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Original Article

Decreased regional left ventricular myocardial strain in type 1 diabetic children: A first sign of diabetic cardiomyopathy?

Amir Hodzic1, Virginie Ribault2, Pascale Maragnes1, Paul Milliez1, Eric Saloux1, Fabien Labombarda1

1Department of Cardiology, Caen CHU, Caen, F-14000, France;
2Department of Pediatrics, Caen CHU, Caen, F-14000, France

ABSTRACT

Background and Objectives: Type 1 diabetes is a major cardiovascular risk factor associated with an excess of mortality in young adults due to premature cardiovascular events, which includes heart failure. The relation between type 1 diabetes and cardiac structure and function in children was poorly documented. Our study investigates (1) whether type 1 diabetic children have echocardiographic signs of subclinical cardiac dysfunction assessed by tissue Doppler strain and (2) whether state of metabolic control and diabetes duration have any influence on the cardiac event. Methods: Standard echocardiography and tissue Doppler imaging were prospectively performed in type 1 diabetic children. Left ventricular dimensions, standard indices of systolic and diastolic function, and septal longitudinal strain were investigated. Results: Thirty consecutive asymptomatic diabetic children (age: 12.4 [5–17] years; males: 53%) were compared to 30 age and sex-matched healthy control subjects. Left ventricular mass index and diastolic septal thickness were significantly increased in diabetic children. There was no difference between two groups as regards the left ventricular ejection fraction and conventional mitral Doppler parameters (E, A, Ea). The global longitudinal systolic strain and strain rate were found to be decreased in children with diabetes. The global longitudinal early diastolic strain rate (Esr) was negatively correlated with metabolic control. Longitudinal strain was not correlated with diabetes duration. Conclusion: Children with Type 1 diabetes had subclinical alterations in left ventricular size and longitudinal myocardial deformation.

Key words: left ventricular size, type 1 diabetes, longitudinal myocardial deformation, children

INTRODUCTION

Type 1 diabetes is a major cardiovascular risk factor. Its prevalence has risen steadily for about 20 years with an increasingly early detection[1]. Currently in France, the incidence of type 1 diabetes is 13.5 per 100,000 children under 15 years old. Type 1 diabetes is associated with excess mortality in young adults due to premature cardiovascular events[2], including heart failure[3,4]. Heart failure is the consequence of myocardial abnormalities specific to diabetes, which occur even in the absence of coronary artery disease or high blood pressure, and is directly related to chronic hyperglycemia. Chronic hyperglycemia induces complex metabolic disturbances in cardiomyocytes, leading to morphological and functional abnormalities of the myocardium, grouped under the term “diabetic cardiomyopathy”[5-9]. Diabetic cardiomyopathy is characterized by the presence of extensive myocardial fibrosis, myocyte hypertrophy, increased oxidative stress, and microangiopathy[5]. While frequent, to date, a specific strategy for early detection or treatment of diabetic cardiomyopathy to improve its prognosis has not yet been established[8]. In adults, echocardiographic or magnetic resonance studies have shown that diabetes led to eccentric left ventricular (LV) hypertrophy with alterations of the diastolic and systolic myocardial function[5-8]. The relationship between type 1 diabetes and cardiac structure and function in children and adolescents was
poorly documented. Most of the previous echocardiographic studies have used standard techniques relatively insensitive to the detection of early myocardial dysfunction[9, 10]. Strain and strain rate, derived from tissue Doppler imaging (TDI), have been proposed as parameters for the early detection of myocardial dysfunction[11]. This technique can detect subclinical changes in myocardial function and represent an independent prognostic factor[12, 13]. Our study investigates (1) whether children with type 1 diabetes have echocardiographic signs of subclinical cardiac dysfunction assessed by color tissue Doppler imaging and (2) whether the state of metabolic control and diabetes duration have an influence on the cardiac event.

METHODS

Population study
The study prospectively recruited patients with type 1 diabetes aged 5 to 18 years followed up at the pediatric department of the Caen Teaching Hospital. Type 1 diabetes was diagnosed according to the World Health Organization criteria[13] together with the permanent need for insulin therapy. Exclusion criteria were the presence of cardiopathy, significant concomitant disease, medication known to modify cardiac function, high blood pressure, smoking, dyslipidemia, and obesity (defined as a body mass index (BMI), adjusted for gender and age, exceeding the 97th percentile according to French reference values[14]). Recently diagnosed (< 1 year) children with diabetes were also not included. Patients with diabetes were compared with healthy control children from our outpatients department of pediatric cardiology selected from children being investigated for physiological cardiac murmur whose echocardiography was normal. To be included in the control group, children had to have no personal antecedents or family history of either high blood pressure or hypercholesterolemia. The study protocol was approved by the hospital ethics review board. Patients provided their informed consent through legal representatives.

Clinical evaluation
Demographic details of age, gender, weight, height, and heart rate were recorded. BMI was calculated according to the formula of weight (kg) divided by height squared (m²) and expressed as a Z score. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured after 10 min at rest with a calibrated automatic blood pressure monitor (Datascope® DUO). Mean blood pressure (MBP) was calculated according to the formula: MBP = (SBP + 2xDBP)/3. SDP, DBP, and MBP were expressed in mmHg. For patients with diabetes, diabetes duration (expressed in years) was considered for each individual based on the full-attained age on the first day of insulin therapy.

Biochemistry
Fasting blood samples were taken from the diabetic children to analyze HbA1c, expressed in percentages. HbA1c was measured by high-performance liquid chromatography (Tosoh Corporation, Tokyo, Japan). This study used the mean quarterly HbA1c (mmol/mol, %) for the year prior to the study.

Echocardiography
Echocardiographic studies were performed using an iE33 (Philips Medical Systems, SS probe, Best, The Netherlands). Each subject was examined in a semisupine left lateral position. The electrocardiogram was recorded continuously. Images were obtained at endexpiratory apnea and stored in cineloop format from three consecutive beats.

Standard Echocardiography and Tissue Doppler imaging
Left ventricular ejection fraction (LVEF) was assessed using the biplane Simpson's method in the apical view. Left ventricular end-diastolic dimension (LV-EDD), interventricular septal end-diastolic dimension (IVS-EDD), and left ventricular posterior wall end-diastolic dimension (PW-EDD) were measured in time motion mode in parasternal long-axis view. Measurements were adjusted for age, sex, height, and weight and expressed as a Z-score. Left ventricular mass (LVM) was calculated by the Devereux formula and indexed by height raised to the power of 2.7. The mitral Doppler signal was recorded in the apical four-chamber view, with the Doppler sample volume placed at the tip of the mitral valve. Peak velocities of early (E) and late (A) filling waves, early/late filling ratio of peak velocities (E/A) were measured on the basis of transmitral flow velocities. Myocardial systolic and diastolic velocities were recorded using the pulsed-wave TDI technique from an apical four-chamber view. The sample volume (4 mm thick) was placed at the basal level of the right ventricular and left ventricular free walls to measure tricuspid peak systolic velocity (ST) and early mitral peak diastolic velocity (Ea).

Strain analysis
For longitudinal strain and strain rate measurements, narrow sector angle acquisitions of the septal wall were obtained in the apical four-chamber view with color TDI (minimum frame rate, 90 Hz) during brief apnea after expiration. Probe movements were maximally limited. Three consecutive beats were stored digitally and analyzed offline using dedicated research software (QLAB; Philips Medical Systems) capable of extracting strain and strain rate from tissue velocity data sets. During processing, manual tagging was performed, and curved M-mode lines (10-mm-thick area of interest) were drawn on the septal wall to obtain the mean strain and
strain rate values of basal and medial septal segments. A tracking of the myocardial region of interest was activated to avoid blood flow artifacts. The peak systolic strain was determined as the nadir of the strain curves (Figure 1). The peak systolic strain rate (Ssr), early (Esr), and late (Asr) peak diastolic strain rates were measured (Figure 1). With our measurement method, strain and strain rates for the septal wall are reliable parameters for both reproducibility and repeatability, as previously reported by our team[15]. Apnea is required for color TDI acquisition and our study limit was age 5 years. In our experience, most children aged under 5 are unable to cooperate for apnea.

**Statistical methods**

Quantitative variables were described using mean and standard deviations (SD), and qualitative variables were described using frequencies and percentages. The two groups were compared using the two-tailed Wilcoxon test for nonparametric paired data and a paired Student’s t-test for normally distributed paired data. A chi-square test was used to estimate the relationship between qualitative variables. Correlations between LVMD indicators and diabetes duration and HBA1c were determined using Pearson coefficient correlation. All tests were two-tailed and their level of significance was defined as $P < 0.05$. R version 2.12.1 was the statistical software used. The statistical review of the study was performed by a biomedical statistician.

**RESULTS**

**Population**

Overall, 30 consecutive children and adolescents with type 1 diabetes (age range [5–17] years, male: 53%) were recruited at our pediatric endocrinology department and enrolled in this prospective cohort. Among children with diabetes, HBA1c ranged from 6.8% to 12.7%, 63% of the patients with diabetes patients had HBA1c > 8% and mean diabetes duration was 5.1 ± 3.1 years. The results in diabetic patients were compared with those in 30 healthy children, matched for age and sex, recruited as a control group over the same time period. SBP was significantly higher in the diabetic group. Both weight and BMI were higher in patients with diabetes but Z score BMI did not differ. The diabetic and control children were comparable with respect to age, gender, heart rate, SBP, DBP, and mean BP. The characteristics of our study population are shown in Table 1.

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**Figure 1:** Measurements of peak strain, peak systolic strain rate (Ssr), early peak diastolic strain rate (Esr) and late peak diastolic strain rate (Asr) for the septal wall, by two-dimensional color-coded tissue imaging.
Table 1: Characteristics in children with type 1 diabetes and controls

<table>
<thead>
<tr>
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<th>Children with diabetes (n = 30)</th>
<th>Controls (n = 30)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>53</td>
<td>47</td>
<td>0.71</td>
</tr>
<tr>
<td>Age (years)</td>
<td>12.4 ± 3.4</td>
<td>12.8 ± 2</td>
<td>0.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>47 ± 17.7</td>
<td>41.1 ± 7.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>151.3 ± 21.2</td>
<td>149.4 ± 11</td>
<td>0.47</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>19.6 ± 3.7</td>
<td>18.2 ± 1</td>
<td>0.02</td>
</tr>
<tr>
<td>Z-score BMI</td>
<td>0.22 ± 0.86</td>
<td>-0.09 ± 0.32</td>
<td>0.08</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>80.5 [76.5;88]</td>
<td>79.5 [72;97]</td>
<td>0.38</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>114.5 [108;122.3]</td>
<td>105 [99.8;115]</td>
<td>0.01</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>65 [59.8;70]</td>
<td>66.5 [60.8;70.3]</td>
<td>0.27</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>80.5 [76.8 ; 88]</td>
<td>79 [75 ; 85]</td>
<td>0.4</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>5.1 ± 3.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HBA1C (%)</td>
<td>8.7 ± 1.4</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SD, percentage or range. BMI: body mass index; bpm: beats per minute; SBP/DBP/MBP: systolic/diastolic/mean blood pressure.

Standard echocardiographic measurements

The results are shown in Table 2. In the diabetic group, Z scores for LV-EDD and LV-ESD were significantly lower, while IVS thickness and LVM were significantly higher. The E wave was lower in the diabetic group without reaching statistical significance (P = 0.053). There were no significant differences between the two study groups in LVEF and other diastolic function parameters (A wave, E/A and E/Ea) and TDI parameters. St was similar in two study groups.

Strain and strain rate analysis

Longitudinal strain (Figure 2, Panel A) as well as Ssr (Figure 2, Panel B) for the septal wall were significantly decreased in patients with diabetes compared with controls. Strain rate diastolic measurements did not differ between the two groups (Figure 1, Panel B). The results are shown in Table 2.

Relation between strain and strain rate parameters, glycemic control and diabetes duration

Among the longitudinal septal strain parameters, Esr was inversely correlated with HBA1C (r = -0.41, P = 0.028). No correlation was found between HBA1C and peak systolic strain (r=0.26, P=0.16) and Ssr (r=0.07, P=0.7). We did not find any correlation between diabetes duration and strain or strain rate measurements.

DISCUSSION

Using longitudinal septal strain measurements, we report subclinical left ventricular functional changes in children with type 1 diabetes associated with LV remodeling. Our results suggest that type 1 diabetes is not only a cardiovascular risk factor in the long term but may be associated, early in childhood, with abnormal LV longitudinal function. We did not find a relationship between both glycemic control and diabetes duration and the impairment of LV longitudinal function.

Left ventricular morphology and function

In our study, children with type 1 diabetes presented an increased LVM. Previous magnetic resonance imaging studies have shown that diabetes was associated with LV hypertrophic remodeling regardless of age and gender[16,17]. These results were confirmed by echocardiographic studies where LV remodeling was associated with abnormalities of diastolic function in patients with type 1 diabetes[18,19]. Previous echocardiographic studies in diabetic children focused on LV diastolic function and suggested a reduction in early diastolic filling based on transmitral flow analysis[20,21]. Although our transmitral Doppler results are consistent with these previous findings, diastolic strain rate parameters failed to identify diastolic dysfunction in the diabetic group. Based on LVEF assessment, all previous studies conducted in children with type 1 diabetes...
concluded the absence of LV systolic dysfunction. Because of cardiac geometry and myofiber arrangements, LV function goes through complex myocardial deformations, or “strains,” and cannot be reduced to a variation of volume, as with assessment of LVEF. Longitudinal strain plays an important role in cardiac pump function. It is primarily controlled by subendocardial longitudinal myofibers, which are more susceptible to fibrosis and ischemia[22]. This explains why subclinical impairment in longitudinal strain represents the first anomaly observed in the setting of many conditions predisposing to heart failure[23]. Our results are consistent with studies in adult diabetic patients, which showed an early impairment of the LV longitudinal strain using TDI[24] and 2D speckle strain analysis[25,26], while LVEF was preserved. However, these studies are difficult to interpret because they mixed patients with type 1 and 2 adult diabetic patients, in whom the influence of comorbidities such as age, coronary artery disease, or high blood pressure could not be formally excluded. Such comorbidities may be considered nonexistent in our cohort of diabetic children, who represent a unique model to investigate the early effects of metabolic disturbances induced by type 1 diabetes on myocardial function. Our results are not consistent with the previous studies reported by Salem et al. and Khattab where the LV longitudinal function analyzed by TDI was preserved in children and adolescents with type 1 diabetes[10,27]. However, these authors analyzed the velocities of displacement of myocardial walls using pulsed TDI modality, which are more influenced by translational cardiac movements and displacement of adjacent myocardial segments[28]. Our results are consistent with those of Abdel-Salam et al. who demonstrated early impairment of LV longitudinal systolic deformation analyzed by 2D speckle strain in young asymptomatic type 1 diabetic adults without associated comorbidities[29]. The consistency of these results suggests that type 1 diabetes may be associated with early longitudinal strain impairment, which may be the first marker of preclinical diabetic cardiomyopathy, as previously suggested in type 2 diabetes[30,31]. The strain measurements reflect myocardial deformation, but they are also dependent on load conditions, ventricular geometry, and elastic properties of myocardial tissue[24]. In our study, we cannot exclude that the SBP, significantly higher in patients with diabetes, was able to reduce the overall septal strain. However, children with diabetes had a decreased peak systolic strain rate, described as a less dependent parameter of load conditions[32].

**Potential mechanisms**

Several pathophysiological mechanisms have been proposed to explain the occurrence of structural and functional myocardial changes observed in diabetic cardiomyopathy[7]. These mechanisms include the metabolic abnormalities of cardiomyocytes associated with excessive use of very long chain fatty acids, chronic hyperglycemia, impaired calcium...
homeostasis, fibrosis, myocyte apoptosis, microcirculation abnormalities, and cardiac autonomic dysfunction[31]. The decrease in longitudinal deformation may reflect structural and functional changes of myocardial fibers due to diabetes through one of these mechanisms, and may constitute the first sign of diabetic cardiomyopathy[31]. A relationship between glycemic control and abnormalities in heart function have been reported in children and adults[33, 34]. The small number of diabetic children and the relatively short diabetes duration may explain why we did not observe a correlation between glycemic control, diabetes duration, and systolic longitudinal strain in our study.

Clinical perspectives
Diabetes generates myocardial changes that remain silent during childhood but are expressed in adulthood by excess cardiovascular mortality, mainly attributed to coronary artery disease and heart failure. Endothelial dysfunction and increased arterial stiffness, both established markers of coronary artery atherosclerosis, are already present in children with type 1 diabetes[35]. Similarly, our results indicate that type 1 diabetes is associated with early abnormalities of the longitudinal myocardial function. These anomalies could be a first step toward the development of heart failure in adulthood. The presence of early myocardial dysfunction enhances the need for active management of diabetes in children with glycemic control as strict as possible. In addition, LV myocardial strain analysis could help assess the beneficial effect of treatment by objectivizing improved myocardial dysfunction as suggested in adults[33]. Further studies are needed to determine the prognostic value of these subclinical abnormalities in heart function and clarify the role of strain in the evaluation and monitoring of diabetic children.

Limitations
Our work had some limitations. We are aware that the small study population represents a limitation to drawing a formal conclusion. Since we included exclusively Caucasian patients, we cannot extend our results to the whole population of diabetic children. We performed a partial longitudinal strain and strain rate analysis with TDI. We thought this modality may be more appropriate for the children overcoming the difficulties of making an extended ultrasound examination. Furthermore, in children a high-quality apical four-chamber view, necessary for LV strain analysis, may be difficult to obtain, especially for the lateral wall analysis. Finally, being a cross-sectional study, the natural history of the development and progression of altered longitudinal deformation was unknown. Longitudinal clinical follow-up will be required in future studies to determine the prognostic value of longitudinal strain abnormalities.

CONCLUSION
Our study has suggested that LV longitudinal function is impaired in young patients with T1D. Further follow-up is necessary to elucidate the clinical significance of the myocardial changes detected by 2D strain imaging in type 1 diabetes children.

Conflict of interest
None

REFERENCES


