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Early Left Atrial Mechanics and Volume Abnormalities in Subjects with Prehypertension: A Real Time Three-Dimensional Echocardiography Study

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The aim of this study was to evaluate left atrial (LA) volume and mechanical functions by real time three-dimensional echocardiography (RT3DE) in prehypertensive subjects. The study included 54 (34 male and 20 female) prehypertensive subjects and 36 (14 male and 22 female) healthy control subjects. Transthoracic echocardiography and RT3DE were performed in all patients. Interventricular septum thickness and isovolumetric relaxation time were significantly higher in prehypertensives than in controls (10.7 ± 0.7 vs. 10.1 ± 0.8 P = 0.001 and 89.9 ± 10 vs. 82.4 ± 11 P = 0.002, respectively). LA maximum volume, volume before atrial contraction, total and active stroke volume, total and active emptying fractions, expansion index, and LA max volume index were significantly higher in prehypertensives when compared with controls ($P < 0.0001$ for all). However, the passive emptying fraction was significantly lower in prehypertensives than controls (45.7 ± 5.6 vs. 48.6 ± 4.1, P = 0.006), and the minimum LA volume between the two groups was similar. The main finding of this study was that although LA volume and LA active systolic functions were significantly increased in prehypertensive people, there was a reduction in passive LA systolic functions. These parameters may be important in showing hemodynamic and structural changes in cardiac tissue caused by prehypertension. (Echocardiography 2012;29:1211-1217)

Key words: full-volume, prehypertension, left atrial abnormalities

The risk of cardiovascular events increases as blood pressure levels increase.[1] Recent studies showed that cohorts with systolic blood pressure (SBP) between 120 and 139 mmHg or diastolic blood pressure (DBP) between 80 and 89 mmHg have a higher risk of cardiovascular disease, stroke, and kidney diseases.[2,3] Therefore, The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommended new definitions and classifications of various blood pressure levels.[4] In addition to simplifying the classification of hypertension into two stages (stage 1, 140/90 mmHg–159/99 mmHg, and stage 2, >160/100 mmHg), the committee designated levels of 120–139/80–89 mmHg as prehypertension. Prehypertension may be a precursor of clinical hypertension that will develop in the future, and also morbidity and mortality levels have been shown to increase in prehypertensive subjects as well as in hypertensive patients.[3,5]

Changes in left atrial (LA) size and function are associated with major adverse cardiovascular outcomes, such as atrial fibrillation, heart failure, stroke, and death.[6–11] Several methods have been used to assess LA function by measuring changes of LA volumes, such as nuclear scintigraphy, two-dimensional echocardiography, pulsed wave Doppler, tissue Doppler imaging, and angiography.[12] However, these techniques have their own limitations, such as higher costs, invasive natures, low temporal resolution, lacking enough information about the volume of LA, and the need for contrast or radiopharmaceutical agents.[12,13] Many studies have shown that real time three-dimensional echocardiography (RT3DE) provides an accurate measurement of the left atrial volume

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and function and could be considered a feasible and reproducible method for its clinical application.[14,15]

In this study, our aim was to evaluate left atrial volume and mechanical functions by RT3DE in prehypertensive subjects who has been largely neglected or not adequately assessed from the clinical point of view on the grounds that they are not symptomatic.

Methods:

The study included 54 (34 male and 20 female) prehypertensive subjects and 36 (14 male and 22 female) healthy control subjects.

Definition of Prehypertension:

Blood pressures were measured during two separate clinical visits using a standardized protocol. Each participant was in a seated position with 5 minutes of rest before the first measurement. Up to 3 brachial systolic and diastolic blood pressures (separated by 30 sec after the 5-min rest period) were taken by trained physicians who were blinded to the study population using appropriate cuff sizes and a mercury sphygmomanometer. Systolic and diastolic blood pressure values were determined according to Korotkoff phase 1 and phase 5.[4] The averages of all of the available measurements for SBP and DBP were used. Prehypertension was defined as an average SBP 120–139 mmHg or DBP 80–89 mmHg according to JNC 7 criteria.

A careful history was taken, and a complete physical examination was performed in all the subjects. A resting 12-lead electrocardiography was obtained. All the patients' demographic parameters, such as age and gender, were recorded.

To avoid confounding by other conditions which affect LA volume, individuals were excluded from both groups on the basis of the following characteristics: age over 65 years, body mass index (BMI) over 31 kg/m^2, systemic hypertension (blood pressure $>$ 140/90 mmHg or ongoing antihypertensive medication), white-coat hypertension, diabetes mellitus (fasting serum glucose level $>$ 126 mg/dL or ongoing diabetes medication), history of coronary artery disease, antiarrhythmic drug use, any valvular diseases, the presence of left bundle branch block, the presence of permanent pacemaker, the presence of active inflammation, obstructive sleep apnea, chronic inflammatory diseases, atrial fibrillation, cardiomyopathies, renal failure, liver disease, and poor-quality imaging on two-dimensional echocardiography and/or RT3DE.

Blood samples were drawn from all study participants under fasting conditions from the left median antecubital vein before echocardiographic examination and placed in vials containing EDTA (1.0 mg/mL). Plasma samples were collected by centrifugation within 2 hours of collection and were studied daily. Serum levels of glucose, total cholesterol, triglycerides, and low-density lipoprotein (LDL) cholesterol were measured using standard laboratory methods. The protocol was approved by the Local Research Ethics Committee.

Echocardiographic Evaluation:

Transthoracic echocardiographic studies, including M-mode, two-dimensional echocardiography, pulsed wave Doppler, color Doppler, tissue Doppler imaging, and real time three-dimensional echocardiography were performed in all study participants. A commercially available machine (IE-33; Philips Medical Systems, Bothell, WA, USA) equipped with broadband S5-1 transducer (Philips Medical Systems) with digital storage software for offline analysis was used. All comprehensive two-dimensional echocardiographic examinations were performed according to the recommendations by the American Society of Echocardiography.[6] The following two-dimensional echocardiographic parameters were measured: left ventricular end-diastolic diameter (LVEDD, mm), left ventricular end-systolic diameter (LVESD, mm), aortic root (mm), LA diameter (mm), interventricular septum thickness in diastole (IVST, mm), and posterior wall thickness in diastole (PWT, mm).

Left ventricular diastolic function was assessed with Doppler echocardiography in accordance with the American and European Societies of Echocardiography recommendations.[16,17] The following variables were measured: peak transmitral flow velocity in early diastole (E), peak transmitral flow velocity in late diastole (A), E/A ratio, E deceleration time (DT) defined as the slope from the peak to zero velocity of the E-wave, and isovolumetric relaxation time (IVRT) defined as the time interval between aortic valve closure to the onset of E-wave. The myocardial systolic (Sm), peak early diastolic (Em), peak late diastolic (Am), early diastolic mitral annulus velocities (E'), and late diastolic mitral annulus velocities (A') were obtained by placing a tissue Doppler sample volume at the septal mitral annulus. The E/Em and Em/Am ratios were subsequently calculated.

Real time three-dimensional echocardiography was performed by 2 experienced investigators blinded to both BD and control groups. RT3DE was performed with an X3 matrix-array transducer (Philips Medical Systems) (1–3 MHz) for acquisition of "full-volume" real time pyramidal volumetric data sets along 4 consecutive cardiac cycles. Individuals were instructed to hold

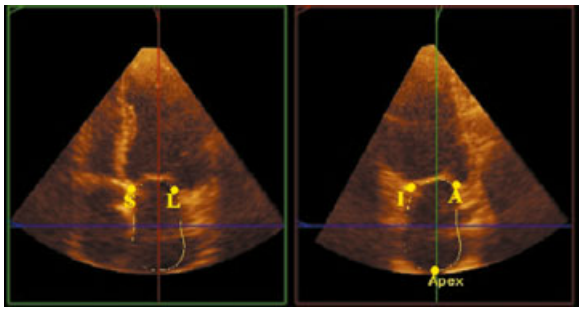

Figure 1. Anatomic landmarks used to calculate left atrial (LA) volumes were manually identified by marking 5 points: at the anterior, inferior, lateral, septal annuli, and the 5th the apex of LA.

their breath, and images were coupled with electrocardiographic recordings. Apical two-chamber and four-chamber views were extracted from the pyramidal data set during expiration. Both left ventricular and LA cavities were included in the pyramidal scan volume. Anatomic landmarks used to calculate LA volumes were manually identified by marking 5 points on the atrial surfaces of the mitral annulus at the anterior, inferior, lateral and septal annuli, and the 5th point at the apex of the LA (Fig. 1). Points determined to represent the pulmonary vein ostia or LA appendage were excluded from the measurement. The LA internal endocardial border of each frame was defined by automated processing and manually adjusted for pulmonary vein ostia and LA appendage exclusion. From these data, a three-dimensional model of LA volume was generated (Fig. 2A–B). The real time three-dimensional echocardiographic data sets were digitally stored and analyzed using analysis software (QLab-Philips version 7.1; Philips Medical Systems). All the stored digital data were analyzed by 2 independent observers who were blinded to the clinical data. (1) Maximum volume (Vmax): at end-systole, the time at which atrial volume was the largest just before mitral valve opening, (2) minimum volume (Vmin): at

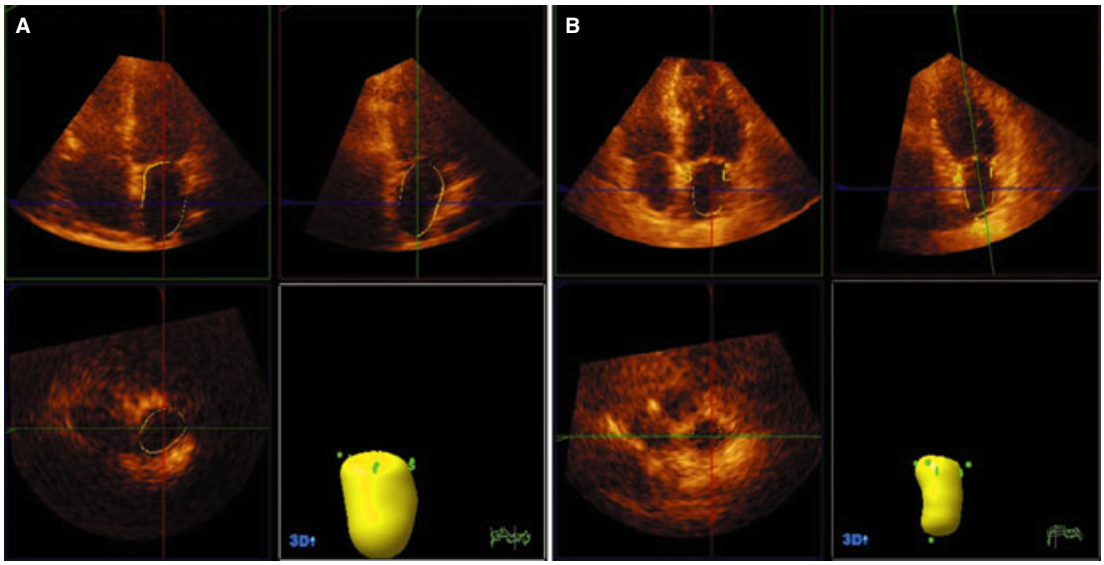

Figure 2. Real time three-dimensional echocardiography recordings. **A.** max left atrial volumes. **B.** min left atrial volumes.

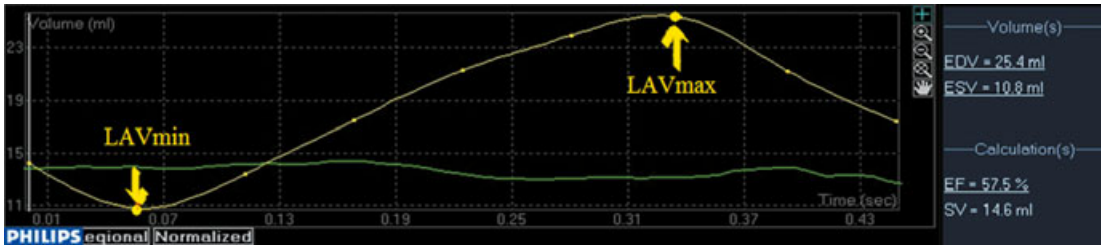

Figure 3. Time-volume curve with indicating max (LA Vmax), and min (LA Vmin) volume. EDV = left atrial end-diastolic volume, ESV = end-systolic volume, EF = ejection fraction, SV = stroke volume.

end-diastole, the time at which atrial volume at its nadir before mitral valve closure (Fig. 3), and (3) volume before atrial contraction (Vpre A): the last frame before mitral valve reopening or at time of P-wave on electrocardiogram. From the three volumes, the following measurements were selected as indices of LA function and calculated according to previous studies.[7,8]

(1) LA Total Stroke Volume (TSV): Vmax−Vmin. (2) LA Total Emptying Fraction (TEF): TSV/Vmax × 100. (3) LA Active Stroke Volume (ASV): Vpre A−Vmin. (4) LA Active Emptying Fraction (AEF): ASV/Vpre A × 100. (5) LA Expansion Index (EI): TSV/Vmin × 100. (6) LA Passive Emptying Fraction (PEF): (Vmax−Vpre A)/Vmax × 100. (7) LA maximum volume index (LA max VI): Vmax/body surface area.

Statistical Analysis:

Statistical analysis was performed using SPSS for Windows version 17.0 software (SPSS, Chicago, IL, USA). All continuous variables were expressed as means ± SD, and categorical variables were defined as numbers and percentages. Differences between groups were assessed with the chi-square test for categorical variables and the Student's *t*-test or Mann-Whitney U test for continuous variables, depending on whether they distributed normally or did not, as tested by the Shapiro-Wilk's test. A P value < 0.05 was considered to be statistically significant.

TABLE I

Clinical Characteristics and Laboratory Data of the Study Population

	Prehypertensive (n = 54)	Controls (n = 36)	P values
Age (year)	49.2 ± 6.5	48.6 ± 4.1	NS
Women/men	20/34	14/22	NS
Body mass index (kg/m^2)	25.6 ± 3.7	25.7 ± 3.1	NS
SBP(mmHg)	134.6 ± 2.4	113.5 ± 6.6	<0.001
DBP(mmHg)	85.4 ± 2	76.4 ± 5	<0.001
Heart rate (beat/min)	76.4 ± 8.4	75.6 ± 6.3	NS
Total cholesterol (mg/dL)	185.6 ± 55.4	189.28 ± 48	NS
LDL cholesterol (mg/dL)	114.7 ± 40	118.6 ± 42.5	NS
Triglycerides (mg/dL)	174.8 ± 40	179.3 ± 64	NS
Blood glucose (mg/dL)	86.3 ± 12	88.7 ± 8	NS

DBP = diastolic blood pressure; LDL = low-density lipoprotein; NS = not significant; SBP = Systolic blood pressure.

Results:

Baseline clinical characteristics and laboratory results of 54 prehypertensive subjects (mean age 48.6 ± 4.1 years) and 36 healthy (mean age 46.2 ± 6.5 years) control subjects are listed in Table I. There were no significant differences between prehypertensives and controls in terms of age, gender, BMI, heart rate, total cholesterol, triglyceride, LDL cholesterol, and blood glucose levels. However, systolic and diastolic blood pressures were significantly higher in prehypertensive subjects when compared with controls (134.6 ± 2.4 vs. 113.5 ± 6 $P < 0.001$, 85.4 ± 2 vs. 76.4 ± 5 $P < 0.001$, respectively).

Two-dimensional echocardiographic results are shown in Table II. There were no significant differences between prehypertensives and controls with regard to ejection fraction, LVEDD, LVESD, aortic diameter, LA diameter, PWT, E/A ratio, DT, Sm, E/Em, E′, A′, and Em/Am ratios. However, IVST and IVRT were significantly higher

TABLE II

Two-Dimensional Echocardiographic and Doppler Parameters of the Study Population

Variable	Prehypertensive (n = 54)	Controls (n = 36)	P values
Ejection fraction (%)	64.9 ± 3	65 ± 3	NS
LVEDD (mm)	47.5 ± 2	46.9 ± 2.6	NS
LVSDD (mm)	28.3 ± 2	28.8 ± 2	NS
Left atrial diameter (mm)	34.6 ± 1.1	33.9 ± 2.1	NS
IVST (mm)	10.7 ± 0.7	10.1 ± 0.8	0.001
Posterior wall (mm)	9.8 ± 0.2	9.6 ± 0.7	NS
Aortic diameter (mm)	32.1 ± 1.6	31.7 ± 1.5	NS
E/A	1.44 ± 0.1	1.4 ± 0.1	NS
DT (ms)	177 ± 11	176 ± 8	NS
IVRT (ms)	89.9 ± 10	82.4 ± 11	0.002
Sm (cm/s)	11.1 ± 1.4	10.7 ± 1.5	NS
E/Em	7.3 ± 1	7.2 ± 1.1	NS
Em/Am	1.7 ± 1.4	1.4 ± 0.3	NS
Peak E′ velocity (cm/s)	9.0 ± 2.1	8.9 ± 4.3	NS
Peak A′ velocity (cm/s)	8.3 ± 3.2	8.1 ± 2.2	NS

A = mitral late diastolic velocity; Am = left ventricular myocardial late diastolic velocity; early diastolic mitral annulus velocity (E′), and late diastolic mitral annulus velocity (A′); DT = mitral E-wave deceleration time; E = mitral early diastolic velocity; Em = left ventricular myocardial early diastolic velocity; IVRT = isovolumetric relaxation time; IVST = interventricular septal thickness; LVEDD = left ventricular end-diastolic dimension; LVESD = left ventricular end-systolic dimension; NS = not significant; Sm = left ventricular systolic myocardial velocity.

TABLE III

Three-Dimensional Echocardiographic Data of the Study Population

Variable	Prehypertensive (n = 54)	Controls (n = 36)	P values
LA maximum volume (mL)	39.5 ± 3.6	35.5 ± 2	0.0001
LA minimum volume (mL)	12.9 ± 1.6	12.5 ± 1.3	NS
LA volume before LA contraction (mL)	21.5 ± 3	18.2 ± 1.3	0.0001
LA total systolic volume (mL)	26.7 ± 3	23 ± 1.6	0.0001
LA total emptying fraction	67.3 ± 3.4	64.8 ± 3	0.0001
LA active stroke volume (mL)	8.6 ± 2.5	5.6 ± 1.4	0.0001
LA active emptying fraction	49.3 ± 7.6	33.1 ± 6.6	0.0001
LA expansion index	209.2 ± 33	185.8 ± 24	0.0001
LA passive emptying fraction	45.7 ± 5.6	48.6 ± 4.1	0.006
LA maxVI	23.9 ± 2.6	20.5 ± 3	0.0001

LA = left atrium; LA maxVI = LA maximum volume index; NS = not significant.

in prehypertensives than in controls (10.7 ± 0.7 vs. 10.1 ± 0.8 P = 0.001 and 89.9 ± 10 vs. 82.4 ± 11 P = 0.002, respectively).

Real time three-dimensional echocardiographic findings are shown in Table III. Vmax, Vpre A, TSV, TEF, ASV, AEF, EI, and LA max VI were significantly higher in prehypertensives when compared with controls (P < 0.0001 for all). However, PEF was significantly lower in prehypertensives than controls (45.7 ± 5.6 vs. 48.6 ± 4.1, P = 0.006), and the minimum LA volume between the two groups was similar. Reproducibility and intra- and interobserver variability results are shown in Table IV.

TABLE IV

Reproducibility for Measurements of Left Atrial Volumes Obtained by Real Time Three-Dimensional Echocardiography Expressed as Coefficient of Variability for 20 Participants Reexamined

	Intraobserver (%)	Interobserver (%)
Vmax	6	8.4
Vmin	5.8	7.8
VpreA	7.3	10.2

Discussion:

LA function actually plays three major physiologic roles in the presence of sinus rhythm: (1) acting as a contractile pump (booster), delivering 15–30% of left ventricular (LV) filling, (2) acting as a reservoir, collecting pulmonary venous return during ventricular systole, and (3) acting as a conduit for passing stored blood from the LA to the LV during early diastolic phase.[18,19] The most important factor which determines these LA functions is the hemodynamics of blood flow across the mitral valve into the LV.

In the previous studies, LA functions were evaluated by pulsed wave Doppler and tissue Doppler in dipper and nondipper hypertensive subjects.[12,20–30] In these studies, maximal and minimal LA volumes, LA active emptying volumes, and LA active emptying fractions were shown to be increased in hypertensives, while LA passive emptying volumes and LA passive emptying fractions were shown to be decreased in the same group.

To the best of our knowledge, our study is the first in which LA volumes and LA mechanical functions were assessed by RT3DE. The main finding of this study was despite LA volume and LA active systolic functions being significantly increased in prehypertensive subjects, there was a reduction in passive LA systolic functions in prehypertensive subjects when compared with the controls.

It is well known that blood flow from left atrium toward the left ventricle deteriorates when left ventricular stiffness increases and left ventricular enlargement capacity decreases,[19,22,28] and in turn, left atrial volumes and left atrial reservoir function increase. In early diastole, passive emptying volume reduces on account of increased left ventricular stiffness and deteriorated diastolic relaxation. The impairment of LA passive emptying volume also contributes to a larger residual LA volume before its active contraction. According to the Frank–Starling mechanism, there is an augmentation of LA contraction force due to LA presystolic volume and fiber length increase. The atrial contraction becomes of crucial importance during LV filling, as suggested by the higher values of LA active emptying volume and LA active emptying fraction in the prehypertensive subjects.

Traditionally, pulsed wave Doppler and tissue Doppler methods were used to assess LA functions. In our study, IVRT was significantly higher in prehypertensives than in controls evaluated by using these methods. However, LA diameter, E/A ratio, E′, A′, DT, Sm, E/Em, and Em/Am were similar between the two groups. Despite lack of a complete deterioration of the parameters

showing diastolic dysfunction evaluated by using pulsed wave Doppler and tissue Doppler methods, we found impaired LA volume and functions assessed by RT3DE. Traditional pulsed wave and tissue Doppler imaging have their own limitations in the assessment of diastolic function, such as the flow dependence of the mitral valve. On the other hand, RT3DE measurements are derived from different phases of the cardiac cycle. Therefore, we think that evaluation of LA functions by RT3DE may be more sensitive and reliable.

In our study, RT3DE parameters showing LA abnormalities cannot be easily used in clinical practice. However, RT3DE has significant clinical potential for demonstrating structural changes caused by prehypertension.

Limitations:

The first limitation of our study was cross-sectional design, and the findings in this study need to be supported by long-term follow-up studies with large patient populations. Another limitation of this study was the potential usage of left ventricular elastance or ventricular early diastolic strain/strain rate may be more significant. Most importantly, our study would have been more meaningful if the levels of atrial natriuretic peptide, which is a volume regulatory neurohormone secreted from the atria in response to atrial volume expansion and pressure overload, were measured together with the assessment of LA by RT3DE.

Conclusions:

We demonstrated a deterioration of LA volume and functions by RT3DE in prehypertensive subjects. However, LA diastolic dysfunction was not present in this group of patients when traditional methods were used. These findings show that LA volume and functions, as evaluated by RT3DE, deteriorate in prehypertensive individuals in the early period before the development of hypertension.

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