS version 22.0.0; IDM Corporation, Armonk, NY). The Shapiro–Wilk test was used to check for normality. Left ventricular volumes were presented as a value indexed to (divided by) FFM because the absolute value of LVESV was not normally distributed. Indexing to FFM restored normality and allowed us to use our preferred statistical model. The need to index LVESV reflects the high degree of body mass variability in these study populations. In fact, Whalley et al. (20) reported that LV dimensions were best expressed when indexed to FFM in this cohort to account for the high degree of variability in body composition. When other variables were nonnormally distributed, log transformation was used to normalize the distribution. Comparisons of key baseline variables were made using the independent student *t*-test.

Group comparisons were performed using two-way repeated-measures (time) ANOVA. For measures obtained during exercise, a two-way repeated-measures (group–time–condition) ANOVA was performed. *Post hoc* tests (Bonferroni) were then conducted and described where appropriate. All data are expressed as the mean ± SE. A P value <0.05 was considered statistically significant. Pearson's correlations were performed using

TABLE 2. Exercise variables before and after the 3-month intervention period.

	T2Dc		T2Dt	
Variable	Pre	Post	Pre	Post
$\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)**	20.1 ± 2.2	19.7 ± 1.9	24.1 ± 2.0	27.6 ± 2.0
Max workload (W)*,**	125 ± 14	125 ± 14	168 ± 17	200 ± 19
HR reserve (bpm)	90.8 ± 9.2	84.5 ± 11.3	97.6 ± 4.7	97.0 ± 5.5
HR recovery 1 min (bpm)	29.8 ± 5.8	28.2 ± 3.9	30.8 ± 3.5	31.4 ± 2.5
HR recovery 2 min (bpm)	50.8 ± 3.6	50.2 ± 4.5	50.8 ± 4.1	53.7 ± 3.4

Values are expressed as means ± SE.
*Significant time effect.
**Significant group–time interaction.

TABLE 3. Resting supine echocardiographic parameters.

Variable		T2Dc	T2Dt
HR (bpm)**	Pre	75.9 ± 5.4	78.2 ± 3.2
	Post	84.4 ± 5.9	72.3 ± 2.9
LVMI (FFM)	Pre	3.54 ± 0.91	3.37 ± 0.19
	Post	3.66 ± 0.64	3.39 ± 0.18
$\dot{Q}$ ($L \cdot min^{-1} \cdot kg_{FFM}^{-1}$)	Pre	0.09 ± 0.00	0.09 ± 0.01
	Post	0.09 ± 0.00	0.09 ± 0.00
LVSV ($mL \cdot kg_{FFM}^{-1}$)**	Pre	1.24 ± 0.11	1.11 ± 0.06
	Post	1.20 ± 0.10	1.23 ± 0.07
EF (%)	Pre	62 ± 2	59 ± 2
	Post	62 ± 2	60 ± 2
LVEDV($mL \cdot kg_{FFM}^{-1}$)**	Pre	2.00 ± 0.16	1.87 ± 0.08
	Post	1.93 ± 0.11	2.06 ± 0.09
LVESV($mL \cdot kg_{FFM}^{-1}$)	Pre	0.75 ± 0.06	0.77 ± 0.06
	Post	0.73 ± 0.03	0.83 ± 0.05
E ($cm \cdot s^{-1}$)	Pre	64 ± 6	63 ± 4
	Post	67 ± 4	68 ± 5
A ($cm \cdot s^{-1}$)	Pre	70 ± 7	70 ± 4
	Post	74 ± 8	71 ± 4
E/A	Pre	0.98 ± 0.16	0.93 ± 0.08
	Post	0.97 ± 0.13	0.95 ± 0.05
E′($cm \cdot s^{-1}$)	Pre	6 ± 0	8 ± 1
	Post	7 ± 1	8 ± 1
E/E′	Pre	9.6 ± 0.5	8.5 ± 0.6
	Post	9.2 ± 0.4	9.9 ± 0.7
S′($cm \cdot s^{-1}$)	Pre	7 ± 0	8 ± 0
	Post	8 ± 1	8 ± 0
TPR ($mm\ Hg \cdot min^{-1} \cdot L^{-1}$)	Pre	18 ± 1	20 ± 1
	Post	20 ± 1	20 ± 1
MABP (mm Hg)	Pre	93 ± 4	101 ± 4
	Post	104 ± 7	101 ± 3
SW ($mL \cdot mm\ Hg^{-1}$)*	Pre	83 ± 8	92 ± 8
	Post	90 ± 11	102 ± 10

Values are expressed as means ± SE.
*Significant time effect.
**Significant group–time interaction.
LVMI, left ventricular mass index; $\dot{Q}$, cardiac output.

GraphPad Prism (version 7.00 for Windows; Graphpad Software, La Jolla, CA).

RESULTS

Baseline comparisons. Participant characteristics are shown in Table 1. There were no differences in any baseline demographic variables (all $P > 0.05$) between the groups, and no participants had evidence of severe cardiac autonomic dysfunction.

Adherence to training. The mean adherence to HIIT training was 78% ± 4% in T2Dt, and 82% ± 9% of these sessions met the >90% age-predicted maximum HR target. There were no differences within or between groups for weight, BMI, FFM, or total fat after the 3-month intervention (all $P > 0.30$). HbA1c and blood volume did not change in either group after the intervention period (both $P > 0.20$).

Peak exercise test. $\dot{V}O_{2peak}$ was not different at baseline but increased ~15% ± 5% in the T2Dt group ($P = 0.002$) (Table 2). Peak workload was higher in the T2Dt group at all time points ($P = 0.04$) and increased 20% ± 6% after the 3-month intervention ($P = 0.04$), but it did not change in the T2Dc group (0% ± 0%). All participants achieved a respiratory exchange ratio (i.e., $\dot{V}CO_2/\dot{V}O_2$) >1.10. HR recoveries at 1 and 2 min were not affected by either intervention (all $P > 0.50$).

Resting parameters: effects of training. LV mass was not different between groups at baseline ($P = 0.68$) and did not change in either group after the intervention period ($P = 0.70$) (Table 3). Resting HR measured during the supine echocardiogram was reduced postintervention in the T2Dt group and increased in the T2Dc group ($P = 0.01$). Resting LVSV and LVEDV increased ($P = 0.05$, $P = 0.03$) after HIIT training, but LVESV did not change in either group ($P = 0.18$). $\dot{Q}$, EF, and total peripheral resistance (TPR) were not different between groups ($P = 0.58$, $P = 0.40$, and $P = 0.62$, respectively) and did not change in either group after the intervention period ($P = 0.58$, $P = 0.82$, and $P = 0.41$, respectively). SW increased in both groups ($P = 0.04$). Doppler indices of mitral inflow (E, $P = 1.00$; A, $P = 0.88$; E/A, $P = 0.78$), tissue Doppler indices of diastolic relaxation (E′, $P = 0.34$; E/E′, $P = 0.75$), or systolic velocity (S′, $P = 0.20$) were not different in either group at any time point.

Exercise response: effects of exercise training. All cardiovascular responses changed significantly across conditions (rest–40% $\dot{V}O_{2peak}$–60% $\dot{V}O_{2peak}$: all $P < 0.01$). TPR did not change in either group after the intervention period ($P = 0.91$). The magnitude of increase in MABP was greater postintervention in T2Dt ($P = 0.05$). The increase in SW across condition amplified in T2Dt but diminished in T2Dc after the intervention period ($P = 0.02$). These data are summarized in Table 4.

Figure 1 summarizes the LV response to exercise before and after HIIT training. HIIT increased LVEDV in all conditions, but there was no change in the T2Dc group ($P = 0.01$; Fig. 1A). HIIT further reduced LVESV across conditions, but the LVESV response did not change in controls ($P = 0.04$; Fig. 1B). LVSV increased at all conditions after HIIT training

TABLE 4. Echocardiographic derived parameters during rest, 40% of $\dot{V}O_{2peak}$, and 60% of $\dot{V}O_{2peak}$.

		T2Dc			T2Dt		
Variable		Rest	40%	60%	Rest	40%	60%
TPR ($mm\ Hg \cdot min^{-1} \cdot L^{-1}$)	Pre	22.6 ± 2.1	15.3 ± 1.7	14.2 ± 1.0	22.0 ± 1.2	16.4 ± 1.4	13.1 ± 0.8
	Post	20.0 ± 1.9	15.8 ± 1.6	11.6 ± 0.2	21.0 ± 1.5	15.7 ± 0.8	12.0 ± 0.9
MABP (mm Hg)*t,**ct	Pre	104 ± 5	108 ± 4	125 ± 3	105 ± 3	100 ± 5	110 ± 3
	Post	102 ± 6	101 ± 4	98 ± 4	102 ± 3	106 ± 3	108 ± 7
SW ($mL \cdot mm\ Hg^{-1}$)**gt	Pre	87.7 ± 5.9	103.8 ± 13.9	123.3 ± 6.10	89.0 ± 6.8	88.6 ± 7.8	106.7 ± 5.1
	Post	86.3 ± 12.2	88.2 ± 6.8	88.2 ± 6.8	94.5 ± 7.8	102.3 ± 5.9	113.0 ± 11.2
EF (%)*g,**gt	Pre	62.7 ± 1.5	69.6 ± 3.2	73.3 ± 1.9	54.8 ± 2.3	56.6 ± 3.0	61.9 ± 2.4
	Post	62.8 ± 2.2	66.5 ± 1.8	69.7 ± 1.8	56.9 ± 2.1	63.0 ± 2.2	68.2 ± 2.2

Values are expressed as means ± SE. All variables had a significant effect across conditions (all $P < 0.05$).
*gSignificant group effect.
*tSignificant time effect.
**gtSignificant group–time interaction.
**ctSignificant condition–time interaction.

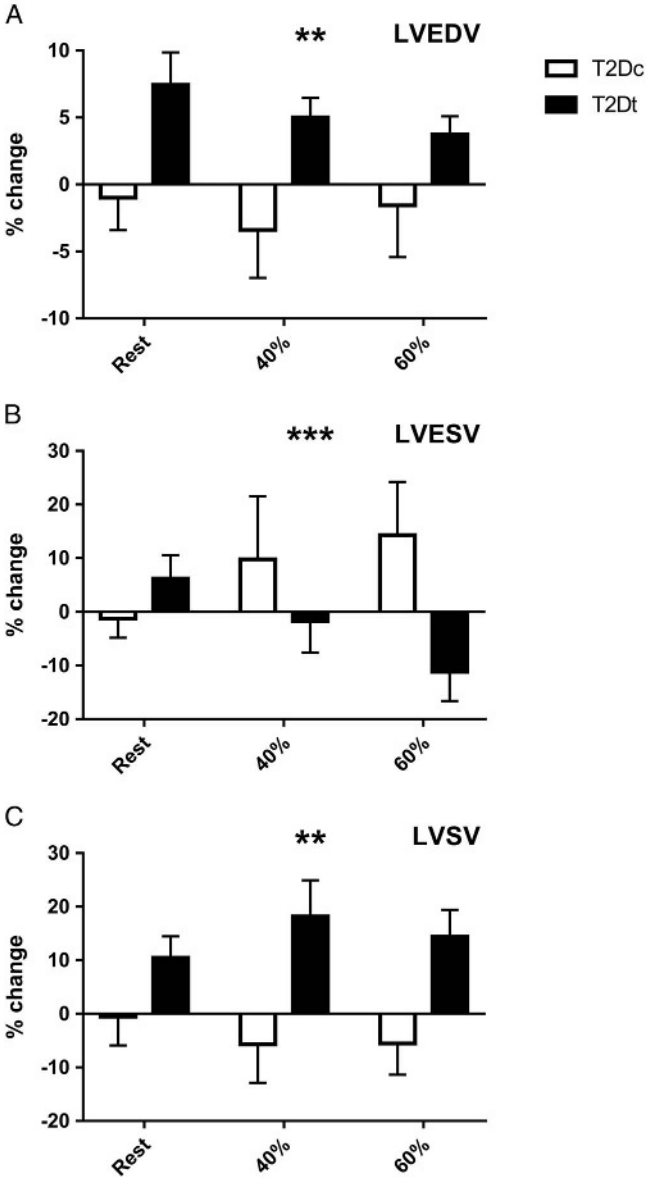

FIGURE 1—The relative ([pre- – post-/preintervention] × 100) change in LVEDV (A), LVESV (B), and LVSV (C) at rest and during low-intensity (40% $\dot{V}O_{2peak}$) and moderate-intensity (60% $\dot{V}O_{2peak}$) exercise after 3 months of HIIT (black bars) or nonexercise control (white bars). **Significant group–time interaction. ***Significant group–time–condition. Values are expressed as means ± SE.

but did not change in the T2Dc group (P = 0.02; Fig. 1C). Exercising HR values were kept constant to eliminate the potential confounding effect of cardiac cycle duration. Consequently, HR did not change as a result of training or in the nontraining control group. HIIT training augmented the rate of increase in $\dot{Q}$ across conditions, but there was no difference in the $\dot{Q}$ response in the T2Dtc group (P = 0.01). EF was smaller in T2Dt across conditions at baseline (P = 0.03), but 3 months of HIIT increased EF so that there were no group differences posttraining (P = 0.03, Table 4).

Figure 2 shows that the change in LVSV during exercise (rest to 40% + rest to 60%) was moderately correlated (R^2 = 0.25) with the corresponding change in LVEDV and inversely associated with LVESV (R^2 = 0.36) when baseline and postintervention values were included in the regression. When only postintervention values were included, there was a stronger correlation between LVSV and LVEDV (R^2 = 0.51) versus LVESV (R^2 = 0.44).

DISCUSSION

T2D alters LV morphology (23), increases the magnitude of end-diastolic pressure development during exercise (11), and may attenuate the contractile response to β-adrenergic activation (24,25). These changes are associated with reduced cardiac reserve and aerobic capacity in people with T2D (1,3). Aerobic exercise training increases cardiac reserve through improved LV function during exercise in nondiabetic individuals (12), but it has been unclear whether exercise has the same effect on the diabetic heart. The main finding of this study is that 3 months of HIIT increased the LVSV response to submaximal semirecumbent exercise in middle-age people with T2D. The increase in LVSV was associated with large, training-induced increases in LVEDV and relatively smaller reductions in LVESV during exercise. There were no effects of training on total blood volume or TPR. These data show that HIIT can improve LV output during exercise in adults with T2D by increased left ventricular filling and, to a lesser extent, augmented systolic emptying.

Our data parallel the findings of Gusso et al. (6) who showed that a 20-wk exercise training program improved the LVSV response to supine exercise in adolescents with type 1 diabetes. They also found that increased LVEDV and reduced LVESV during exercise explained training-induced increases in LVSV. However, it is unclear whether type 1 diabetes and T2D induce similar changes in the heart, and whether adolescents have had sufficient diabetic exposure to induce the biochemical changes described in diabetic adults with long-duration diabetic diagnoses (23). In this context, our findings that HIIT induced a 4%–7% increase in LVEDV and augmented the reduction in LVESV during exercise are the first to show that the LV volume response to semirecumbent exercise can be improved by training in adults with T2D.

We observed no changes in resting Doppler-derived indices of LV diastolic function after HIIT. This contradicts two studies reporting "improved" indices of resting diastolic function after training in adults with T2D (14,26). Some have suggested that the ratio of resting peak early to late mitral inflow (E/A) is associated with aerobic capacity (10,27). However, others have found that the ratio of peak early to late mitral inflow velocity (E/A) is inversely proportional to LVSV during exercise (28). We found that $\dot{V}O_{2peak}$, exercising LVSV, and LVEDV increased in all conditions after HIIT without changes in resting E, A, or E′. This may indicate that changes in LV capacity cannot be estimated by the pattern of LV filling during rest and instead suggest that left ventricular dimensions have a greater influence on the LV exercise responses. In support of this theory, Roberts et al. (29) recently found that LV volumes,

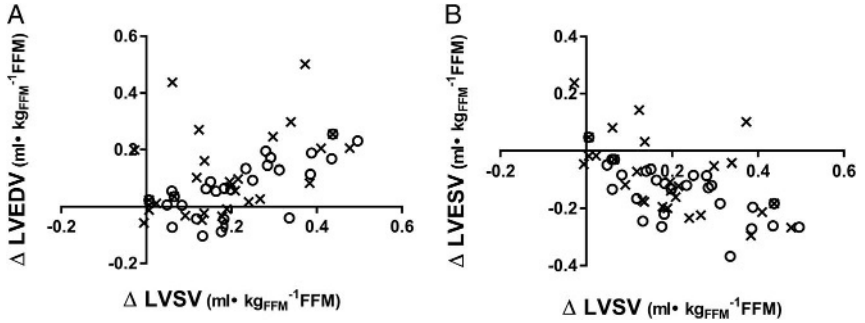

FIGURE 2—A, Linear association between change in LVEDV and LVSV during exercise (rest to 40% and 60% of $\dot{V}O_{2peak}$). R^2 = 0.25 for all samples and R^2 = 0.51 for postintervention only. B, Linear association between change in ESV and SV during exercise. R^2 = 0.36 for all samples and R^2 = 0.44 for postintervention only. X = preintervention and O = postintervention.

particularly LVEDV, were the best predictors of exercise capacity in a mixed group of people with type 1 and 2 diabetes.

Previous studies have reported that total blood volume is reduced (9,30) and is strongly correlated with LVEDV (9) and LVSV (30) in people with diabetes when compared with nondiabetic controls. We did not compare diabetic versus nondiabetic groups in this study; however, HIIT training increased LVEDV and LVSV (at rest and during exercise) without significant changes in total blood volume (P = 0.80). Our findings contradict studies in nondiabetic cohorts reporting total blood volume increases of ~8% after similar training regimens (31). We do not believe our lack of significant changes in total blood volume or HR responses reflect an insufficient training stimulus because the ~15% increase in $\dot{V}O_{2peak}$ in the present study is comparable with many moderate-intensity training studies of similar duration (32). Moreover, similar increases in $\dot{V}O_{2peak}$ have been associated with increased total blood volume (12,33) in nondiabetic cohorts. Instead it is possible that diabetes independently affects these parameters, preventing adaptations normally seen in nondiabetic cohorts.

Cardiac autonomic dysregulation may affect the exercise response in diabetes (16,24,34) and has been associated with exercise intolerance (35). Increased resting HR (3,9) and reduced peak HR and HR reserve (1,3,36) are common findings in people with diabetes that are associated with altered autonomic regulation of the heart. We found a significant (7 beats) reduction in resting HR; however, 3 months of HIIT increased $\dot{V}O_{2peak}$ and $\dot{Q}$ without changing HR reserve or HR recovery at 1 and 2 min postexercise. MABP and TPR, which are also regulated by the autonomic responses to exercise, were similarly unchanged after HIIT. These findings (and no change in total blood volume) suggest that augmented LV performance during exercise was not the result of improved peripheral vascular function or cardiac autonomic control.

Clinical implications. People with diabetes have a higher incidence of congestive heart failure (37), which has led to the somewhat contentious (38) theory that there is unique diabetes-specific cardiomyopathy (39). These definitions are ambiguous but usually share an inability to adequately fill the ventricle, resulting in reduced cardiac reserve (3) and increased prevalence of heart failure with preserved EF (39). Experimental drugs that target "fibrosis" pathways have not conclusively improved LV filling or compliance in humans (40); therefore, our finding that LVSV and LVEDV are increased after HIIT training has promising implications as a method of attenuating diabetic cardiac dysfunction and potentially preventing diabetic heart failure/diabetic cardiomyopathy.

In conclusion, HIIT increased aerobic capacity and improved the LV response to submaximal exercise in adults with well-controlled T2D. These changes occurred independently of improved indices of resting diastolic function, autonomic control, or total blood volume. Improved LV performance appeared to be explained completely the ability to increase LVEDV and decrease LVESV during exercise. The findings of this study suggest that diabetes-specific impairment of diastolic and systolic LV function can be reversed by HIIT training, resulting in greater cardiac reserve.

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