Exercise Training Improves but Does Not Normalize Left Ventricular Systolic and Diastolic Function in Adolescents With Type 1 Diabetes

Silmara Gusso,[1] Teresa Pinto,[2] James C. Baldi,[3] José G.B. Derraik,[1,4] Wayne S. Cutfield,[1,4] Tim Hornung,[5] and Paul L. Hofman[1]

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OBJECTIVE

To determine the impact of 20 weeks of exercise training in aerobic capacity on left ventricular function and glycemic control in adolescents with and without type 1 diabetes.

RESEARCH DESIGN AND METHODS

Fifty-three adolescents with type 1 diabetes (aged 15.6 years) were divided into two groups: exercise training (n = 38) and nontraining (n = 15). Twenty-two healthy adolescents without diabetes (aged 16.7 years) were included and, with the 38 participants with type 1 diabetes, participated in a 20-week exercise-training intervention. Assessments included VO_{2max} and body composition. Left ventricular parameters were obtained at rest and during acute exercise using MRI.

RESULTS

Exercise training improved aerobic capacity (10%) and stroke volume (6%) in both trained groups, but the increase in the group with type 1 diabetes remained lower than trained control subjects. Increased stroke volume in adolescents with type 1 diabetes resulted from greater left ventricular contractility (9% increase in ejection fraction and an 11% reduction in end-systolic volumes) and, to a lesser extent, improved left ventricular filling (6%), suggesting that impaired diastolic function can be affected by exercise training in adolescents with type 1 diabetes. Insulin use decreased by ∼10%, but no change in glycemic status was observed.

CONCLUSIONS

These data demonstrate that in adolescents, the impairment in left ventricular function seen with type 1 diabetes can be improved, although not normalized, with regular intense physical activity. Importantly, diastolic dysfunction, a common mechanism causing heart failure in older subjects with diabetes, appears to be partially reversible in this age group.

Regular physical activity has many potential health benefits, and there is strong evidence of its role in the primary and secondary prevention of chronic diseases such as cardiovascular disease and diabetes (1). In particular, exercise training improves exercise capacity and cardiac output by increasing left ventricular function (2–5). Training increases left ventricular stroke volume by enhancing intrinsic cardiac contractility

[1]Liggins Institute, University of Auckland, Auckland, New Zealand
[2]IWK Health Centre, Dalhousie University, Halifax, Nova Scotia, Canada
[3]Department of Medicine, University of Otago, Otago, New Zealand
[4]A Better Start–a National Science Challenge, University of Auckland, Auckland, New Zealand
[5]Department of Paediatric Cardiology, Starship Children's Hospital, Auckland, New Zealand

Corresponding author: Silmara Gusso, s.gusso@auckland.ac.nz.

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(decreased end-systolic volume and increased ejection fraction) and improving left ventricular filling (increased end-diastolic volume) (6,7).

Adults and adolescents with type 1 diabetes have reduced exercise capacity (8–10), which increases their risk for cardiovascular morbidity and mortality (11). The causes for this reduced exercise capacity are unclear. However, recent studies have shown that adolescents with type 1 diabetes have lower stroke volume during exercise, which has been attributed to alterations in left ventricular function (9,10). Reduced left ventricular compliance resulting in an inability to fill the left ventricle appropriately during exercise has been shown to contribute to the lower stroke volume during exercise in both adults and adolescents with type 1 diabetes (12).

Exercise training is recommended as part of the management of type 1 diabetes. However, the effects of exercise training on left ventricular function at rest and during exercise in adolescents with type 1 diabetes have not been investigated. In particular, it is unclear whether exercise training improves cardiac hemodynamics during exercise in adolescents with diabetes. Therefore, we aimed to assess left ventricular volumes at rest and during exercise in a group of adolescents with type 1 diabetes compared with adolescents without diabetes before and after a 20-week exercise-training program. We hypothesized that exercise training would improve exercise capacity and exercise stroke volume in adolescents with diabetes.

RESEARCH DESIGN AND METHODS

Study Participants

Baseline data comparing adolescents with type 1 diabetes and healthy control subjects have been previously published (10). This study reports the effects of 20 weeks of exercise training on the left ventricular function in this population. Adolescents with type 1 diabetes or healthy control subjects without diabetes aged 14–18 years and matched for sex, body composition, pubertal stage, and reported physical activity levels were recruited for this study. Participants with diabetes were sequentially recruited from the Auckland Adolescent Diabetes Clinic, whereas the control subjects were friends or siblings without diabetes with similar reported levels of physical activity. All participants were healthy with no evidence of hypertension, microvascular complications such as retinopathy, neuropathy, or microalbuminuria, and no chronic diseases other than type 1 diabetes. None of the adolescents with type 1 diabetes was taking regular medications other than insulin. This study was approved by the Northern X Regional Ethics Committee-Ministry of Health (reference number NTX/07/12/125) and registered at the Australian New Zealand Clinical Trials Registry (ACTRN12608000075381). All participants provided written informed consent, and it was compulsory for those under the age of 16 to have written parental consent to participate in the study.

Ninety adolescents with type 1 diabetes were eligible from the Auckland Adolescent Diabetes Clinic, of whom 53 (27 males) agreed to participate in our study. Twenty-seven healthy control subjects were contacted from the community (friends or family members of participants with diabetes), and 22 agreed to participate. Note that apart from examining between-group differences, we were also interested in assessing possible effects of exercise within the training group with type 1 diabetes, particularly in regards to associations with HbA_{1c}. Thus, we adopted a 2:1 randomization strategy so that we would have approximately twice as many participants with diabetes training, which would increase the statistical power to detect within-group differences. Participant randomization was performed using an electronically generated random list allocating adolescents with type 1 diabetes to the exercise or nonexercise group. Because of timeline restrictions, recruitment was ceased once 75 participants were enrolled, thus the unbalanced group numbers. Consequently, 38 (20 male) participants with type 1 diabetes were then randomized to engage in a 20-week exercise program, whereas the remaining 15 acted as a nontraining control group. The 22 healthy control subjects (10 males) who were matched for sex, body composition, and reported physical activity levels also engaged in the 20 weeks of exercise training. All posttraining assessments were conducted between 5 and 7 days after the last exercise session. Note that all procedures were not carried out and therefore rescheduled if the participant's blood glucose levels were <5 or >12 mmol/L.

Body Composition

Body composition was determined by DXA (GE Lunar Prodigy, Madison, WI) using the standard manufacturer's software (Encore v.4) as formerly described (10). BMI was calculated as weight in kilograms divided by height in meters squared. Abdominal adiposity was estimated by the ratio of android fat to gynoid fat, which was measured automatically by the Prodigy enCORE software. Antecubital venous blood samples were collected to determine HbA_{1c}.

Functional Aerobic Capacity

Functional aerobic capacity was assessed by pedaling to exhaustion on an electronically braked cycle ergometer (Schiller, Baar, Switzerland) as previously described (TrueOne 2400 Metabolic Measurement System; Parvo Medics, Sandy, UT) (10).

Left Ventricular Function at Rest and During Exercise

Cardiac MRIs were obtained at rest and during acute exercise using a 1.5T Magnetom Avanto MRI scanner (Siemens, Erlangen, Germany) as previously described (10,13). Left ventricular exercise images were obtained once 1 min of steady-state heart rate (110 $\pm$ 5 bpm) was reached. Images were acquired during breath-hold maneuvers at midexpiration. Ergometer resistance and participants' cycling speed (revolutions per minute) were adjusted to maintain the target heart rate of $\pm$5 bpm. Blood pressure measurement was obtained after resting cardiac images were obtained and during pedaling, at the end of exercise measurements.

Analyses of cardiac MRI analyses were performed with the Cardiac Image Modeler software (University of Auckland, Auckland, New Zealand). Parameters obtained included ejection fraction, stroke volume, cardiac output, end-systolic volume, and end-diastolic volume. Stroke work was calculated by dividing stroke volume by mean arterial pressure. Total peripheral resistance was calculated by dividing mean arterial pressure by cardiac output. The O_2 pulse was calculated by dividing oxygen consumption per heartbeat. The analyses of MRI data were performed blinded. However, data on maximal aerobic capacity analysis were not blinded, as the group with diabetes required blood glucose testing before and after the procedures, and data were collected by assessor. All assessments

were performed by the same experienced exercise physiologist.

Exercise Training

Exercise training consisted of four 60-min (including warm-up and cool-down periods) exercise sessions per week over 20 weeks. Sessions were performed individually or with a friend, under the supervision of an exercise physiologist. Training was progressively adjusted to achieve 85% of the participant's maximal heart rate (obtained during the VO_{2peak} test) during aerobic exercise training (weeks 1–4). After that (weeks 5–20), participants were asked to exercise at the target heart rates of 85% of the maximal heart rate for a minimum of 40 min/session during the aerobic sessions. Participants were instructed to perform at least three sessions a week of aerobic training (combination of treadmill, cycling, and rowing machine with interval training) followed by weekly resistance training (weight training and core exercises) from weeks 1–12. From weeks 12–20, participants engaged in four exercise sessions a week of combined aerobic and resistance training (circuit training). This planned change in exercise regimen aimed at sustaining the participant's engagement with the program, so that compliance with the exercise protocol was maximized. Participants had up to 30-s rest (to catch their breath) between exercise/mode of exercise.

Each participant in the training group received a downloadable heart rate monitor (Polar S625X; Polar Electro, Kempele, Finland) that was used to record their exercise sessions. These records provided a quantitative assessment of compliance and ensured that participants were exercising at appropriate target heart rates. Data were downloaded into a research database using a Polar infrared device (Polar Electro, Hong Kong).

Data Analyses

Age and diabetes duration data were compared using one-way ANOVA and sex ratio with a χ^2 test. All other study parameters were compared using linear regression models, controlling for age and sex. For specific cardiac parameters (ejection fraction, stroke volume, cardiac output, end-systolic volume, end-diastolic volume, stroke work, and total peripheral resistance), fat-free mass was also included as a covariate. Analyses were carried out in SAS version 9.3 (SAS Institute, Cary, NC). All statistical tests were two-tailed. Significance level was maintained at $P < 0.05$, with no adjustments for multiple comparisons. Age and diabetes duration data are reported as means ± SD; all other data are means and 95% CIs adjusted for confounders in the multivariate models.

RESULTS

From the 75 participants enrolled at baseline, 3 participants with type 1 diabetes (1 male and 2 female) did not complete the study (because of the time commitment required). The final study population consisted of 72 participants: 37 with type 1 diabetes in the exercise-training group; 13 with type 1 diabetes in the control group; and 22 adolescents without diabetes in the exercise-training group.

Participants' Characteristics and Body Composition

Table 1 shows the participants' characteristics before and after training. The training group without diabetes was ~1 year older than the groups with type 1 diabetes at the start of the study. There were no other baseline differences between groups. After 20 weeks, both groups with type 1 diabetes significantly increased their total body weight. Interestingly, the control group with type 1 diabetes gained weight by accumulating fat, as seen by an increase in percentage body fat, whereas in the training group with type 1 diabetes, the increase in body weight was because of greater fat-free mass. Exercise training had a positive impact on body composition, with both training groups reducing their percentage body fat and increasing fat-free mass and bone mineral density. Exercise training did not modify HbA_{1c} levels on the study groups, but it reduced daily insulin consumption by ~10% in the training group with type 1 diabetes.

Functional Aerobic Capacity

Overall compliance in the exercise-training groups was high, with an average completion of 84.7% of the total exercise sessions prescribed (84.1% with type 1 diabetes and 85.7% in the group without diabetes), with all participants achieving up to 85% of their VO_{2peak} heart rate during exercise sessions. Table 2 shows the functional aerobic capacity outcomes measured during the maximal oxygen consumption test.

VO_{2peak} expressed by liters per minute adjusted for age, sex, and fat-free mass was lower in the groups with diabetes at baseline. Exercise training increased in exercise capacity in both training groups (12% in the group with type 1 diabetes and 13% in the group without diabetes).

Exercise training did not alter resting and maximal exercise systolic, diastolic, or mean arterial pressure (Table 2). However, the maximal exercise mean arterial pressure increased in the control group with type 1 diabetes after 20 weeks. Exercise training improved maximal O_2 pulse and workload achieved on both training groups. Resting heart rate was comparatively higher at baseline on both groups with type 1 diabetes compared with adolescents without diabetes; this parameter remained higher in the control group with type 1 diabetes, but not in the training group with type 1 diabetes after 20 weeks.

Left Ventricular Function During MRI Scanning

Table 3 shows the MRI scan outcomes for left ventricular function at rest and during supine submaximal exercise, both at baseline and posttraining.

Heart Rate, Blood Pressure, and Mean Arterial Pressure

After training, there was a significant reduction in the resting heart rate in both training groups (Table 3). Resting mean arterial pressure, submaximal exercise systolic blood pressure, and resting diastolic blood pressure decreased in the training group with type 1 diabetes after 20 weeks of exercise.

Left Ventricular Function (Resting)

The exercise intervention significantly improved the left ventricular function of both training groups at rest (Table 3). There was an increase in stroke volume and a decrease in heart rate in the supine position, with no changes in cardiac output. The increase in stroke volume was attributed to changes in left ventricular filling capacity, as shown by larger end-diastolic volume in training groups. There was no change in end-systolic volume observed in those with diabetes who exercise trained in contrast to an increase observed in the adolescents with diabetes who did not train. In agreement with these findings, resting ejection fraction increased in adolescents with diabetes who trained, but decreased in those who did not.

Table 1—Demography, clinical characteristics, and body composition at baseline and after 20 weeks (posttraining) in adolescents with type 1 diabetes who trained (T1D Tx), with type 1 diabetes who did not train (T1D Con), and without diabetes who trained (ND Tx)

	Baseline			Posttraining		
	T1D Con	T1D Tx	ND Tx	T1D Con	T1D Tx	ND Tx
N (% female)	15 (53)	38 (47)	22 (55)	13 (46)	37 (49)	22 (55)
Age (years)	15.5 ± 0.9*	15.6 ± 1.3*	16.7 ± 1.5	—	—	—
Diabetes duration (years)	7.5 ± 4.0	5.4 ± 3.4	—	—	—	—
HbA_{1c} (%)	8.57 (7.84–9.31)****	8.80 (8.36–9.25)****	5.15 (4.43–5.88)	8.67 (8.06–9.28)****	8.50 (8.13–8.86)****	5.14 (4.45–5.83)
HbA_{1c} (mmol/mol)	70 (62–78)	73 (68–78)	33 (25–41)	71 (65–78)	69 (65–73)	33 (25–40)
Insulin (units/day)	73.8 (60.4–87.3)	64.8 (57.5–72.2)	—	80.3 (64.5–96.1)	59.1 (50.3–67.9)†,#	—
Weight (kg)	69.2 (63.3–75.1)	69.8 (66.1–73.6)	64.6 (59.5–69.7)	71.0 (65.0–77.0)#	70.2 (66.6–73.8)#	65.7 (60.9–70.5)
BMI (kg/m^2)	24.6 (22.8–26.4)	23.5 (22.4–24.7)	23.0 (21.4–24.5)	25.0 (23.1–26.9)	23.5 (22.4–24.7)	23.1 (21.5–24.6)
Bone mineral density (g/cm^2)	1.184 (1.140–1.229)	1.141 (1.113–1.169)	1.136 (1.110–1.174)	1.181 (1.138–1.122)	1.146 (1.120–1.172)####	1.154 (1.120–1.189)####
Percent fat-free mass	74.2 (70.0–78.3)	74.3 (71.7–76.9)	73.1 (69.5–76.6)	72.6 (68.0–77.1)	75.3 (72.6–78.1)####	73.9 (70.3–77.6)##
Percent total body fat	27.3 (23.0–31.6)	26.8 (24.0–29.5)	27.9 (24.2–31.6)	28.6 (24.0–33.2)#	25.7 (22.9–28.5)##	26.8 (23.0–30.5)##
Android fat to gynoid fat ratio	0.884 (0.791–0.976)	0.855 (0.797–0.913)	0.827 (0.748–0.906)	0.897 (0.789–1.00)	0.841 (0.776–0.905)	0.844 (0.758–0.931)

Age and diabetes duration data are means ± SD; other data are means and 95% CIs adjusted for age and sex. †$P < 0.05$ for comparisons between the two groups with diabetes. *$P < 0.05$; ****$P < 0.0001$ for comparisons with ND Tx. #$P < 0.05$; ##$P < 0.01$; ####$P < 0.0001$ for a change from baseline within group.

Left Ventricular Function (Submaximal Exercise)

Submaximal exercise cardiac output, stroke volume, end-diastolic volume, and ejection fraction increased significantly in the two training groups (Table 3). The training group without diabetes and, to a lesser extent, the training group with type 1 diabetes required an increased workload to maintain their target heart rate during the submaximal exercise MRI scan. Interestingly, the training group with type 1 diabetes also showed improvement in contractility with a significant decrease in end-systolic volume after the intervention that was not observed in the training group without diabetes. Table 3 also illustrates the left ventricular volumes indexed for participants' fat-free mass. Twenty weeks of exercise training improved indexed cardiac output, stroke volume, and end-diastolic volume during exercise in the group with diabetes.

Left Ventricular Outcomes as Percentage Change

To gain a better understanding of the alterations that occurred in the left ventricular function, we calculated the percentage change of cardiac output, stroke volume, end-diastolic volume, end-systolic volume, and ejection fraction from rest to submaximal exercise at baseline and after 20 weeks of training (Fig. 1). There were improvements in both training groups, but greater improvements overall were observed in those with diabetes.

Total Peripheral Resistance

Total peripheral resistance at rest did not alter with training intervention (Table 3). The total peripheral resistance during submaximal exercise, however, was higher in the groups with diabetes prior to the intervention and significantly reduced in the training group with type 1 diabetes. Although total peripheral resistance improved in the training group with type 1 diabetes, it remained elevated compared with the training group without diabetes.

Training and Glycemic Control

There were no associations between glycemic control (HbA_{1c}) and diabetes duration with the MRI variables posttraining. However, higher HbA_{1c} levels were associated with worse functional aerobic capacity outcomes including higher resting heart rate ($P = 0.007$ for the control group with type 1 diabetes and $P = 0.003$ for the

Table 2—Results from VO_{2peak} tests carried out at baseline and after 20 weeks (posttraining) in adolescents with type 1 diabetes who trained (T1D Tx), with type 1 diabetes who did not train (T1D Con), and without diabetes who trained (ND Tx)

		Baseline			Posttraining		
	Time	T1D Con	T1D Tx	ND Tx	T1D Con	T1D Tx	ND Tx
N (% female)		15 (53)	38 (47)	22 (5)	13 (46)	37 (49)	22 (55)
Heart rate (bpm)	At rest	76.5 (70.1–82.9)*	74.5 (70.5–78.5)*	67.1 (61.7–72.6)	78.7 (72.1–85.4)**	72.1 (68.1–76.1)	65.9 (60.6–71.3)
	Maximal exercise	182.6 (177.4–187.7)	188.6 (185.4–191.8)†	185.7 (181.3–190.1)	181.7 (176.6–186.8)	187.8 (184.7–190.8)	187.4 (183.3–191.5)
Systolic BP (mmHg)	At rest	110.3 (106.3–114.3)	110.2 (107.7–112.7)	106.3 (102.9–109.8)	109.5 (105.4–113.7)	110.2 (107.7–112.7)	106.1 (102.7–109.4)
	Maximal exercise	169.1 (159.7–178.5)	170.2 (164.3–176.1)	160.3 (152.3–168.3)	173.6 (164.9–182.3)**	171.0 (165.7–176.2)*	158.9 (151.9–165.9)
Diastolic BP (mmHg)	At rest	63.3 (59.6–67.0)	63.5 (61.2–65.9)	61.2 (58.0–64.4)	63.3 (59.5–67.1)	63.0 (60.7–65.3)	60.2 (57.1–63.2)
	Maximal exercise	67.5 (63.3–71.7)	67.0 (64.4–69.7)	67.5 (63.9–71.1)	70.6 (66.0–75.3)*	64.9 (62.1–67.7)†	64.7 (60.9–68.4)
Mean arterial pressure (mmHg)	At rest	79.0 (75.5–82.4)	79.1 (76.9–81.2)	76.2 (73.2–79.2)	78.7 (75.2–82.3)	78.7 (76.6–80.9)	75.5 (72.6–78.3)
	Maximal exercise	101.4 (97.0–105.8)	101.4 (98.6–104.2)	98.5 (94.7–102.2)	105.0 (100.6–109.3)**,#	100.3 (97.6–102.9)	96.1 (92.6–99.6)
O_2 pulse	Maximal exercise	12.3 (11.0–13.6)	12.3 (11.5–13.2)	12.3 (11.2–13.4)	12.5 (11.0–14.0)	14.0 (13.1–14.9)####	13.8 (12.6–15.0)####
Respiratory exchange ratio	Maximal exercise	1.21 (1.18–1.23)	1.20 (1.19–1.22)	1.24 (1.22–1.26)	1.19 (1.15–1.23)*	1.21 (1.19–1.23)	1.25 (1.22–1.27)
VO_{2peak} (L/min)	Maximal exercise	2.19 (2.00–2.38)*	2.24 (2.12–2.36)*	2.47 (2.30–2.63)	2.26 (2.07–2.46)***	2.51 (2.39–2.64)*,†,####	2.79 (2.63–2.96)####
VO_{2peak} (mL/kg FFM/min)	Maximal exercise	43.8 (40.4–47.1)*	45.0 (42.9–47.1)*	48.5 (45.7–51.4)	44.2 (40.5–47.8)***	49.9 (47.7–52.1)*,††,####	53.6 (50.6–56.5)####
Workload (watts)	Maximal exercise	190.7 (166.6–214.9)	197.9 (182.7–213.1)	192.1 (171.4–212.8)	187.7 (161.5–214.0)	214.2 (198.4–230.1)####	218.5 (197.4–239.6)####

Data are adjusted means and 95% CIs from multivariate models. BP, blood pressure; FFM, fat-free mass. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ for comparisons with ND Tx. †$P < 0.05$; ††$P < 0.01$ for comparisons between the two groups with diabetes. #$P < 0.05$; ###$P < 0.001$; ####$P < 0.0001$ for a change from baseline within group.

training group with type 1 diabetes), higher resting diastolic blood pressure ($P = 0.031$), and higher resting mean arterial pressure ($P = 0.035$) overall. Glycemic control was also inversely associated with VO_{2peak} in both groups with diabetes ($P = 0.029$ for the control group with type 1 diabetes and $P = 0.009$ for the training group with type 1 diabetes).

CONCLUSIONS

To our knowledge, this is the first study to investigate the effects of exercise training on the cardiac performance at rest and during exercise in adolescents with type 1 diabetes using exercise MRI. This study confirms that aerobic capacity is reduced in these adolescents and that this, at least in part, can be attributed to impaired left ventricular function and a blunted cardiac response to exercise (9). Importantly, although an aerobic exercise-training program improved the aerobic capacity and cardiac function in adolescents with type 1 diabetes, it did not normalize them to the levels seen in the training group without diabetes. Both left ventricular filling and contractility improved after exercise training in adolescents with diabetes, suggesting that aerobic fitness may prevent or delay the well-described impairment in left ventricular function in diabetes (9,10).

The increase in peak aerobic capacity (~12%) seen in this study was consistent with previous exercise interventions in adults and adolescents with diabetes (14). However, the baseline peak aerobic capacity was lower in the participants with diabetes and improved with training to a level similar to the baseline observed in the participants without diabetes; therefore, trained adolescents with diabetes remained less fit than equally trained adolescents without diabetes. This suggests there are persistent differences in the cardiovascular function in adolescents with diabetes that are not overcome by exercise training. Consistent with our findings, studies in rodents showed that training-induced increases in cardiac output, stroke volume, and end-diastolic volume in diabetic animals have only reached values equivalent to untrained nondiabetic rodents (15). Thus, although there is some reversibility in cardiac function with exercise training, these adaptations do not achieve levels found in healthy adolescents without diabetes.

Table 3—Cardiac MRI parameters at rest and during submaximal exercise at baseline and after 20 weeks (posttraining) in adolescents with type 1 diabetes who trained (T1D Tx), with type 1 diabetes who did not train (T1D Con), and without diabetes who trained (ND Tx)

		Baseline			Posttraining		
	Time	T1D Con	T1D Tx	ND Tx	T1D Con	T1D Tx	ND Tx
N (% female)		15 (53)	38 (47)	22 (55)	13 (46)	37 (49)	22 (55)
Left ventricular mass (g)	At rest	129.5 ± 4.8	128.4 ± 3.1	133.7 ± 4.3	130.8 ± 5.2	131.6 ± 3.2###	141.7 ± 4.4####
Left ventricular mass (g/kg FFM)		2.59 (2.39–2.78)	2.58 (2.45–2.70)	2.72 (2.55–2.88)	2.58 (2.39–2.77)	2.60 (2.49–2.71)	2.77 (2.62–2.92)
Heart rate (bpm)	At rest	72.9 (67.4–78.5)	75.2 (71.7–78.7)	70.1 (65.3–74.8)	73.7 (67.6–79.8)	69.8 (66.2–73.5)##	65.0 (60.1–69.8)#
	Submaximal exercise	109.4 (106.6–112.3)	109.8 (108.0–111.6)	108.9 (106.5–111.4)	108.3 (106.0–110.6)	108.2 (106.8–109.6)##	107.9 (106.0–109.7)
Systolic blood pressure (mmHg)	At rest	108.2 (103.0–113.3)	110.4 (107.1–113.6)**	102.7 (98.3–107.1)	109.6 (104.4–114.8)	107.9 (104.7–111.0)	102.9 (98.7–107.1)
	Submaximal exercise	128.2 (119.8–136.6)	128.2 (123.0–133.5)	119.3 (112.1–126.5)	123.5 (115.8–131.1)	123.0 (118.4–127.6)#	119.3 (113.2–125.4)
Diastolic blood pressure (mmHg)	At rest	60.3 (56.2–64.5)	60.7 (58.1–63.3)*	56.0 (52.4–59.5)	60.8 (56.7–64.8)	56.4 (53.9–58.8)##	58.0 (54.8–61.3)
	Submaximal exercise	66.2 (60.8–71.5)	65.9 (62.6–69.3)	60.7 (56.2–65.3)	66.1 (61.4–70.8)	64.7 (61.9–67.5)	60.8 (57.0–64.5)
Mean arterial pressure (mmHg)	At rest	76.3 (72.7–79.9)*	77.2 (75.0–79.5)**	71.5 (68.5–74.6)	77.0 (73.5–80.6)	73.5 (71.4–75.7)##	73.0 (70.1–75.8)
	Submaximal exercise	86.8 (81.4–92.2)	86.7 (83.3–90.1)	80.3 (75.6–84.9)	85.2 (80.5–89.9)	84.1 (81.3–86.9)	80.3 (76.5–54.1)
Cardiac output (L/min)	At rest	6.66 (6.04–7.27)	7.00 (6.61–7.39)	6.67 (6.13–7.22)	6.62 (5.87–7.36)	7.02 (6.56–7.48)	6.65 (6.03–7.27)
	Submaximal exercise	10.25 (9.49–11.00)*	10.30 (9.82–10.79)**	11.45 (10.78–12.12)	10.03 (9.08–10.98)***	11.40 (10.81–11.99)*,†,####	12.56 (11.76–13.35)##
Cardiac output (mL/kg FFM)	At rest	133.5 (118.8–146.3)	141.0 (132.3–149.6)	142.3 (130.6–154.1)	130.4 (116.0–144.7)	137.9 (129.2–146.5)	134.8 (123.3–146.3)
	Submaximal exercise	206.5 (190.8–222.1)**	207.7 (197.8–217.5)**	235.9 (222.5–249.3)	198.2 (180.4–216)****	225.8 (215.1–236.6)**,††,###	252.4 (238.0–266.7)##
Stroke volume (mL)	At rest	91.9 (84.7–99.1)	92.9 (88.3–97.5)	96.3 (89.9–102.7)	91.2 (82.4–99.9)*	100.5 (95.1–105.9)####	104.9 (97.6–112.2)##
	Submaximal exercise	93.9 (87.1–100.7)*	93.7 (89.4–98.0)**	105.9 (99.9–111.9)	92.8 (84.0–101.6)***	105.5 (100.1 –110.9)*,†,####	116.7 (109.3–124.0)##
Stroke volume (mL/kg FFM)	At rest	1.82 (1.67–1.98)*	1.87 (1.77–1.97)*	2.05 (1.92–2.19)	1.80 (1.64–1.96)**	1.98 (1.89–2.08)*,###	2.08 (1.95–2.21)
	Submaximal exercise	1.89 (1.76–2.03)**	1.90 (1.82–1.99)***	2.17 (2.05–2.28)	1.83 (1.67–1.99)****	2.09 (1.99–2.19)**,††,####	2.34 (2.21–2.47)###
End-diastolic volume (mL)	At rest	143 (133–153)	147 (141–154)	157 (148–166)	150 (138–162)	150 (143–157)#	163 (153–173)#
	Submaximal exercise	135 (126–145)*	139 (133–145)*	153 (144–161)	138 (126–149)**	147 (140–154)*,##	161 (151–171)#
End-diastolic volume (mL/kg FFM)	At rest	2.88 (2.67–3.08)*	2.96 (2.84–3.09)*	3.20 (3.03–3.38)	2.97 (2.75–3.18)	2.98 (2.85–3.11)*	3.21 (3.04–3.39)
	Submaximal exercise	2.73 (2.54–2.92)**	2.81 (2.69–2.93)**	3.09 (2.93–3.25)	2.72 (2.51–2.92)***	2.93 (2.81–3.05)*,#	3.18 (3.02–3.34)
End-systolic volume (mL)	At rest	51.5 (46.3–56.6)*	54.3 (51.0–57.6)*	60.4 (55.9–65.0)	55.7 (49.7–61.8)#	50.2 (46.5–54.0)*	58.0 (53.0–63.0)
	Submaximal exercise	41.2 (35.6–46.7)	45.2 (41.7–48.8)	46.5 (41.6–51.4)	44.2 (38.6–49.7)	40.1 (36.6–43.6)#	43.6 (39.0–48.3)
End-systolic volume (mL/kg FFM)	At rest	1.04 (0.94–1.14)*	1.09 (1.03–1.16)*	1.21 (1.12–1.30)	1.11 (0.99–1.23)	1.00 (0.93–1.07)*,##	1.13 (1.04–1.23)#
	Submaximal exercise	0.83 (0.72–0.94)	0.92 (0.85–0.98)	0.91 (0.82–1.01)	0.88 (0.76–0.99)	0.81 (0.74–0.87)##	0.85 (0.76–0.94)##
Ejection fraction (%)	At rest	64.4 (61.9–66.9)	63.0 (61.4–64.5)	62.8 (60.6–64.9)	61.8 (59.2–64.4)##	66.3 (64.8–67.9)††,###	64.7 (62.6–66.8)
	Submaximal exercise	69.4 (64.7–74.1)	66.1 (63.2–69.1)	69.9 (65.9–73.9)	67.5 (64.7–70.4)**,#	72.1 (70.4–73.8)††,####	73.4 (71.1–75.6)###
Stroke work	At rest	95.2 (86.4–104.0)	97.6 (92.0–103.3)	94.4 (86.6–102.2)	95.5 (84.5–106.5)	101.0 (94.2–107.8)	104.6 (95.5–113.8)##
	Submaximal exercise	111.5 (99.4–123.5)	110.5 (102.8–118.2)	118.8 (108.2–129.4)	108.1 (96.4–119.9)*	120.5 (113.2–127.7)##	128.5 (118.7–138.3)#
Total peripheral resistance	At rest	11.9 (10.7–13.0)	11.5 (10.7–12.2)	11.0 (10.0–12.0)	12.1 (11.0–13.1)	11.1 (10.4–11.7)	11.4 (10.5–12.3)
	Submaximal exercise	8.5 (7.8–9.4)*	8.7 (8.2–9.2)**	7.2 (6.5–7.9)	8.8 (8.0–9.5)****	7.6 (7.2–8.1)*,†,####	6.6 (5.9–7.2)
Workload (watts)	Submaximal exercise	37.7 (30.7–44.7)	35.4 (31.2–39.6)	34.9 (28.7–41.1)	32.5 (25.0–40.1)*	41.5 (37.1–45.8)**,†,#	49.0 (42.8–55.2)####

Data are means and 95% CIs adjusted for age and sex. FFM, fat-free mass. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ****$P < 0.0001$ for comparisons with ND Tx. †$P < 0.05$; ††$P < 0.01$ for comparisons between the two groups with diabetes. #$P < 0.05$; ##$P < 0.01$; ###$P < 0.001$; ####$P < 0.0001$ for a change from baseline within group.

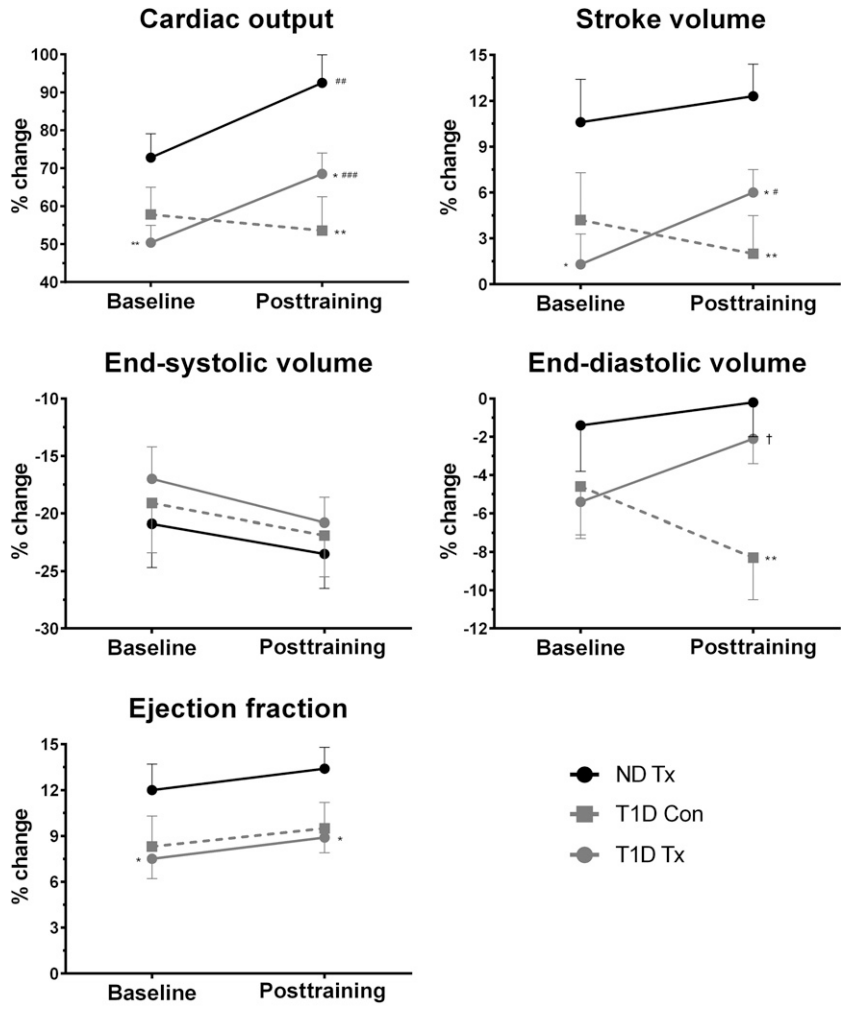

Figure 1—Percentage changes in cardiac outcomes from rest to exercise at baseline and after 20 weeks (posttraining) in adolescents with type 1 diabetes who trained (T1D Tx), with type 1 diabetes who did not train (T1D Con), and without diabetes who trained (ND Tx). *$P < 0.05$; **$P < 0.01$ for comparisons with ND Tx; †$P < 0.05$ for comparisons between the two groups with diabetes; #$P < 0.05$; ##$P < 0.01$; ###$P < 0.001$ for differences from baseline within groups.

A novel observation from this study was that regular exercise reverses the diastolic effects of type 1 diabetes. Left ventricular filling patterns (16) and end-diastolic volume (10) are reduced in adolescents with well-controlled type 1 diabetes. Although we did not quantify filling patterns, we found that exercise training increased end-diastolic volume and stroke volume to levels found in healthy untrained adolescents without diabetes both at rest and during moderate-intensity exercise. Supine exercise exposes the heart to elevated left ventricular preload and large end-diastolic volume (6); therefore, increasing end-diastolic volume under these conditions requires greater left ventricular compliance, increased left ventricular filling pressure, or both (17). We did not measure left ventricular pressure, but others have shown that left ventricular compliance increases after endurance training and is reduced by inactivity (18). Thus, it is possible that the improvements in end-diastolic volume in the trained group with diabetes were because of improved left ventricular compliance.

Blood volume was not measured in this study, but a training-induced increase in blood volume may have influenced our findings. Blood volume increases with chronic exercise training (19), and endurance-trained athletes rely on increased total blood volume and increased rates of diastolic filling to achieve greater stroke volume during exercise (20,21). Type 1 (22) and type 2 diabetes (23) are associated with reduced blood volume and smaller end-diastolic volume. Thus, a preload reduction caused by a smaller blood volume in adolescents with diabetes may have contributed to lower end-diastolic volume and stroke volume at baseline, whereas training-induced plasma volume expansion may have combined with changes in left ventricular relaxation to increase end-diastolic volume and stroke volume after 5 months of exercise training.

The improved ejection fraction seen with training in our adolescent population agrees with previous studies in healthy individuals (24). However, unlike adults, in whom changes in end-diastolic volume underlie improved ejection fraction (25), the adolescents with type 1 diabetes in this study appeared to rely more on reductions in end-systolic volume to increase stroke volume and ejection fraction after training (24). Indeed, the reductions in resting end-systolic volume and ejection fraction, without changes in total peripheral resistance or arterial blood pressure, are consistent with increased resting contractility.

We note that although the control with diabetes in our cohort was not within the International Society for Pediatric and Adolescent Diabetes guidelines (HbA_{1c} <7.5%), they were in a range consistent with glycemic control in adolescents internationally. The DCCT trial indicated that among intensively treated adolescents, the average HbA_{1c} was 8.1%, and this changed little over time (26). A large cohort of 27,035 with type 1 diabetes in Austria in 2008 showed a mean HbA_{1c} of 8.0% between 12 and 16 years of age (27). Similarly, a study of patients on insulin pumps and continuous glucose monitoring showed mean HbA_{1c} levels between 8.0 and 8.2% among adolescents (28). The SWEET registry of multiple European sites in 2016 demonstrated a mean HbA_{1c} of 8.2% for patients on multiple daily injections (interquartile range 7.3–9.4%) in children aged 12–18 years (29). Thus, the range of HbA_{1c} levels in this group is similar to those reported internationally. Although we accept that this is not an ideal glycemic control, it is extremely difficult to achieve better control in adolescents. There were no associations between glycemic control and cardiac function (at baseline or during exercise) in the current study, although glycemic control was inversely associated with aerobic capacity in the adolescent cohort. Similarly, data

on adult elite athletes with diabetes indicated that better glycemic control resulted in improved cardiovascular performance (12). Specifically, Baldi and Hofman (12) showed that athletes with diabetes were able to achieve a similar cardiopulmonary response as those without diabetes, but this response was reduced by poor glycemic control. Thus, our data cannot be extrapolated to patients with good glycemic control. In addition, Niranjan et al. (30) showed in a small 7-year follow-up study in nonathlete adults with diabetes that those with higher HbA_{1c} had decreased exercise capacity, maximal heart rate, and cardiac and stroke indices.

Although regular exercise potentially could improve HbA_{1c}, the majority of studies have failed to show this (31–34). Exercise training improved aerobic capacity in this study without affecting glucose control in the participants with diabetes, suggesting that the effects of glycemic status and exercise training may work independently to improve aerobic capacity. Nadeau et al. (35) have recently shown that insulin resistance may independently decrease exercise capacity in nonobese youth with type 1 diabetes, being a stronger correlate than HbA_{1c}. We did not directly measure insulin resistance in our study, but insulin dose decreased by ~10% after training, an indirect measure of insulin sensitivity.

It is important to note that our study has a few limitations. Our sample size was relatively small. However, to our knowledge, this is the largest study ever performed using MRI scans to examine the effects of exercise on cardiac function in subjects with diabetes. There were also a large number of pairwise statistical comparisons carried out without adjustment for multiple comparisons. This is a potential limitation that would have inflated the likelihood of type 1 errors. Thus, our findings need to be interpreted accordingly. The age difference between groups (mean difference of 1 year) could have contributed to the baseline differences seen in the study, although this is unlikely, as the cardiac parameters were controlled for age during analysis. Moreover, previous studies have shown that aerobic capacity does not substantively change with age in adolescence, and, when adjusted for body weight, it actually declines slightly (36). The participants in this study also had HbA_{1c} levels above the recommended limits (<7.5%); therefore, interpretation of our findings cannot be extended to well-controlled youth with diabetes.

In summary, regular intense exercise over 20 weeks was associated with clinically relevant improvements in aerobic capacity and improved left ventricular function. However, in trained adolescents with diabetes, these improvements only achieved levels similar to untrained control subjects without diabetes. In trained adolescents with type 1 diabetes, increased stroke volume was achieved by both increased end-diastolic volume and reduced end-systolic volume, consistent with improved filling and increased left ventricular contractility after training. Given the potential to prevent or reverse the progressive diastolic abnormalities that occur in diabetes, our data support regular intense exercise in adolescents with diabetes.

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