Two-dimensional speckle-tracking echocardiography evaluation of left atrial function according to glycemic state in patients with coronary artery disease

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Objectives Prediabetes and diabetes are dysglycemic conditions associated with increased cardiovascular risks and subtle myocardial injuries. The aim of our study was to evaluate left atrial (LA) function by two-dimensional speckle-tracking echocardiography in prediabetic and diabetic patients with coronary artery disease (CAD) and compare the results with those in euglycemic patients with CAD.

Methods The study population comprised 205 consecutive patients with CAD: 104 diabetic, 51 prediabetic, and 50 euglycemic patients. LA function was evaluated with two-dimensional speckle-tracking echocardiography and the longitudinal deformation indices of the LA were measured.

Results Our results showed that early diastolic strain was lower in the diabetic patients than in the prediabetic and euglycemic patients. The absolute value of early diastolic strain rate was reduced in the diabetic patients compared with the euglycemic patients. Late diastolic strain was increased in the diabetic patients compared with the

prediabetic and euglycemic patients. The multivariate analysis showed that diabetes was a determinant of early diastolic strain and strain rate, but not late diastolic strain.

Conclusion LA conduit function, as evaluated in terms of early diastolic strain and strain rate, was impaired in the diabetic CAD patients compared with the prediabetic and euglycemic CAD patients. *Cardiovasc Endocrinol* 6:101–108 Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

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Keywords: diabetes, left atrium, prediabetes, two-dimensional speckle-tracking echocardiography

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Introduction

Prediabetes is a state of impaired glucose metabolism that stands between normal glycemic state and diabetes mellitus in the glycemic state spectrum. Prediabetes has been defined by the American Association of Diabetes as a fasting plasma glucose level between 100 and 125 mg/dl or a 2-h plasma glucose level after 75 g of oral glucose of between 140 and 199 mg/dl or a hemoglobin A1c (HbA1c) level of between 5.7 and 6.4% [1]. The prevalence of prediabetes has been reported to be about 28% in the general population [2]. One study estimated that the incidence of prediabetes was ~32.3/1000 person-years [3]. Also, a prevalence rate of prediabetes of up to 65% has been reported in patients admitted for selective coronary angiography [4].

Prediabetes is related to increased cardiovascular risks of mortality and morbidity [5,6] and subclinical myocardial injuries as assessed by high-sensitive cardiac troponin T [7]. The effects of prediabetes on the functions of the cardiac chambers have been evaluated in a few studies [8–10]. In most of these studies, two-dimensional speckle-tracking echocardiography (2DSTE) was the main method for the evaluation of the function of the cardiac chambers. 2DSTE is an angle-independent method, in comparison with color-coded tissue Doppler

imaging, for the assessment of myocardial deformation [11]. 2DSTE is a feasible and reproducible method for the evaluation of left atrial (LA) function and has been used in several conditions such as coronary artery disease (CAD) [12,13] and diabetes [9,14–17]. In studies on the effects of diabetes on LA function, CAD has been an exclusion criterion [9,14–17]. However, there is no study in the existing literature on LA function in prediabetic and diabetic patients with CAD. We used 2DSTE to evaluate our hypothesis that LA function is impaired in prediabetic and diabetic patients with CAD in comparison with euglycemic patients with CAD. Accordingly, we evaluated systolic strain (SS) and strain rate as the markers of reservoir function, the difference between SS and early diastolic strain and also early diastolic strain rate as the markers of conduit function, and the difference between early diastolic strain and late diastolic strain and also late diastolic strain rate as the markers of contraction function.

Methods

Study population

Our study population consisted of 205 patients admitted to our hospital for a coronary artery bypass graft surgery between February 2015 and December 2015. After hospital

admission, assessment of history, review of previous medical records, and physical examinations were performed. The inclusion criteria were candidacy for coronary artery bypass graft surgery, left ventricular (LV) ejection fraction more than 50%, and sinus rhythm. The exclusion criteria were the presence of any degree of valvular stenosis; more-than-mild valvular regurgitation; grades II and III diastolic dysfunction according to the recommendations of the American Society of Echocardiography (ASE) [18]; history of thyroid, hepatic, and autoimmune diseases; cancer; type 1 diabetes mellitus; cardiomyopathy; pericardial disease; acute coronary syndrome in the previous 3 months; cardiac surgery; permanent pacemaker implantation; history of atrial tachycardia, or flutter, or fibrillation; bundle branch block; estimated systolic pulmonary artery pressure more than 35 mmHg by echocardiography; creatinine more than 1.5 mg/dl; and poor echocardiography window. Eight patients were excluded from the study because of poor echocardiography window. Blood venous samples were obtained after 12 h of overnight fasting.

Diabetes mellitus was determined as fasting blood sugar more than 126 mg/dl in at least two separate samples or a history of oral antidiabetic agent or insulin usage. Prediabetes was determined as HbA1c between 5.7 and 6.4% and a euglycemic state was defined as HbA1c less than 5.7%. Finally, we enrolled 104 diabetic, 51 prediabetic, and 50 euglycemic patients. The research proposal was approved by the institutional review board and informed consent was obtained from all the patients.

Standard and two-dimensional speckle-tracking echocardiography

All echocardiographic examinations were performed by one experienced echocardiologist, blinded to the patients' glycemic state, using a commercial echocardiography setting (EKO 7; Samsung Medison, Seoul, South Korea) with a 2–4 MHz probe. These echocardiographic examinations were performed in the left lateral decubitus position while one lead of ECG monitoring with a maximal obtainable P-wave height was recorded. The scale of ECG was increased to the maximal possible level to maximize the height of the P wave. Septal and posterior wall thickness and LV mass were measured according to the ASE's recommendations [19]. Next, LV ejection fraction was measured in the apical four-chamber and two-chamber views according to the modified Simpson method. Mitral flow wave velocities at early and late diastole (*E* and *A* wave, respectively), deceleration time of the mitral *E* wave, and pulmonary vein velocities in systole and diastole (*S* and *D*, respectively) were obtained by pulsed-wave and measured according to the ASE's recommendations [18], and the average of three cardiac cycle measurements was calculated. Septal and lateral mitral annulus velocities in systole and early and late diastole (*s'*, *e'*, and *a'*, correspondingly) were obtained by pulsed-wave tissue Doppler and measured according to

the ASE's recommendations [18], and the average of septal and lateral values was presented. These indices were measured in three cardiac cycles and the average of these measurements was calculated. The ratio of *E*/averaged *e'* was computed.

Maximal, minimal, and pre-A (at the initiation of P wave in ECG) LA volumes were measured using the 'auto EF' option, which presented changes in the LA volume curve according to time. These LA volumes were measured in the apical two-chamber and four-chamber views, and then their average was calculated. Accordingly, the following indices were calculated for the evaluation of LA function: filling volume = maximal LA volume – minimal LA volume; expansion index = $100 \times (\text{maximal LA volume} - \text{minimal LA volume}) / \text{minimal LA volume}$; diastolic emptying index = $100 \times (\text{maximal LA volume} - \text{minimal LA volume}) / \text{maximal LA volume}$; as the indices of LA reservoir function, emptying percent of total emptying = $100 \times (\text{maximal LA volume} - \text{pre-A volume}) / (\text{maximal LA volume} - \text{minimal LA volume})$; passive emptying index = $100 \times (\text{maximal LA volume} - \text{pre-A volume}) / \text{maximal LA volume}$; as the indices of LA conduit function and booster active emptying percent total emptying = $100 \times (\text{pre-A volume} - \text{minimal volume}) / (\text{maximal LA volume} - \text{minimal LA volume})$; and active emptying index = $100 \times (\text{pre-A volume} - \text{minimal volume}) / \text{pre-A volume}$, as the indices of LA contraction function.

For the evaluation of LA function by 2DSTE, three cardiac cycles of the apical two-chamber and four-chamber views with a frame rate of 50–80/s at the end of the expiratory phase of respiration were obtained and then stored in the echocardiography setting. Maximal effort was made to eliminate the LA appendage and pulmonary vein orifices in the apical two-chamber and four-chamber views. At the end of systole, the internal LA border was traced from one side of the mitral annulus to its other side. Thereafter, the epicardial border of the LA was determined by echocardiography setting software and the defined region of interest was adjusted manually if it did not include LA wall thickness correctly. After the confirmation of the region of interest, each LA wall was automatically segmented into three sections using software, and the following of the region of interest from the LA borders was checked. If this following was impaired, these stages were repeated. The sections with a poor-quality signal were deleted after several attempts. If more than three sections of the LA were deleted, the patient was excluded from the study. Five patients were excluded from our study because of this reason. Zero level was set at the initiation of the QRS wave of ECG. LA strain curve had one dominant positive systolic peak (SS), one plateau at early diastole (ED), and one negative peak at late diastole (LD; after P wave in ECG). The difference between SS and ED was termed 'EDS', and the difference between ED and LD was termed 'LDS' (Fig. 1). The strain rate

curve comprised one positive peak in systole (SRS), one negative peak at early diastole (SRE), and one at late diastole (SRA) (Fig. 2). Each of these 2DSTE-derived indices of LA function for a patient was calculated by averaging the values of the accepted sections and was subsequently reported as global strain or strain rate. The reservoir function of the LA was evaluated by SS and SRS, conduit function of the LA by EDS and SRE, and contraction function of the LA by LDS and SRA. Overall, 2349 (95.5%) sections were approved for analysis.

Statistical analysis

The normally distributed continuous data are shown as mean $\pm$ SD; otherwise, they are presented as medians and

Fig. 1

Global longitudinal strain of the left atrium shows peak systolic strain (SS), early diastolic strain (EDS), and late diastolic strain (LDS).

Fig. 2

Global Longitudinal strain rate of the left atrium shows peak systolic strain rate (SRS), early diastolic strain rate (SRE), and late diastolic strain rate (SRA).

interquartile boundaries (25th–75th). The Kolmogorov–Smirnov test was used to determine the normal distribution of the data. The one-way analysis of variance was utilized to compare the mean of the normally distributed data; otherwise, the nonparametric Kruskal–Wallis H -test was used. The Bonferroni-adjusted method was used for pairwise comparisons if the omnibus test was statistically significant. The categorical data are shown as absolute frequencies and percentages. The χ^2 -test or the Fisher exact test, whichever was appropriate, was used to compare this type of data. Multivariable linear regression models were drawn upon to determine the association between glycemic state and the 2DSTE-derived indices of LA function adjusted for sex, hypertension, heart rate, hematocrit, and e' and E/e' (markers of LV diastolic function) as the potential confounders. The 2DSTE-derived indices of LA function were entered into the multivariable analysis. If they showed a skewed distribution after having been transformed logarithmically for normalization, they were entered into this analysis. The statistical analyses were carried out using IBM SPSS statistics for Windows (version 23.0; IBM Corp., Armonk, New York, USA). P values of up to 0.05 were considered statistically significant.

Results

Our study population consisted of 137 men and 68 women, with a mean age of 61.3 ± 8.4 and 60.2 ± 8.2 years, respectively. The demographic, clinical, and laboratory characteristics of the study population, divided into three groups according to their glycemic state, are shown in Table 1. These groups were different in the male sex ratio, history of cigarette smoking, functional capacity class, heart rate, hematocrit, and lipid profile. The number of involved vessels was similar between these groups. There were no statistically significant differences in the other mentioned characteristics between these groups. The echocardiographic data are shown in Table 2. A-wave velocity, e' -wave velocity, E/A ratio, E/e' ratio, and e'/a' ratio were different between the three groups. There were no statistically significant differences in the LA volumetric parameters of LA function. SRE was statistically significantly different between the euglycemic group and the diabetic group ($P=0.011$). EDS was statistically significantly different between the diabetic group and the nondiabetic groups (diabetic vs. euglycemic; $P<0.001$; and diabetic vs. prediabetic; $P=0.003$). Also, LDS was statistically significantly different between the diabetic group and the nondiabetic groups (diabetic vs. euglycemic; $P=0.049$; and diabetic vs. prediabetic; $P=0.008$). The multivariable analysis (Table 3) showed that after adjustment for the aforementioned confounders, diabetes, female sex, hematocrit, and e' were the independent determinants of the absolute amount of SRE, whereas female sex, diabetes, and e' and E/e' were the independent determinants of the absolute value of log EDS and heart rate was the only independent determinant of log LDS.

Table 1 Baseline demographic, clinical, and laboratory characteristics in the coronary artery disease patients with diabetes, prediabetes, and euglycemic state

Characteristics	Euglycemic patients (n = 50)	Patients with prediabetes (n = 51)	Patients with diabetes (n = 104)	P value
Sex (male) (%)	42 (84)	39 (77)	56 (54)	< 0.001
Age (years)	60.9 ± 8.4	59.7 ± 9.2	61.6 ± 7.9	0.388
SBP (mmHg)	123.2 ± 16.1	126.8 ± 12.9	124.5 ± 12.8	0.395
DBP (mmHg)	77.7 ± 9.7	78.5 ± 7.6	75.1 ± 9.5	0.063
HR (bpm)	66.4 ± 10.6	68.1 ± 9.9	72.8 ± 13.4	< 0.001
BMI (kg/m ²)	26.8 ± 2.7	28.0 ± 3.8	27.3 ± 4.0	0.237
Body surface area (m ²)	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	0.058
NYHA class				0.011
I	7 (14)	8 (16)	36 (35)	
II	38 (76)	33 (64)	57 (55)	
III	5 (10)	10 (20)	11 (10)	
Hyperlipidemia (%)	24 (48)	32 (63)	55 (53)	0.309
Hypertension (%)	29 (58)	35 (69)	66 (64)	0.541
Cigarette smoking (%)	20 (40)	25 (49)	19 (18)	< 0.001
FH (%)	15 (30)	13 (26)	16 (15)	0.085
ACE or ARB use (%)	40 (80)	32 (63)	73 (70)	0.163
Calcium-channel blocker use (%)	6 (10)	10 (20)	26 (25)	0.171
β-Blocker use (%)	41 (82)	41 (80)	75 (72)	0.303
Statin use (%)	47 (94)	46 (90)	92 (89)	0.555
Nitrate use (%)	38 (76)	35 (69)	81 (78)	0.450
Aspirin use (%)	45 (90)	41 (80)	94 (90)	0.175
Insulin or OA use (%)	0 (0)	0 (0)	90 (87)	–
Degree of vessel diseased				0.541
One-vessel disease	1 (2)	4 (8)	5 (5)	
Two-vessel disease	11 (22)	12 (23)	31 (30)	
Three-vessel disease	38 (76)	35 (69)	68 (65)	
LAD (%)	50 (100)	51 (100)	104 (100)	> 0.999
LCX (%)	44 (88)	42 (83)	83 (80)	0.457
RCA (%)	43 (86)	38 (75)	84 (81)	0.344
Hemoglobin level (mg/dl)	14.5 ± 1.7	14.4 ± 1.7	13.1 ± 1.8	< 0.001
Hematocrit level (%)	41.7 ± 4.4	41.8 ± 4.2	38.8 ± 5.0	< 0.001
FBS level (mg/dl)	86.0 (78.0–90.3)	91.0 (87.0–103.0)	130.5 (103.3–169.0)	< 0.001
Serum triglyceride level (mg/dl)	119.0 (92.0–148.0)	146.0 (100.5–184.5)	145.0 (101.0–207.3)	0.024
Serum cholesterol level (mg/dl)	141.0 (119.0–162.0)	154.0 (128.5–202.0)	149.0 (128.5–179.3)	0.042
Serum HDL level (mg/dl)	37.7 ± 8.3	37.7 ± 11.3	37.2 ± 9.4	0.933
Serum LDL level (mg/dl)	82.0 (62.0–108.0)	98.0 (76.5–140.0)	87.0 (70–115.8)	0.016
Serum urea level (mg/dl)	35.0 (30.8–44.3)	36.0 (29.0–45.0)	36.0 (29.0–45.0)	0.835
Serum creatinine level (mg/dl)	0.9 ± 0.2	0.9 ± 0.2	0.8 ± 0.2	0.481
Serum hemoglobin A1c (mmol/mol) (%)	5.4 ± 0.7	6.0 ± 0.5	7.9 ± 1.6	< 0.001

Data are presented as mean ± SD for the normally distributed continuous variables, medians (25th–75th interquartile) for the continuous variables with skewed distributions, and frequencies (%) for the categorical variables.

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; DBP, diastolic blood pressure; FBS, fasting blood sugar; FH, family history of coronary artery disease; HDL, high-density lipoprotein; HR, heart rate; LAD, left anterior descending artery; LCX, left circumflex artery; LDL, low-density lipoprotein; NYHA, New York Heart Association; OA, oral antidiabetes agents; RCA, right coronary artery; SBP, systolic blood pressure.

Thirty-one patients were reanalyzed to determine intraobserver variability after 3 months. The corresponding intraobserver variability as a coefficient variation for SS, EDS, LDS, SRS, SRE, and SRA was 8.4, 5.8, 6.9, 8.4, 6.7, and 10.0%, respectively.

Discussion

To our knowledge, our study is the first of its kind to compare LA function in patients with CAD according to their glycemic state (i.e. euglycemic, prediabetes, and diabetes). In our study, we assessed LA function in patients with CAD in terms of volumetric indices and 2DSTE-derived parameters. Our findings showed that in the diabetic patients, LA conduit function parameters (i.e. EDS and SRE) were reduced. Moreover, diabetes (not prediabetes) was an independent determinant of EDS and SRE. In addition, LA contraction function parameter (LDS) was decreased in the diabetic patients compared with the nondiabetic patients (prediabetic and

euglycemic). However, diabetes was not an independent determinant of LDS in the multivariate analysis.

Two studies compared LA function between CAD and non-CAD patients [12,13]. One of these studies [12] considered diabetes an exclusion criterion and diabetic patients constituted about one-third of the small study population of the other one [13]. One of these studies showed a reduction in SRE in the nondiabetic CAD patients compared with the nondiabetic non-CAD patients [12], whereas the other study reported reductions in SS and SRS, SRE, and SRA in the patients with CAD [13].

Although several studies have compared LA function between diabetic and nondiabetic patients [9,14–17], the glycemic state (euglycemic or prediabetes) in nondiabetic patients is still obscure [14–17]. In the only available study on this topic, Tadic *et al.* [9] evaluated LA function between prediabetic, diabetic, and euglycemic patients.

Table 2 Echocardiographic parameters in the coronary artery disease patients with diabetes, prediabetes, and euglycemic state

Characteristics	Euglycemic patients (n = 50)	Patients with prediabetes (n = 51)	Patients with diabetes (n = 104)	P value*
LVEDV index (ml/m ²)	67.3 ± 14.9	64.4 ± 19.0	61.1 ± 16.0	0.082
LVESV index (ml/m ²)	26.6 ± 7.2	27.3 ± 9.7	24.6 ± 7.9	0.114
LVEF (%)	60.1 ± 7.9	57.7 ± 7.2	59.6 ± 8.0	0.248
Posterior wall thickness (mm)	9.0 ± 1.1	9.0 ± 1.3	9.3 ± 1.3	0.202
Septal wall thickness (mm)	9.0 ± 1.2	9.0 ± 1.4	9.5 ± 1.4	0.087
LV mass index (g/m ²)	83.3 ± 17.7	80.0 ± 22.3	82.8 ± 21.6	0.921
E (cm/s)	62.2 ± 15.2	61.9 ± 11.7	64.2 ± 14.9	0.569
A (cm/s)	69.9 ± 15.9	71.1 ± 17.3	80.8 ± 20.7	0.001
DT (ms)	216.0 ± 52.0	236.5 ± 65.2	247.0 ± 62.6	0.014
E/A ratio	0.8 (0.7–1.0)	0.8 (0.7–1.1)	0.8 (0.7–0.9)	0.050
S (cm/s)	52.0 ± 9.9	52.1 ± 13.0	54.4 ± 13.4	0.468
D (cm/s)	35.8 ± 9.9	35.0 ± 10.2	34.8 ± 9.7	0.847
SPAP (mmHg)	26.7 ± 4.6	26.0 ± 5.5	25.8 ± 4.7	0.559
s' (cm/s)	7.7 ± 1.6	7.8 ± 1.5	7.7 ± 1.4	0.964
e' (cm/s)	7.8 ± 1.8	7.9 ± 1.7	7.1 ± 1.6	0.007
a' (cm/s)	9.1 ± 1.8	9.5 ± 1.4	9.6 ± 1.7	0.229
E/e' ratio	8.3 ± 2.6	8.2 ± 2.4	9.4 ± 2.7	0.015
e'/a' ratio	0.9 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.001
Maximum LA volume (ml)	52.7 ± 14.5	50.4 ± 14.2	49.4 ± 14.3	0.396
Maximum LA volume index (ml/m ²)	29.6 ± 8.6	27.6 ± 7.9	28.1 ± 8.0	0.438
Minimum LA volume (ml)	14.6 (11.2–20.2)	14.5 (11.9–19.0)	14.5 (10.6–19.3)	0.951
Pre-A LA volume (ml)	32.1 ± 10.2	32.1 ± 11.1	32.0 ± 11.0	0.995
Filling volume (ml)	37.3 ± 10.9	34.5 ± 10.4	33.6 ± 9.4	0.102
Diastolic emptying index (%)	70.9 ± 9.7	68.2 ± 6.6	68.3 ± 10.4	0.227
Expansion index (%)	260.8 (185.2–349.6)	209.9 (172.4–269.6)	225.9 (172.3–305.1)	0.134
Passive emptying percent (%)	54.4 (48.8–63.4)	52.3 (42.9–61.3)	50.0 (39.7–62.4)	0.186
Passive emptying index (%)	38.1 (31.8–48.0)	36.1 (28.8–44.5)	34.5 (27.3–44.7)	0.152
Booster active emptying percent total emptying (%)	45.6 (36.6–51.2)	47.7 (38.7–57.1)	50.0 (37.6–60.3)	0.186
Active emptying index (%)	55.7 (45.6–58.2)	51.3 (41.1–57.0)	54.1 (44.9–60.8)	0.199
SS (%)	40.3 ± 11.1	38.3 ± 7.0	38.5 ± 11.9	0.551
EDS (%)	24.0 (21.1–27.3)	22.7 (19.7–28.1)	18.0 (13.8–24.5)	<0.001*
LDS (%)	18.2 (15.8–21.7)	17.2 (14.7–21.3)	20.7 (16.2–26.5)	0.004**
SRS (s ⁻¹)	2.7 ± 1.0	2.5 ± 0.6	2.6 ± 0.8	0.422
SRE (s ⁻¹)	2.1 ± 0.6	1.9 ± 0.4	1.8 ± 0.6	0.001***
SRA (s ⁻¹)	2.6 (2.2–3.0)	2.5 (2.2–2.9)	2.8 (2.2–3.4)	0.101

Data are presented as mean ± SD for the normally distributed continuous variables and medians (25th–75th interquartile) for the continuous variables with skewed distributions.

DT, deceleration time; EDS, left atrial early diastolic longitudinal strain; LA, left atrial; LDS, left atrial late diastolic longitudinal strain; LVEF, left ventricle ejection fraction; LVEDV, left ventricular end-diastolic volume index; LVESV, left ventricular end-systolic volume index; SPAP, systolic pulmonary artery pressure; SRA, left atrial late diastolic longitudinal strain rate; SRE, left atrial early diastolic longitudinal strain rate; SRS, left atrial systolic longitudinal strain rate; SS, left atrial systolic longitudinal strain.

*Diabetic versus euglycemic, $P < 0.001$; diabetic versus prediabetic, $P = 0.003$.

**Diabetic versus euglycemic, $P = 0.049$; diabetic versus prediabetic, $P = 0.008$.

***Diabetic versus euglycemic, $P = 0.011$.

Table 3 Multivariable analysis of left atrial conduit and contraction function indices

Variables	SRE		Log EDS		Log LDS	
	β	P value	β	P value	β	P value
Diabetes	-0.20	0.019	-0.20	0.012	0.03	0.701
Prediabetes	-0.15	0.075	-0.03	0.716	-0.06	0.499
Sex	-0.25	0.002	-0.22	0.003	0.01	0.881
Hypertension	0.06	0.406	0.04	0.593	-0.03	0.716
Heart rate	0.12	0.085	-0.12	0.081	0.30	<0.001
e'	0.40	<0.001	0.43	<0.001	-0.16	0.083
E/e'	0.12	0.186	0.20	0.018	-0.02	0.868
Hematocrits	-0.21	0.006	-0.03	0.694	0.04	0.656

EDS, left atrial early diastolic longitudinal strain; LDS, left atrial late diastolic longitudinal strain; SRE, left atrial early diastolic longitudinal strain rate.

In all the mentioned studies [14–17], CAD patients were excluded by several methods with different sensitivity. At one end of the spectrum, the exclusion criteria for CAD in the study by Tadic *et al.* [9] were the signs and symptoms of myocardial infarction and at the other end of

the spectrum, the exclusion criterion in the study by Liu and colleagues was significant coronary artery stenosis in coronary computed tomography angiography. It, therefore, seems that CAD patients were included in most of these studies inadvertently [9,14–16] and that the populations of the studies were mixed with respect to the presence of CAD. In our study, all the patients had documented significant CAD and the absence of other similar data in the existing literature precluded us from comparing and contrasting our results.

Muranaka and colleagues reported that SRS and SRE were reduced in their diabetic patients compared with the nondiabetic patients. In that study, the researchers used color-coded tissue Doppler imaging and evaluated LA myocardial deformation only in some segments (mid part) of the LA walls. Color-coded tissue Doppler imaging is an angle-dependent method compared with 2DSTE. Mondillo and colleagues showed that SS, SRS, EDS, SRE, and LDS were reduced in their diabetic

patients with a normal LA size ($<28 \text{ ml/m}^2$) compared with their nondiabetic individuals. Nonetheless, the new guideline sets the limit for LA enlargement at more than 35 ml/m^2 . Kadappu and colleagues reported that SS, SRS, SRE, and SRA were decreased in their diabetic patients. The authors evaluated only some segments of the LA (septal and lateral walls), and their study population included patients with an advanced grade of diastolic function. We excluded patients with an advanced grade of diastolic function from our study. Also, the LA size of the diabetic patients was greater than that of the nondiabetic patients. In our study, there were no statistically significant differences in LA size between the three groups. Liu and colleagues showed that EDS and SRE were reduced in their hypertensive diabetic patients compared with their nondiabetic hypertensive patients. In that study, diabetes was not an independent determinant of EDS and SRE, but early diastolic LV strain rate was one of the several determinants of EDS and SRE. Tadic and colleagues reported that SS, SRS, EDS, and SRE were reduced in their diabetic patients compared with their euglycemic patients, whereas LDS and SRA increased in their diabetic cases. In addition, the authors found that although SS, SRS, and EDS were reduced in their prediabetic patients compared with their normal patients, SRA was increased in the prediabetic patients compared with their euglycemic peers. In addition, EDS was reduced in the diabetic patients compared with the prediabetic ones. It seems that according to the results of the study by Tadic and colleagues, with the progression of impairment in glucose metabolism, EDS is reduced, but SS and SRS decrease after reaching the status of critical impairment in glucose metabolism (prediabetes). Moreover, LDS and SRA increase after reaching this critical point (prediabetes). It should, however, be noted that Tadic and colleagues did not report whether or not prediabetes or diabetes was an independent determinant of the reservoir, conduit, and contraction functions of the LA.

In contrast to the findings of Tadic and colleagues, our results vis-à-vis EDS support the hypothesis that EDS (marker of LA conduit function) is reduced after reaching critical impairment in glucose metabolism (diabetes) in patients with CAD. This difference in the results can be explained by this conceivable point that CAD may modulate the effects of diabetes on LA function. Consequently, the pattern of the effects of impaired glucose metabolism on LA function may be different in CAD patients by comparison with non-CAD patients.

LA contraction function increases in the presence of significant LV systolic dysfunction for the compensation of reduced LV stroke work [20,21], but our study population had preserved LV systolic function. Also, it has been shown that whereas LA contraction increases in the presence of acute induced ischemia and significant stenosis in the proximal portion of the left anterior

descending artery, LA contraction decreases in the presence of significant stenosis in the proximal portion of the left circumflex artery. This is probably because of the affected LA branch artery [12,22]. In our study, the left anterior descending artery had significant stenosis in all the participants and there was no statistically significant difference in the involvement of the left circumflex artery. Nonetheless, research has shown that the occurrence of LV diastolic dysfunction precedes that of LV systolic dysfunction in diabetic patients [23]. It can, therefore, be postulated that in diabetic patients with CAD and in the presence of preserved LV systolic function – similar to the LV – LA conduit function impairment may precede the occurrence of LA contraction function. This hypothesis was discussed previously by Liu *et al.* [17] and supported by some previous studies on LA function in diabetic patients [14,17].

The main myocardial fibers in the subendocardial layer of the LA are longitudinal myocardial fibers [24]. It can be postulated that diabetes can be detrimental to these myocardial fibers by mechanisms that damage the subendocardial LV myocardial fibers. These include altered calcium regulation [25], oxidative stress [26], and microvasculopathy [27]. There is evidence that diabetes is linked to fibrosis and apoptosis in the atrium [28,29]. Fibrosis and apoptosis are also associated with LA conduit function [30]. This evidence may be explained by our findings.

It has been proposed that although LV diastolic function is one of the determinants of LA conduit function [31], it is not the only determinant of LA function and that LA structural changes (e.g. the aforementioned changes) can also be determinants. It has been shown that there is impairment in LV diastolic function in postmenopausal women and that estrogen is the main agent involved in this process by several mechanisms such as altered rennin-angiotensin activity, brain natriuretic peptide regulation, Ca handling, myocardial matrix turnover, adrenergic receptor system, and nitric oxide system [32]. Most of the women in our study population were postmenopausal (60.4 ± 8.2 years); this can explain our findings of the negative effects of the female sex on the 2DSTE-derived markers of LA conduit function.

It has been shown that chronic anemia is linked to LV diastolic dysfunction in patients with CAD or diabetes [33,34]. Also, myocardial ultrastructures such as mitochondria and sarcomere fibers can be affected by chronic anemia [35]. Early diastolic LV relaxation is an energy-consuming phase and is dependent on oxidative metabolism [36,37]. Consequently, in patients with significant CAD, as was the case in our study population, anemia can prove detrimental to LV diastolic function. As was also mentioned previously, early LV relaxation is one of the major determinants of LA conduit function, of which SRE is a marker. Such evidence supports our findings

that hematocrit can be independently one of the determinants of SRE as a marker of LA conduit function. There is evidence that with an increased heart rate, atrial contraction function is increased [38]. Our finding for LDS (a marker of atrial contraction function) is aligned with this evidence.

Limitations

First and foremost among the limitations of the present study is its small sample size. Another major weakness of the current study is the evaluation of LA function with software designed for the assessment of LV function. That we could not assess LA function by three-dimensional STE constitutes another drawback that is noteworthy. In addition, our study population comprised CAD patients who were candidates for coronary artery bypass graft surgery; our findings, therefore, are restricted only to this group of patients.

Conclusion

Our findings showed that EDS and SRE, as the indices of LA conduit function, were reduced in the diabetic CAD patients compared with the euglycemic and prediabetic CAD patients. Diabetes was one of the independent determinants of these indices of LA conduit function. LDS, as a marker of LA contraction function, was increased in the diabetic CAD patients compared with the euglycemic and prediabetic CAD patients, but diabetes was not an independent determinant of this index of LA contraction function.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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