Complex evaluation of left atrial dysfunction in patients with type 1 diabetes mellitus by three-dimensional speckle tracking echocardiography: results from the MAGYAR-Path Study

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Abstract

Objective: Changes in left atrial (LA) function can be observed in type 1 diabetes mellitus (T1DM). Three-dimensional (3-D) speckle tracking echocardiography (STE) seems to be a promising tool for volumetric and functional evaluation of LA. The objective of the present study was to compare 3DSTE-derived LA volumetric and strain parameters between T1DM patients and matched healthy controls.

Methods: This prospective study consists of 17 subcutaneous insulin pump-treated non-obese patients with T1DM (mean age: 33.5±8.2 years, 8 males). To exclude possible cardiovascular disease, patients with complaints of chest pain, dyspnea, or signs of cerebrovascular disease or peripheral artery disease were not included. Their results were compared with 20 age-matched and gender-matched healthy controls (mean age: 36.9±11.0 years, 9 males). Independent sample Student t-test and Fisher's exact test were used for comparisons. Bland–Altman method was used for evaluating intraobserver and interobserver correlations.

Results: Anemia and impaired renal function were not confirmed in T1DM patients. Calculated LA maximum and minimum volumes and LA volume before atrial contraction were significantly increased in T1DM patients. Total atrial stroke volume was increased (23.6±6.9 mL vs. 19.6±4.6 mL, p=0.04), whereas mean segmental circumferential peak strain was decreased (28.9%±11.4% vs. 37.3%±12.5%, p=0.04). Segmental basal longitudinal and area strains were increased, whereas segmental superior circumferential and area strains and midatrial 3-D strain were decreased in T1DM.

Conclusion: Both 3DSTE-derived volumetric and strain analysis confirmed alterations in LA function, suggesting early LA remodeling in patients with T1DM. *(Anatol J Cardiol 2016; 16: 587-93)*

Keywords: echocardiography, function, left atrium, three-dimensional, diabetes mellitus, speckle-tracking

Introduction

Type 1 diabetes mellitus (T1DM) is characterized by a progressive destruction of pancreatic beta cells via apoptosis induced by an irreversible autoimmune process. Left ventricular (LV) dysfunction is a known feature in T1DM, and it is considered to be the result of diabetic microangiopathy affecting the small vessels of the heart, progressive fibrosis, and cardiac autonomic neuropathy (1). Diastolic dysfunction is reported to start as early as 6 years after the onset of T1DM, whereas systolic dysfunction is reported to occur after an average of 18 years after the onset of T1DM (1, 2). In earlier studies, changes were demonstrated in left atrial (LA) function in patients with T1DM, suggesting an increased significance of the contribution of LA to LV filling (3–5).

Three-dimensional (3D) speckle tracking echocardiography (STE) is a promising non-invasive tool based on "block-matching algorithm" by strain analysis (6). Its usefulness in the assessment of volumes, strains, and rotational/dyssynchrony indices of the cardiac chambers in the various phase of the cardiac cycle has been demonstrated (7). The objective of the present study was to assess and compare 3-DSTE-derived LA volumetric and strain parameters in patients with T1DM and healthy matched controls.

Methods

Patient population

Seventeen subcutaneous insulin pump-treated non-obese patients with T1DM (mean age: 33.5±8.2 years, 8 males, duration of T1DM: 17.0±11.1 years, body mass index: 23.3±3.0 kg/m^2, daily

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insulin dose: 39.0±7.3 IU) were included in this prospective study. To exclude possible cardiovascular disease, patients with complaints of chest pain, dyspnea, or signs of cerebrovascular or peripheral artery disease were not included. For comparisons, 20 age-matched and gender-matched healthy controls (mean age: 36.9±11.0 years, 9 males, body mass index: 23.1±1.2 kg/m^2) were included. Disorders that may influence the results were ruled out in the healthy controls. The definition of T1DM was based on the American Diabetes Association (8) and World Health Organization (9) criteria. Hypertension was defined when subjects had a systolic blood pressure of ≥140 mm Hg, diastolic blood pressure of ≥90 mm Hg, or were receiving antihypertensive therapy. Data of T1DM patients and controls were obtained from the MAGYAR-Path Study (Motion Analysis of the heart and Great vessels bY three-dimensionAl speckle-tRacking echocardiography in Pathological cases), which had the aim of clarifying the diagnostic and prognostic impact of 3-DSTE-derived parameters ("magyar" means "Hungarian" in Hungarian language). The Institutional Human Research Committee approved the study and all patients and control subjects provided informed consent. The study complied with the Declaration of Helsinki (10).

Biochemical measurements

To evaluate routine blood parameters, including plasma glucose, HbA1c, hematocrit, hemoglobin, creatinine, and glomerular filtration rate (GFR), blood samples were obtained by venipuncture following 8 h of fasting.

Two-dimensional Doppler and tissue Doppler echocardiography

In the left lateral decubitus position, all T1DM patients and healthy subjects underwent a complete 2-dimensional (2-D) Doppler echocardiography and tissue Doppler study using a commercially available Toshiba Artida™ echocardiography device (Toshiba Medical Systems, Tokyo, Japan). This device had a PST-30SBP phased-array transducer with a center frequency of 3.5 MHz (ranged between 1–5 MHz depending on the necessities and changing automatically). LV internal dimensions were measured by M-mode echocardiography using Teichholz method (11). Significant (>grade 1) valvular regurgitations and stenoses were excluded by Doppler echocardiography. Following Doppler assessment of E/A, the ratio of transmitral E velocity to early diastolic mitral annular velocity (E/E') was measured by tissue Doppler imaging. Echocardiographic studies were performed by examiners who were blinded regarding the physical condition of subjects and the knowledge of whether they were T1DM patients and healthy controls.

Three-dimensional speckle-tracking echocardiography

3D echocardiographic acquisitions were performed using a commercially available fully sampled PST-25SX matrix-array transducer (Toshiba Medical Systems, Tokyo, Japan) by two experienced investigators (AK, PD) (7). The full-volume mode, in which six wedge-shaped subvolumes were acquired over six consecutive cardiac cycles during a single-breathold, was used. Care was taken to avoid movement of the patient or the examination table during the acquisitions. The sector width was decreased as much as possible to improve temporal and spatial image resolutions. Pyramidal 3D datasets were analyzed offline using 3-D Wall Motion Tracking software version 2.7 (Toshiba Medical Systems, Tokyo, Japan) by experienced investigators (AK, PD). Apical 4-chamber (AP4CH) and 2-chamber (AP2CH) views as well as three short-axis views at different LA levels (basal, midatrial, and superior regions) were automatically selected by the software from the 3D dataset (Fig. 1). Anatomically correct non-foreshortened optimal views by optimizing longitudinal planes in AP4CH and AP2CH views were created. Then, LA boundaries were manually traced, starting at the mitral valve level of the LA going toward the LA superior region at end-diastole. Pulmonary veins and the LA appendage were excluded from the cavity. The epicardial border was manually adjusted. Subsequently, 3-D wall motion tracking was automatically performed for the whole cardiac cycle.

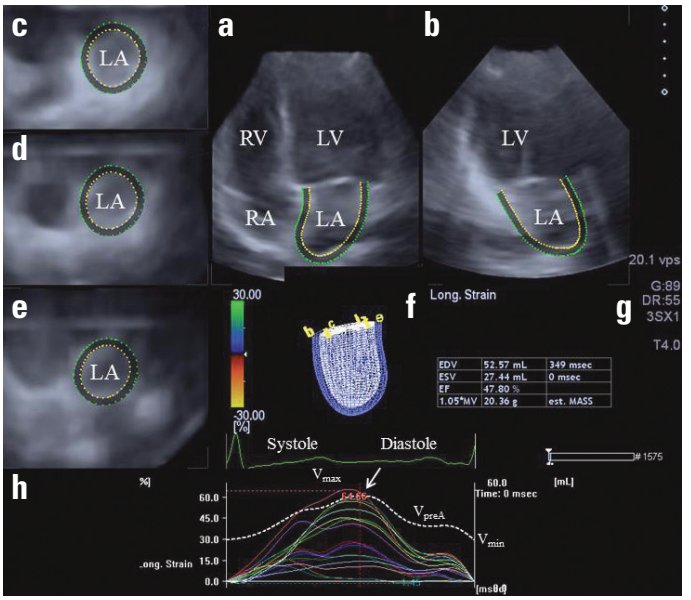

Figure 1. Images from three-dimensional (3-D) full-volume dataset showing left atrium (LA) in a patient with type 1 diabetes mellitus is shown: (a) apical four-chamber view, (b) apical two-chamber view, (c) short-axis view at basal, (d) mid-atrial, and (e) superior left atrial levels. A 3D cast (f), volumetric data (g), time–global volume, and time–segmental strain curves (h) of the LA are also shown. Dashed curve (h) represents LA volume changes during the cardiac cycle with maximum LA volume (V_{max}), minimum LA volume (V_{min}), and LA volume before atrial contraction (V_{preA}). White arrow represents peak strain (h).
LA - left atrium; LV - left ventricle; RA - right atrium; RV - right ventricle

3DSTE-derived LA volumetric measurements

From the acquired 3D echocardiographic datasets, time–global LA volume change curves were initially generated. From these curves, end-systolic maximum LA volume (V_{max}), end-diastolic minimum LA volume (V_{min}), and early diastolic LA volume before atrial contraction (V_{preA}) were calculated (12–15) (Fig. 1). V_{max} and V_{min} were obtained automatically by the software, whereas V_{preA} was obtained from the time–volume change curve (Fig. 1). From

Table 1. Calculation of left atrial stroke volumes and emptying fractions in each phase of left atrial motion

Functions	Stroke volumes (mL)	Emptying fractions (%)
Reservoir	Total atrial SV= $V_{max} - V_{min}$	Total atrial EF= Total atrial SV/V_{max}
Conduit function	Passive atrial SV= $V_{max} - V_{preA}$	Passive atrial EF= Passive atrial SV/V_{max}
Active contraction	Active atrial SV= $V_{preA} - V_{min}$	Active atrial EF= Active atrial SV/V_{preA}

EF - emptying fraction; SV - stroke volume; V_{max} - maximum left atrial volume; V_{min} - minimum left atrial volume; V_{preA} - left atrial volume before atrial contraction

Table 2. Baseline demographic and two-dimensional echocardiographic data in patients with type 1 diabetes mellitus and controls

	Type 1DM patients (n=17)	Controls (n=20)	*P*
Risk factors			
Age, years	33.5±8.2	36.9±11.0	0.15
Male gender, %	8 (47)	9 (45)	1.00
Hypertension, %	4 (24)	0 (0)	0.04
Hypercholesterolemia, %	4 (24)	0 (0)	0.04
Two-dimensional echocardiography			
LA diameter, mm	33.2±6.6	33.1±3.4	0.92
LV end-diastolic diameter, mm	46.3±5.5	47.8±7.1	0.41
LV end-diastolic volume, mL	100.5±28.2	101.2±21.3	0.97
LV end-systolic diameter, mm	29.3±4.4	31.0±4.1	0.58
LV end-systolic volume, mL	34.2±12.0	34.9±11.2	0.88
Interventricular septum, mm	9.1±1.9	9.6±2.0	0.61
LV posterior wall, mm	9.1±0.9	9.4±2.2	0.52
LV ejection fraction, %	66.1±7.6	66.1±7.1	0.89
LV mass index, kg/m^2	97.7±14.6	104.6±33.4	0.44
E/A	1.47±0.50	1.30±0.17	0.14
E/E'	6.3±2.0	5.2±1.8	0.32

DM - diabetes mellitus; LA - left atrial; LV - left ventricular. Student t-test and Fisher's exact test were applied

the three volumes, several measurements were selected as indices of LA function, as demonstrated in Table 1 (14, 15).

3-DSTE-derived LA strain assessments

Form the same 3-D echocardiographic datasets, time curves of segmental unidirectional radial strain (RS), longitudinal strain (LS), circumferential strain (CS), multidirectional area strain (AS), and 3D (3DS) strain were generated using the 16-segment model obtained for the LV (15, 16). AS is the ratio of endocardial area change during the cardiac cycle. On the other hand, 3DS is a special 3DSTE-derived strain in the direction of wall thickening; actually, it can be considered as a combination of "unidirectional strains." On each time–segmental strain curve, peak strains characterizing LA reservoir function were measured. Global strains were calculated by the software taking into consideration the whole LA, whereas mean segmental strains were obtained as the average of strains of 16 segments. The software calculated these parameters automatically (Fig. 1).

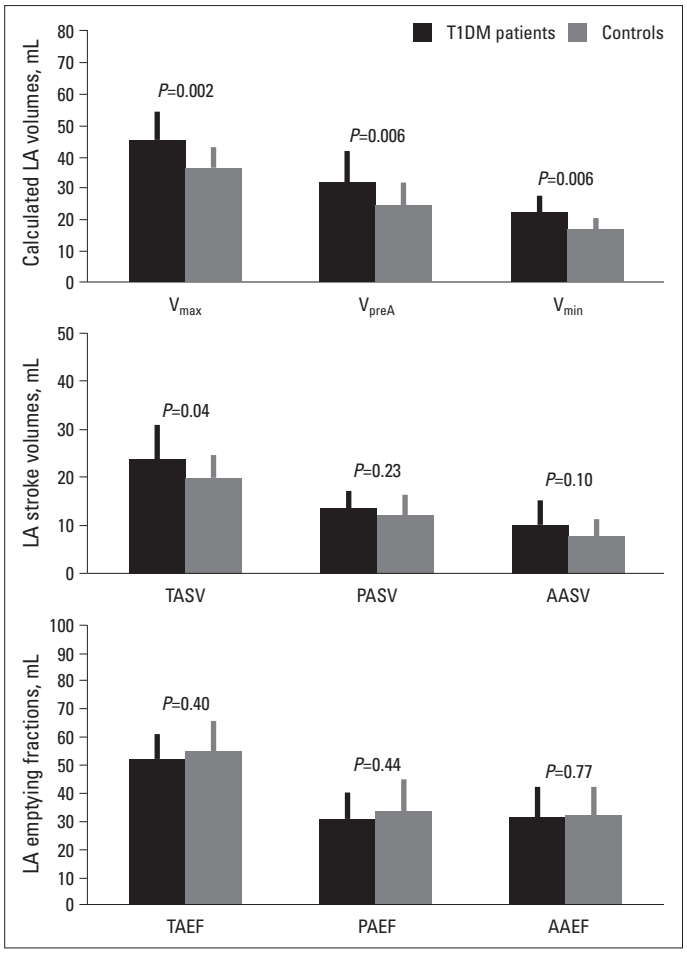

Figure 2. Calculated left atrial volumes and volume-based functional properties (stroke volumes and emptying fractions) are shown in type 1 diabetes mellitus patients and matched healthy controls.

V_{max} - maximum left atrial volume; V_{min} - minimum left atrial volume; V_{preA} - left atrial volume before atrial contraction; TASV - total atrial stroke volume; PASV - passive atrial stroke volume; AASV - active atrial stroke volume; TAEF - total atrial emptying fraction; PAEF - passive atrial emptying fraction; AAEF - active atrial emptying fraction; LA - left atrial; T1DM - type 1 diabetes mellitus. Student t-test was applied

Statistical analysis

Statistical analyses were performed using the MedCalc software (MedCalc, Mariakerke, Belgium). All continuous variables are expressed as mean±standard deviation. Statistical significance was determined as a p value of <0.05. The Shapiro–Wilk test was used to check the normality of data. The independent-samples Student t-test was used to compare continuous variables. Fisher's exact test was used for comparison of categorical variables. Pearson's coefficient was used for intraobserver and interobserver correlations. Intraobserver and interobserver

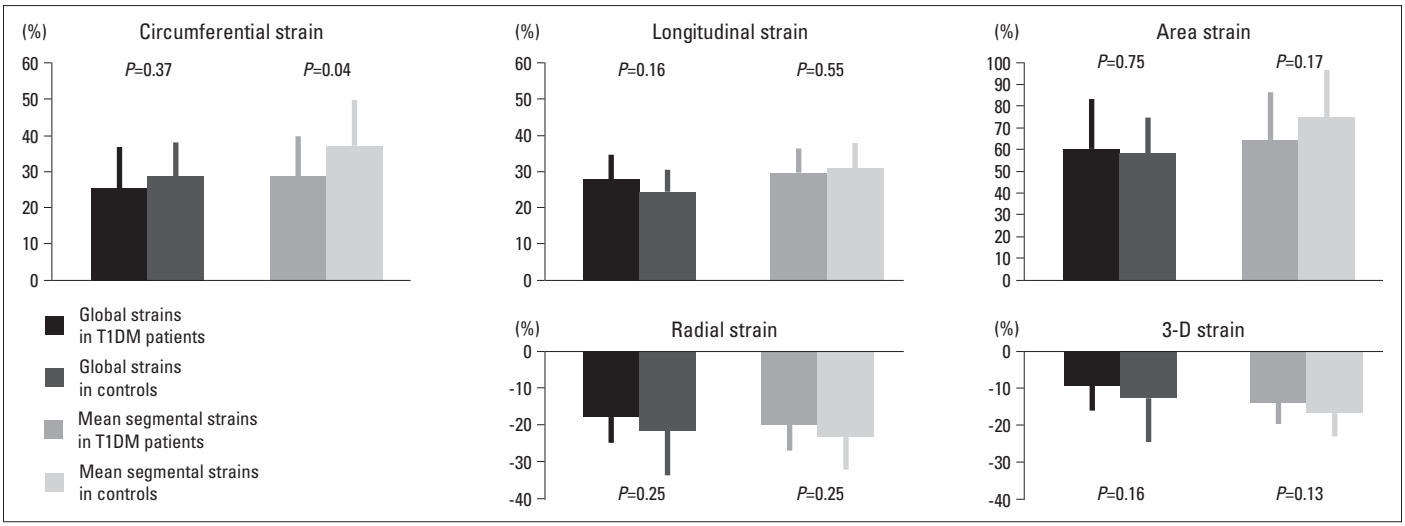

Figure 3. Left atrial global and mean segmental peak circumferential, longitudinal, area, radial and three-dimensional strains are shown in type 1 diabetes mellitus patients and matched healthy controls.

T1DM - type 1 diabetes mellitus

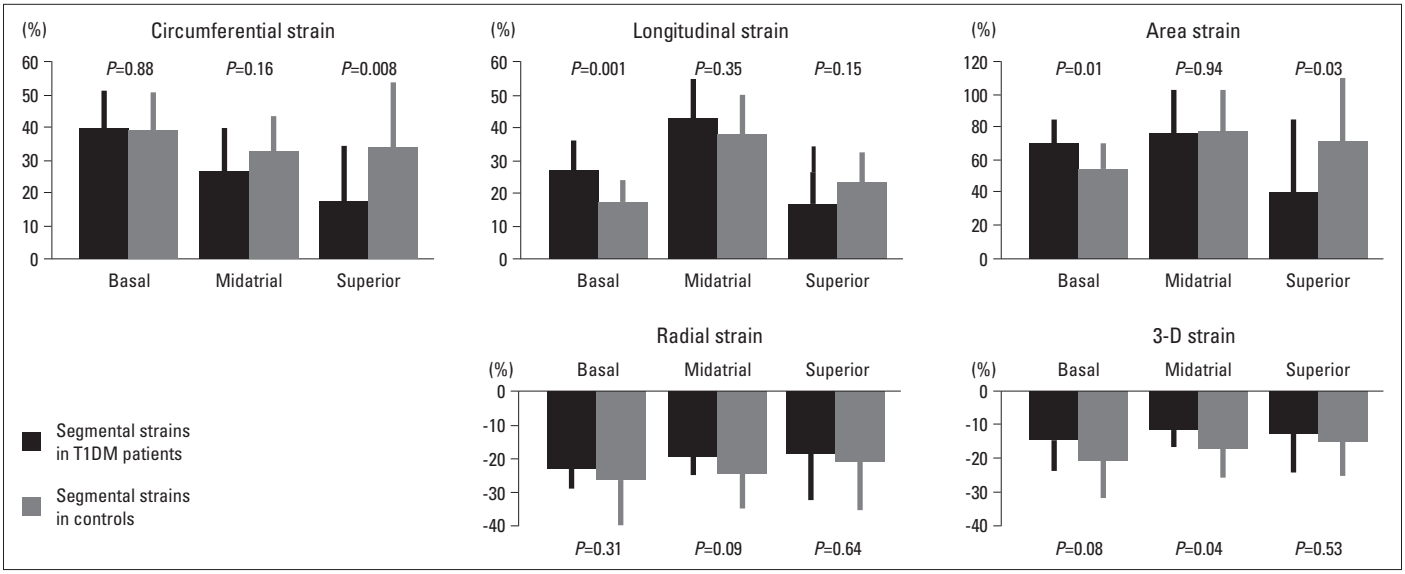

Figure 4. Left atrial segmental basal, midatrial, and superior peak circumferential, longitudinal, area, radial and three-dimensional strains are shown in type 1 diabetes mellitus patients and matched healthy controls

agreements were evaluated using the Bland–Altman method (17). In a recent study, excellent intraobserver and interobserver agreement were demonstrated for 3-DSTE-derived volumetric data (14).

Results

Demographic, biochemical, and two-dimensional echocardiographic data

Hypertension and hypercholesterolaemia were frequent in T1DM patients. No significant differences were demonstrated in standard echocardiographic parameters between the groups (Table 2). Fasting plasma glucose (5.3±0.6 mmol/L vs. 5.1±0.8 mmol/L, p=0.93), creatinine (75±5 μmol/L vs. 78±3 μmol/L, p=0.91), hematocrit (41%±2% vs. 40%±1%, p=0.90), and hemoglobin (134±3 mmol/L vs. 132±4 mmol/L, p=0.88) levels did not differ between T1DM patients and controls; GFR of >60 mL/min/1.73 m^2 was observed in both the groups. However, HbA1c was significantly increased in T1DM patients (8.1%±1.5% vs. 5.2%±1.0%, p<0.05). These results suggest that anemia or impaired renal function were not confirmed in this T1DM patient population.

3-DSTE-derived volumes and volume-based functional properties

Significantly increased LA maximum volume (45.2±10.3 mL vs. 35.9±6.3 mL, p=0.002), LA minimum volume (21.6±6.3 mL vs. 16.3±4.8 mL, p=0.006), and LA volume before atrial contraction (31.5±9.1 mL vs. 24.0±6.6 mL, p=0.006) were detected in T1DM patients compared with controls. Total atrial stroke volume

Table 3. Intraobserver and interobserver variability for the most important parameters in patients with type 1 diabetes mellitus

	Intraobserver agreement		Interobserver agreement	
	Mean±SD difference in values obtained by two measurements of the same observer	Correlation coefficient between measurements of the same observer	Mean±SD difference in values obtained by two observers	Correlation coefficient between independent measurements of two observers
Volumetric data				
V_{max}	0.9±4.7 mL	0.97 (p=0.0001)	1.0±6.4 mL	0.95 (p=0.0001)
V_{min}	–1.1±6.5 mL	0.85 (p=0.0001)	–1.2±7.4 mL	0.83 (p=0.0001)
V_{preA}	0.3±3.7 mL	0.98 (p=0.0001)	0.2±5.3 mL	0.95 (p=0.0001)
Global strains				
Radial strain	–2.5±11.1%	0.68 (p=0.003)	–0.6±9.6%	0.75 (p=0.0005)
Circumferential strain	3.8±14.8%	0.77 (p=0.0003)	3.6±18.0%	0.73 (p=0.0009)
Longitudinal strain	0.6±8.5%	0.67 (p=0.003)	–2.0±15.7%	0.54 (p=0.02)
Area strain	10.2±37.1%	0.59 (p=0.01)	2.3±38.0%	0.75 (p=0.0005)
3-D strain	–1.1±10.4%	0.62 (p=0.008)	1.4±9.5%	0.71 (p=0.001)

SD - standard deviation; 3D - three-dimensional; V_{max} - maximum left atrial volume; V_{min} - minimum left atrial volume; V_{preA} - left atrial volume before atrial contraction. Pearson's correlation coefficient was calculated and Bland–Altman method was used

(SV) was increased (23.6±6.9 mL vs. 19.6±4.6 mL, p=0.04) in patients with T1DM. Other volume-based LA functional properties showed no significant differences between the groups (Fig. 2).

3-DSTE-derived peak strain parameters

Global; mean segmental; and segmental basal, midatrial, and superior segmental peak strain parameters of T1DM patients and control subjects are shown in Figures 3 and 4. Only mean segmental circumferential peak strain showed significant difference between the groups (37.3%±12.5% vs. 28.9%±11.4%, p=0.04). In T1DM patients, segmental basal longitudinal (26.8%±9.2% vs. 17.3%±6.7%, p=0.001) and area (69.1%±16.0% vs. 54.4%±16.4%, p=0.01) strains were increased, whereas segmental superior circumferential (33.8%±18.5% vs. 17.2%±16.8%, p=0.008) and area (71.1%±38.8% vs. 39.7%±45.1%, p=0.03) strains and midatrial 3-D strain (-16.8%±8.8% vs. -11.2%±6.8%, p=0.04) were decreased.

Reproducible measurements

Table 3 shows the mean±standard deviation difference in values obtained by two measurements of the same observer and two observers for the measurements of 3-DSTE-derived V_{max}, V_{min}, V_{preA}, RS, CS, LS, AS, and 3-DS, along with the respective correlation coefficients.

Discussion

The present study features a novel aspect of early LA remodeling in T1DM patients with the aid of 3-DSTE. Changes in LA volumes and functional properties according to the various phases of the cardiac cycle indicative of LA remodeling could highlight our attention on the importance of early diagnosis, treatment, and follow-up of young patients with T1DM who have not yet been diagnosed with overt cardiovascular disease.

It is known that LA shows phasic function during cardiac cycle: it works as a reservoir during LV systole (reservoir function), it is a conduit for blood transiting from the pulmonary veins to the LV during early diastole (conduit function), and it acts as an active contractile chamber that augments LV filling in late diastole (active contraction) (18). Several methodologies, including different echocardiographic, computed tomographic (CT), and cardiac magnetic resonance imaging (cMRI) techniques, are used in clinical practice for the evaluation of LA dimensions, volumes, and function (19). 3-DSTE has just been introduced and seems to be reliable method for the evaluation of LA volumes and volume-based functional properties according to the phases of the cardiac cycle (14, 15, 20, 21) as well as LA strain parameters (15, 16, 22). It is based on the "block-matching algorithm" by strain analysis. It is known that 3-DSTE suffers in inherently lower image quality than 2-D echocardiography because of the low volume rate. Moreover, no reference values for 3-DSTE-derived LA volumetric and strain parameters are available at this moment; therefore, our LA data could differ from the results of other studies for control cases.

3-DSTE is suitable for measuring LA features according to the phases of the cardiac cycle. Reservoir, conduit, and active contraction phases of LA function could be characterized by total, passive, and active atrial SVs and EFs, respectively. Global; mean segmental; and segmental basal, midatrial, and superior peak strain parameters, derived from the same 3-D dataset, could also be calculated for the characterization of LA reservoir function.

In the present study total atrial SV was found to be increased along with decreased mean segmental circumferential peak strain in T1DM patients. Segmental analysis revealed that basal longitudinal and area strains were increased, whereas supe-

rior circumferential and area strains were decreased, in T1DM patients. This suggests that augmented basal and decreased superior LA deformations in the reservoir phase of LA function. However, alterations in conduit and active contraction phases of LA function were not confirmed by 3-DSTE in this patient subset.

Our results are only partially in agreement with previous findings. Acar et al. (3) found decreased LA passive EF as well as increased LA active emptying volume and LA active EF in T1DM patients. In another study, during the cold pressor test in T1DM patients, isovolumetric relaxation time increased, peak early LV filling velocity (E) decreased, E deceleration time decreased, and LA contribution (A) increased significantly. A marked increase in LA ejection force was also seen in this study. This LA hyperactivity was hypothesized to be because of the decreased size of the LV in combination with incipient autonomic neuropathy (4). Peterson et al. (5) found that T1DM is related to A wave velocity, late myocardial velocity (Am global), LA ejection fraction, and LA systolic ejection fraction.

The prevalence of hypertension was frequent in our diabetic patient population, which is a common finding in T1DM. In a recent 2DSTE study, hypertension was found to be associated with impaired LA function even before LA enlargement develops and after LV remodeling is accounted for (23). Badran et al. (24) found that in hypertension, LA conduit function is chiefly affected and LA dysfunction is linked to a more advanced disease.

The actual mechanism underlying the LA volumetric and functional alterations and LA remodeling in T1DM is not yet known. However, in our study, diabetes-related hormonal changes, necrosis, progressive fibrosis, hemodynamic reasons, and the effect of diastolic dysfunction, etc., were not excluded. Moreover, the effects of diabetes-related hypertension should also be considered.

Study limitations

The present single-center study covered a small number of T1DM patients, which should be considered as the most important limitation. Only a limited number of 3-DSTE-derived LA validation studies are available at this moment, therefore further studies are warranted. Finally, one quarter of T1DM patients had treated hypertension and/or hypercholesterolemia, and HbA1c levels of T1DM patients was significantly increased, which could theoretically affect the results.

Conclusion

3-DSTE seems to be a promising, non-invasive, easy-to-perform tool for detailed assessment of LA (dys) function. Both 3-DSTE-derived volumetric and strain analysis confirmed alterations in LA function in young patients with T1DM in comparison with matched controls. These results suggest early remodeling of the LA even in young patients with T1DM before other cardiovascular alterations occur.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept – A.N.; Design – A.N., T.F.; Supervision – T.F.; Funding – A.N.; Materials – C.L., T.T.V., G.A.P.; Data collection &/or processing – G.A.P., P.D., A.K.; Analysis and/or interpretation – A.N.; Literature search – A.N.; Writing – A.N., C.L., T.T.V., T.F.; Critical review- C.L., T.T.V., T.F.

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