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Original Research

# Cardiac Function is Preserved in Adolescents With Well-Controlled Type 1 Diabetes and a Normal Physical Fitness: A Cross-sectional Study

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**Key Messages**

- Previous studies showed cardiac dysfunction and reduced exercise capacity in adolescents with poorly controlled type 1 diabetes (T1D).
- Studies are scarce in well-controlled T1D adolescents and have not addressed exercise capacity, which strongly affects morbidity and mortality.
- Left ventricular ejection fraction is negatively affected by disease duration (not glycemic control) despite a normal exercise capacity.

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ABSTRACT

*Objectives:* Cardiovascular diseases and exercise intolerance elevate mortality in type 1 diabetes (T1D). Left ventricular systolic and diastolic function are already affected in T1DM adolescents, displaying poor glycemic control (glycated hemoglobin [A1C]>7.5%) and exercise intolerance. We investigated to the extent to which left ventricular function is affected by disease severity/duration and whether this is related to exercise capacity.

*Methods:* Transthoracic echocardiography was performed in 19 T1DM adolescents (14.8±1.9 years old, A1C 7.4±0.9%) and 19 controls (14.4±1.3 years old, A1C 5.3±0.2%), matched for age and Tanner stage. Diastolic and systolic (ejection fraction [EF]) function were assessed. Cardiopulmonary exercise testing was used to evaluate exercise capacity, as measured by peak oxygen uptake ($VO_{2peak}$).

*Results:* $VO_{2peak}$ and left ventricular systolic and diastolic function were similar in both groups. Within the T1D group, EF was negatively associated with disease duration (r=−0.79 corrected for age, standardized body mass index, glucose variability and $VO_{2peak}$; p=0.011). Regression analyses revealed that 37.6% of the variance in EF could be attributed to disease duration.

*Conclusions:* Although left ventricular systolic and diastolic function are preserved in T1D with adequate exercise capacity, disease duration negatively affects EF. The detrimental effects of T1D seem to be driven by disease duration, rather than by disease severity, at least during adolescence. Young T1D patients may, therefore, benefit from cardiovascular evaluation in order to detect cardiovascular abnormalities early in the disease course, and therefore, improve long-term cardiovascular health.



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RÉSUMÉ

*Objectifs :* Les maladies cardiovasculaires et l'intolérance à l'effort haussent la mortalité lors de diabète sucré de type 1 (DST1). Les fonctionnements systolique et diastolique du ventricule gauche sont déjà affectés chez les adolescents atteints du DST1 qui montrent une mauvaise régulation de la glycémie (hémoglobine glyquée [A1c] > 7,5 %) et une intolérance à l'effort. Nous avons examiné dans quelle mesure le fonctionnement ventriculaire gauche est affecté par la gravité ou la durée de la maladie, et si ceci est associé à la capacité à l'effort.

*Méthodes :* Dix-neuf adolescents atteints du DST1 (14,8 ± 1,9 ans, A1c 7,4 ± 0,9 %) et 19 témoins (14,4 ± 1,3 ans, A1c 5,3 ± 0,2 %), appariés selon l'âge et la classification de Tanner ont passé une échocardiographie transthoracique. Nous avons évalué les fonctionnements diastolique et systolique (fraction d'éjection [FE]). L'épreuve d'effort cardiorespiratoire a été utilisée pour évaluer la capacité à l'effort, c'est-à-dire la consommation maximale d'oxygène ($VO_{2max}$).

*Résultats :* Les 2 groupes montraient une $VO_{2max}$ et des fonctionnements diastolique et systolique similaires. La FE des adolescents atteints du DST1 était associée de façon négative à la durée de la maladie ($r = -0{,}79$ corrigé en fonction de l'âge, de l'indice de masse corporelle normalisé, de la variabilité glycémique et de la $VO_{2max}$; $p = 0{,}011$). Les analyses de régression ont révélé que 37,6 % de la variance de la FE pouvaient être attribués à la durée de la maladie.

*Conclusions :* Bien que les fonctionnements systolique et diastolique du ventricule gauche soient préservés en présence du DST1 et d'une bonne capacité à l'effort, la durée de la maladie affecte la FE. Les effets néfastes du DST1 semblent attribuables à la durée de la maladie, plutôt qu'à la gravité de la maladie, du moins à l'adolescence. Les jeunes patients atteints du DST1 peuvent donc tirer avantage de l'évaluation cardiovasculaire pour la détection des anomalies cardiovasculaires au début de la maladie et ainsi voir leur santé cardiovasculaire à long terme améliorée.



## Introduction

Diabetes mellitus affects about 463 million people worldwide and its prevalence continues to increase (1). Type 1 diabetes (T1D) accounts for approximately 5% to 10% of all cases, and the incidence is rapidly increasing in younger children (<10 years old) (2,3). T1D is an autoimmune disorder that leads to dysfunction and destruction of pancreatic beta cells, and ≥85% of all diabetes cases develop before 20 years of age (4). Although its exact mechanisms are not fully elucidated, T1D is considered to result from a complex multifactorial interplay between (epi)genetics, metabolism, the immune system and multiple organs, such as the kidneys and heart (5). T1D is known to shorten life expectancy (by up to 13 years), which is at least partly driven by the development of cardiovascular diseases (6–10).

Indeed, diabetes doubles the risk of developing cardiovascular diseases, but also intrinsically increases the cardiovascular mortality rate (11,12). Both hyper- and hypoglycemic episodes can lead to long-term cardiac dysfunction. Repetitive hyperglycemic events are known to enhance oxidative stress and (systemic) inflammation, which can lead to myocardial fibrosis and inappropriate cardiomyocyte $Ca^{2+}$ handling (13). In addition, the formation and deposition of advanced glycation end-products causes cardiac remodelling, resulting in impaired diastolic function (14–17).

The detrimental effects of diabetes seem to be established early in life, as shown by impaired endothelial function, and even relate to metabolic control (18). Multiple studies have reported the detrimental effects of T1D on left ventricular systolic and diastolic function, more specifically on diastolic function (18–23). Altun et al demonstrated increased late diastolic flow velocity (A wave), typically an early marker of diastolic dysfunction (22). Eltayeb et al reported a decreased early diastolic flow velocity (E wave) and E/A ratio, further confirming the hypothesized detrimental effect of diabetes on diastolic function (18). On the other hand, systolic function seems to be preserved in this population (23). A major limitation is the lack of studies performed on well-controlled T1D patients (glycated hemoglobin [A1C]≤7.5%).

Recently, Yoldas et al described anomalies in diastolic function and myocardial deformation in well-controlled T1D adolescents (13). Cardiac dysfunction was observed to be related to disease duration, a relationship already described in T1D adults but not yet in T1D adolescents (24). This emphasizes the importance of disease duration in addition to metabolic control.

The interplay between left ventricular systolic and diastolic function and physical fitness remains another area that requires further elucidation. Exercise capacity (maximal oxygen uptake [$VO_{2peak}$]) is up to 22% lower in T1D adolescents displaying poor glycemic control (25). This is of great clinical importance, because, in the long term, mortality risk is up to 2.49-fold higher in T1D (adults) displaying low levels of activity compared with more active patients (26).

The primary objective of this study was to investigate left ventricular systolic and diastolic function and exercise capacity in young T1D patients and whether these are related. Posthoc analyses were performed to investigate the extent to which disease severity and duration relate to the primary outcomes (left ventricular systolic and diastolic function and exercise capacity). We hypothesized that exercise capacity and left ventricular systolic and diastolic function would be negatively affected by disease severity and/or duration.

## Methods

### *Study design and subjects*

This cross-sectional study was a collaboration between the Departments of Pediatrics and Cardiology at the Jessa Hospital (Hasselt, Belgium). T1D adolescents were recruited at the Department of Pediatrics (February 2018 to August 2019). T1D patients were compared with healthy controls (HCs), matched for age (±1.5 years), Tanner stage (pubertal stage, ±1 stage), in an attempt to match body mass index (BMI, in $kg/m^2$) and sex. Data for the matched HCs were obtained retrospectively, taken from a study population of a previous clinical trial by our research group (Clinical

Trials No. NCT03516721, November 2016 to May 2017). Thus, data for the T1DM adolescents were compared with historical data.

*Inclusion criteria*

Inclusion criteria for this study were: a diagnosis of T1D by a pediatrician according to the criteria of the American Diabetes Association; age 12 to 18 years; ability to perform a maximal incremental exercise test; and no diagnosis of other chronic cardiovascular, renal, pulmonary or orthopedic diseases. Except for diagnosis of T1D, the same criteria were applied to the HC group.

The study protocol was approved by the medical ethical committee of the Jessa Hospital (Hasselt, Belgium) and Hasselt University (Hasselt, Belgium) and was performed in accordance with the Declaration of Helsinki (2013). All participants and their parents/legal guardians provided informed consent and gave their permission before execution of the clinical assessments. The study is registered at ClinicalTrials.gov (Clinical Trials No. NCT04052919).

*Clinical characteristics: Physical examination, anthropometric assessment and glycemic control*

Both groups underwent clinical examination. Body length was measured to the nearest 0.1 cm using a wall-mounted Harpenden stadiometer (ICD 250 DW; De Grood Metaaltechniek, Nijmegen, The Netherlands) and body weight was assessed using a digital-balanced weighing scale to the nearest 0.1 kg (Model 770; Seca, Hamburg, Germany), as described in a previous study from our laboratory (27). Systolic and diastolic blood pressure levels were measured in the supine position after a resting period of at least 5 minutes, using an electronic sphygmomanometer (Omron Healthcare, Lake Forest, Illinois, United States). Tanner stage was assessed by a pediatrician who provided an estimation of the pubertal stage of each adolescent (28,29). BMI and body surface area (in $m^2$) were calculated using a formula from Dubois and Dubois (30). In addition, BMI corrected for standard deviation score (BMI-SDS) was calculated by Growth Vision version 3.0 (Novo Nordisk, Bagsværd, Denmark) and using of Flemish reference values (31). A1C values were assessed via ion-exchange chromatography (Menarini HA-8180 A1c Auto-analyser; Menarini Diagnostics, Diegem, Belgium). In the T1D group, glucose variability was estimated using coefficients of variation covering the last 84 days before the first assessments (calculated by standard deviation [SD] of glucose concentrations divided by mean glucose concentrations).

*Cardiac evaluation*

Transthoracic echocardiographic assessments were performed using a phased-array probe (Vivid E90 cardiovascular ultrasound system and M5S 1.5- to 4.5-MHz probe; GE Healthcare, Milwaukee, Wisconsin, United States). Echocardiographic images of the controls consisted of historical assessments, whereas T1D echocardiographic assessments were performed by one of the researchers (L.V.R.). All images were digitally stored until analyses using EchoPac software (GE Healthcare), also executed by L.V.R. Participants were placed in the left lateral decubitus position and images of at least 3 cardiac cycles were collected from apical 4- and 5-chamber views (AP4C and AP5C) and parasternal long- and short-axis views (PLAX and PSAX). Conventional echocardiography was used to evaluate dimensions of the left ventricle (LV) and atrium (interventricular septum thickness end-diastole [IVSd], LV posterior wall thickness end-diastole [LVPWd], LV diameter end-diastole [LVDd], LV relative wall thickness [LVRWT] and left atrial diameter end-systole [LAsys diameter]). LV mass (LVM) was calculated according to the Devereux formula and indexed for body surface area (LVMi) (32). Pulsed-wave Doppler was used to obtain the mitral inflow pattern (early [E] and late [A] diastolic flow, deceleration time [Dt], E/A ratio and isovolumic relaxation time [IVRT]). Septal annular velocities of the mitral valve (early [e′] and late [a′] annular velocities) and LV filling pressures (E/e′ ratio) were evaluated using tissue Doppler imaging. Longitudinal strain (LS) was evaluated using 2-dimensional speckle-tracking analyses. The region of interest (ROI) was defined at end of diastole (endocardial and epicardial borders traced and epicardium avoided). Speckle tracking of the 6 individual segments (basal, middle and apical inferoseptal, apical and middle and basal lateral) was quantitatively and qualitatively checked (automated software and researcher, respectively). Measurements were only included in the analyses if tracing was accepted in all 6 segments (using automated software). LV ejection fraction (EF) was calculated using automated software according to the monoplane Simpson method. Left ventricular outflow tract (LVOT) was determined as the cross-sectional area of the aortic valve in the PLAX view in midsystole. Cardiac output (CO) was measured using the velocity-time integral of the flow through the aortic valve in the AP5C view for the left ventricular outflow tract and heart rate (HR).

*Physical activity and fitness*

Physical activity levels were determined using the validated Dutch Physical Activity Questionnaire for Adolescents (PAQ-A) (33). A maximal incremental exercise test (cardiopulmonary exercise test) was performed as described elsewhere (27). The cardiopulmonary exercise test was performed up to volitional exhaustion on an electronically braked cycle ergometer (eBike; GE Healthcare, Milwaukee, Wisconsin, United States). Electrocardiographic activity was monitored continuously using electrocardiography software and 12-lead electrocardiography (CardioSoft version 6.6; GE Medical Systems, Freiburg, Germany). HR reserve was calculated as the difference between maximal attained HR and resting HR, and HR percentage was measured as the achieved percentage of theoretical maximal HR. The test (ramp stage protocol; initial workload of 40 W, increased by 20 W/min) consisted of a 1-minute pre-exercise resting period, a 1-minute unloaded warmup cycling phase, an incremental exercise cycling phase and cooldown phase at 45 W. During the test, a cycling frequency of 60 to 70 revolutions per minute was requested. Participants were verbally encouraged to achieve maximal effort (aiming to reach a respiratory gas exchange ratio [RER] of $\geq$1.10) and the test was discontinued when participants failed to sustain the required cycling frequency. Breath-by-breath analyses were performed (Jaeger MasterScreen CPX Metabolic Cart; CareFusion Germany GmbH, Hoechberg, Germany) for assessment of peak oxygen uptake ($VO_{2peak}$). In addition, peak workload capacity ($W_{peak}$) was used to estimate exercise tolerance. In case of hypoglycemia in the T1D group (capillary blood glucose concentrations $<$100 mg/dL [$<$5.6 mmol/L]), the test was postponed. Supplementation of monosaccharides was applied until blood glucose increased to $>$100 mg/dL ($>$5.6 mmol/L), allowing for safe execution of the exercise test.

*Study size and statistical analysis*

The estimation of the required sample size was based on a study by Nadeau et al (25), who investigated exercise capacity in (poorly controlled) T1D adolescents and compared the latter with HCs. Study sample calculations (G*Power version 3.1.9.2) revealed that a minimum of 30 study subjects (15 in each group) would ensure sufficient statistical power ($\geq$80) to detect differences in exercise capacity ($VO_{2peak}$, in mL/min; 2,319$\pm$530 mL/min vs 1,813$\pm$416 mL/min) and relations between exercise capacity and metabolic control ($VO_{2peak}$ [mL/min] and A1C [%]; r=$-$0.53) and LV systolic and diastolic function ($VO_{2peak}$ [mL/min] and E/A; r=$-$0.41). All statistical

analyses were performed using SPSS version 24 (IBM SPSS Armonk, New York, United States). Data are expressed as mean ± standard deviation. Normality was checked using the Shapiro-Wilk test. As participants were matched, paired t tests were used (in the case of normally distributed data). A nonparametric alternative (Wilcoxon signed-rank test) was used for non–normally distributed data. Pearson correlations (and partial correlations) were performed for LV systolic and diastolic function and clinical parameters. Linear regression was applied for significant correlations to explain the variance. In case of non–normally distributed variables, nonparametric partial correlations were calculated. $p<0.05$ was considered significant (two-tailed).

## Results

### *Clinical characteristics: Physical examination and anthropometric assessment*

Nineteen T1D adolescents were eligible and, therefore, included in the study and compared with 19 HCs, matched for age and Tanner stage. As summarized in Table 1, groups were similar with regard to age, Tanner stage, sex and BMI. General characteristics, including body length, body weight, BMI-SDS and the systolic and diastolic blood pressure, were similar between groups. Evidently, A1C was significantly higher in the T1D group (7.4±0.9% vs 5.3±0.2%).

### *LV systolic and diastolic function*

Characteristics of LV systolic and diastolic function are summarized in Table 2. Groups were similar ($p>0.05$) with regard to cardiac dimensions and structure (IVSd, LVDd, LVPWd, LAsys, LVM, LVMI and LVRWT). No differences were observed for parameters of diastolic function (mitral inflow pattern and tissue Doppler imaging) and systolic function (EF, LS, CO) between groups ($p>0.05$).

### *Physical activity and fitness*

As illustrated by the PAQ-A score, groups were similar with regard to physical activity levels (Table 3). HRrest was significantly higher in the T1DM group (88±14 vs 73±12 beats/min; $p<0.05$). Exercise performance and oxygen uptake were similar between the 2 groups, as reflected by $W_{peak}$, $VO_{2peak}$ and $VO_2$/HR. Although RER was significantly higher in the control group (1.24±0.06 vs 1.16±0.08; $p<0.001$), such differences were not clinically meaningful as both exceeded the cutoff for a maximal test (RER>1.10).

### *Correlations and regression*

Correlations were assessed for both groups with regard to clinical parameters (age, BMI-SDS, A1C, $VO_{2peak}$ and Tanner stage) and LV systolic and diastolic function. Except for EF, no significant correlations were observed for LV systolic and diastolic function (LS, E, A, E/A, E/e′, Dt, IVRT, a′ and CO), structure (IVSd, LVDd, LVPWd, LAsys, LVM, LVMI and LVRWT) or clinical parameters. Within the T1D group, EF was significantly negatively correlated with disease duration, even when corrected for age, A1C, BMI-SDS, glucose variability and $VO_{2peak}$ (r=−0.595 and r=−0.79; $p<0.05$; Table 4). Linear regression for disease duration and EF revealed that

**Table 1**
Subjects' characteristics

| | Healthy controls (n=19) | T1D (n=19) | p Value |
|---|---|---|---|
| Gender, females/males, n | 5/14 | 6/13 | – |
| Age, years | 14.4±1.3 | 14.8±1.9 | 0.5 |
| Tanner stage * | 3.8±1.2 | 4±1.2 | 0.56 |
| Body length, cm | 168.6±8.8 | 169.6±7.7 | 0.72 |
| Body weight, kg | 58±13.5 | 59±12.1 | 0.81 |
| BMI, kg/m$^2$ * | 20.2±3.8 | 20.7±3.7 | 0.54 |
| BMI-SDS | −0.02±1.08 | 0.15±0.91 | 0.61 |
| BSA, m$^2$ | 1.65±0.22 | 1.67±0.18 | 0.75 |
| Systolic BP rest, mmHg | 116±9 | 122±14 | 0.13 |
| Diastolic BP rest, mmHg | 70±9 | 68±11 | 0.73 |
| A1C concentration, % * | 5.3±0.3 | 7.4±0.9 | <0.001 † |
| Glucose variability, % | | 48.1±8.8 | – |
| Time since diagnosis, months | – | 69±36 | – |
| Age at diagnosis, years | – | 9±3 | – |

*A1C*, glycated hemoglobin; *BMI*, body mass index; *BMI-SDS*, standardized body mass index; *BP*, blood pressure; *BSA*, body surface area; *T1D*, type 1 diabetes.
*Note:* Data expressed as mean ± standard deviation, unless noted otherwise.
* Data abnormally distributed. Wilcoxon signed-rank test used.
† $p<0.005$ for significant difference between 2 groups.

**Table 2**
Echocardiographic data

| | HC group (n=19) | T1D group (n=19) | p Value |
|---|---|---|---|
| E, m/s * | 0.82±0.13 | 0.85±0.19 | 0.4 |
| A, m/s | 0.5±0.12 | 0.46±0.08 | 0.41 |
| E/A | 1.72±0.4 | 1.86±0.38 | 0.42 |
| DT, ms | 155±24 | 152±39 | 0.79 |
| IVRT, ms | 59±7 | 62±11 | 0.6 |
| EF, % | 58±4 | 61±5 | 0.07 |
| e′, m/s | 0.11±0.02 | 0.12±0.02 | 0.1 |
| a′, m/s * | 0.06±0.02 | 0.06±0.01 | 0.82 |
| e′/a′ | 2.1±0.85 | 2.16±0.58 | 0.8 |
| E/e′ | 7.43±1.3 | 7.06±1.77 | 0.52 |
| LVOT, cm | 1.9±0.2 | 2±0.2 | 0.07 |
| LS, % | 19.7±2.4 | 20.1±2.3 | 0.62 |
| IVSd, cm * | 0.93±0.16 | 0.93±0.14 | 0.64 |
| LVDd, cm | 4.27±0.41 | 4.5±0.41 | 0.14 |
| LVPWd, cm | 0.99±0.13 | 0.98±0.14 | 0.83 |
| LAsys diameter, cm | 2.93±0.28 | 3±0.31 | 0.42 |
| LVM, g | 133±33 | 146±38 | 0.22 |
| LVMi, g/m$^2$ | 79.5±14 | 87±18.5 | 0.16 |
| LVRWT | 0.47±0.07 | 0.44±0.06 | 0.29 |
| CO, L/min | 4.8±0.8 | 4.7±1.1 | 0.85 |

*a′*, late annular velocity; *A*, late diastolic flow; *CO*, cardiac output; *DT*, deceleration time; *e′*, early annular velocity; *E*, early diastolic flow; *E/e′*, left ventricular filling pressures; *EF*, ejection fraction; *HC*, healthy control; *IVRT*, isovolumetric relaxation time; *IVSd*, interventricular septum thickness end-diastole; *LAsys*, left atrial diameter end-systole; *LS*, longitudinal strain; *LVDd*, left ventricular diameter end-diastole; *LVM*, left ventricular mass; *LVMi*, left ventricular mass index; *LVOT*, left ventricular outflow tract; *LVPWd*, left ventricular posterior wall thickness end-diastole; *LVRWT*, left ventricular relative wall thickness; *T1D*, type 1 diabetes.
*Note:* Data expressed as mean ± standard deviation.
* Data abnormally distributed. Wilcoxon signed-rank test used.

**Table 3**
Physical activity and physical fitness

| | HC group (n=19) | T1D group (n=19) | p Value |
|---|---|---|---|
| PAQ-A score | 2.47±0.45 | 2.64±0.65 | 0.41 |
| HRrest, bpm * | 73±12 | 88±14 | 0.006 † |
| HRpeak, bpm | 186±11 | 192±7 | 0.05 |
| HRreserve, bpm | 113±12 | 105±16 | 0.06 |
| $HR_{Achieved\ percentage\ of\ maximal\ HR,\ \%}$ | 94±3 | 91±5 | 0.08 |
| $Workload_{peak}$, W * | 192±46 | 180±40 | 0.29 |
| $VO_{2peak}$, mL/min * | 2,286±578 | 2,493±511 | 0.1 |
| $VO_{2peak}$, mL/kg per min | 40.5±8.7 | 43.8±9.9 | 0.28 |
| RER | 1.24±0.06 | 1.16±0.08 | <0.001 ‡ |
| $VO_2$/HR, mL/beat * | 13±2.7 | 12.3± 3.1 | 0.21 |

*HC*, healthy control; *HR*, heart rate; *PAQ-A*, Physical Activity Questionnaire for Adolescents; *RER*, respiratory exchange ratio; *T1D*, type 1 diabetes; *$VO_{2peak}$*, maximal oxygen uptake; *$VO_2$/HR*, oxygen pulse.
*Note:* Data expressed as mean ± standard deviation.
* Data abnormally distributed. Wilcoxon signed-rank test used.
† $p<0.05$ for significant difference between 2 groups.
‡ $p<0.001$ for significant difference between 2 groups.

**Table 4**
Correlation of ejection fraction with clinical parameters in healthy controls and T1DM patients

| | HC group | | | T1D group | | |
|---|---|---|---|---|---|---|
| | r | p Value | Sample size | r | p Value | Sample size |
| Age, years | −0.255 | 0.34 | 16 | −0.234 | 0.421 | 15 |
| BMI-SDS | −0.162 | 0.548 | 16 | −0.219 | 0.452 | 15 |
| A1C concentration, % | 0.34 | 0.214 | 15 | −0.39 | 0.169 | 15 |
| $VO_{2peak}$, mL/min | −0.35 | 0.184 | 16 | 0.426 | 0.129 | 14 |
| Tanner stage | −0.041 | 0.881 | 16 | −0.355 | 0.234 | 14 |
| Glucose variability | — | — | — | 0.046 | 0.882 | 14 |
| Disease duration, years | — | — | — | −0.595 | 0.025 * | 15 |
| Disease duration (years) corrected for age, BMI-SDS, glucose variability and $VO_{2peak}$ | — | — | — | −0.79 | 0.011 * | 12 |

*A1C*, glycated hemoglobin; *BMI-SDS*, standardized body mass index; *HC*, healthy control; *T1D*, type 1 diabetes; *$VO_{2peak}$*, maximal oxygen uptake.
* $p<0.05$ (statistically significant).

37.6% of the variance (adjusted $R^2=32.9\%$) in EF could be attributed to disease duration ($F_{1,13}=7.85$, $p<0.05$; see Supplementary Figure 1).

*Observed power of statistical analyses*

Posthoc (observed) power analyses were performed (G*Power version 3.1.9.2) as the study sample size was based on an earlier study (25). Although analyses for LVEF were sufficiently powered (0.975 for paired t test), other parameters of LV systolic and diastolic function, as well as exercise capacity, were underpowered to detect differences between groups (<0.80 for paired t tests). The linear regression for LVEF and disease duration was sufficiently powered (0.88 for actual sample size, n=15).

## Discussion

In this study, we have compared LV systolic and diastolic function and exercise capacity between T1D adolescents and healthy controls, matched for age and Tanner stage. The comparable BMI and physical fitness levels in the groups allowed for a thorough comparison. Our data show that systolic and diastolic function were well preserved in adolescents with well-controlled T1D. LV function proved to be related to disease duration, a relationship already described in adult diabetes patients (24). Such findings point toward the intrinsic deteriorating effects of long-term diabetes on cardiovascular health.

Indeed, every 10-year accumulation of disease duration accounts for a 23% higher risk of developing CVD in T2D patients (34). Recently, such a relation was also described in T1D patients (35). In our study, we reported a strong negative relation between systolic function (EF) and disease duration in T1D adolescents ($r=-0.79$, $p=0.011$, corrected for age, BMI-SDS, glucose variability and $VO_{2peak}$), although most of the EF data were within the normal range (36). Nevertheless, surprisingly, such results are in line with those of Yoldas et al, the first study to show a negative relation between disease duration and LV function in T1D adolescents with well-controlled (A1C≤7.5%) diabetes (13). In the latter, myocardial deformation (longitudinal, radial and circumferential strain) and diastolic function were impaired in T1D adolescents when compared with HCs, and impairments in myocardial deformation were even more prominent with prolonged disease duration. Such differences were not observed in our study. However, Yoldas et al reported global longitudinal strain (based on apical 4C, apical long-axis and apical 2C views), whereas our study reported longitudinal strain (apical 4C), which impedes any full comparison between both studies. Furthermore, group differences for BMI may have (partially) contributed to the differences in diastolic function in the study by Yoldas et al. Indeed, BMI is of great clinical importance, as obesity was shown to be related to diastolic dysfunction in adolescents, even in the absence of diabetes (27).

Although not investigated in our study, longer disease duration is likely to be accompanied by more hypo- and hyperglycemic events, which may in turn cause myocardial dysfunction. Indeed, hypoglycemia acutely results in decreased myocardial blood flow reserve, whereas hyperglycemia negatively affects contractility (37,38). The contribution of metabolic control is undeniable as the majority of studies displaying LV dysfunction showed that glycemic status was poorly controlled (A1C>7.5%). Khattab et al even reported diastolic dysfunction in recently diagnosed T1D adolescents (disease duration <3 years), >80% of whom displayed poor metabolic control (21–23,39). Hyperglycemia and the associated accumulation of advanced glycation end-products could contribute to such findings, as demonstrated by Berg et al, who described increased heart stiffness in their study group (40). Interestingly, we did not find any correlations between indicators of glycemic control (A1C and glycemic variability) and LV function, neither diastolic function nor contractility (longitudinal strain). This may have been related to the limited A1C range, in contrast to previous studies (18,21,22,41).

Evaluating exercise capacity is crucial, as exercise intolerance is associated with higher mortality risk in diabetes patients (26). Previous studies reported impaired exercise capacity in T1D adolescents (25,42). Nadeau et al also reported diastolic dysfunction, emphasizing the interplay with exercise capacity and its clinical relevance (25). In contrast to findings by Nadeau et al, we did not observe impaired exercise capacity or impaired LV function in T1D adolescents. It is doubtful whether this could be attributed to the adequate glycemic control in our study (in contrast to the study of Nadeau et al), as A1C values have previously been reported not to influence $VO_{2peak}$ (43). Nevertheless, the pivotal role of regular physical activity is widely accepted and specific recommendations have been established for young diabetes patients (44,45).

The detrimental effects of diabetes are not limited to LV systolic and diastolic function but instead can affect the entire cardiovascular system. Indeed, hyperglycemia has also been shown to be related to impaired endothelial function (up to 50% smaller flow-mediated dilation) (18). Impaired flow-mediated dilation was already broadly described in adults with diabetes (46). However, strikingly, these results indicate a distinct diabetes-related effect on endothelial function as most of the modifiable risk factors (e.g. tobacco smoking and physical inactivity) develop later in life (44).

In combination with previous studies, we have shown that, even if lifestyle factors (physical fitness/activity) and glycemic status are well controlled, anomalies in cardiovascular function manifest early in life and/or in the disease process even though LV function may be preserved. This could explain why cardiac dysfunction is more prevalent in adults with T1D compared with adolescents with T1D (47). Given the risk-increasing effect of A1C on heart failure later in life, tight glycemic control is clearly warranted in this population (48). Thus, our results suggest that young T1D patients could benefit from cardiovascular evaluation in order to detect early changes in cardiac function. Larger cohort studies are warranted to further elucidate how the different aspects of diabetes (such as disease duration and glycemic control) affect long-term cardiovascular health and exercise capacity in T1D patients.

*Limitations*

Our study included a relatively small study group and, although sample calculations were performed, statistical power was lacking for some analyses. Caution is, therefore, warranted when interpreting these findings. To properly compare our study with the study by Yoldas et al, which is the only investigation (to our knowledge) in which glycemic status was well controlled, global longitudinal strain analyses should have been performed (including the apical long-axis and apical 5C views). However, the control groups consisted of historical assessments, and apical long-axis and apical 5C images were not included in the assessments. As A1C only reflects glycemic control of the previous 3 months, the use of continuous glucose monitoring systems that provide the ambulatory glucose profile may be helpful to unravel the pathophysiologic mechanisms of T1D in LV systolic and diastolic function and structure.

In conclusion, our study has shown that LV systolic and diastolic function is preserved in T1D adolescents displaying adequate physical fitness and glycemic control. However, although LVEF was in the normal range, a prolonged disease duration was related to lower values of the latter. Young T1D patients may, therefore, benefit from cardiovascular evaluation so cardiovascular abnormalities can be detected early in the disease course and long-term cardiovascular health can be improved.

## Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Diabetes* at www.canadianjournalofdiabetes.com.

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## Disclosure Statement

Conflict of interest: None.

## Author Contributions

L.V.R. was responsible for conceptualization, formal analysis, investigation and writing of the original manuscript draft. W.M.A.F. provided formal analysis. E.V. was responsible for project administration and formal analysis. J.I. and F.D.V. provided project administration and investigation. J.V. and P.D. provided writing, review and editing. V.B. provided visualization, writing, review and editing. D.H. conceptualization, writing, review and editing.

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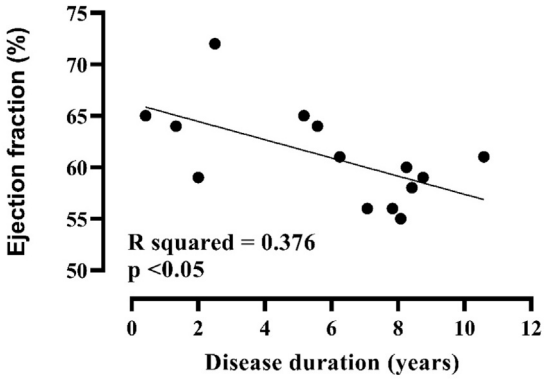


**Supplementary Figure 1.** Linear regression showing the negative relation between disease duration and ejection fraction.