doi: 10.4183/aeb.2015.470

USEFULNESS OF STRAIN MEASUREMENT IN THE ASSESSMENT OF CAROTID ARTERIES STIFFNESS IN TYPE 1 DIABETES PATIENTS

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Abstract

Context. Increased arterial stiffness is an independent risk factor of cardiovascular events in patients with diabetes mellitus (DM).

Objective. We aimed to evaluate elastic properties of common carotid arteries (CCA) in patients with DM type 1 (T1DM) by means of ultrasonographically based technique – two-dimensional speckle tracking.

Design. Case-control observational study.

Subjects and Methods. Examination of both CCA was performed in 50 patients with T1DM. The mean age of patients was 36.1 (±11.9) years and duration of diabetes was 8.9 (±11.9) years. 28 controls (mean age 38.6 ± 10.8) were examined according to the same protocol. Strain and strain rate reflected arterial wall stiffness and intima-media complex thickness (IMCT) indicate presence of morphological changes. Parameters were compared between groups and regression analysis was performed to predict determinants of evaluated parameters.

Results. Patients with T1DM had significantly more elastic CCA arteries than the healthy control (mean strain [%]: 6.05 ± 2.55 *vs.* 5.19 ± 1.79, p=0.0295; mean strain rate [1/s]: 0.91 ± 0.33 *vs.* 0.78 ± 0.25, p= 0.0142; respectively), but no significant differences in IMCT were revealed (0.49mm ± 0.12mm *vs.* 0.49mm ± 0.10mm, p=0.9893; respectively). Women had significantly decreased strain parameters in comparison with men, although the difference in IMCT was not significant.

Conclusions. Two-dimensional speckle tracing revealed increased elasticity of CCA in patients with T1DM with no deterioration of arterial wall.

Key words: Atherosclerosis, Type 1 diabetes mellitus, Two-dimensional speckle tracking, Sonography, Intima-media complex thickness.

INTRODUCTION

Although not appreciated enough, T1DM - similarly to type 2 diabetes - is associated with increased risk of CVD (1-3). Early detection of vascular dysfunction is of utmost importance in CVD prevention in individuals with diabetes. Arterial stiffness develops at the initial stage of diabetes vascular complications, largely due to the gradually increasing formation of advanced glycation endproducts (2). Arterial stiffness may be non-invasively assessed by means of pulse wave velocity measurement (3-5). Moreover, morphological surrogate of sub-clinical atherosclerosis - IMCT - can be evaluated by ultrasound scanning of the CCA (6,7). 2DST is a relatively new ultrasonographic method that enables improved evaluation of arterial stiffness. By using this technique a vascular strain, defined as a percentage of the object spatial deformation (in this case vascular wall) during systolic-diastolic cycles, can be measured. Strain assessment with ultrasound is angle and pressure independent, it also helps analyse the elasticity of all segments of the arterial wall, thus it has clear advantages over classical arterial stiffness assessment methods (8).

The aim of this study was to assess vascular function as well as structure in type 1 diabetes patients by strain evaluation and IMCT measurement.

MATERIALS AND METHODS

The study population consisted of 50 individuals with T1DM. Main inclusion criteria were age >18 years, T1DM duration > 1 year, and absent history of ischemic heart disease. Twenty-eight age-, gender- and BMI-matched healthy individuals served as controls. Four T1DM patients suffered from macro- and 14 from microangiopathy. Fourteen patients were taking cardiovascular medications; 2 were treated with ACEI, 4 with ACEI and statin, 1 with ACEI and β-blocker, 4 with ACEI, statins and β-blocker, and 1 patient was receiving statin and β-blocker. Patients taking cardiovascular medications were significantly

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older than the remainder of the diabetic patients (49±13 *vs.* 32±13; p=0.001). Baseline characteristics of the study participants are presented in Table 1.

Study protocol

Each individual underwent full medical examination with body height and weight measurements (for BMI calculation). The patients with T1DM were assessed towards the presence of chronic diabetes complications. Medication used on regular basis was recorded. Ultrasonographic examination of right and left CCA was performed in supine position with the Vivid 7 ultrasound system (GE Medical System, Germany), equipped with a 7.5–10 MHz linear probe. Once an ECG trace was obtained, CCAs were examined in long and short axis for presence of atherosclerotic plaques. If no pathology occurred cine loop of three cardiac cycles in short axis of each CCA, about one centimetre below its bifurcation, was obtained. Afterwards cine loop in long axis of another three cardiac cycles was acquired. All acquisitions were performed during short breath-holding at the end of exhalation, to minimize the presence of motion artefacts.

Off-line data analysis was performed on a workstation equipped with dedicated software (EchoPac PC, GE Vingmed Ultrasound, Horten, Norway). Two-dimensional speckle tracking algorithm was used to perform the strain analysis on cine loops of short axis of the CCA. A ROI was circumscribed manually along the intima–blood interface and its width was adjusted to overlie the full thickness of the CCA wall. If not all segments were traced properly the width of ROI was extended and further analysis was performed only if all six segments of the CCA were traced. Mean peak systolic circumferential strain and strain rate (physical deviation of the arterial wall [expressed in mm per second]) for the whole circumference of the CCA were considered. They were recognised as the peaks following the R-wave on ECG. Amplitude of the strain parameters for three consecutive heart cycles were computed and averaged. Measurement of IMCT was performed on the cine loop of the long axis of the CCA. By means of the semi-automatic calculation system, farther wall of the CCA was marked over a distance of 2 cm, immediately before the carotid bulb, at the moment of R-wave on ECG.

Within a week from ultrasound examination, blood was drawn in all subjects upon fasting for total CH, HDL and LDL, TG and HbA1c measurements.

Statistical analysis

Normality of data distribution was evaluated with the Shapiro-Wilk test. The $\chi 2$ test with Yates correction was applied to compare differences in qualitative data between groups. Continuous variables were analysed by means of the Student t-test for independent samples or the Mann-Whitney test. Differences in strain parameters and IMCT between the right and left side were evaluated with the Wilcoxon sing rank test. Multiple stepwise regression analysis was used to analyse the determinants affecting the carotid artery parameters (dependent variables), with T1DM presence, gender, smoking status, systolic and diastolic blood pressure and age as

Table 1. Differences in characteristics between T1DM patients and controls. In continuous variables mean and standard deviations are presented

Features		T1DM Patients (n=50)	Control (n=28)	p -value
Gender	Female	31	17	0.8425
	Male	19	11	
T1DM duration [years]		8.9 (11.9)		
Age [years]		36.1 (14.5)	38.6 (10.8)	0.2658
SBP [mmHg]		130 (19.2)	130 (15.2)	0.8319
DBP [mmHg]		77.3 (9.4)	76.2 (10.4)	0.4380
HR [1/min]		75 (11.9)	70 (11.4)	0.1236
BMI [kg/m^2]		23.9 (3.7)	24.3 (4.6)	0.5512
Current smokers		12	4	0.2232
Pack-year		9.9 (8.0)	10.5(11.0)	0.8615
Daily Dose of Insulin [IU]		42.7 (16.3)		
HbA1c [%]		9.1 (2.2)		
Total CH [mg/dL]		191.4 (37.3)	196.0 (34.0)	0.7012
HDL [mg/dL]		58.8 (18.8)	102.0 (58.0)	0.3537
LDL [mg/dL]		110.3 (30.0)	59.7 (14.7)	0.6343
TG [mg/dL]		118.6 (70.7)	117.3 (33.9)	0.4923

T1DM: Type 1 Diabetes Mellitus; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HR: heart rate; BMI: Body Mass Index; CH: Cholesterol; HDL: High-Density Lipoproteins; LDL: Low-Density Lipoproteins; TG: Triglycerides; HbA1c: Glycated Haemoglobin.

Table 2. Comparison of vascular parameters between groups (mean ± SD)

Parameters		T1DM Patients (n=50)	Control (n=28)	p -value
LCCA and RCCA (n=156)	Strain [%]	6.05 ± 2.55	5.19 ± 1.79	0.0295
	Strain rate [1/s]	0.91 ± 0.33	0.78 ± 0.25	0.0142
	IMCT [mm]	0.49 ± 0.12	0.49 ± 0.10	0.9893
LCCA (n=78)	Strain [%]	6.05 ± 2.52	5.22 ± 1.84	0.2484
	Strain rate [1/s]	0.92 ± 0.36	0.79 ± 0.26	0.0974
	IMCT [mm]	0.52 ± 0.13	0.52 ± 0.11	0.8076
RCCA (n=78)	Strain [%]	6.16 ± 2.53	5.15 ± 1.77	0.0775
	Strain rate [1/s]	0.90 ± 0.31	0.77 ± 0.25	0.0857
	IMCT [mm]	0.47 ± 0.11	0.47 ± 0.08	0.5815

T1DM: Type 1 Diabetes Mellitus; LCCA: left common carotid artery; RCCA: right common carotid artery; IMCT: Intima-Media Complex Thickness.

Table 3. Differences in vascular parameters between genders (mean ± SD)

Parameters		Males (n=30)		Females (n=47)		p-value
LCCA (n=78)	Strain [%]	6.65	2.60	5.20	1.93	0.0053
	Strain rate [1/s]	0.99	0.36	0.80	0.29	0.013
	IMCT [mm]	0.09	0.04	0.11	0.04	0.1755
RCCA (n=78)	Strain [%]	6.49	2.78	5.36	1.87	0.0394
	Strain rate [1/s]	0.93	0.30	0.80	0.29	0.0654
	IMCT [mm]	0.10	0.06	0.11	0.05	0.7788

LCCA: left common carotid artery; RCCA: right common carotid artery; IMCT: Intima-Media Complex Thickness.

Table 4. Differences in vascular parameters between body sides (mean ± SD)

Parameter	Total (n=78)			T1DM Patients (n=50)			Control (n=28)		
	LCCA	RCCA	p	LCCA	RCCA	p	LCCA	RCCA	p
Strain	5.8 ± 2.3	5.8 ± 2.3	0.9642	6 ± 2.5	6.2 ± 2.5	0.8735	5.3 ± 1.9	5.2 ± 1.8	0.7317
Strain rate	0.88 ± 0.33	0.85 ± 0.3	0.24	0.92 ±0.36	0.90 ± 0.31	0.3371	0.80 ± 0.26	0.77 ± 0.25	0.402
IMCT	0.52 ± 0.12	0.47 ± 0.1	0.0000	0.52 ± 0.13	0.47 ± 0.11	0.0005	0.52 ± 0.11	0.47 ± 0.08	0.0095

T1DM: Type 1 Diabetes Mellitus; LCCA: left common carotid artery; RCCA: right common carotid artery; IMCT: Intima-Media Complex Thickness.

independent variables. Additionally, in T1DM group further evaluation included disease duration, mean daily dose of insulin, HbA1c, presence of micro- or macroangiopathy, mean plasma total CH, HDL, LDL and TG and used medication as independent variables. $p<0.05$ was considered significant.

The study protocol was approved by the Bioethics Committee of the Medical University of Łódź, and all subjects participating in the study signed an informed consent form.

RESULTS

Contrary to what was expected, strain and strain rate were significantly increased in patients with T1DM in comparison with the controls (strain: 6.05±2.55 *vs.* 5.19±1.79; p=0.0295 and strain rate: 0.91±0.33*vs.* 0.78±0.25; p=0.0142, respectively), with no significant differences between left or right CCA (Table 2). The intima-media complex thickness was not significantly different between both groups. No carotid stenosis or atheromatic plaques were found in any subject. Strain and strain rate for left CCA, and strain for right CCA were significantly greater in males than in females in both groups (Table 3).

Due to the fact that there was no significant difference in any of the analysed parameters between body sides (Table 4), mean values of parameters for left and right CCA were included in regression analysis. When data for both groups were pooled, model for prediction of mean strain value explained 43.7% ($p<0.001$) of its variance and included age, SBP, DBP, T1DM presence, gender and smoking status, although last two determinants were not statistically significant. Model for strain rate value prediction explained 50.4% ($p<0.001$) of the variance and included the same first four determinants as for strain and additionally BMI and gender. In the analysis of IMCT determinants age, BMI, DBP and smoking status were included, explaining 43.7% of variance, however only age was a significant predictor. The details of regression analysis are shown in Table 5. In T1DM patients any of the independent variables has an effect on strain and strain rate (p=0.126 and p=0.127, respectively).

Table 5. Multiple stepwise regression analysis of the determinants of the changes in mean carotid artery parameters analysed for all patients

Dependent Variable	Parameters	In	R^2 - Increment	β - Coefficient (±SD)	P Value
Mean Strain	age	Yes	0.216	-0.083 (0,016)	<0.001
	DBP	Yes	0.115	-0.096 (0.021)	<0.001
	SBP	Yes	0.08	0.032 (0.012)	0.014
	group affiliation	Yes	0.034	0.836 (0.383)	0.033
	gender	No			0.072
	Smoking status	No			0.195
Mean Strain rate	age	Yes	0.299	-0.013 (0.002)	<0.001
	DBP	Yes	0.096	-0.012 (0.003)	<0.001
	SBP	Yes	0.085	0.004 (0.002)	0.007
	group affiliation	Yes	0.038	0.129 (0.05)	0.012
	BMI	No			0.149
	gender	No			0.168
Mean IMCT	age	Yes	0.428	0.004 (0.0007)	<0.001
	BMI	No	0.023	-0.004 (0.002)	0.053
	Smoking status	No	0.016	0.040 (0.022)	0.075
	DBP	No	0.019	0.001 (0.0009)	0.123

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; BMI: Body Mass Index; IMCT: Intima-Media Complex Thickness

However, in IMCT prediction the model explained 35.3% of the variance (p=0.004) including HDL concentration (β=0.0025 ± 0.001; R^2 Increment=0.241; p=0.005), presence of angiopathy (β=0.1 ± 0.04; R^2 Increment=0.096; p=0.054) as well as LDL and HbA1c although they were not significant (p=0.079 and p=0.251, respectively).

DISCUSSION

The main finding of the study was that the T1DM patients in 2DST examination presented with more elastic CCAs and the same IMCT as the individuals from the control group. Moreover, in both groups women had less elastic CCAs than men.

Diabetes mellitus is associated with formation of advanced glycosylation end products, increased collagen cross-linking and endothelial dysfunction, which influences functional stiffness (2). Moreover, the structure of the blood vessels is altered by an increase in type IV collagen, fibronectin, and laminin, which leads to changes in the elastic properties of the basement membrane. Chronic hyperglycemia severely damages endothelial cells, which results in significant impairment of vascular function regulation, eg. through decrease in nitric oxide production (9). Hence, the abnormal glucose metabolism is significantly associated with increased cardiovascular risk.

The exact course of changes in arterial wall morphology during T1DM in relation to the duration of the disease is not well studied. It was hypothesised that the increase in arterial wall stiffness in diabetic women is rather an early event in the disease process, soon reaching a plateau and then it is not increasing any further (6). Although reduced vascular compliance was suspected in patients with early stages of T1DM, Romney *et al.* (5) observed it only in patients without microangiopathy. However, when patients with microangiopathy were included and variables that differed between groups (age, smoking and systolic blood pressure) were added as covariables, there was no difference in pulse wave velocity between T1DM patients and controls (5). It should be noted, though, that in the study by Romney *et al.* (5) twenty patients with microangiopathy were taking medications that are known to affect compliance (10) (ACEIs, ARBs, calcium channel blockers and β-blockers). In our study 14 patients were also taking medications that might have affected arterial wall properties and thus prevent the detection of increased arterial stiffness due to T1DM.

In general, though, the results of our study are discordant with the majority of similar studies. Berry *et al.* (11) in a cohort of 25 young T1DM patients, with similar characteristics to those presented in this research, reported decreased arterial compliance in comparison to the control group. Gordin *et al.* (4) and Wilkinson *et al.* (3) suggested that T1DM patients had increased stiffness in the resistance arteries, however actually the differences were found only in the augmentation index (AI) that represents arterial stiffness in the small arteries. Pulse wave velocity, reflecting arterial stiffness in large and intermediate-sized arteries, was only estimated as a higher (3) or did not differ between T1DM patients

and healthy controls (4). These findings confirm the common view that unlike in type 2 diabetes, in T1DM microangiopathy precedes macroangiopathy. This may also explain increased strain parameters observed in our group of relatively young patients (mean age of 36 years) with short or intermediate duration of the disease (mean of 9 years). The absence of differences in IMCT, that has typically been reported as increased in DM patients (7,10,12,13), and in offspring of T2DM patients, (14) also supports this theory. Probably, poor metabolic control of diabetes (mean HbA1c of 9.0%) clearly has not yet affected large arteries, and led to the development of microangiopathy in a subgroup of individuals with T1DM enrolled to this study.

Some observations support our findings. Barchetta *et al.* (1) in a comparison of 26 healthy subjects *vs.* 23 T1DM patients, with similar characteristics to presented in this research, reported no difference in small and large arteries elasticity properties evaluated by means of tonometry. The difference becomes significant only when patients with duration of T1DM longer than 10 years were compared with the controls. Furthermore, in a group of patients with shorter duration of diabetes a trend towards an increased small artery elasticity compared to controls was noted. In other studies there was no difference in CCA and aortic wall elasticity between 30 patients with uncomplicated T1DM of mean 9.7 years' (0.5-23.5) duration and 30 healthy subjects (15). In another study of 39 T1DM patients the carotid wall stress analysis also showed no difference in comparison with controls (16). Gordin *et al.* (4), in their study conducted in T1DM male patients without diabetic complications, found no difference in either brachial or aortic pulse wave velocity in comparison with healthy controls.

We have also noted decreased arterial elasticity in women with diabetes as compared to the controls. In other research, increased aortic stiffness was observed in pregnant women diagnosed with gestational DM (17). Typically, premenopausal women are protected against CVD, however this gender-related effect is attenuated by diabetes, and thus e.g. the coronary heart disease incidence is similar among men and women with diabetes (6). Our finding of increased arterial stiffness in women may confirm the loss of protective gender influence on vasculature in diabetes.

Two-dimensional speckle tracking has already been used in evaluation of CCA strain parameters in DM patients. In two studies published by Yang *et al.* (8,13) the authors described decreased strain in 21 diabetic patients in comparison with healthy controls.

However, those patients were much older (mean age 57 years) than the subjects participating in our study. Moreover, there was no significant difference in CCA strain values derived from measures of luminal dimensions (8,13).

Models predicted in this research include variables that are commonly accepted as determinants of the arterial wall stiffness. Age is the most important predictor of arterial wall deterioration (4,6). However, there is no agreement on the role of disease duration and glycaemic control (1,18).

Despite using a relatively novel technique of arterial imaging, our study has some limitations. We have only conducted the CCAs evaluation, and it may be assumed that CCAs status does not reflect the general condition of vasculature in T1DM patients. Giannattasio *et al.* (12) in 2 years follow-up study of 60 T1DM patients observe decreased distensibility of the radial artery and aorta, but not the CCA. Moreover, many studies documenting increased arterial wall stiffness in T1DM patients were performed with the assessment of aorta (evaluation of PVW or AIx) (5,11). Drawing comparisons with other studies is also often infeasible as many of them were conducted in a poorly defined population of pooled T1DM and T2DM patients. Moreover, study sample was relatively small, thus in future research a bigger study group should be examined to confirm our findings.

In conclusion, 2D-Speckle Tracking technique is a precise and reliable method of assessing arterial stiffness in common carotid arteries. It revealed that in young palatines, with short course of T1DM, arteries may be more elastic than in healthy control. Moreover, no corresponding changes in morphological properties of arteries (IMCT) were noted. However, due to the fact that diabetes-related changes in large arteries develop relatively late, further research should be performed in a larger, and more diverse study sample.

Conflict of interest

The authors declare that they have no conflict of interest concerning this article.

Acknowledgement

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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