Research Article

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Assessment of Left Atrial Functions in Patients with Prediabetes

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Abstract

Background: LA volumes and functions are reported to be independent predictors of cardiovascular events in general and diabetic population. The aim of this is to evaluate the effects of prediabetes on LA volumes and functions and parameters that effect LA volumes and functions in patients with prediabetes.

Methods: 114 patients (83 female, mean age 48.6 ± 7.4 years) with prediabetes and 70 controls (46 female, mean age 46.5 ± 9.4 years) were included in the study. LA volumes (indexed maximal LA volume-V_{max}, pre-atrial contraction volume-V_{olp}, minimal LA volume-V_{min}) and functions (passive emptying volume-fraction (PEV-PEF), active emptying volume-fraction (AEV-AEF), total emptying volume-fraction (TEV-TEF) were evaluated with 2-dimentional echocardiography and indexed to body surface area.

Results: LA diameter, indexed V_{max}, V_{olp}, V_{min}, AEV, and TEV were found to be significantly higher in preDM group compared with control group (P<0.05). There were significant positive correlation between all three LA volumes and body mass index (BMI), triglyceride, HbA1c, fasting glucose, high sensitive C-reactive protein, mitral A wave and deceleration time. Additionally, there were positive correlation between AEV, TEV and BMI. Multivariate analysis showed that the BMI had statistically significant effect on LA diameter, indexed V_{max}, indexed V_{olp}, indexed PEV and indexed TEV whereas prediabetes had statistically significant effect on indexed V_{max}, indexed V_{olp} and indexed V_{min}. HT had only statistically significant effect on indexed V_{max}.

Conclusion: BMI and prediabetes have significant effect on LA volumes, but BMI is the only factor that has significant effect on LA functions. On the basis of these findings, we speculate that impairment of LA volumes and functions may be present before overt DM begins and this finding was mainly due to prediabetes and BMI.

Keywords: Left atrial volume; Left atrial function; Prediabetes; Transthoracic echocardiography

Introduction

Prediabetes (preDM) can be defined as an intermediate stage between normal glucose tolerance (NGT) and overt type 2 diabetes mellitus (DM) [1]. It has been well described that type 2 DM is associated with a marked increase in cardiovascular events (CVE). Recently, it has been shown that individuals with prediabetes are also at high risk to experience adverse CVE later in life [1,2]. Moreover, preDM is associated with left ventricular (LV) structure abnormalities and diastolic dysfunction even in the presence of normal systolic function in patients without coronary artery disease [3-5]. Assessment of left atrium (LA) functions is a groving interest as LA serves as a reservoir during ventricular systole, as a conduit during early diastole, and as an active contractile chamber that augment left ventricular filling in late diastole [6,7]. Recently published trial by Kadappu et al demonstrated that LA dilatation and dysfunction may be a coexistent diastolic dysfunction marker in patients with DM [8]. Additionally, most investigators reported LA volumes and functions are independent predictors of CVE in general and diabetic population

[9-17]. However, there is limited data about the effects of preDM on LA volumes and functions.

In this study, we examined 1. The effects of preDM on LA volumes and functions and 2. The parameters that effect LA volumes and functions in patients with preDM.

Methods and Materials

Study population

One hundred fourteen patients (83 female, mean age 48.6 ± 7.4 years) with preDM who were requited from endocrinology department (impaired fasting glucose-IFG defined as elevated fasting plasma glucose concentration, 100 and 126 mg/dL and impaired glucose tolerance test-IGT defined as elevated 2-hour plasma glucose concentration, 140-200 mg/dL according to American Diabetes Assocation (ADA) 2013 criteria) and 70 age-matched healthy volunteers (46 female, mean age 46.5 ± 9.4 years) who were requited from cardiology department were included in the study [18]. A detailed medical history, physical examination and 12-lead electrocardiography were obtained from the study population. All subjects underwent treadmill exercise test according to Bruce protocol or myocardial perfusion scintigrapyh to rule out latent ischemia.

Patients with evidence of ischemia, arrhythmia on electrocardiogram, LV dysfunction with an ejection fraction of <50%, significant valvular diseases, history of coronary artery disease, suspicion of secondary hypertension, thyroid disorders, pulmonary diseases, and renal failure (defined as decreased glomerular filtration rate of <60 mL/min/1.73m^2 for at least 3 months), electrolyte imbalance, technically insufficient echocardiographic and electrocardiographic data were excluded. The study protocol was approved by our local ethical committee. All participants gave informed consent before participation into the study.

Transthoracic echocardiography

Transthoracic echocardiographic examinations were performed using commercially available cardiac ultrasound scanner equipped with a multifrequency transducer and Doppler imaging program (Acuson Sequoia 512 System with 2.5 to 4.0 MHz transducer, Siemens Mountain View, California, USA) in the left lateral position according to the criteria of the American Society of Echocardiography [19]. During echocardiography, one-lead ECG recording was recorded continuously.

Left ventricular end-diastolic and end-systolic volumes were determined from the apical 4- and 2- chamber views, and stroke volume and ejection fraction (EF) were measured using the modified Simpson equation [19]. The LV mass was calculated with the Devereux Formula as LVM (g)=1.04 [(LVID + PWT + IVST)^3 - LVID^3] - 14 (LVID: LV internal dimension; PWT: posterior wall thickness; IVST: interventricular septum thickness) and indexed to the body surface area (BSA) (dividing LVM by body surface area). The peak early diastolic (E) velocity, and atrial contraction (A) velocity and E wave deceleration time (DT) were measured from the transmitral pulsed wave Doppler spectrum and E/A ratio was calculated. The pulsed wave tissue Doppler imaging (TDI) was performed in apical four-chamber window with a sample volume of 5 mm. The monitor sweep speed was set at 100 mm/sec to optimize the spectral display of myocardial velocities and all Doppler spectral velocities were averaged over three consecutive beats. The average pulsed wave TDI derived early (E') diastolic myocardial velocity was obtained from the lateral and septal sides of mitral annulus. Then, E/E' ratio was calculated to provide an estimation of LV filling pressures. The TDI derived late diastolic wave (A') was obtained from the mitral lateral annulus [20].

The LA diameter was measured from the parasternal long axis with M-mode echocardiography. Left atrial volumes were traced and calculated by means of a modified Simpson method from apical 4- and 2- chamber views according to the guidelines of the American College of Cardiology [19]. LA volumes were measured as: 1) maximal LA volume (V_{max}): just before mitral valve opening, at end-sytole 2) pre-atrial contraction volume (V_{olp}): at the onset of the P-wave on electrocardiography; and 3) minimal LA volume (V_{min}): at mitral valve closure, at end-diastole. All LA volumes were indexed to BSA in all patients. From these, the following measurements were calculated to estimate LA functions:

1.   LA passive emptying volume (PEV) = V_{max}-V_{olp};
2.   LA passive emptying fraction (PEF) = PEV/V_{max} × 100;
3.   LA active emptying volume (AEV) = V_{olp}-V_{min};
4.   LA active emptying fraction (AEF) = AEV/V_{olp} × 100;
5.   LA total emptying volume (TEV) = V_{max}-V_{min}.
6.   LA total emptying fraction (TEF) = TEV/V_{max} × 100. Left atrial volumes were indexed to body surface area (BSA) in all patients [21].

Statistical analysis

The statistical analyses were performed with the MedCalc Statistical Software version 12.7.7 (MedCal Software bvbv, Ostend, Belgium; 2013). All continuous variables were expressed as mean ± standard deviation, and categorical variables were defined as frequency and percentages. All continuous variables were checked with Kolmogorov-Smirnov normality test to show their distributions. Continuous variables with normal distributions were compared using the unpaired Student t test. For categorical variables, the chi-square test was used. Pearson and Spearman correlation analysis was used to evaluate correlations between LA volumes and functions and various laboratory parameters, and 2D echocardiographic diastolic parameters. Multivariate evaluations were performed by using Lineer Regression Analysis. The confounders that were found to be statistically significant impact on the dependent variable upon univariate analysis were described as the independent variables in multivariate linear regression analysis model. The P values <0.05 was considered significant.

Sample size justification: According to the article 'Atrial conduction times and left atrial mechanical functions and their relation with diastolic function in prediabetic patients" study (ref no 22) V_{min} value at prediabets was 9.6 ± 6.1 mL and for the control group 13.1 ± 4.3 mL. The mean difference was assumed as 3.5 and the standard deviation of the prediabetes group was 6.1 and of the control group 4.3. With the assumption of 5% of type I error (a) and 90% of power (1-b), 49 patients for each group was calculated as the sample size. With a 25% drop-out rate, minimum 62 patients (in total 124) patients should be enrolled to the study.

Results

Patient characteristics analyzed according to groups are shown in Table 1. A total of 184 patients with mean age 47.8 ± 8.3 years and 129 (70.1%) female were included in this study. There were no significant differences between both groups in age and sex distribution (p>0.05). Hypertension was present in 49 (43%) patients in preDM group, and 6 (8.6%) individuals in control group (p<0.05). 27 (14.7%) patients in preDM group were taking oral antidiabetics. In preDM group, patients were taking more frequent medications of acetylsalicylic acid, angiotensin-converting enzyme inhibitors, beta-blockers and statins than control group. Body mass index (BMI), triglyceride, high sensitive C-reactive protein (hsCRP), uric acid, fasting glucose, HbA1c were significantly higher in preDM group compared with control group (p<0.05). There were no significant difference regarding total cholesterol, LDL, HDL levels (p>0.05).

Both groups were compared to each other with respect to 2D echocardiographic parameters. Diastolic dysfunction was present in 33 (28.9%) patients in preDM group, and 12 (17.1%) individual in control group (p=0.08). There were no significant differences between the groups regarding EF and mitral E wave. However, LV mass, mitral A and A' waves, E/E' ratio, deceleration time were significantly higher and mitral E' wave was significantly lower in preDM group compared with control group (p<0.05) (Table 2).

Characteristics	PreDM group n=114	Control Group n=70	P
Age, year	48.6 ± 7.4	46.5 ± 9.4	0.083
Female, n (%)	83 (72.8)	46 (65.7)	0.324
BMI (kg/m^2)	25.2 ± 5.2	22.3 ± 1.9	<0.001
Tobacco use, n (%)	21 (18.4)	9 (12.9)	0.412
Hypertension, n (%)	49 (43)	6 (8.6)	<0.001
Hyperlipidemia, n (%)	68 (59.6)	11 (15.7)	<0.001
Medications, n (%)			
ACEI	40 (35.1)	5 (7.1)	<0.001
Betablockers	15 (13.2)	1 (1.4)	0.006
Statins	49 (43)	5 (7.1)	<0.001
ASA	23 (20.2)	3 (4.3)	0.002
OAD	27 (14.7)	-	-
Fasting glucose (mg/dL)	105.6 ± 8.8	92.7 ± 6.9	<0.001
HbA1C (%)	5.7 ± 0.6	4.8 ± 0.5	<0.001
Total cholesterol (mg/dL)	217.5 ± 33.9	207.7 ± 39.6	0.076
HDL (mg/dL)	51.4 ± 15.2	48.8 ± 12.8	0.55
LDL (mg/dL)	137.6 ± 32.8	128.2 ± 36.7	0.72
TG (mg/dL)	159.5 ± 75.4	133.2 ± 79.2	0.025
hsCRP (mg/L)	3.4 ± 2.1	1.8 ± 1.1	<0.001
Uric acid (mg/dL)	5.6 ± 1.7	4.6 ± 1.0	<0.001

BMI: Body Mass Index, ACEI: Angiotensin Converting Enzyme Inhibitors, ASA: Acetylsalisilic Acid, OAD: Oral Antidiabetics, HbA1C: Glycosylated Hemoglobin, HDL: High Density Lipoprotein, LDL: low density Lipoprotein, TG: Triglyceride, hsCRP: High Sensitive C-reactive Protein

Table 1: Demographic characteristics and laboratory parameters of the groups.

Parameters	PreDM Group n=114	Control Group n=70	P
Ejection fraction (%)	62.7 ± 5.8	62.1 ± 5.0	0.526
Left ventricular mass (g/m^2)	110.1 ± 11.8	106.0 ± 10.3	0.015
Mitral E (cm/s)	81.5 ± 14.3	81.8 ± 15.8	0.887
Mitral A (cm/s)	74.6 ± 17.3	66.9 ± 14.7	0.002
E/A ratio (cm/s)	1.1 ± 0.2	1.2 ± 0.3	0.002
Deceleration time (s)	210.7 ± 24.5	198.6 ± 23.3	0.001
Mitral lateral E' (cm/s)	16.6 ± 3.9	18.2 ± 3.7	0.008
Mitral lateral A' (cm/s)	14.8 ± 4.0	13.1 ± 2.6	0.002
E/E' ratio (cm/s)	5.1 ± 1.4	4.4 ± 0.9	0.001
Diastolic dysfunction, n (%)	33 (28.9)	12 (17.1)	0.079

Table 2: Echocardiographic parameters of the groups.

Table 3 shows the 2D echocardiographic evaluation of LA volumes and functions. LA diameter, indexed V_{max}, V_{olp}, V_{min} were significantly higher in preDM group compared with control group (p<0.05). Regarding parameters reflecting LA functions, indexed AEV, TEV were significantly higher in preDM group compared with control group, whereas there were no significant difference between the groups regarding indexed PEV, AEF, PEF and TEF (p>0.05).

Parameters	PreDM Group n=114	Control Group n=70	P
LA diameter (mm)	37.3 ± 5.9	33.8 ± 4.9	<0.001
Indexed Vmax (mL/m²)	24.0 ± 5.3	19.8 ± 4.8	<0.001
Indexed Volp (mL/m²)	15.5 ± 4.7	12.4 ± 4.0	<0.001
Indexed Vmin (mL/m²)	9.4 ± 3.5	7.4 ± 2.7	<0.001
Indexed PEV (mL/m²)	8.4 ± 3.6	7.4 ± 3.7	0.064
Indexed AEV (mL/m²)	6.0 ± 2.9	4.9 ± 2.6	0.012
Indexed TEV (mL/m²)	14.5 ± 3.7	12.4 ± 3.8	<0.001
LA Passive emptying fraction (%)	35.1 ± 12.4	36.9 ± 14.5	0.367
LA Active emptying fraction (%)	38.4 ± 12.7	39.5 ± 13.5	0.583
LA Total emptying fraction (%)	60.7 ± 9.0	62.4 ± 10.7	0.238
LA: Left Atrium, PEV: Passive Emptying Volume, AEV: Active Emptying Volume, TEV: Total Emptying Volume			

Table 3: The echocardiographic parameters for the LA volumes and functions of the groups.

There were weak but significant correlation between indexed V_{max}, V_{olp}, V_{min} and BMI, triglycerides, HbA1c, fasting glucose, hsCRP, mitral A wave and deceleration time. There were also weak, positive correlation between indexed V_{olp}, indexed V min and E/E' ratio. Additionally, there were weak positive correlation between indexed AEV, indexed TEV and BMI (Table 4). The univariate analysis showed that preDM, HT, BMI, and hs-CRP levels had statistically significant impact on the LA diameter, indexed V_{max}, indexed V_{olp}, indexed V_{min}, and indexed TEV. According to the multivariate analysis when adjusted with other confounders BMI had statistically significant effect on LA diameter, indexed V_{max}, indexed V_{olp}, indexed PEV and indexed TEV, whereas prediabetes has statistically significant effect on indexed V_{max}, indexed V_{olp} and indexed V_{min}. HT had only statistically significant effect on indexed V_{max} (Table 5).

Parametes		Indexed V_{max} (ml/m²)	Indexed V_{olp} (ml/m²)	Indexed V_{min} (ml/m²)	Indexed AEV (ml/m²)	Indexed TEV (ml/m²)
Glucose (mg/dL)	r	0.19	0.183	0.216	0.043	0.079
	P	0.01	0.013	0.003	0.56	0.289
HbA1C (%)	r	0.249	0.244	0.215	0.143	0.163
	p	0.001	0.001	0.003	0.053	0.027
BMI (kg/m²)	r	0.385	0.267	0.22	0.175	0.349
	p	<0.001	<0.001	0.003	0.017	<0.001
TG (mg/dL)	r	0.181	0.166	0.202	0.033	0.078
	p	0.014	0.024	0.006	0.655	0.294
hsCRP (mg/L)	r	0.252	0.179	0.211	0.043	0.171
	p	0.001	0.015	0.004	0.562	0.02
Uric acid (mg/dL)	r	0.154	0.061	0.108	-0.027	0.122
	p	0.037	0.411	0.146	0.714	0.099

Mitral A (cm/s)	r	0.233	0.199	0.196	0.092	0.156
	p	0.001	0.007	0.008	0.213	0.034
Mitral E' (cm/s)	r	-0.94	-0.046	-0.095	0.036	-0.05
	p	0.202	0.532	0.201	0.628	0.5
Mitral A' (cm/s)	r	0.198	0.129	0.103	0.089	0.188
	p	0.007	0.08	0.164	0.229	0.01
E/E' ratio (cm/s)	r	0.144	0.167	0.22	0.013	0.11
	p	0.051	0.024	0.003	0.859	0.879
E/A ratio (cm/s)	r	0.233	-0.139	-0.144	-0.56	-0.188
	p	0.002	0.06	0.05	0.451	0.011

BMI: Body Mass Index, TG: Triglycerides, hs-CRP: High Sensitive C-reactive Protein,PEV: Passive Emptying Volume, AEV: Active Emptying Volume, TEV: Total Emptying Volume.

Table 4: Correlation analysis of left atrial volumes and functions with 2D echocardiographic parameters and laboratory findings.

Parameters	Univariate Analysis							Multivariate Analysis						
	preDM	HT	HL	Age	BMI	hsCRP	Uric Acid	preDM	HT	HL	Age	BMI	hsCRP	Uric Acid
LA diameter (mm)	0.004	<0.001	0.373	0.089	<0.001	0.032	0.177	0.189	0.061	-	-	<0.001	0.484	-
Indexed V_{max} (mL/m²)	<0.001	<0.001	0.073	0.084	<0.001	0.001	0.041	0.011	0.028	-	-	<0.001	0.136	0.732
Indexed V_{olp} (mL/m²)	<0.001	0.003	0.068	0.012	0.008	0.007	0.337	0.008	0.323	-	0.229	0.026	0.483	-
Indexed V_{min} (mL/m²)	<0.001	0.006	0.006	0.031	0.004	0.006	0.149	0.009	0.107	0.059	0.168	0.126	0.156	0.149
Indexed PEV (mL/m²)	0.064	0.014	0.405	0.798	0.017	0.26	0.048	-	0.143	-	-	0.01	-	-
Indexed AEV (mL/m²)	0.012	0.134	0.155	0.187	0.097	0.105	0.728	-	-	-	-	-	-	-
Indexed TEV (mL/m²)	<0.001	0.003	0.036	0.309	<0.001	0.034	0.073	0.168	0.108	0.881	-	<0.001	0.429	-
LA Passive emptying fraction (%)	0.367	0.537	0.693	0.314	0.6	0.727	0.095	-	-	-	-	-	-	-
LA Active emptying fraction (%)	0.583	0.67	0.462	0.741	0.496	0.668	0.492	-	-	-	-	-	-	-
LA Total emptying fraction (%)	0.238	0.863	0.807	0.2	0.938	0.253	0.645	-	-	-	-	-	-	-

DM: Diabetes Mellitus, HT: Hypertension, HL: Hyperlipidemia, BMI: Body Mass Index, hsCRP: High Sensitive C-reactive Protein, LA: Left Atrium, PEV: Passive Emptying Volume, AEV: Active Emptying Volume, TEV: Total Emptying Volume

Table 5: Univariate and multivariate analysis for predictors of LA volumes and functions of the study population.

Discussion

The purpose of the present study was to investigate the changes in LA volumes and functions and the parameters that effect LA volumes and functions in patients with preDM based on 2D echocardiography. In this study, we demonstrated that indexed LA volumes and AEV, TEV increase significantly in preDM even which is mainly due to BMI and preDM and BMI was the only factor that had significant effect on LA functions.

Assessment of LA volumes and functions is a growing interest since changes in LA size and functions are associated with CVE such as atrial fibrillation, stroke, diastolic dysfunction and LV failure in general and diabetic population [9-17]. 2D echocardiography derived LA volume provides more accurate assessment of LA size because of the irregular geometry of LA as it often enlarges asymmetrically, resulting in variable shape that may underestimate LA size [6]. Cardiovascular imaging modalities for determination of LA functions like computed tomography (CT), cardiac magnetic resonance imaging (CMRI), and 3D echocardiography are still evolving. Although the main advantage

of CMRI and CT over echocardiography is determination of all parts of LA, including LA appendage, usage of iodine and radiation during CT, and usefulness of CMRI in patients with pacemakers limit their usage [6]. Therefore, we preferred to use 2D echocardiography which is a non-invasive, easy applicable and accessible method to evaluate LA volumes and functions.

LA volumes are evaluated by measuring V_{max}, V_{olp} and V_{min} and indexed to BSA, whereas LA functions are evaluated by calculating TEV, TEF, AEV, AEF, PEV and PEF from these three volumes. TEV describes reservoir, PEV describes conduit, and AEV describes pump functions of LA. Indexed V_{max} <29 ml/m^2 and indexed LA diameter <24 mm/m^2 for both sexes were defined as normal LA volume and LA diameter for 2D-echocardiographic evaluation [22]. Impairment of LA functions in patients with DM was demonstrated in previous studies by using 2D, 3D echocardiography, myocardial strain imaging, and CMRI.6 [16,17,23-25]. Moreover, Kadappu et al. reported that LA dilatation in DM was independent of associated hypertension and diastolic dysfunction which was called atrial cardiomyopathy [8]. Atrial structural and functional remodeling in DM can be explained with several mechanisms: LV diastolic dysfunction, oxidative stress, and inflammation, autonomic nervous system disbalance with enhanced sympathetic activation, increased blood pressure, and subendocardial fibrosis [6]. Recently Gudul et al reported that LA diameter; LA AEV and LA AEF were significantly higher in preDM group than control group [22]. In this study, we found that although LA volume and LV filling pressure were within normal limits LA reservoir and pump function were impaired and conduit function was similar in patients with preDM compared to controls. Moreover, we found that V_{max}, V_{olp}, V_{min} were associated with BMI, hsCRP, uric acid, fasting glucose, HbA1c, and mitral A wave which might indicate inflammation, impaired glysemic control, LV diastolic dysfunction may alter LA volumes in preDM. We also found that BMI was the only factor that had significant effect on LA functions. On the basis of these findings, we suggest that weight control has additional importance for LA functions in patients with preDM.

Limitations

Our study had some limitations. As this was a cross-sectional study, follow-up of the patients for CVE could not be done. Therefore, we cannot comment if increased LA volumes and impaired LA functions precipitated AF or diastolic heart failure in patients with preDM. Also, as the population size was relatively small we could not evaluate IFG and IGT patients separately for LA volumes and functions and we could not analyse the effects of medications on LA volumes and functions. For this reason, long-term follow-up and large-scale prospective studies are needed to determine the clinical predictive value of LA volumes and functions in this population.

Conclusion

The results of our study showed impaired LA functions may be present in patients with preDM. BMI and preDM had significant effect on LA volumes, but BMI was the only factor that had significant effect on LA functions. We determined that impairment of LA volumes and functions might be present in patients with preDM and this finding was mainly due to preDM and BMI. 2D echocardiography can be a valuable method to assess the LA functions in preDM. Further studies with larger sample size are needed to better define the underlying mechanism and to reach a final conclusion.

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