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Original Article

Evaluation of left atrial volume and functions by 3D echocardiography in patients with prediabetes and investigation of its correlation with NT-pro ANP levels*

Prediyabetli hastalarda sol atriyal hacim ve fonksiyonlarının 3D ekokardiyografi ile değerlendirilmesi ve NT-pro ANP düzeyleri ile korelasyonunun araştırılması

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ABSTRACT

Background: An increased burden of cardiovascular disease is observed in prediabetes compared to normoglycemic. In this study, we aimed to evaluate left atrium (LA) volume indices and mechanical functions in prediabetes patients by real-time three-dimensional echocardiography (3DE) and examine the relationship of these parameters with N-terminal pro-atrial natriuretic peptide (NT-pro-ANP) levels.
Methods: 41 patients diagnosed with prediabetes by the oral glucose tolerance test in the endocrinology outpatient clinic and 43 healthy controls were included in this study. We evaluated the volume indices and mechanical functions of the LA using 3DE. Plasma NT-proANP was evaluated by the enzyme-linked immunosorbent assay method.
Results: Median NT-pro-ANP level was higher in the prediabetes group than the control group (1.5 vs 0.7 nmol/L, p<0.001). Levels of LA volume index (LAVI), minimum and maximum of LA volume (Vmin, Vmax; respectively), pre- atrial contraction volume (VpreA), active emptying fraction, and total and active emptying volume, each reflects reservoir and pump functions of LA, were higher in the prediabetes group. In contrast, the LA passive emptying fraction (PEF) level was lower (p<0.05). There was a positive correlation between levels of NT-pro-ANP and Vmax (r= 0.352, p=0.024), Vmin (r= 0.563, p<0.001), VpreA (r= 0.504, p<0.001), and LAVI (r= 0.338, p=0.031), while negative correlation existed between levels of NT-pro-ANP and total emptying fraction (r = -0.522, p<0.001) and PEF (r= -0.349, p=0.025) was found.
Conclusion: LA volume and mechanical functions are impaired in prediabetes patients, and this deterioration was positively correlated with NT pro-ANP levels. The current findings demonstrate that cardiac structural deterioration in prediabetes patients is just initiated before overt diabetes onset.

Keywords: glycemia, left atrium, N-terminal pro-atrial atriuretic peptide, prediabetes, three-dimensional echocardiography

ÖZ

Giriş ve Amaç: Prediyabet hastalarında kardiyovasküler hastalık riski normoglisemili bireylere göre daha yüksektir. Bu çalışmada prediyabet hastalarında sol atriyum (LA) hacim indekslerini ve mekanik fonksiyonları gerçek zamanlı üç boyutlu ekokardiyografi (3DE) ile değerlendirmeyi ve bu parametrelerin N-terminal proatriyal natriüretik peptid (NT-pro-ANP) seviyeleri ile ilişkisini araştırmayı amaçladık.
Yöntem ve Gereçler: Çalışmaya endokrinoloji polikliniğine başvuran ve oral glukoz tolerans testi yapılan ve prediyabet tanısı konulan 41 hasta ve 43 sağlıklı kontrol dahil edildi. 3DE kullanarak LA'nın hacim indekslerini ve mekanik fonksiyonlarını değerlendirdik. Plazma NT-proANP, ELISA yöntemiyle ölçüldü.

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Bulgular: Medyan NT-pro-ANP seviyeleri, prediyabet grubunda kontrol grubuna kıyasla daha düşüktü (1.5 vs 0.7 nmol/L, p<0.001). SA rezervuarını ve pompasını fonksiyonlarını yansıtan SA volüm indeksi (SAVI), SA minimum ve maksimum hacim (sırasıyla; Vmin, Vmax), preatriyal kasılma hacmi (VpreA), aktif boşalma hacmi, toplam boşalma hacmi ve aktif boşalma fraksiyonu seviyeleri prediyabet grubunda da daha yüksek, SA pasif boşaltma fraksiyonu (PEF) seviyeleri daha düşüktü (p<0.05). NT-pro-ANP düzeyleri ile Vmax (r= 0.352, p=0.024), Vmin (r= 0.563, p<0.001), VpreA (r= 0.504, p<0.001) ve SAVI (r= 0.338, p=0.031) düzeyleri arasında pozitif korelasyon saptandı, toplam boşalma fraksiyonu (r = -0.522, p<0.001) ve PEF (r= -0.349, p=0.025) arasında negatif korelasyon saptandı.
Tartışma ve Sonuç: Prediyabetli hastalarda LA hacmi ve mekanik fonksiyonlar bozulur ve bu bozulma NT pro-ANP seviyeleri ile pozitif korelasyon gösterir. Mevcut bulgular, prediyabetli hastalarda kardiyak yapısal bozulma sürecinin henüz aşikar diyabet başlangıcından önce başladığını göstermektedir.

Anahtar kelimeler: glisemi, sol atriyum, N-terminal pro-atriyal natriüretik peptit, prediyabet, üç boyutlu ekokardiyografi

INTRODUCTION

Prediabetes, which is involved in the etiopathogenesis of cardiovascular diseases, is a clinical condition with deteriorated glucose tolerance (GT) or fasting blood glucose (FBG) and with a high risk of developing diabetes (1). Similar to diabetes, prediabetes can have several negative effects on both the vascular structures and the mechanics of the heart. These negative effects include left ventricular (LV) systolic and diastolic dysfunction (2). Left atrial (LA) volume and mechanical function parameters indicate the severity of LV diastolic dysfunction (3). Although the LA is a transport cavity that transmits blood via pulmonary veins to the LV during both active and passive diastolic filling, it also has volume-sensing physiological functions. The function of LA and LV are affected by cardiomyopathies, hypertension, arrhythmias, and valvular diseases (4).

Three-dimensional echocardiography (3DE) assures an easier, more accurate, and repeatable interpretation of complex cardiac anatomy than conventional echocardiography (5). Furthermore, it provides a better assessment of LA and LV cavity parameters (volume, function, and synchronization) than two-dimensional echocardiography (2DE). It was reported that 3DE provided results comparable to those of magnetic resonance imaging (the gold-standard method) to measure left atrial volume (6). Although it is known that silent ischemia in diabetes is a crucial risk factor for cardiovascular diseases, it is important to shed light on the extent of the risk of developing cardiac dysfunction in prediabetes, also called 'silent' diabetes (7,8). The atrial natriuretic peptide (ANP) system is activated in response to cardiac decompensation with increased LV end-diastolic pressure and atrial diameter (9). Diastolic dysfunction is one of the first predictors of cardiac dysfunction in diabetes, indicating the importance of evaluating LA volume and atrial mechanical functions concerning ANP levels to demonstrate a diastolic dysfunction.

Therefore, our study aimed to assess LA's volume and mechanical functions in prediabetes individuals using 3DE and examine the association between these parameters and NT-pro-ANP.

MATERIALS AND METHODS

Study population

This cross-sectional study was executed between January 2012 and September 2012 after the local Ethics Committee approval (Decision Date-No: 10.2012-46). All aspects of the research were carefully designed to comply with the Declaration of Helsinki and the principles of good clinical practices. The consent of all participants was obtained in verbal and written form before the study began.

The study enrolled 53 patients over 18 years of age diagnosed with prediabetes by performing an oral GT test (OGTT) in patients with FBG of 100-126 mg/dL (deteriorated fasting glucose) in the outpatient clinic of the Endocrinology Department. Impaired GT is defined according to glucose levels of 140 to 200 mg/dL at the 120th minute by the American Diabetes Association (ADA) criteria (10). Patient have deteriorated fasting glucose or impaired GT are accepted as prediabetic. Twelve patients were excluded with coronary artery disease (CAD) (n:2), LV

hypertrophy (n:3), EF <60% (n:3), aortic stenosis (n:1), and hypertension (n:4). Thus, the study included 41 patients diagnosed with prediabetes. The control group included 43 healthy subjects without prediabetes based on the OGTT. They had no existing co-morbidities and were matched for age and gender compared to prediabetes.

The exclusion criteria included known cardiovascular diseases; diseases that may cause diastolic dysfunction (e.g., hypertension, chronic renal failure, CAD, aortic stenosis); LV hypertrophy, or an EF of <60% or a deterioration in regional wall motion or moderate or severe valvular disease; FBG level of 126 mg/dL or higher; and blood glucose level of 200 mg/dL or higher at 120 minutes after a 75-g OGTT.

Demographic and clinical characteristics, including anthropometric measurements, were recorded after detailed anamnesis and physical examination. In the morning, after resting for at least 10 minutes or a sufficient time, blood pressure was performed by mercury sphygmomanometer in a sitting position. The evaluation was based on the Joint National Committee VII report (11).

Laboratory parameters

Blood samples were collected from 08:00 to 09:00 in the morning after a 12-hrs period of fasting and were centrifuged at 5000 rpm for 15 mins to discrete the serum and plasma fractions. Subsequently, the NT-pro-ANP levels of these samples were measured simultaneously by the same person in the same laboratory. We determined the urea concentration by an enzymatic, kinetic UV method; levels of creatinine by Jaffe's kinetic method; cholesterol levels by a homogeneous enzymatic colorimetric method; albumin levels using the bromocresol green method on a Hitachi modular P800 autoanalyzer (Roche Diagnostic Corp., IN, USA); white blood cell count with optical laser scattering; and hemoglobin levels photometrically on a Sysmex XE 2100 analyzer of hematology (Roche Diagnostic Corp., IN, USA).

The ELISA kit measured plasma NT-pro-ANP levels (Catalog No. BI-20892, Biomedica, Vienna, Austria).

The OGTT procedure included blood sampling to measure the baseline glucose level at 09:00 following a three-day unrestricted carbohydrate diet, followed by ingestion of 75 g of glucose solution (300 mL of 25% dextrose solution) within 5 minutes and re-measurement of the blood glucose level after 120 minutes.

Transthoracic echocardiographic evaluation

The same cardiologist performed the echocardiographic evaluation using an iE 33 system (Philips Medical Systems, WA, USA) according to the AHA/ESC Guidelines of Cardiac Chamber Quantification (12). The 2D data was obtained by a 2.5-MHz S5-1 transducer. In a left lateral supine position, all images were obtained via views of apical 4- and 2-chamber. The patients were subjected to M-mode and 2DE measurements, respectively. In the M-mode evaluation, the end-diastolic dimension (LVEDD) and left ventricular end-systolic dimension (LVESD) of LV were performed perpendicular via the long axis of LV on the mitral valve leaflet tips level, and posterior wall thickness levels were performed in parasternal long-axis view. Furthermore, LV borders of endocardial were drawn dynamically on end-diastole and -systole via views of apical 4- and 2-chamber. The LVEDD, LVESD, cardiac output, and LVEF were assessed via views of apical 4- and 2-chamber according to the modified Simpson method. Subsequently, LV diastolic functions were performed using pulsed-wave (PW) tissue Doppler imaging of the mitral annulus. In addition, early diastolic peak conduction flow velocity (E) and late diastolic peak conduction flow velocity (A) were obtained via PW tissue Doppler imaging, and the E/A ratio was measured. The E wave's deceleration time (DT) was measured in msec. Mitral lateral annulus peak early (EM) and late (Am) diastolic and systolic wave velocities (S) were calculated in cm/sec using tissue Doppler imaging from the

apical 4-chamber view. After that, myocardial isovolumetric relaxation (IVRT) and contraction time (IVCT), and also ejection time (ET) were calculated in msec. The ratio of E/Em and Em/Am were obtained.

Real-time 3D echocardiographic evaluation

After electrocardiographic monitoring, real-time pyramidal volumetric images were acquired at each of four consecutive heartbeats during an end-inspiratory breath-hold via an X3 matrix-array transducer (1-3 MHz). The acquired images were recorded on CD for evaluation in views of apical 4- and 2-chamber, as in 2DE evaluation.

The acquired apical 4- and 2-chamber images were analyzed by an observer blinded to the clinical information of patients and 2DE measurements via 3D analysis software (QLAB, Philips Medical Systems, Version 7.1). LA volumes were calculated via anatomical landmarks, and five reference points were tagged at the atrial aspect of the mitral valve: anterior (A), inferior (I), lateral (L), septal (S), and LA apex. The software then automatically determined the endocardial borders for each frame. A 3D model of the LA volume was derived based on these data (Figure 1). After this step, the following parameters were calculated automatically with the software: Vmax with calculated at T wave end and fair before mitral valve opening, Vmin with calculated during mitral valve closure at QRS wave beginning, and VpreA with calculated at P wave beginning and fair before mitral valve reopening (Figure 1). After these measurements, LA functions were performed with specified formulas (13,14). Accordingly, LA volume parameters were obtained with the following formulas:

1. LA Total Emptying Volume (TEV) = Vmax - Vmin.
2. LA Total Emptying Fraction (TEF) = TEV / Vmax × 100.
3. LA Active Emptying Volume (AEV) = VpreA - Vmin.
4. LA Active Emptying Fraction (AEF) = AEV / VpreA × 100.
5. LA Passive Emptying Fraction (PEF) = (Vmax - VpreA) / Vmax × 100.
6. LA Expansion Index (EI) = TEV/ Vmin × 100.
7. LA maximum volume index (LAVI) = Vmax / Body Surface Area.

Statistical analysis

The normal distribution condition was evaluated with the Kolmogorov-Smirnov test in the statistical analysis. Those that met the condition were shown as mean ± standard deviation and those that did not were shown as median (min-max). Categorical data were shown as numbers and percentages. The parametric data were compared between groups with the Student's T test, while nonparametric data were compared with the Mann-Whitney U test. Furthermore, categorical data were compared with Chi-square, Yates correction, and Fischer tests. The relationship between NT pro-ANP and LA volume and functions was evaluated by Spearman correlation analysis. $P < 0.05$ was accepted for statistical significance. All analyzes were evaluated with IBM SPSS Statistics (IBM Corp., Armonk, NY, USA).

Sample size justification: In the literature, the Vmin value was approximately 2 mL higher in diabetes patients than in the control group (15). The sample size was calculated as at least 40 patients in each group, with 5% Type I error and 80% power.

RESULTS

The clinical and demographic characteristics are shown in Table 1 in detail. Mean fasting glucose level (104.2±5.6 vs 94.2±15.2 mg/dL, p<0.001), mean HbA1c level (5.8±0.6 vs 5.1±0.4 %, p<0.001), and median NT-pro-ANP level (1.5 vs 0.7 nmol/L, p<0.001) were higher in the prediabetes group than the control group (Figure 2).

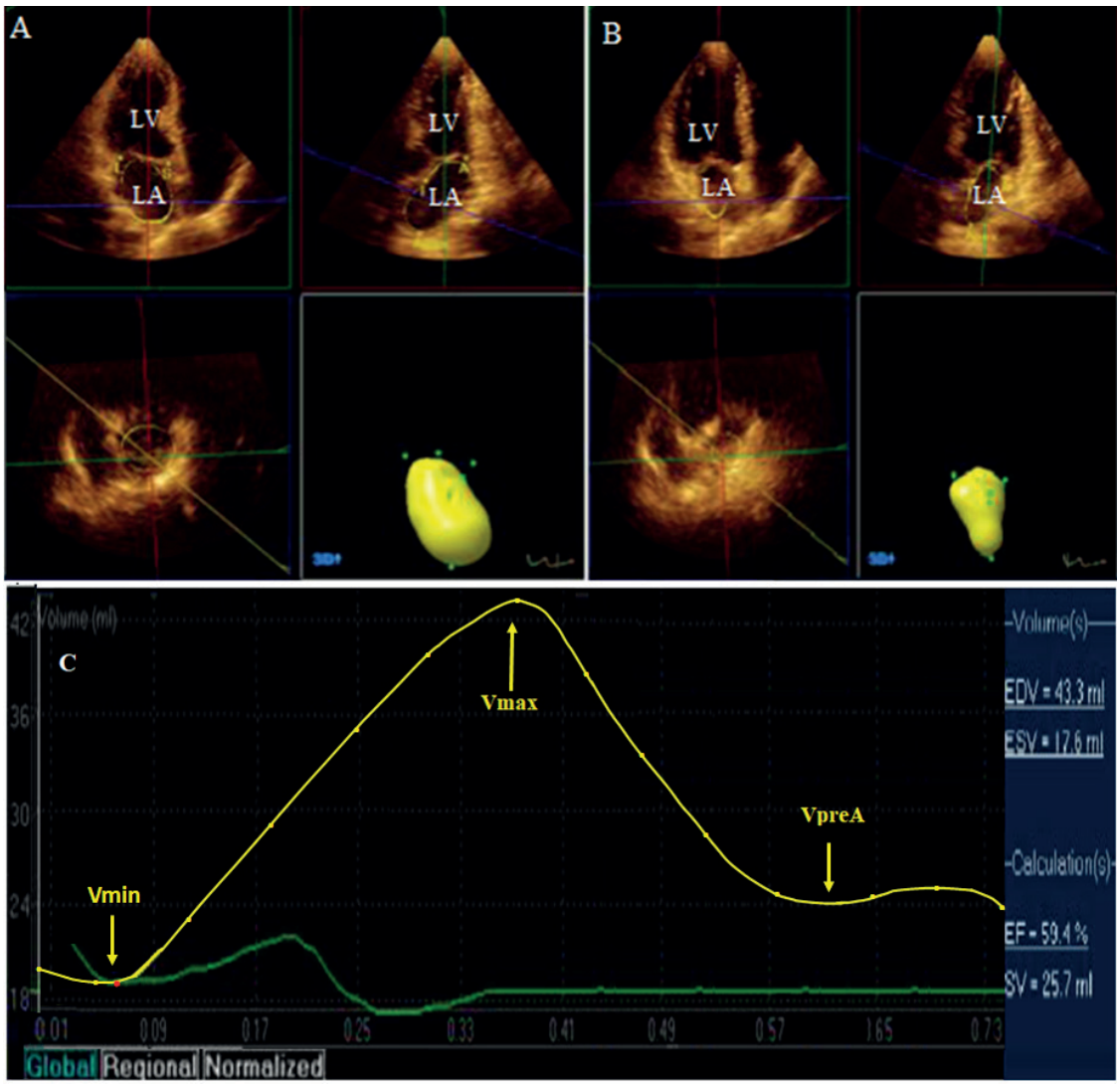

Figure 1. Real-time 3DE recordings of LA maximal volume (A), LA minimal volume (B), and time–volume curve (C).
Abbreviations: EDV, end-diastolic volume; EF, Ejection fraction; ESV, end-systolic volume; LA, Left atrium; LV, Left ventricle; Vmax, maximal volume; Vmin, minimal volume; VpreA, before left atrial contraction volume; 3DE, Three-dimensional echocardiography

The mean E/A ratio and mean Em/Am ratios were lower in prediabetes patients than control group, while mean IVRT level was higher ($p<0.001$ for each parameter) (Table 2). The mean Vmax (39.0±4.6 vs 35.2±2.8 mL, $p<0.001$), Vmin (14.9±2.7 vs 13.2±1.9 mL, $p = 0.002$), VpreA (23.2±4.1 vs 19.3±2.0 mL, respectively; $p<0.001$), ASV (8.3±2.6 vs 6.1±1.4 mL, $p < 0.001$), TEV (24.2±3.1 vs 21.9±2.7 mL, $p<0.001$), AEF (35.6 ± 7.0 vs 31.5 ± 7.1 %, $p=0.006$), and LAVI (21.1±2.5 vs 19.2±1.5 mL/m^2, $p<0.001$) levels were higher in the prediabetes group than control group, while PEF level was lower (40.5±7.6 and 44.9±5.5 %, $p=0.003$) (Table 3).

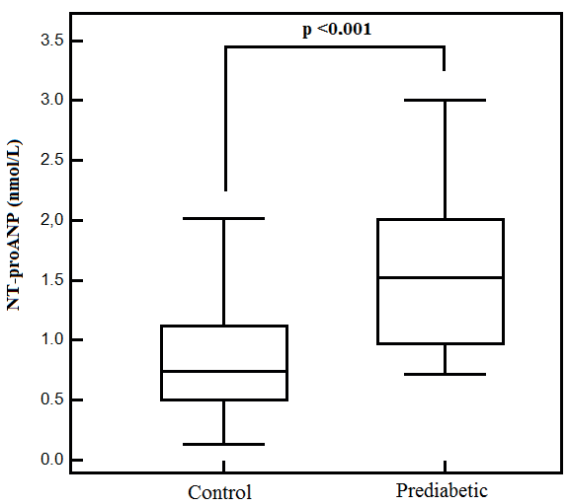

Figure 2. Distribution of NT-proANP levels in prediabetes and control groups.

Table 1. Demographic and laboratory findings.

Variables	Prediabetes n=41	Control n=43	p-value
Demographic findings			
Age, years	55.2 ±3.9	53.7±4.4	0.122
Gender, n (%)			
Female	17 (47.1)	16 (48.5)	0.824
Male	24 (51.5)	27 (52.9)	
Smoke, n (%)	12 (54.5)	10 (45.5)	0.623
BMI, kg/m^2	27.7±2.8	27.3±2.3	0.476
BSA, m^2	1.9±0.4	1.8±0.3	0.197
SBP, mm Hg	115.2±16.8	111.5±13.5	0.268
DBP, mm Hg	66.2±12.4	63.5±10.8	0.290
Laboratory findings			
WBC, x10^3/mL	7.4±1.8	8.2±2.3	0.081
Hemoglobin, gr/dL	13.8±1.6	14.3±1.0	0.144
Total cholesterol, mg/dL	192.0±31.7	186.6±44.1	0.522
LDL, mg/dL	122.8±25.3	120.5±36.6	0.738
HDL, mg/dL	39.7±6.9	42.3±10.4	0.189
Triglyceride, mg/dL	151 (64-321)	168 (66-339)	0.757
BUN, mg/dL	13.4±4.1	12.5±3.3	0.272
Creatinine, mg/dL	0.7±0.1	0.7±0.2	0.219
FBS, mg/dL	104.2±5.6	94.2±15.2	*<0.001*
OGTT 0.minute, mg/dL	112.2±9.5	96.4±8.0	*<0.001*
OGTT 120. minutes, mg/dL	167.6±13.5	103.3±10.9	*<0.001*
HbA1c, %	5.8±0.6	5.1±0.4	*<0.001*
C-peptid, pmol/mL	2.8±0.8	1.7±0.5	*<0.001*
NT- proANP, nmol/L	1.5 (0.7-3.0)	0.7 (0.1-2.1)	*<0.001*

Numerical variables were shown as mean ± standard deviation or median (min-max) according to normality distribution.
Categorical variables were shown as numbers (%).
Abbreviations: BMI, Body mass index; BSA, Body surface area; BUN, Blood urea nitrogen; FBS, Fasting blood sugar; HbA1c, Glycated Hemoglobin; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; NT-proANP, N-terminal pro-atrial natriuretic peptide; OGTT, Oral glucose tolerance test; SBP, Systolic blood pressure; WBC, White blood cells

Table 2. Evaluate of 2D echocardiography findings.

Variables	Prediabetes n=41	Control n=43	p-value
Conventional echocardiography			
LVEF, %	64.3±2.0	64.4±2.0	0.447
LVEDD, cm	4.6±0.2	4.6±0.2	0.374
LVESD, cm	2.8±0.2	2.8±0.1	0.513
IVST, cm	1.0±0.1	1.0±0.1	0.274
PWT, cm	1.0±0.1	0.9±0.1	0.281
LAD, cm	3.5±0.2	3.4±0.2	0.197
Doppler echocardiography			
E/A ratio	0.9±0.2	1.3±0.2	*<0.001*
E/Em ratio	6.8±1.5	6.7±1.1	0.675
Em/Am ratio	1.0±0.3	1.4±0.3	*<0.001*
DT, msec	196.1±55.2	181.8±30.1	0.158
IVRT, msec	87.8±7.8	75.7±10.2	*<0.001*
IVCT, msec	72.7±14.0	70.5±10.8	0.419
ET, msec	293.9±32.8	292.6±40.7	0.875
Sm, cm/sec	9.8±1.7	10.4±1.8	0.121

Numerical variables with normal distribution were shown as mean ± standard deviation.
Abbreviations: A, Late diastolic transmitral flow velocity; Am, Late diastolic mitral lateral annulus velocity; E, Early diastolic transmitral flow velocity; EDD, End-diastolic diameter; EF, Ejection fraction; Em, Early diastolic mitral lateral annulus velocity; ESD, End-systolic diameter; ET, Ejection time; DT, Deceleration time of the mitral E-wave; IVCT, Isovolumic contraction time; IVRT, Isovolumetric relaxation time; IVST, Interventricular septum thickness; LAD, Left atrium diameter; LV, Left ventricular; PWT, Posterior wall thickness; Sm, Peak systolic myocardial velocity

Table 3. Left atrial volume and function parameters by 3D echocardiography.

Variables	Prediabetes	Control	p-value
	n=41	n=43	
Heart rate, bpm	70.4±6.8	69.6±5.7	0.560
Vmax, mL	39.0±4.6	35.2±2.8	*<0.001*
Vmin, mL	14.9±2.7	13.2±1.9	*0.002*
VpreA, mL	23.2±4.1	19.3±2.0	*<0.001*
TEV, mL	24.2±3.1	21.9±2.7	*<0.001*
TEF, %	62.0±4.3	62.3±5.0	0.769
AEV, mL	8.3±2.6	6.1±1.4	*<0.001*
AEF, %	35.6±7.0	31.5±7.1	*0.006*
PEF, %	40.5±7.6	44.9±5.5	*0.003*
EI, %	166.2±28.9	169.5±34.7	0.638
LAVI, mL/m^2	21.1±2.5	19.0±1.8	*<0.001*

Numerical variables with normal distribution were shown as mean ± standard deviation.
Abbreviations: AEF, Active emptying fraction; AEV, Active emptying volume; EI, Expansion index; LAVI, Left atrial volume index; PEF, Passive emptying fraction; Vmax, Maximum volume; Vmin, Minimum volume; VpreA, Pre-atrial contraction volume; TEV, Total emptying volume; TEF, Total emptying fraction

Table 4. The relationship between NT-proANP levels and 3D echocardiography parameters in prediabetes patients.

Variables	NT- proANP	
	R	p-value
Vmax	0.352	*0.024*
Vmin	0.563	*<0.001*
VpreA	0.504	*<0.001*
TEV	0.038	0.415
TEF	-0.522	*<0.001*
AEV	0.192	0.295
AEF	-0.136	0.344
PEF	-0.349	*0.025*
EI	-0.084	0.493
LAVI	0.338	*0.031*

Abbreviations: see Table 3.

There was a positive correlation between levels of NT-pro-ANP and Vmax (r= 0.352, p=0.024), Vmin (r= 0.563, p<0.001), VpreA (r= 0.504, p<0.001), and LAVI (r= 0.338, p=0.031), while negative correlation between levels of NT-pro-ANP and TEF (r = -0.522, p<0.001) and PEF (r= -0.349, p=0.025) was found (Table 4).

DISCUSSION

This is the first study to evaluate LA volume and mechanical functions with 3DE in prediabetes patients to the best of our knowledge. Herein, Vmax, Vmin, VpreA, TEV and AEV were higher in the prediabetes patients, which indicates deterioration reservoir and booster pump functions of LA. Furthermore, PEF was lower in the prediabetes patients, which reflect the changed conduit function of LA. The current findings show increased LA volume and impaired LA mechanical function in prediabetes patients.

Significant changes of structural and functional occur in the heart due to hyperglycemia, which leads to deterioration of diastolic functions (16). Diastolic dysfunction may develop from normal fasting glucose levels to the onset of diabetes (17). The role of various mechanisms has been proposed for LV diastolic dysfunction in hyperglycemia. Chronic hyperglycemia leads to non-enzymatic glycosylation of myocardial macromolecules and leads to enhanced glycosylation end products. This process leads to the formation of irreversible end products over time. LV relaxation may be impaired due to the accumulation of advanced glycosylation end products in the myocardium (18,19). Potential structural changes in the atrium are the first expected findings associated with the onset of diastolic dysfunction. Measurement via the apical 4-chamber view in 2DE using the Simpson technique has been reported to be the best-known method for measuring the volume of the LA (20). Recent advances in 3DE imaging have eliminated most of the limitations in assessing LA volume associated with 2DE imaging and have led to significant improvement in the accuracy of measurements. For the reason that 3DE provides dynamic volumetric information, it has come to

the forefront in the evaluation of cardiac functions. 3DE is superior to 2DE because it eliminates errors caused by the apical biplane summation method (21).

The increase in Vmin is more pronounced than in Vmax with worsening diastolic dysfunction (22). Vmin has been suggested to be the best independent predictor of future potential major adverse cardiac events in outpatients (23). Therefore, Vmin has become much more valuable. It has been reported that in diastolic dysfunction, the increase in Vmax is mainly due to increased LV filling pressure. In contrast, the increase in Vmin is mainly due to atrial contraction failure (23). LA volume indices (Vmax and Vmin) were significantly higher in the prediabetes patients. In addition, a strong positive correlation was found between Vmin and NT-pro-ANP, which is a parameter of left atrial strain. These findings suggest that Vmin and other related parameters in the assessment of volume and mechanical functions may guide the follow-up of prediabetic patients.

Mechanical functions of the LA include reservoir, conduction, and pump functions on distinct phases of the cardiac cycle. The function of the reservoir is activated in the ventricular systolic phase, the conduit function in the ventricular early diastolic phase, and the pump function in the ventricular diastolic phase (24). In LV dysfunction, sufficient cardiac output is maintained by readjustment of the LA's reservoir, conduit, and pump functions (25). Potential changes in the LA volume and function may be associated with diastolic dysfunction in prediabetes patients. A study of this hypothesis suggested that the relationship between active and passive ejection of the LA, as assessed by 3DE, may be a sensitive indicator of LA functioning and may reflect the LV diastolic dysfunction severity (26). Herein, we found that prediabetes patients have increased LA reservoir, impaired booster pump functions, and altered LA conduit function. The alterations in the LA's PEF and AEF volume indices can indicate impaired atrial conduit and pump functions. Decreased PEF and increased AEF in patients with prediabetes suggest that a compensatory mechanism that results in increased LA contraction is also important in these patients. Furthermore, these findings are consistent with the Frank-Starling law.

The active function of the LA is associated with the contractility of the myocardium and part by VpreA based on the Frank-Starling law (27,28). The LA's passive ejection dysfunction also leads to a large residual LA volume prior to active contraction. Based on the Frank-Starling principle, there is an increase in LA contraction force due to the increase in LA pre-systolic volume and fiber length in the pre-systolic phase. Atrial contraction is vital during LV filling, and AEF is expected to be increased in patients with cardiovascular risk (26,29). Consistently, AEF was higher in prediabetes patients (30). TEF levels were similar between prediabetes patients and controls. The increase in LA pre-systolic volume due to increased LA stroke volume in prediabetes patients may be a compensatory mechanism to achieve ventricular filling. A higher TEV in prediabetes could be interpreted as an increase in stroke volume secondary to increased left atrial preload. However, our results also suggest the necessity of supporting the possible relationship between this hypothesis and diastolic dysfunction in prediabetes patients in further advanced studies.

Tissue Doppler imaging is another method of assessing LV diastolic functions. The progression of diastolic dysfunction leads to the maintenance of the decrease in Em and Am velocities (31). Prediabetes patients had a decreased E/A ratio, which is suggestive of diastolic dysfunction. Oki et al. (32) found a correlation between LV end-diastolic pressure and IVRT on PW tissue Doppler imaging. Similar to studies showing a prolongation of IVRT in conjunction with other echocardiographic parameters in diastolic dysfunction (33), we showed a prolongation of IVRT in prediabetes. These findings indicate a relaxation disorder that has not yet been fully established. The underlying mechanism may

be calcium handling disturbances and cardiac hypertrophy, important factors in diabetic cardiomyocytes (34). Secondly, in light of increasing evidence, NT pro-ANP is involved in glucose metabolism and serves as a connection between the metabolism and the cardiovascular system (35,36). Increased NT pro-ANP levels might have effect on the impaired LA functions response (37-39). Furthermore, increased ventricular end-diastolic pressure and atrial distension are likely to cause an increase in ANP release. These hypotheses explain the increased NT pro-ANP levels in prediabetes patients.

There are some important limitations of our study. Firstly, as with all Doppler techniques, the quality of the evaluation depends on the operator's knowledge, skills, and experience. On 3DE imaging, poorly recognized endocardial boundaries, a smaller display size, and an angle-dependent measurement lead to a decrease in the accuracy of volumetric estimates. In addition, operator-dependent manual tracing of endocardial borders affects the quality of the measurements. The limitations of the 3DE technique, including the use of apical view and careless use of scanning plans, also reduce the accuracy of the volumetric estimates of the LA. Another limitation is the low number of patients.

LA volume and mechanical functions are impaired in prediabetes patients, and this deterioration was positively correlated with NT pro-ANP levels. The present findings suggest that cardiac structural deterioration in prediabetes patients is initiated just before overt diabetes onset. An impairment of LA functions may be a potential marker of disease pathogenesis, which can also have benefits in management of the patients before the development of overt heart failure or atrial arrhythmia. 3DE imaging is a sensitive, easily applicable, noninvasive, and advantageous method for assessing LA volume and mechanical functions.

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