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Two-Dimensional Speckle Tracking Versus Applanation Tonometry in Evaluation of Subclinical Atherosclerosis in Children with Type 1 Diabetes Mellitus

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Manuscript Preparation E
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Background: Patients with type 1 diabetes mellitus (T1DM) often develop atherosclerosis at an early age. In the subclinical stage of the process, minimal/non-morphological changes can be noticed, but the arterial wall function can be impaired. Applanation tonometry allows to assess the arterial tree stiffness; however, the Two-Dimensional Speckle Tracking (2DST) is an increasingly accepted alternative. This study evaluated arterial wall stiffness using these 2 techniques in children with T1DM.

Material/Methods: We performed applanation tonometry and carotid arteries sonography with evaluation of the carotid intima-media thickness (cIMT) and use of the 2DST in 50 children with T1DM and in 50 healthy sex- and age-matched controls. We also assessed the reliability of 2DST in 10 random subjects.

Results: Children with T1DM had increased arterial wall stiffness, which was confirmed by tonometry (PWV: p=0.0386) and 2DST (Strain: p=0.0004; Strain rate: p=0.0081). There was no significant difference in cIMT between groups (0.45±0.06 *vs.* 0.43±0.05, p=0.073 in children with T1DM and controls, respectively). 2DST presented good intraclass correlation coefficient between researchers and within a single researcher.

Conclusions: Children with T1DM presenting with subclinical stage of atherosclerosis were found to have arterial wall stiffening. The 2DST, the same as applanation tonometry, allows to recognize this condition but in a more accessible and reproducible manner.

MeSH Keywords: **Arteriosclerosis • Carotid Intima-Media Thickness • Diabetes Mellitus, Type 1 • Pediatrics • Ultrasonography**

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Background

Patients with type 1 diabetes mellitus (T1DM) are at risk of developing atherosclerosis at an early age [1]. This is partly because T1DM onset generally starts in childhood and thus has a longer duration than diabetes mellitus type 2 (T2DM). The etiopathology of atherosclerosis is probably based on prolonged non-enzymatic glycosylation of arterial wall proteins and the overproduction of superoxide, both of which result in dysfunction of the epithelium (with lower bioavailability of nitric oxide), stiffening of the arterial wall, and further atherosclerotic changes [1]. However, in this multifactorial process, interactions between genetic, environmental, and biological factors contribute as well [2].

Although cardiovascular diseases rarely affect children, autopsy studies suggest that subclinical disease is already present in pediatric patients with T1DM [3,4]. The subclinical stage of vascular pathologies is reflected only in the form of discreet morphological changes (thickening of intima-media complex [5,6]), while the function of the arterial walls may have been significantly impaired. The criterion standard technique for evaluation of arterial wall stiffening is applanation tonometry. Pulse wave velocity (PWV) and augmentation index (AI) are 2 standard measures that reflect the mechanical properties (elasticity) of the entire arterial tree (consisting of large central elastic arteries as well as muscular and resistance arteries). In pediatric patients with T1DM, tonometry has already confirmed accelerated arterial aging [1]. However, this technique is not widely used in clinical practice, as the examinations are time-consuming and can be difficult to perform in agitated/hyperactive children. There are reports that in adults, 2-dimensional speckle tracking (2DST) can be an alternative [7,8].

2DST is a sonographic technique that allows evaluation of strain and strain rate of the arterial wall, which deforms due to the flowing of the pulse wave. It is a quick examination because it requires storing of the common carotid artery cross-section during 3 consecutive heartbeats. The short duration of the examination is an important advantage when examining children. Moreover, use of sonography allows for visual inspection of the examined area and assessment of other markers of arterial wall stiffness. Nevertheless, validation of this technique has not previously been performed in pediatric patients with T1DM.

The present study evaluated strain parameters of carotid arteries in T1DM patients and compared them with parameters derived from applanation tonometry. We hypothesized that both these techniques can recognize abnormalities in patients with T1DM in comparison with healthy controls, and that the results of these 2 tests will agree with each other. Confirmation of this hypothesis would show the utility of the 2DST technique as an alternative to tonometry.

Material and Methods

This cross-sectional study included 50 children with T1DM (31 girls and 19 boys, mean age 13.4 years old, age range 7.2–18.0 years) and 50 healthy, sex- and age-matched children in a control group. Diabetes was diagnosed according to WHO guidelines. Exclusion criteria were duration of diabetes shorter than 2 years [6] and known thyroid pathologies.

The study protocol required a fasting patient to arrive at the hospital in the morning. First, the blood sample was obtained to assess glucose, HbA1c, and lipid profile. Then, sonographic and tonometric examinations were performed within a short time interval (about 15 min). The local Bioethics Committee approved the study protocol, and all the participants/participants' guardians signed an informed consent.

Sonographic analysis

All participants were measured and weighed in light clothing and without shoes to calculate BMI. Then, they were positioned supine and studied in the morning hours in a quiet, semi-dark room with a comfortable temperature. The ECG trace was obtained, and the blood pressure was measured under resting conditions with an automatic sphygmomanometer. Examinations were performed by 2 independent researchers (with 6 and 10 years of experience in pediatric sonography) who were blinded to the group assignments. We used a Samsung RS80 device with a high-frequency linear probe (L3–12A) and Arterial Analysis™ software.

First, we scanned the carotid arteries for signs of significant atherosclerotic changes (focal IMC thickening of more than 50% of the adjacent parts of the IMC layer [6]). Then, longitudinal B-mode images of the common carotid artery (CCA) were obtained just below the carotid bulb. We positioned the focus below the far wall of the artery. Cine loops of 3 consecutive heartbeats were obtained for each side when the patient was holding breath at the end of expiration. Afterwards, the probe was turned 90° to show the cross-section of the CCA at the level of about 10 mm below the carotid bulb, and another cine loop of 3 consecutive heartbeats was stored. The patients were also asked to hold their breath at the end of expiration to minimize motion artifacts. Data analysis was performed immediately after the examination (Figure 1).

For each CCA, the carotid intima-media thickness (cIMT) was assessed semi-automatically during end-diastole (R-wave of the ECG) at the distance of 150–250 points, with the quality index (QI) >0.9. The mean value of the mean IMC obtained by 2 researchers on both sides was included in the analysis. For the evaluation of strain and strain rate, the circular region of interest (ROI) was placed along the border of the IMC and the

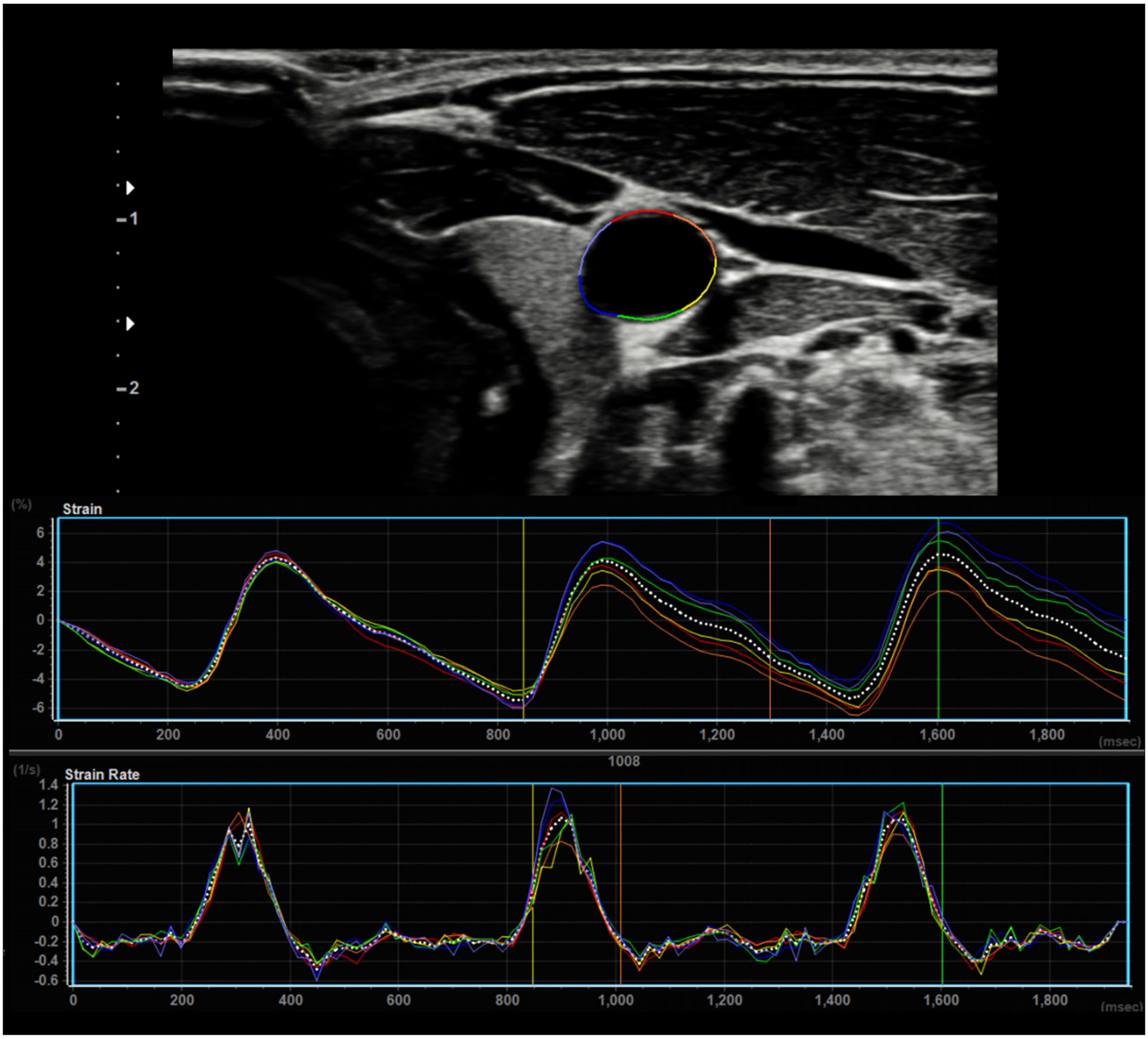

Figure 1. Arterial Analysis™ software with ROI in left common carotid artery and plots of strain and strain rate during 3 consecutive heart beats.

arterial lumen. The analysis was performed automatically and mean results from 12 heartbeats (3 for each side performed twice by 2 researchers) were included in the analysis.

Applanation tonometry

The PWV and AI were evaluated using a SphygmoCor applanation tonometer (SphygmoCor, AtCor Medical, New South Wales, Australia) by a researcher with 9 years of experience in this method. First, the patient was seated, and after 5 min of rest, the AI was evaluated using 2 measurements of the brachial artery pressure (analysis of the brachial artery waveform). Then, the patient was laid supine. The distance between places of measurements was measured (from the jugular notch to the site of the strongest carotid artery pulsation and to the groin where the femoral artery was pulsating best). Then, we measured the PWV by recording the arterial pressure waveform at the carotid and femoral artery sampling sites. Operator index was a measure of quality, and, if lower than 75%, the measurements were repeated.

Reliability

Although the reliability of the sonographic strain assessment was confirmed in previous studies [7,8], this is the first research in CCAs of children, in whom examination conditions are different (e.g., quality of tissues, and dimensions and range of movement of measured structures). Thus, in 10 random subjects from both groups, the sonographic examination was repeated according to the same protocol within 8 weeks after the initial

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Table 1. Clinical characteristics of the patients in both groups.

Feature		Children with DMT1		Control		P-value
Age [years (SD)]		13.4	(3.8)	13.1	(4.1)	0.7894
Gender	Females [n (%)]	24	(48)	25	(50)	0.8414
	Males [n (%)]	26	(52)	25	(50)	
BMI [kg/m² (SD)]		23.5	(3.7)	22.6	(3.1)	0.1906
SBP arm [mmHg (SD)]		113	(9)	118	(12)	0.1331
DBP arm [mmHg (SD)]		67	(9)	73	(11)	0.0981
SBP central [mmHg (SD)]		97	(8)	101	(9)	0.0563
DBP central [mmHg (SD)]		68	(9)	71	(7)	0.2367
Mean IMCT [mm (SD)]		0.45	(0.06)	0.43	(0.05)	0.0732
PWV [m/s (SD)]		4.04	(0.61)	3.72	(0.98)	0.0386*
AI [% (SD)]		18.8	(9.5)	21.2	(10.1)	0.2239
Strain [% (SD)]		13.7	(3.8)	15.4	(3.5)	0.0220*
Strain rate [1/s (SD)]		1.71	(0.45)	1.95	(0.61)	0.0274*

* Statistically significant differences; DBP – diastolic blood pressure; SBP – systolic blood pressure; IMCT – intima media complex thickness; PVW – pulse wave velocity; AI – augmentation index.

test. Both the cIMT and strain were assessed without knowledge of the previous values. For the cIMT, the intra-class correlation coefficient (ICC) between researchers was 1.0 (95% CI 0.996–1.00), and the ICCs were 0.98 (95% CI 0.976–0.995) and 0.97 (95% CI 0.972–0.982) for the first and second researcher, respectively. For the strain, the ICC between researchers was 0.90 (95% CI 0.863–0.949), and the ICCs were 0.91 (95% CI 0.872–0.952) and 0.89 (95% CI 0.843–0.947) for the first and second researcher, respectively.

Statistical analysis

Continuous variables are presented as mean and standard deviation, while categorical variables are presented as number and percentages. Normality of data distribution was evaluated with the Shapiro-Wilk test. If distribution was other than normal, comparison of means between 2 groups was performed with the Mann-Whitney U test, and Spearman correlation coefficient was used to assess correlations between means from 2 techniques. The analysis was performed with Statistica 12 software (StatSoft Polska, Cracow, Poland). A p-value lower than 0.05 was considered significant.

Results

The mean duration of T1DM was 6.5±3.8 year and the age at onset was 5.4±2.7 years. Thirty-six patients were treated with continuous subcutaneous insulin infusion and the remaining 14 were treated with multiple injections. Most of the patients presented good diabetes control: mean values of glucose level were 85±7 [mg/dl] and HbA1c was 7.64±1.2% (60±14 mmol/mol). They also did not present significant abnormalities in lipid profile (total cholesterol 163±21 [mg/dl], triglycerides 71±14 [mg/dl]). Patients from both groups did not differ significantly in BMI and blood pressure parameters (Table 1).

Analysis of morphological changes in arterial walls indicated a trend towards greater cIMT in patients with T1DM in comparison with healthy controls, but the level of significance was not reached (p=0.0732). However, assessment of arterial wall stiffness confirmed that these patients had significantly decreased elasticity of the arterial tree in general (PWV: 4.04±0.61 m/s *vs.* 3.72±0.98 m/s, for patients with T1DM *vs.* healthy controls, respectively; p=0.0386) and locally in carotid arteries (Strain: 13.7±3.8% *vs.* 15.4±3.5, p=0.0220; Strain rate: 1.71±0.45 *vs.* 1.95±0.61, for patients with T1DM *vs.* healthy controls, respectively; p=0.0274). A comparison of results between groups is presented in Table 1. In cumulative analysis of both groups, stiffness parameters derived from tonometry and sonography were significantly correlated with each other (Table 2, Figure 2).

Discussion

We confirmed that the children with T1DM present a subclinical stage of atherosclerosis, particularly arteriosclerosis. However, this can be diagnosed not only with applanation tonometry but also with sonography using 2DST.

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Table 2. Correlation between arterial wall stiffness markers.

	Strain		Strain rate	
	R	P-value	R	P-value
PWV	0.6294	<0.001	0.5979	<0.001
AI	0.5886	<0.001	0.5826	<0.001

PVW – pulse wave velocity; AI – augmentation index.

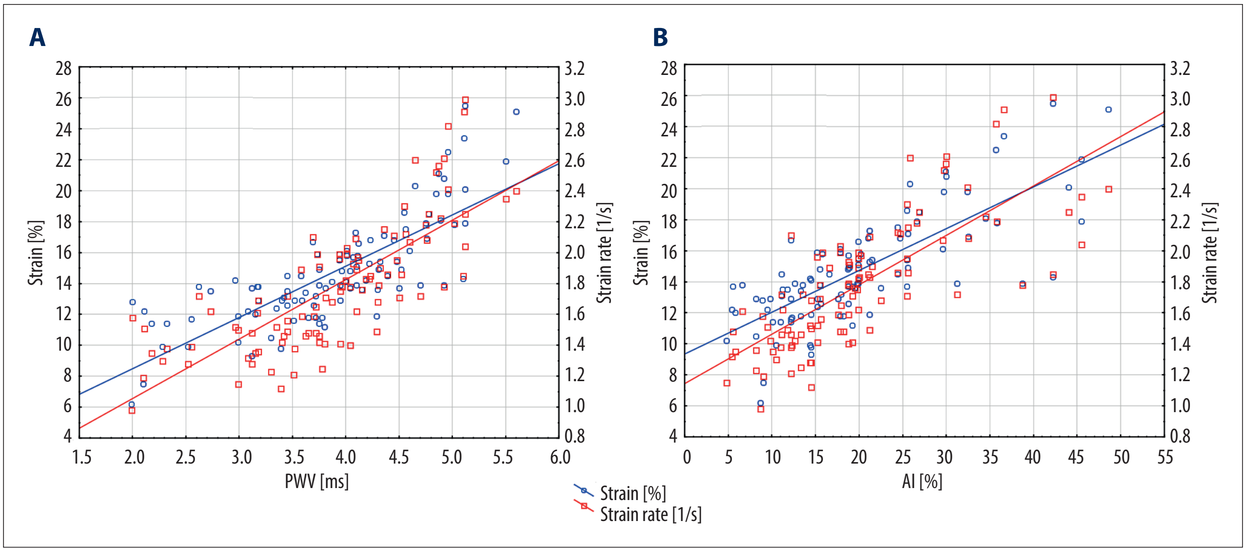

Figure 2. Plots of correlation between 2DST strain parameters and results of applanation tonometry.

In pediatric patients, sonography is a method of choice in all possible diagnostic scenarios. It gives high spatial resolution in real time and without exposing patients to radiation. Moreover, in contrast to applanation tonometry, it can provide morphological data (in this context cIMT). Studies have reported a significant increase in cIMT in children with T1DM [5,9–11] Our results are closest to those obtained by Margeirsdottier et al. [6] in a group of 314 children with T1DM, showing cIMT to be 0.45±0.054 mm in comparison with 0.44±0.045 mm in healthy controls (p=0.11). We also observed that the cIMT was increased in children with T1DM, but results were just on the verge of significance (0.45±0.06 *vs.* 0.43±0.05, p=0.073), possibly due to the very short duration of the disease and its good control, which was also proposed to be a cause in other studies in which children with T1DM did not have increased cIMT [12, 13].

However, the subclinical stage of atherosclerosis has only minimal morphological changes. In this context, ultrasound can be successfully applied in the functional assessment of arteries through the Flow-Mediated Dilation (FMD) test. It was confirmed that the children with T1DM had significantly impaired FMD in comparison with healthy controls [14,15]. Nevertheless, this test requires compression of the forearm to produce ischemic stress; this discomfort may be intolerable for children, especially those who are younger. Furthermore, FMD evaluates the function of the epithelium and not the arterial wall elasticity *per se*. 2DST can be an alternative to sonography, evaluating arterial wall stiffness without causing discomfort.

This technique is derived from cardiology. Interestingly, it can be applied in diagnosing subclinical left ventricular systolic dysfunction in children with T1DM [16], even when they present good metabolic control [17]. However, this is the first study showing that 2DST can be successfully applied in the evaluation of carotid arteries. Although it can be applied in other locations (e.g., the aorta), carotid arteries are the most appropriate place for the assessment of atherosclerosis in children with T1DM [18].

We showed that results from 2DST agreed with those from applanation tonometry, and they both showed increased arterial stiffness in children with T1DM, but the repeatability of the strain evaluation was higher than that reported for tonometry. In the research of Lowenthal et al., conducted in a group of pediatric patients, the ICCs for PWV was 0.61 (95% CI=0–0.86) and 0.78 (95% CI=0.58–0.88) for Aix, suggesting moderate intervisit reproducibility of PVW and AI in children and adolescents [19]. In our study, the between-study ICC was 0.90 (95% CI 0.863–0.949), and the ICC within-study was above 0.89. We think that the better reproducibility of the 2DST technique

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might be caused by the easier and shorter acquisition method that requires recording of only 3 consecutive heartbeats of the CCA cross-section.

Application of sonography in children with a subclinical stage of atherosclerosis is tempting because this method is widely available and relatively easy to handle. However, it might affect the management and be useful in a follow-up of treated patients. In our opinion, 2DST would be also helpful in the evaluation of children from other risk groups (e.g., obese ones or with family hypercholesterolemia); however, it should be further analyzed in future studies.

Our study has certain limitations. We did not consider the physical activity of children; however, due to similar BMI and laboratory testing within limits in both groups, we assume that it would not affect the results. In the analysis of reproducibility, the differences in heart rate and blood pressure were not included. These differences could explain some of the ICC variances, but it was not our goal in this study to determine these causes. Finally, there are non-normal limits of cIMT and strain parameters for children. Thus, we were able only to show a significant difference between children with T1DM and healthy controls, but the prognostic value of the obtained results remain unknown. This should be addressed in future studies, and it is especially important to assess whether subclinical atherosclerosis is a significant risk factor for development of cardiovascular diseases [20].

Conclusions

Children with T1DM and no significant morphological signs of atherosclerosis have stiffer arteries than their healthy counterparts. These findings indicate that assessment of functional changes in the arterial tree is crucial in the subclinical stage of atherosclerosis in pediatric patients. It can be performed with applanation tonometry and by sonography with the application of 2DST. The second technique seems to be more user-friendly and presents better reproducibility; therefore, it has the potential to displace tonometry, but further studies are required to confirm its usability in larger groups and in a broader spectrum of patients.

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