Diastolic Function Is Reduced in Adolescents With Type 1 Diabetes in Response to Exercise

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OBJECTIVE—To determine whether adolescents with type 1 diabetes have left ventricular functional changes at rest and during acute exercise and whether these changes are affected by metabolic control and diabetes duration.

RESEARCH DESIGN AND METHODS—The study evaluated 53 adolescents with type 1 diabetes and 22 control adolescents. Baseline data included peak exercise capacity and body composition by dual-energy X-ray absorptiometry. Left ventricular functional parameters were obtained at rest and during acute exercise using magnetic resonance imaging.

RESULTS—Compared with nondiabetic control subjects, adolescents with type 1 diabetes had lower exercise capacity (44.7 ± 0.9 vs. 48.5 ± 1.4 mL/kg fat-free mass [FFM]/min; P < 0.05). Stroke volume was reduced in the diabetes group at rest (1.86 ± 0.04 vs. 2.05 ± 0.07 mL/kg FFM, P = 0.02) and during acute exercise (1.89 ± 0.04 vs. 2.17 ± 0.06 mL/kg FFM, P = 0.01). Diabetic adolescents also had reduced end-diastolic volume at rest (2.94 ± 0.06 vs. 3.26 ± 0.09 mL/kg FFM, P = 0.01) and during acute exercise (2.78 ± 0.05 vs. 3.09 ± 0.08 mL/kg FFM, P = 0.01). End-systolic volume was lower in the diabetic group at rest (1.08 ± 0.03 vs. 1.21 ± 0.04 mL/kg FFM, P = 0.01) but not during acute exercise. Exercise capacity and resting and exercise stroke volumes were correlated with glycemic control but not with diabetes duration.

CONCLUSIONS—Adolescents with type 1 diabetes have reduced exercise capacity and display alterations in cardiac function compared with nondiabetic control subjects, associated with reduced stroke volume during exercise.

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Diabetes in adults is associated with increased cardiovascular risk and altered cardiovascular function independent of hypertension or other coronary artery disease (1). Diastolic dysfunction is characterized by reduced early diastolic relaxation, changes in ventricular filling patterns (2,3), increases in left ventricular filling pressure during exercise (4), and decreases resting and exercising end-diastolic volume (EDV) (5). At a more advanced stage, these changes are collectively defined as diabetic cardiomyopathy, which may be a precursor to diastolic heart failure (1).

Cardiac dysfunction may be exacerbated by physiologic stressors such as exercise. Previous studies in diabetic adults showed that aerobic capacity and left ventricular stroke volume during exercise are associated with diastolic dysfunction in adults (5,6). Adults with asymptomatic type 1 diabetes have reduced exercise capacity and lower stroke volume at peak exercise compared with nondiabetic peers, limitations that are strongly associated with diastolic dysfunction (6,7) and reduced EDV during exercise (5,6). It remains unclear whether diabetic adolescents present similar alterations in left ventricular function.

Although current evidence is equivocal, healthy adolescents with diabetes may also have lower aerobic capacity (8,9) and lower exercise stroke volume (8). Abnormalities in myocardial function have also been described in healthy adolescents with type 1 diabetes at rest (10–12) but not during exercise. Thus, this study aimed to determine the left ventricular responses at rest and during acute submaximal exercise in adolescents with type 1 diabetes compared with nondiabetic control subjects with a comparable sex distribution using magnetic resonance imaging (MRI). We also sought to determine whether left ventricular performance was associated with metabolic control and/or diabetes duration.

RESEARCH DESIGN AND METHODS—Healthy adolescents (n = 53) with type 1 diabetes were recruited from the Auckland Adolescent Diabetes Clinic. All subjects were healthy, with no evidence of hypertension, microvascular complications (e.g., retinopathy, neuropathy, and microalbuminuria), or chronic diseases other than type 1 diabetes. Diabetic retinopathy and nephropathy were regularly checked at the Auckland Adolescent Diabetes Clinic. The initial examination was performed in subjects with a diabetes duration of more than 2 years. Retinopathy was assessed binurally using digital retinal photography, and nephropathy was annually assessed using a urinary microalbumin-to-creatinine ratio. None of the subjects were taking regular medications other than insulin. A group of 22 healthy nondiabetic adolescents was recruited from friends and relatives of the diabetic cohort. This study was approved by the Northern X Regional Ethics Committee (reference number NTX/0712/125). Written informed consent was obtained from all participants and from the guardians of those aged <16 years.

Body composition was determined by dual-energy X-ray absorptiometry (DEXA; GE Lunar Prodigy, Madison, WI) using standard manufacturer’s software (version Encore 4). BMI was calculated as weight in kilograms divided by height in meters squared. Antecubital venous blood samples were collected after an overnight fast. Each sample was used to determine glycosylated...
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hemoglobin (HbA1c), total cholesterol, triglycerides, HDL and LDL cholesterol, and total cholesterol-to-HDL ratio. Insulin sensitivity in the diabetic group was indirectly calculated by dividing the units of insulin per kilogram per day. Outpatient glycemic control was assessed using HbA1c, which was recorded every 3 months. Diabetes control was assessed using the current HbA1c and the mean HbA1c over the previous year.

Functional aerobic capacity (V\textsubscript{O2peak} test)

Before and after functional capacity testing, participants with diabetes verified their glucose levels to avoid hypoglycemia during the test. Participants were also asked to report the occurrence of hypoglycemic events in the 48 h preceding the test, and testing was postponed in the case of such events. All subjects had glucose levels between 5.6 and 13.9 mmol/L, with no sign of ketosis during the V\textsubscript{O2peak} test and the MRI assessments, in accordance with published guidelines (13). Functional aerobic capacity was assessed by pedaling to volitional exhaustion on an electronically-braked cycle ergometer (Schiller, Baar, Switzerland) with simultaneous breath-by-breath measurement of expired and inspired O\textsubscript{2} and CO\textsubscript{2} gas volumes using the ParvoMedics TrueOne 2400 Metabolic Measurement System (ParvoMedics, Sandy, UT). Blood pressure was recorded at test initiation and termination. The exercise protocol consisted of 1-min stages starting at 55 W with increments of 15 W per stage. Rates for V\textsubscript{O2} and V\textsubscript{CO2} were recorded every 30 s. The average of the highest two consecutive V\textsubscript{O2} values was defined as V\textsubscript{O2peak}. The test was terminated when participants were unable to continue because of exhaustion or discomfort. This protocol was designed to last no more than 15 min.

MRI assessment

Between 2 and 7 days after functional aerobic capacity testing, cardiac structure and function were evaluated at rest and during acute exercise using a 1.5-T Magnetom Avanto MRI scanner (Siemens, Erlangen, Germany) and a phased-array surface coil with retrospective electrocardiographic gating. Exercising images were obtained while subjects pedaled a purpose-built MRI-compatible cycle ergometer.

Resting left ventricular function

Left 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 (5). Images were acquired during breath-hold maneuvers. Participants performed breath-hold at midexpiration at each image acquisition to eliminate respiratory motion artifacts. Blood pressure measurement was obtained at the end of the resting protocol.

Submaximal exercise left ventricular function

After resting measurements were completed, participants were instructed to start pedaling. The target heart rate for the exercise was 60% of the maximal heart rate obtained during the V\textsubscript{O2peak} test. 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 participants’ cycling speed (revolutions per minute) were adjusted to maintain the target heart rate. Once the heart rate was in steady state, participants were instructed to hold their breath and stop pedaling for 5 to 7 s while images (as described above) were obtained. Participants resumed cycling as soon as the image was obtained. Blood pressure measurement was obtained during pedaling, at the end of measurements.

Cardiac MRI images analyses were performed using three-dimensional volumetric modeling software by members of the research team blinded to the participant’s details (Cardiac Image Modeler Software, Auckland, New Zealand). Endocardial limits of each slice were manually identified at end-diastole and end-systole for each time point through the cardiac cycle. Mean arterial pressure was calculated by the formula: [(2 × diastolic blood pressure) + systolic blood pressure]/3]. Cardiac output was determined by multiplying stroke volume by heart rate. The MRI data were used to calculate left ventricular mass, EDV, end-systolic volume (ESV), stroke volume, ejection fraction, and cardiac output. Values for V\textsubscript{O2peak}, cardiac output, stroke volume, EDV, ESV, and left ventricular mass were indexed for participants’ fat-free mass (FFM) (14).

Statistical analyses

ANOVA were used to compare baseline characteristics of participants. General linear models were used to determine whether there were differences in cardiovascular function and structure between the diabetic and nondiabetic groups. Current exercise levels, sex, and age were controlled for in the analyses. General linear models were also used to examine the associations between HbA1c and diabetes duration with the response parameters of interest. A P value ≤ 0.05 was considered statistically significant. All analyses were performed with SPSS 15.0 software (SPSS Inc., Chicago, IL). Data are expressed as mean ± SEM.

RESULTS

Baseline data

The study comprised 53 adolescents with type 1 diabetes and 22 nondiabetic control individuals. The groups were similar in sex ratio, weight, height, body fat percentage, BMI, and lipid profile (Table 1). Diabetic adolescents were younger than control subjects (P = 0.005) and had higher resting heart rates (P = 0.02; Table 1). Resting systolic blood pressure was higher in adolescents with type 1 diabetes, but diastolic blood pressure and mean arterial pressure were similar (Table 1). HbA1c was higher in diabetic adolescents than in control subjects (P = 0.01). The diabetic subjects had higher HbA1c levels at study enrolment compared with the mean HbA1c over the previous year (8.68 ± 0.18% vs. 8.23 ± 0.26%, P = 0.04). Average daily insulin dose per kilogram per day was 0.99 ± 0.33. No participant was hypoglycemic or near hypoglycemia immediately before testing or at its termination or had any history of hypoglycemia in the 48 h before testing.

Despite similar self-reported levels of physical activity, adolescents with type 1 diabetes had lower relative exercise capacity (V\textsubscript{O2}) than control subjects (P = 0.03; Table 1). Resting seated heart rate (P = 0.02) and systolic blood pressure (P = 0.02) were higher among adolescents with diabetes, as were peak systolic blood pressure (P = 0.001) and mean arterial pressure (P = 0.05; Table 1).

Left ventricular structure and function

There were no differences in left ventricular mass, resting and acute exercise supine heart rates, or ejection fractions between groups after adjustment for sex, age, and fitness level (Table 2). The diabetic group showed elevated systolic blood pressure at rest (P = 0.001) and during acute exercise (P = 0.03; Table 2). Supine diastolic blood pressure was higher in the diabetic group at rest (P = 0.05) and also tended to be higher during exercise (P = 0.06; Table 2). As a result, resting (P = 0.002) and acute exercise (P = 0.02) mean arterial pressures were both significantly elevated in the
Table 1—Characteristics of participants and their baseline functional aerobic capacity

|                     | Type 1 diabetes | Control | P   |
|---------------------|-----------------|---------|-----|
| n                   | 53              | 22      |     |
| Female (n)          | 26              | 12      |     |
| Age (years)         | 15.6 ± 0.2      | 16.6 ± 0.2 | 0.005 |
| Diabetes duration (years) | 6 ± 4 (1.2–15) | —       | —   |
| Weight (kg)         | 69.4 ± 1.6      | 65.2 ± 2.6 | 0.20 |
| Height (m)          | 1.70 ± 0.09     | 1.67 ± 0.01 | 0.06 |
| BMI (kg/m²)         | 23.7 ± 0.5      | 23.3 ± 0.8 | 0.64 |
| Body fat (%)        | 26.4 ± 1.1      | 29.0 ± 1.2 | 0.24 |
| HbA1c (%)           | 8.68 ± 0.18     | 5.32 ± 0.35 | 0.001 |
| Triglycerides (mmol/L) | 1.09 ± 0.09  | 0.777 ± 0.17 | 0.13 |
| HDL cholesterol (mmol/L) | 1.53 ± 0.04 | 1.50 ± 0.08 | 0.74 |
| LDL cholesterol (mmol/L) | 2.32 ± 0.11 | 2.32 ± 0.20 | 0.98 |
| Vo2 (L/min)         | 2.30 ± 0.07     | 2.29 ± 0.11 | 0.96 |
| Vo2 (ml/kg FFM/min) | 44.7 ± 0.9      | 48.5 ± 1.4 | 0.03 |

Data are mean ± SEM with exception of diabetes duration, which is mean ± SD (range). The P values in boldface indicate statistical significance (P ≤ 0.05).

diabetic group (Table 2). Despite different maximal aerobic capacities, exercise workloads eliciting 60% maximal heart rate were similar between groups (Table 2).

Stroke volume was reduced in subjects with diabetes at rest (P = 0.02) and during acute exercise (P = 0.01; Table 2). When the components of stroke volume were examined separately, EDV in diabetic adolescents was reduced at rest (P = 0.01) and during acute exercise (P = 0.01; Table 2). ESV was also significantly lower in the diabetic group at rest (P = 0.01) but not during acute exercise (P = 0.73; Table 2). No differences were observed between groups in response to exercise (P > 0.05).

HbA1c was associated with resting (P = 0.02) and exercise stroke volumes (P = 0.01), resting heart rates (P = 0.03), and maximal exercise capacity (P = 0.004; Table 3). Diabetes duration was associated only with ESV at rest (P = 0.02) and during acute exercise (P = 0.05; Table 3). The mean HbA1c over the preceding 12-month period was negatively associated with exercise capacity (β coefficient = −1.20 [SE 0.54]; P = 0.03) but not with cardiac outcomes. Insulin per kilogram per day was not associated with study outcomes.

CONCLUSIONS—This study shows that despite a relatively short duration of diabetes (mean, 6 years), adolescents with type 1 diabetes have decreased left ventricular performance at rest and during acute exercise. Specifically, the reductions in exercise stroke volume reflected lower EDV. This impairment was compensated at rest by a smaller ESV, which did not occur during exercise. These data are the first to describe an impaired left ventricular stress response in otherwise healthy adolescents with type 1 diabetes. As previously described in adults (15), left ventricular function was inversely associated with HbA1c, which suggests that this response may be modifiable.

Our finding that adolescents with diabetes displayed a 10% reduction in maximal exercise capacity compared with healthy adolescents is consistent with previous studies, which show reductions ranging from 8 to 20% (8,9,12,16). Studies in adults with type 1 or type 2 diabetes have also reported reductions in exercise capacity, but their reductions are usually greater than 20% compared with matched control subjects (17–20). Therefore, it can be inferred that adolescents and adults with type 1 diabetes may reflect a continuum of reduced exercise capacity that worsens with the duration of diabetes. Importantly, the reduction in exercise capacity was associated with metabolic control, because subjects with higher levels of HbA1c showed worse fitness levels. The reduction in exercise capacity likely reflects the restrictions in cardiac output and, in particular, the abnormalities in stroke volume noted in this study.

Table 2—Cardiovascular parameters at rest and during submaximal exercise among control subjects and subjects with type 1 diabetes

|                     | Type 1 diabetes | Control | P   |
|---------------------|-----------------|---------|-----|
| n                   | 53              | 22      |     |
| Heart rate (bpm)    | 74 ± 1          | 71 ± 2  | 0.27 |
| Left ventricular mass (g/kg FFM) | 2.58 ± 0.05 | 2.72 ± 0.08 | 0.16 |
| Ejection fraction (%) | 63.5 ± 0.7    | 62.5 ± 1.1 | 0.45 |
| Stroke volume (mL/kg FFM) | 1.89 ± 0.04 | 2.05 ± 0.07 | 0.02 |
| EDV (mL/kg FFM)     | 2.94 ± 0.06     | 3.26 ± 0.09 | 0.01 |
| ESV (mL/kg FFM)     | 1.08 ± 0.03     | 1.21 ± 0.04 | 0.01 |
| Blood pressure (mmHg) |                     |         |     |
| Systolic            | 110 ± 1         | 101 ± 2 | 0.001 |
| Diastolic           | 65.0 ± 1        | 56 ± 1  | 0.05 |
| Mean arterial pressure (mmHg) | 77 ± 1     | 71 ± 1  | 0.002 |
| Workload (W)        | —               | —       | 36.5 ± 1.3 | 34.6 ± 2.2 | 0.54 |

Data are mean ± SEM. The P values in boldface indicate statistical significance (P ≤ 0.05).
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Table 3—The association of individual parameters on HbA1c and diabetes duration

| Parameter            | β Coefficient | SE  | P     |
|----------------------|---------------|-----|-------|
| HbA1c                |               |     |       |
| V02peak              | −1.284        | 0.431 | 0.004 |
| Resting heart rate   | 1.941         | 0.849 | 0.03  |
| Resting stroke volume| −0.052        | 0.022 | 0.02  |
| EDV                  | −0.053        | 0.031 | 0.09  |
| ESV                  | −0.001        | 0.014 | 0.92  |
| Exercise stroke volume| −0.050       | 0.020 | 0.01  |
| EDV                  | −0.030        | 0.027 | 0.28  |
| ESV                  | 0.024         | 0.014 | 0.09  |
| Diabetes duration    |               |     |       |
| V02peak              | 0.123         | 0.21  | 0.55  |
| Resting heart rate   | 0.362         | 0.41  | 0.38  |
| Resting stroke volume| 0.002         | 0.01  | 0.82  |
| EDV                  | −0.013        | 0.01  | 0.37  |
| ESV                  | −0.016        | 0.01  | 0.02  |
| Exercise stroke volume| −0.002       | 0.01  | 0.81  |
| EDV                  | −0.016        | 0.01  | 0.24  |
| ESV                  | −0.013        | 0.01  | 0.05  |

The P values in boldface indicate statistical significance (P ≤ 0.05).

As previously observed (8), stroke volume was reduced in adolescents with type 1 diabetes at rest as well as during exercise. Our MRI scans showed that filling of the left ventricle was reduced in adolescents with diabetes independent of sex, age, and fitness level. This study was not designed to investigate detailed diastolic function and systolic function, such as ventricular relaxation and filling patterns; however, previous echocardiography assessments in adults and youth with diabetes found altered filling patterns, impaired left ventricular relaxation, and higher filling pressures at rest (10,21,22), all of which may alter resting EDV. We therefore speculate that the abnormal filling pattern previously observed in adolescents with diabetes at rest is maintained or perhaps worsened during exercise, reducing filling volumes (and consequently, stroke volume) during exercise (10,22).

Diastolic volumes can also be affected by heart rate and preload. The reduction in EDV in our study cannot be attributed to changes in heart rate between groups and therefore less diastolic filling time, because both groups had similar resting and exercise heart rates, as well as workloads, during MRI scanning. Nonetheless, reductions in EDV may also be attributed to decreased blood volume. Endurance-trained athletes, for example, rely on increased rates of diastolic filling attributable to larger blood volume, to achieve greater stroke volume during exercise (23,24). Lalonde et al. (5) found that total blood volume was 20% lower in adults with diabetes, which was associated with reduced stroke volume and lower EDV. Thus, a preload reduction caused by a smaller blood volume could possibly affect the ability to increase or maintain EDV in adolescents with diabetes.

An interesting finding in this study was that the group with type 1 diabetes had increased systolic function at rest (lower ESV) but not during exercise. This suggests that diabetic adolescents are already “recruiting” systolic reserve at rest, impairing their ability to further improve systolic function to compensate for the diastolic changes (and therefore maintain cardiac output) during exercise. Ejection fractions were similar between groups in both conditions, which may reflect a sympathetically mediated increase in contractility at rest to compensate for a decreased EDV. Increased resting sympathetic outflow has been reported in patients with diabetes (25) and has been associated with elevated heart rate (26) and altered left ventricular relaxation (21). The adolescents with type 1 diabetes in this study had elevated heart rate while upright, and although it was not the aim of the current study, we and others have previously reported impaired left ventricular relaxation in adolescents with diabetes (10,22). Nevertheless, Huggett et al. (25) have shown that basal muscle sympathetic nervous activity (MSNA) is elevated in some adults with type 2 diabetes and responds normally to baroreceptor activation. MSNA is strongly correlated with myocardial sympathetic activity (27); thus, the smaller ESV we observed at rest may reflect elevated basal sympathetic activation in diabetic adolescents. Another possibility is that a prior hypoglycemic event might have altered the catecholamine response of diabetic participants. Studies have shown that individuals with diabetes may have a deficient catecholamine response to hypoglycemia (28,29), which may affect cardiac function (30). Although this study did not measure catecholamine response to exercise, it is unlikely that autonomic responses to hypoglycemia affected our results because none of the subjects with type 1 diabetes had experienced a hypoglycemic episode in the 48 h before data collection.

In agreement with previous studies using Doppler echocardiography (10,21), we observed no changes in left ventricular mass. Whalley et al. (22) showed that a group of girls with type 1 diabetes had similar left ventricular mass (indexed for body FFM) compared with healthy girls. Furthermore, Suys et al. (10) compared girls and boys with diabetes with a respective control group, and again, no differences in left ventricular mass index adjusted for body surface area were noted. Thus, the increase in left ventricular mass observed in diabetic adults is likely to occur later in life in association with diabetes progression.

Peripheral vascular dysfunction may also contribute to the decreased exercise capacity and poor left ventricular performance observed in adolescents with diabetes. Assuming ventricular contractility was similar between groups, the increased systolic blood pressure in diabetic adolescents (at rest and during exercise) indicates greater peripheral vascular resistance. Previous studies have demonstrated impaired peripheral vascular function in diabetic youth, including decreased blood flow and increased intima media thickness (31–33). Thus, changes in vascular function may possibly reduce preload and increase afterload, consequently impairing left ventricular performance.

The literature on the association between glycemic control and diabetes duration with cardiovascular function is conflicting (10,15,34). However, most studies show that glycemic control is correlated with exercise capacity and resting cardiac outcomes in diabetic individuals (15,17,35). In adults with type 1 diabetes, the change in stroke volume during exercise was inversely correlated with HbA1c (35). Therefore, the correlation observed in our study between reduced stroke volume and
VO2peak with current HbA1c, but not diabetes duration, is in agreement with previous findings in adults (17,35). Interestingly, the average HbA1c in the previous year was associated with exercise capacity but not with any cardiac outcomes, suggesting that the cardiac abnormalities are associated with more recent glycemic control.

Hyperglycemia increases the formation of advanced glycation end products (AGEs), which leads to irreversible changes in myocardial structure and may thus be responsible for the cardiac changes associated with diabetes (36,37). AGEs form protein cross-links with collagen and elastin, causing irreversible alterations by inducing fibrosis and decreased connective tissue flexibility (38–40). These changes may result in ventricular stiffness, and consequently interfere with diastolic and systolic function (39). As a result, the decreased EDV may be explained by abnormalities in left ventricular relaxation and filling velocities, which have been observed in adolescents with diabetes at rest in studies using echocardiography (10,12,22). Thus, an increase in collagen accumulation in the myocardium may be already creating a stiffer and less compliant heart chamber in youth with diabetes, without altering myocardium mass (38). A study by Nadeau et al. (12) has recently shown that insulin resistance may play an important role in the decreased exercise capacity in nonobese type 1 diabetic youth, being a stronger correlate than HbA1c. Although we did not directly measure insulin resistance, the indirect assessment using insulin per kilograms per day was not correlated with the study outcomes.

MRI has some temporal limitations (left ventricular assessments were obtained after a brief breath-hold pause) but offers a number of advantages over other noninvasive cardiac assessments and is considered the “gold standard” for left ventricular structure and function assessment. In contrast to echocardiography, MRI has superior spatial resolution and provides a more accurate assessment of cardiac volume and mass. MRI scans allow for three-dimensional assessments that are not adversely affected by patient size, body composition (especially greater adiposity), chest deformities or scar tissue, preload conditions, or variability between technicians. Nonetheless, we acknowledge that the breath-hold maneuver can potentially influence left ventricular filling capacity, and if accompanied by the Valsalva maneuver, a change in filling pressure may happen and possibly alter EDV. However, the study personnel did instruct and practice with each participant before MRI scanning to prevent the Valsalva maneuver from occurring. Moreover, the exercise heart rates were maintained at target levels during scanning (target heart rate ± 5).

In conclusion, our study showed that adolescents with type 1 diabetes have an impaired left ventricular diastolic response to acute exercise, which was associated with glycemic control. Lower stroke volume contributes to the VO2peak reduction in adolescents with type 1 diabetes, indicating that diastolic impairment may reduce their functional capacity. This is the first report of left ventricular dysfunction during exercise in adolescents with diabetes, suggesting functional (but not morphologic) cardiac changes early in the progression of diabetes. Notably, these alterations were present despite a relatively short duration of diabetes and in the absence of any associated complications. Little emphasis has been placed on cardiovascular function in children and youth with diabetes to date, and a greater understanding of the cardiovascular effects of diabetes and potential therapies is needed.

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