Systolic and Diastolic Abnormalities Reduce the Cardiac Response to Exercise in Adolescents With Type 2 Diabetes

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OBJECTIVE

To better understand the cardiac limitations during exercise in adolescents with type 2 diabetes mellitus (T2DM), we measured left ventricular performance with magnetic resonance imaging (MRI) during exercise in diabetic and nondiabetic adolescents.

RESEARCH DESIGN AND METHODS

Thirteen subjects with T2DM, 27 overweight/obese nondiabetic (ObeseND) subjects, and 19 nondiabetic nonobese control subjects were recruited. Cardiac (left ventricular) MRI scans were performed at rest and during submaximal exercise.

RESULTS

V_{O_2} peak indexed to fat-free mass was reduced in T2DM and ObeseND subjects compared with control subjects ($P < 0.0001$). Indexed cardiac output increased less during exercise and was 20% lower in T2DM subjects due to reduced stroke volume. This was a consequence of reduced ventricular filling with smaller end-diastolic volume, which decreased further during exercise in T2DM subjects, but not in ObeseND or control subjects. End-systolic volume was also smaller in T2DM subjects. These changes were associated with increased resting and exercise diastolic blood pressure, and total peripheral resistance in T2DM subjects.

CONCLUSIONS

Independently of obesity, T2DM impairs cardiac function during exercise in adolescents.

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Exercise is a standard recommendation in the management and prevention of type 2 diabetes mellitus (T2DM) (1,2). Regrettably, people with diabetes often have reduced cardiac reserve (3,4) and a resultant decrease in aerobic capacity (3,5). Adults with T2DM have smaller left ventricular stroke volume (6) and reduced heart rates (3,7) during peak exercise. These factors may present a barrier to exercise participation because recommended "moderate intensity" exercise (2) requires a greater proportion of their aerobic capacity (8).

Several authors suggest that reduced early left ventricular diastolic filling (i.e., diastolic dysfunction) is responsible for lower aerobic capacity in people with T2DM,

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presumably by a reduction in stroke volume (9–11). Lalande et al. (6) found that a small group of men with T2DM had shorter diastolic duration and an increased reliance on late diastolic filling that accompanied smaller end-diastolic and stroke volumes. However, resting measurements may be misleading because they do not represent the loading conditions during exercise, when left ventricular pressure gradients increase and left ventricular filling time is reduced (12–15). Adults with T2DM also have impaired resting systolic function (16), independent of diastolic dysfunction or changes in left ventricular morphology (17). Therefore, it is unclear how diastolic and/or systolic impairment affect cardiac responses to exercise.

The cardiac consequences of diabetes, particularly diastolic dysfunction and left ventricular stiffness (18,19) are associated with diabetes duration, due to the progressive accumulation of permanent advanced glycation end products (20,21), and possibly cardiac steatosis and increased left ventricular free fatty acid metabolism (22). It is therefore hypothesized that early interventions may prevent or delay changes in cardiac function and reduce the elevated risk of developing microvascular and macrovascular morbidity in adolescents with diabetes (21,23). However, adolescents with T2DM also have reduced cardiovascular capacity (24,25), and, thus, preventing diabetes-related complications depends on the assumption that either the cardiovascular consequences of diabetes are not evident in early-stage diabetes or early changes in cardiac function can be reversed.

The aim of this study was to determine whether the cardiac exercise response is impaired in adolescents with a relatively short diagnosis of T2DM. To achieve this, we used magnetic resonance imaging (MRI) to examine the myocardial responses to moderate-intensity exercise in obese diabetic, obese nondiabetic (ObeseND), and lean nondiabetic adolescents using a customized MRI-compatible supine cycle ergometer (26). We hypothesized that T2DM would independently reduce cardiovascular capacity in adolescents and would result in an attenuated stroke volume and end-diastolic volume during steady-state moderate-intensity exercise. Because cardiac performance appears to be affected by glycemic control (27), we also hypothesized that cardiac reserve would be associated with glycated hemoglobin (HbA_{1c}) level.

RESEARCH DESIGN AND METHODS

Study Population

Adolescents with T2DM were recruited from adolescent diabetes clinics in Auckland, New Zealand. Otherwise, healthy overweight or obese adolescents (BMI >90th percentile for age and sex; ObeseND) and nonobese adolescents without diabetes (control subjects) were recruited from schools within the Auckland area. T2DM had been previously diagnosed in all subjects based on a fasting plasma glucose level of ≥7.0 mmol/L, a 2-h plasma glucose level of ≥11.1 mmol/L during an oral glucose tolerance test, or a random plasma glucose level of ≥11.1 mmol/L, as well as on symptoms of hyperglycemia in the face of acanthosis nigricans, and an absence of anti–glutamic acid decarboxylase and anti-insulinoma–associated protein 2 antibodies (28). Exclusion criteria included weight >150 kg (due to physical restrictions of MRI equipment), known cardiac disease, musculoskeletal disease that might limit the ability to exercise maximally, regular drug use (including tobacco), and pregnancy. Subjects with T2DM were also excluded if they had evidence of diabetes complications, including retinopathy, autonomic neuropathy, nephropathy, and microalbuminuria, or if they were taking ACE inhibitors.

Of the 37 patients with T2DM treated in Auckland adolescent clinics, 20 agreed to participate. The following seven subjects were excluded: three with diabetes complications (microalbuminuria and/or retinopathy), two because of medications, and two who failed to attend all study sessions. Thirteen T2DM (6 male subjects), 27 ObeseND (11 male subjects), and 19 control subjects (9 male subjects) were recruited into this study.

Among the subjects with diabetes, six were taking metformin, six were diet-controlled, and one was taking insulin. One of the subjects taking metformin was also taking gliclazide. Among the overweight/obese subjects, six were taking metformin (two of whom were also taking an oral contraceptive pill), one was taking doxycycline for acne, and the remainder were not taking any medications.

This study was approved by the Northern X Regional Ethics Committee. All participants, or their parent/legal guardian if they were <16 years of age, provided written informed consent.

Physical and Physiological Parameters

Clinical assessments were carried out at the Maurice & Agnes Paykel Clinical Research Unit (Liggins Institute, University of Auckland). Fasting blood samples were obtained to determine HbA_{1c} levels, and total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride concentrations. ObeseND subjects underwent an oral glucose tolerance test (using 1.75 g/kg [maximum 75 g] in a 20% dextrose solution) and had fasting insulin concentrations assessed to exclude the existence of undiagnosed T2DM. As a result, two female subjects from the obese/overweight group received diagnoses of impaired glucose tolerance based on oral glucose tolerance test results.

All subjects had height and weight, as well as hip and waist circumferences (at the level of the umbilicus), measured by the same researcher during their first assessment, and BMI was calculated. Percentage of body fat, fat mass, lean mass, and fat-free mass (FFM), as well as android and gynoid percentage of fat, were obtained using dual-energy X-ray absorptiometry scans (Lunar Prodigy 2000; General Electric, Madison, WI).

Exercise Protocol and Peak Exercise Capacity

All subjects performed an incremental exercise test on a cycle ergometer (Schiller, Baar, Switzerland), in which participants were asked to cycle to exhaustion. Exercise testing was performed as per Gusso et al. (29). In brief, the exercise protocol consisted of 1-min stages starting at 55 W, with increments of 15 W per stage. Oxygen uptake, carbon dioxide level, and

minute ventilation were measured, and calculated using a breath-by-breath analyzer (TrueOne 2400 Metabolic Measurement System; Parvo Medics, Sandy, UT). The rates of V_{O_2} and V_{CO_2} were recorded every 30 s. The highest V_{O_2} and heart rate measurements attained were considered to be the peak values. All subjects attained a respiratory exchange ratio of >1.1, and the test was terminated when participants were unable to continue as a result of exhaustion or discomfort. This protocol was designed to last no more than 15 min.

Cardiac MRI

Cardiac images were obtained using a 1.5 Tesla MRI scanner (MAGNETOM Avanto; Siemens, Erlangen, Germany). This methodology has been previously described in detail (26). Briefly, the exercise cycle ergometer was attached, and participants were prepared for imaging. Once cardiac images were obtained, participants were instructed to start pedaling. The target heart rate for the exercise was 60% of the maximal heart rate obtained during a V_{O_2} peak test (110 ± 5 bpm). Left ventricular exercise images were obtained once 1 min of steady-state heart rate (target heart rate ± 5 for 1 min) was reached. Ergometer resistance and participant cycling speed (in revolutions per minute) were adjusted to maintain the target heart rate. Once heart rate was in the steady state, participants were instructed to hold their breath and stop pedaling for 5–7 s while images (as described below) were obtained. Participants resumed cycling as soon as the image was obtained. Blood pressure was measured during pedaling and at the end of MRI measurements.

Ventricular volumes were calculated from steady-state free-precession cine acquisitions, using six parallel short-axis acquisitions and three long-axis acquisitions at 0°, 60°, and 120°, as previously described (26,29,30). These data were analyzed by members of the research team who were blinded to subject details and group allocation, using three-dimensional volumetric modeling software (Cardiac Image Modeller; Auckland MRI Research Group, Auckland, New Zealand). Participants performed a breath-hold at midexpiration for each image acquisition to eliminate respiratory motion artifacts (31,32). Resting images were obtained with 100% phase resolution (256 × 256), so that breath-holds at rest varied by 10–15 s, while for postexercise images we adopted a 50% phase resolution to lower the breath-hold time (because of exercise exertion) to 5–7 s (29).

Statistical Analysis

Anthropometric measurements, lipid profiles, and HbA_{1c} concentrations were compared using general linear models, controlling for age and sex. Cardiovascular parameters at rest and during exercise, and percentage changes resulting from exercise testing were compared between groups using general linear models controlling for sex; in the case of blood pressure parameters, height was also added as a covariate. Possible differential responses between groups as a result of exercise testing were assessed using random-effect mixed models with repeated measures. All analyses were carried out in SAS version 9.3 (SAS Institute, Cary, NC). All statistical tests were two-tailed and maintained at a 5% significance level. Age and diabetes duration data are reported as means ± SDs; all other data are reported as means ± SEMs.

RESULTS

Baseline Data

Participants were 15.7 ± 1.9 years of age (age range 12.3–19.9 years), with the control group being slightly older than the ObeseND and T2DM groups (Table 1). The mean duration of diabetes in the T2DM group was 2.4 ± 2.3 years. BMI, percentage of body fat, and android-to-gynoid fat ratio were higher in the ObeseND and T2DM groups (Table 1). ObeseND and T2DM groups also had lower HDL cholesterol and higher triglyceride concentrations than control subjects (Table 1). Triglyceride concentrations were also higher in T2DM group vs. ObeseND group (Table 1). The HbA_{1c} concentration was higher in the T2DM group compared with the ObeseND and control groups. Although still within the normal range, ObeseND

Table 1—Demographics, anthropometry, lipid profile, and glycemic control of study participants

Parameters	Control subjects (n = 19)	ObeseND subjects (n = 27)	T2DM subjects (n = 13)
Demographics			
Age (years)	16.9 ± 1.5	15.1 ± 1.6*	15.4 ± 2.2†
Female sex (%)	47	56	54
Anthropometry			
Height (cm)	167.8 ± 2.1	170.7 ± 1.6*	167.7 ± 1.9
Weight (kg)	62.3 ± 2.0	103.7 ± 3.8‡	102.7 ± 6.4‡
BMI (kg/m^2)	22.1 ± 0.7	35.5 ± 1.0‡	36.5 ± 2.1‡
Total body fat (%)	24.8 ± 13.0	45.2 ± 6.6‡	41.7 ± 6.9‡
Body surface area (m^2)	1.70 ± 0.03	2.21 ± 0.05‡	2.16 ± 0.07‡
Android-to-gynoid fat ratio	0.79 ± 0.04	1.16 ± 0.02‡	1.21 ± 0.03‡
Left ventricular mass (g)	126.5 ± 10	154.4 ± 7.2§	140.4 ± 6.9†
Left ventricular mass/FFM ratio (g/kg)	2.63 ± 0.10	2.66 ± 0.05	2.34 ± 0.08†,‖
Lipid profile			
Total cholesterol (mmol/dL)	4.23 ± 0.20	4.35 ± 0.17	4.83 ± 0.37
HDL-C (mmol/dL)	1.58 ± 0.07	1.10 ± 0.04‡	1.09 ± 0.06‡
LDL-C (mmol/dL)	2.26 ± 0.18	2.65 ± 0.16	2.95 ± 0.28†
Triglycerides (mmol/L)	0.77 ± 0.08	1.31 ± 0.13*	2.04 ± 0.31‡,¶
HbA_{1c}			
%	5.22 ± 0.09	5.61 ± 0.08*	7.42 ± 0.41‡,#
mmol/mol	33.5 ± 3.7	37.8 ± 4.4*	57.6 ± 4.4‡,#

Age data are given as the mean ± SD; all other data are given as the mean ± SEM. HDL-C, HDL cholesterol; LDL-C, LDL cholesterol. *P < 0.01 for comparisons with the control subjects. †P < 0.05 for comparisons with the control subjects. ‡P < 0.0001 for comparisons with the control subjects. §P < 0.001 for comparisons with the control subjects. ‖P < 0.01 for comparisons with ObeseND subjects. ¶P < 0.05 for comparisons with ObeseND subjects. #P < 0.0001 for comparisons with ObeseND subjects.

subjects had higher HbA_{1c} levels than control subjects (Table 1). There were no differences in reported activity levels among groups, with mean weekly durations of physical activity of 2.7 h in the T2DM group, 2.0 h in the ObeseND group, and 2.8 h in control subjects.

Exercise Testing

Data from the maximal aerobic capacity tests are provided in Table 2. The V_{O_2} peak, expressed as liters per minute, was not different among groups, but when indexed for FFM (or weight), V_{O_2} peak was 26% lower in the T2DM group ($P < 0.0001$) and 20% lower in the ObeseND group ($P < 0.0001$) than in the control group. Upright resting heart rate was not different among groups, but maximum heart rate was ~10 bpm lower in the T2DM ($P = 0.004$) and ObeseND ($P = 0.004$) groups, despite comparable maximum workloads. Consequently, heart rate reserve was lower in T2DM and ObeseND subjects than in control subjects. Resting and peak systolic, diastolic, and mean arterial blood pressure were higher in the T2DM group than in the ObeseND and control groups ($P < 0.05$).

MRI Cardiac Function

Table 3 summarizes the left ventricular responses to submaximal exercise. The exercise workloads performed to achieve target heart rate (~110 bpm) were not different between groups; however, the average exercise heart rate during measurements was 3 bpm lower in T2DM and ObeseND subjects than in control subjects ($P = 0.058$ and $P = 0.016$, respectively). During submaximal exercise, diastolic and mean arterial blood pressure were higher in the T2DM group than in the ObeseND ($P = 0.050$) and control ($P < 0.001$) groups. Cardiac output was not different among groups at rest, but increased less in T2DM (+41%, $P < 0.001$) and ObeseND (+53%, $P = 0.007$) subjects than in control subjects (+77%) with exercise (Fig. 1). As a result, cardiac output during exercise was lower in the T2DM group (194 mL/kg FFM) than in the ObeseND (225 mL/kg FFM; $P = 0.003$) and control (240 mL/kg FFM; $P < 0.0001$) groups (Fig. 1). The smaller increase in cardiac output and greater increase in mean arterial blood pressure resulted in increased total peripheral resistance during exercise in the T2DM group ($P = 0.006$), so that it was greater than in the ObeseND ($P = 0.011$) and control ($P = 0.041$) groups (Table 3).

Because heart rate was controlled during exercise, stroke volume explained the differences in cardiac output. Mean stroke volume at rest was lower in T2DM subjects (1.83 mL/kg FFM) than in ObeseND subjects (2.03 mL/kg FFM; $P = 0.029$), but was not different from that in control subjects (1.97 mL/kg FFM; $P = 0.14$) (Fig. 1). Stroke volume did not change in the T2DM group during exercise (−0.9%; $P = 0.98$), but increased in both the ObeseND (+3.9%; $P = 0.046$) and control (+10%; $P < 0.0001$) groups (Fig. 1). The resting ejection fraction was within the normal range for all subjects, but was greater in the T2DM (68%; $P = 0.013$) and ObeseND (67%; $P = 0.012$) subjects than in control subjects (63%; Fig. 1). There was a greater increase in ejection fraction during exercise in control subjects (13%) than in T2DM (7%; $P = 0.045$) and ObeseND (7%; $P = 0.006$) subjects (Fig. 1). Resting end-diastolic volume was lower in the T2DM group (2.71 mL/kg FFM) than the control (3.12 mL/kg FFM; $P = 0.003$) and ObeseND (3.02 mL/kg FFM; $P = 0.013$) groups (Fig. 1). End-diastolic volume decreased during exercise in the T2DM group (−8%; 2.54 mL/kg FFM; $P = 0.015$), but not in the control (−1%; 3.10 mL/kg FFM; $P = 0.66$) and ObeseND (−3%; 2.98 mL/kg FFM; $P = 0.50$) groups (Fig. 1). Resting end-systolic volume was also lower in the T2DM (0.89 mL/kg FFM; $P < 0.001$) and ObeseND (1.00 mL/kg FFM; $P = 0.018$) groups than in the control group (1.15 mL/kg FFM), and remained lower during exercise in the T2DM group (0.70 mL/kg FFM) vs. the control group (0.88 mL/kg FFM; $P = 0.027$) (Fig. 1). Stroke work was greater in T2DM and ObeseND subjects at rest ($P < 0.0001$) and during exercise ($P < 0.01$) compared with control subjects (Table 3).

Table 2—Cardiovascular parameters associated with maximal exercise test

Parameters	Control subjects	ObeseND subjects	T2DM subjects
Heart rate*			
Resting (bpm)	67.4 ± 2.4	71.2 ± 2.1	71.6 ± 3.2
Maximum (bpm)	185.6 ± 2.2	175.7 ± 2.2†	174.2 ± 3.1†
Change (%)	181 ± 11	153 ± 8‡	149 ± 13‡
Systolic blood pressure§			
Resting (mmHg)	106.6 ± 2.0	115.8 ± 2.0†	120.8 ± 2.1‖,¶
Maximum (mmHg)	163.0 ± 5.0	161.5 ± 4.2	178.9 ± 3.4‡,#
Change (%)	53 ± 3	40 ± 3†	49 ± 4¶
Diastolic blood pressure*			
Resting (mmHg)	61.8 ± 1.8	65.1 ± 1.2	71.2 ± 2.1¶,**
Maximum (mmHg)	66.8 ± 1.4	78.6 ± 2.8†	93.5 ± 3.6‖,††
Change (%)	9 ± 3	22 ± 5‡	33 ± 6†
Mean arterial pressure§			
Resting (mmHg)	76.7 ± 1.7	82.0 ± 1.4‡	87.7 ± 1.9‖,¶
Maximum (mmHg)	98.9 ± 2.0	106.2 ± 2.8	121.9 ± 2.7‖,††
Change (%)	29 ± 2	30 ± 3	40 ± 4
Maximum workload (W)	200.8 ± 17	177 ± 5.3‡	170.0 ± 5.9‡
V_{O_2}/FFM ratio (mL/kg/min)	48.2 ± 1.8	38.4 ± 1.0‖	35.8 ± 1.2‖
V_{O_2} (L/min)	2.33 ± 0.19	2.20 ± 0.07	2.12 ± 0.07
V_{O_2}/weight ratio (mL/kg/min)	37.0 ± 2.3	21.8 ± 0.7‖	21.4 ± 1.2‖

Values are given as mean ± SEM. *$P < 0.01$ for an interaction between terms indicating a differential response to exercise among groups. †$P < 0.01$ for comparisons with the control group. ‡$P < 0.05$ for comparisons with the control group. §$P < 0.05$ for an interaction between terms indicating a differential response to exercise among groups. ‖$P < 0.0001$ for comparisons with the control group. ¶$P < 0.05$ for comparisons with the ObeseND group. #$P < 0.01$ for comparisons with the ObeseND group. **$P < 0.001$ for comparisons with the control. ††$P < 0.001$ for comparisons with the ObeseND group.

CONCLUSIONS

This study shows that adolescents with T2DM, like their adult counterparts, are less able to increase cardiac performance during exercise. T2DM subjects had smaller resting left ventricular end-diastolic and end-systolic volumes. During supine

Table 3—Cardiovascular parameters during submaximal exercise test in the MRI

Parameters	Control subjects	ObeseND subjects	T2DM subjects
Heart rate*			
Resting (bpm)	69.7 ± 2.2	74.0 ± 1.9	77.2 ± 2.9
Exercise (bpm)	109.0 ± 0.9	105.8 ± 1.4†	106.0 ± 1.6‡
Change (%)	59 ± 5	45 ± 3§	40 ± 6§
Systolic blood pressure*			
Resting (mmHg)	102.5 ± 2.8	112.5 ± 2.4†	119.4 ± 3.6‖,¶
Exercise (mmHg)	122.3 ± 4.2	122.0 ± 3.8	125.9 ± 6.2
Change (%)	20 ± 3	9 ± 3†	5 ± 6†
Diastolic blood pressure			
Resting (mmHg)	57.3 ± 1.8	63.8 ± 2.1†	70.9 ± 3.2¶,#
Exercise (mmHg)	60.4 ± 1.7	70.7 ± 3.2‡	79.8 ± 5.9¶,#
Change (%)	7.0 ± 4.3	11.4 ± 3.4	15.8 ± 10.2
Mean arterial pressure			
Resting (mmHg)	72.4 ± 6.9	80.1 ± 9.9†	87.0 ± 9.8‖,¶
Exercise (mmHg)	81.0 ± 9.3	87.8 ± 16.2	95.2 ± 18.7§
Change (%)	13 ± 14	10 ± 14	10 ± 25
Total peripheral resistance*			
Resting (mmHg · min/L)	11.7 ± 0.5	9.6 ± 0.3§	10.7 ± 0.6
Exercise (mmHg · min/L)	7.4 ± 0.3	7.0 ± 0.2	8.5 ± 0.6†,¶
Change (%)	−36 ± 3	−27 ± 3†	−19 ± 6§
Stroke work			
Resting (mmHg · mL)	92.4 ± 6.3	128.3 ± 7.0‖	128.7 ± 5.7‖
Exercise (mmHg · mL)	115.5 ± 9.2	150.6 ± 11#	142.2 ± 13§
Change (%)	24 ± 4	16 ± 4	10 ± 8
Exercise workload (W)	36.7 ± 4.8	32.0 ± 4.2	36.1 ± 2.2

Values are given as mean ± SEM. *$P < 0.01$ for an interaction between terms, indicating a differential response to exercise among groups. †$P < 0.05$ for comparisons with the control group. ‡$P < 0.06$ for comparisons with the control group. §$P < 0.01$ for comparisons with the control group. ‖$P < 0.0001$ for comparisons with the control group. ¶$P < 0.05$ for comparisons with the ObeseND group. #$P < 0.001$ for comparisons with the control group.

exercise, end-diastolic volume decreased more and end-systolic volume decreased less in T2DM subjects, consistent with impaired left ventricular filling and reduced contractile reserve. Consequently, T2DM subjects failed to achieve the normal exercise-induced increase in stroke volume that was evident in control and ObeseND subjects. Left ventricular stroke work, mean arterial blood pressure, and total peripheral resistance were higher during exercise in T2DM subjects. Thus, asymptomatic adolescents with T2DM already show evidence of impaired left ventricular filling, reduced contractile reserve, and impaired vascular function, which contribute to reduced cardiovascular reserve.

Like adults with longer diabetes duration, adolescents who have had T2DM for <3 years appear to have less compliant left ventricles than their peers. Nearly 40 years ago, Regan et al. (19) combined left and right heart catheterization and left ventricular biopsies to show that extravascular myocardial glycoprotein deposition was associated with increased left ventricular filling pressure and reduced end-diastolic and stroke volumes in adults with diabetes. Their data provided the foundation for a "diabetes-specific" cardiomyopathy that is characterized by impaired diastolic filling of the left ventricle. In the current study, left ventricular function was measured with subjects in supine posture, which is associated with high ventricular preload and large end-diastolic volumes in healthy adults (33). Therefore, our finding that resting left ventricular end-diastolic volume was 10–13% smaller during supine rest in diabetic vs. nondiabetic adolescents is consistent with increased left ventricular stiffness and diastolic dysfunction. Whalley et al. (34) previously showed clinical indications of elevated left ventricular filling pressure when they found that adolescent girls with T2DM have left atrial distension and left ventricular dilation. These findings suggest that adolescents with a relatively short time since the diagnosis of diabetes already exhibit the early stages of compensation for impaired left ventricular filling, as reported in healthy adults who have had diabetes for longer duration (9,19).

An unexpected finding was that the T2DM subjects in this study had increased resting contractility (i.e., increased ejection fraction and lower end-systolic volume) but attenuated contractile and heart rate responses to exercise. By achieving smaller end-systolic volumes, T2DM subjects had resting left ventricular stroke volumes similar to those of control subjects despite reduced left ventricular filling (i.e., systolic compensation). However, control subjects had a greater capacity to increase their ejection fraction and to further reduce end-systolic volume during exercise. Control subjects also achieved higher maximal heart rates than T2DM subjects. Similar findings have been reported in adults with T2DM (3) and adolescents with type 1 diabetes (29), who also had impaired left ventricular filling. Based on these findings, it appears that an early diabetes-specific impairment of the left ventricle affects both diastolic and systolic function, and reduces cardiac reserve.

The primary aim of our study was to examine the cardiac responses to exercise; nonetheless, altered vascular responses appear to have influenced cardiac function in the adolescents with T2DM. Total peripheral resistance was 15–20% higher during exercise in adolescents with T2DM. Therefore, the left ventricles of the T2DM subjects needed to overcome greater left ventricular afterload in order to achieve the same increase in cardiac output. Instead, the T2DM subjects achieved a smaller increase in cardiac output, despite having higher left ventricular stroke work during exercise. Vascular function is impaired in adults with T2DM (35,36) and ObeseND adolescents (37). Therefore, it appears that attenuated peripheral vasodilation during exercise, combined with a limited ability to increase cardiac contractility may have contributed to a smaller increase in

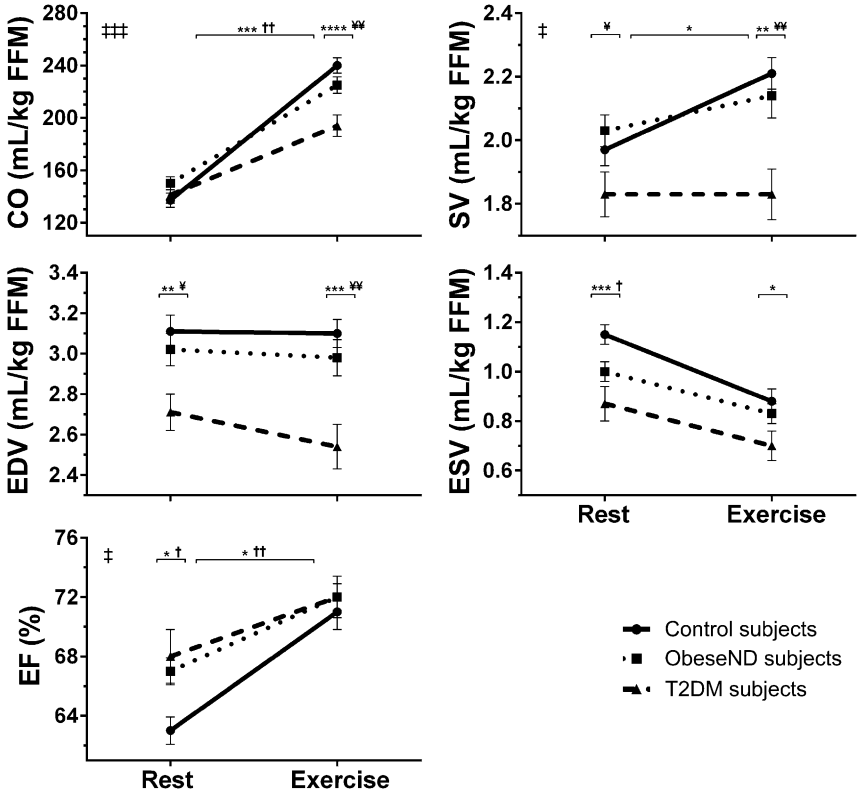

Figure 1—Cardiac function parameters. Data are mean ± SEM. CO, cardiac output; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; SV, systolic volume. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, and ****$P < 0.0001$ for control vs. T2DM subjects; ¥$P < 0.05$ and ¥¥$P < 0.01$ for T2DM vs. ObeseND subjects; †$P < 0.05$ and ††$P < 0.01$ for control vs. ObeseND subjects; ‡$P < 0.05$ and ‡‡‡$P < 0.001$ for an interaction between terms indicating a differential response to exercise among groups.

cardiac output during steady-state exercise.

From a clinical perspective, adolescents with T2DM may provide the best opportunity for successful intervention because of their relatively short exposure to hyperglycemia. It has been suggested that diastolic dysfunction and left ventricular stiffening result from the chronic, irreversible accumulation of advanced glycation end products (38) or cardiac steatosis in patients with T2DM (22). Though we did not see an association between diabetes duration and cardiac reserve in this study, we do not believe our data strongly refute such an association. The T2DM participants in this study only had diabetes for 0.3–6.7 years, which may not have provided a sufficient range of duration to identify the compounding effects of hyperglycemia on the cardiovascular system. A review of the available data in adults with T2DM suggests that cardiovascular morbidity increases with diabetes duration (39); however, the duration of diabetes in these studies is considerably longer than reported in our cohort. Nonetheless, smaller end-diastolic volumes in adolescents with T2DM in our and other studies (7,27,40) suggest that reduced left ventricular filling is an early consequence of diabetes that affects cardiac function after relatively short diabetes duration.

While this study has focused on adolescents with T2DM, it is notable that similar, less severe abnormalities in exercise capacity and cardiovascular indices were found in ObeseND adolescents. Cardiovascular and exercise changes in obese adolescents have previously been documented (41,42). The current study highlights that obese adolescents are also at risk for early cardiovascular changes that may also impair their capacity to exercise effectively. These changes, at least during adolescence, appear to be modifiable with exercise interventions improving cardiovascular responses (41). These encouraging results suggest that similar programs in youth with T2DM may also be beneficial.

In summary, adolescents with T2DM did not achieve the normal increase in left ventricular stroke volume seen in lean and ObeseND adolescents during steady-state leg ergometry. Smaller stroke volumes were associated with a lower end-diastolic volume and a smaller decrease in end-systolic volume during exercise, suggesting impaired left ventricular filling and reduced "systolic reserve" in adolescents with T2DM. ObeseND patients (matched with the T2DM group for body composition and activity levels) also had lower aerobic capacity than lean control subjects, but showed none of the changes in left ventricular function seen in adolescents with T2DM.

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