Left atrial volume and function in patients with white-coat hypertension assessed by real-time three-dimensional echocardiography

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Background **White-coat hypertension (WCH) is a disease based on the disparity of a patient's blood pressure measurements between the physician's office and the patient's home environment. The aim of the present study is to evaluate the left atrial (LA) volume and functions in WCH.**

Methods **In total, this study included 37 WCH (17 women, 20 men, mean age 48.4 ± 5.7 years) and 30 healthy individuals (18 women, 20 men, mean age 47.9 ± 7.5 years). All patients underwent real-time three-dimensional and comprehensive two-dimensional echocardiography (2DE) with tissue Doppler evaluation to estimate left atrial volumes and mechanical functions.**

Results **LA diameters were significantly higher in the patients compared with the controls (37 ± 2.8 vs. 35 ± 3.1 mm, $P = 0.017$). LA total systolic volume and LA maximal volume were significantly higher in the patients. (41.1 ± 6.9 vs. 35.5 ± 3.7 ml, $P < 0.001$; 25.8 ± 5.4 vs. 21.3 ± 3.3 ml, $P < 0.001$, respectively). LA volume before LA contraction and LA active stroke volume were significantly higher in the patients with WCH than in the normotensives (24.4 ± 6.3 vs. 20.9 ± 2 ml, $P = 0.002$; 9.1 ± 4.8 vs. 6.7 ± 2.5 ml, $P = 0.007$, respectively). Moreover, the LA expansion index was significantly higher in the patients with WCH than in the normotensives (178.7 ± 53.6 vs. 155.3 ± 36.3, $P = 0.037$). However, the total emptying volume fraction of the LA was similar between the two groups.**

Conclusion **We showed that LA structural functions and volumes were increased in the WCH group. Although increased LA volume has been observed in many diseases, structural changes in LA may be accepted as an early sign for clinical cardiac remodeling in patients with WCH, suggesting the necessity of early intervention for preventing clinical cardiovascular disease.** ***Blood Press Monit*** **21:231–237**

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Introduction

White-coat hypertension (WCH) is a clinical condition in which patients have persistently high blood pressure (BP) levels when measured at a medical office despite having normal BP levels during their daily lives [1,2]. The patient's BP level peaks within 2–4 min at the beginning of the visit and remains high during the physician visit. The overall prevalence is 13% in the 2013 European guidelines report. However, a recent review reported that 30–40% of patients who are diagnosed with hypertension only with standard office BP measurements have normal out-of-office BP according to ambulatory BP measurements [2].

WCH is associated with an increased risk of developing persistent hypertension, and the effect of WCH both on target organ damage and its prognostic significance are being debated. There is a widespread view that a transient increase in BP such as that triggered by stress-induced sympathetic activation may modulate cardiac growth, compliance, and stiffness. Moreover, some recent studies reported increased left ventricular (LV) mass, higher LV filling pressure, carotid atherosclerosis, reduced LV deformation, and aortic elastic properties in patients with WCH [1,3–7].

Longitudinal investigations have consistently reported that changes in left atrial (LA) size and function are known to be associated with major cardiovascular outcomes such as atrial fibrillation, heart failure, stroke, and death [8–17]. Several methods have been used to assess LA function by measuring changes in LA volumes, such as nuclear scintigraphy, 2DE, pulsed wave Doppler, tissue Doppler imaging, and angiography. However, these techniques have limitations such as higher costs, invasive nature, low temporal resolution, lack of sufficient

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information on LA volume, and need for contrast or radiopharmaceutical agents. Recently, many studies have shown that real-time three-dimensional echocardiography (RT3DE) provides a correct measurement of the LA volume and function and could be considered a feasible and reproducible method for its clinical application [18,19]. The aim of the present study was to evaluate the LA volume and functions using RT3DE in patients with WCH.

Methods

Study design and patient population

We carried out a cross-sectional and observational study focusing on the evaluation of the effect of WCH on LA volume and function with RT3DE. The present study included 37 patients with WCH and age-matched 38 healthy individuals. All the demographic parameters of the patients such as age, sex, and BMI were recorded. All patients were fully observed and a complete physical examination was performed in the Turgut Özal Medical Center; an ambulatory BP monitoring evaluation was also performed. A resting 12-lead ECG was obtained. Transthoracic echocardiographic studies, including M-mode, 2DE, pulsed wave Doppler, color Doppler, tissue Doppler imaging, and RT3DE, were carried out in all patients. Patients' blood samples were obtained under fasting conditions from the left median antecubital vein before echocardiographic examination and placed in ethylene diamine tetra-acetic acid-containing vials (1.0 mg/ml). Plasma samples were collected by centrifugation within 2 h of collection and were studied daily. Serum levels of glucose, total cholesterol, triglycerides, HDL, and LDL cholesterol were measured using standard laboratory methods and expressed as mg/dl. High-sensitivity C-reactive protein levels were calculated using the nephelometric method (BN II nephelometer; Dade Behring Holding GmbH, Liederbach, Germany) and expressed as mg/l. According to the 2013 European Society of Hypertension/Society of Cardiology guidelines, WCH is diagnosed in individuals with office systolic/diastolic BP measurements of 140/90 mmHg or higher on at least three occasions, with normal ambulatory or home BP readings (24 h ambulatory BP, 130/80 mmHg, or a home BP reading of 135/85 mmHg) [2,20]. To ensure that other conditions did not affect the LA volume, individuals were excluded from both groups on the basis of the following criteria: age more than 65 years, BMI greater than 31 kg/m^2, systemic hypertension (BP > 140/90 mmHg or ongoing antihypertensive medication), diabetes mellitus (fasting serum glucose level > 126 mg/dl or ongoing diabetes medication), history of coronary artery disease (>30% luminal diameter narrowing of ≥ 1 coronary artery shown by angiography, history of coronary revascularization, an abnormal myocardial perfusion scan or dobutamine stress echocardiogram, regional LV akinesia and/or dyskinesia on echocardiogram, or pathologic Q waves on 12-lead ECG), antiarrhythmic drug use, valvular heart diseases, obstructive sleep apnea, chronic inflammatory diseases, atrial fibrillation, cardiomyopathies, renal failure, liver disease, and poor-quality imaging on 2DE and/or RT3DE. This study was carried out in compliance with the Helsinki Declaration and the Local Research Ethics Committee approved the protocol; written informed consent was obtained from all the patients.

Echocardiographic assessment

Transthoracic echocardiography was performed using a commercially available machine (iE 33; Philips Medical Systems, Bothell, Massachusetts, USA) equipped with broadband S5-1 transducer by a trained, registered cardiologist according to a standardized protocol. LV end-diastolic diameter, interventricular septum thickness, and posterior wall thickness were measured. LV ejection fraction was calculated using the biplane modified Simpson's rule. Transmitral pulsed-wave Doppler velocities were recorded from the apical four-chamber view with the Doppler sample placed between the tips of the mitral leaflets. Peak velocities of the early (E) and late (A) phases of the mitral inflow, E deceleration time (DT), defined as the slope from the peak to the zero velocity of the E wave, and isovolumetric relaxation time (IVRT), defined as the time interval between aortic valve closure to the onset of the E wave from Doppler recordings, were measured and their ratio (E/A) was calculated. Tissue Doppler pulsed wave sample volume was placed on the septal mitral annulus in the apical four-chamber view, and myocardial systolic (S_m), peak early diastolic (E_m), peak late diastolic (A_m) velocities, and E_m/A_m ratio were determined. The E/E_m and E_m/A_m ratios were subsequently calculated. The peak early diastolic (E') and late diastolic (A') velocity of the lateral and the septal mitral annulus by pulsed-tissue-Doppler imaging were measured and the average value was calculated.

LA volume measurements were performed by RT3DE. A full-volume loop was acquired from an apical window using an X3 matrix array transducer (Philips Medical Systems, Bothell, Massachusetts, USA) (1–3 MHz) over four consecutive cardiac cycles. Patients were instructed to hold their breath and images were coupled with ECG recordings. Both apical two-chamber and four-chamber views were extracted from the pyramidal data set during expiration. Also, both LV and LA cavities were included in the pyramidal scan volume.

Anatomic landmarks used to calculate LA volumes were identified manually by marking five points on the atrial surfaces of the mitral annulus (anterior and inferior mitral annulus, septal, lateral, and posterior wall of the LA) by the operator, semiautomated border detection was performed by the software, and LA borders were tracked throughout the entire cardiac cycle. The pulmonary vein ostium or the LA appendage point was excluded from the measurement. From these data, a 3D model of the LA volume was generated. Measurements of 3D LA volumes

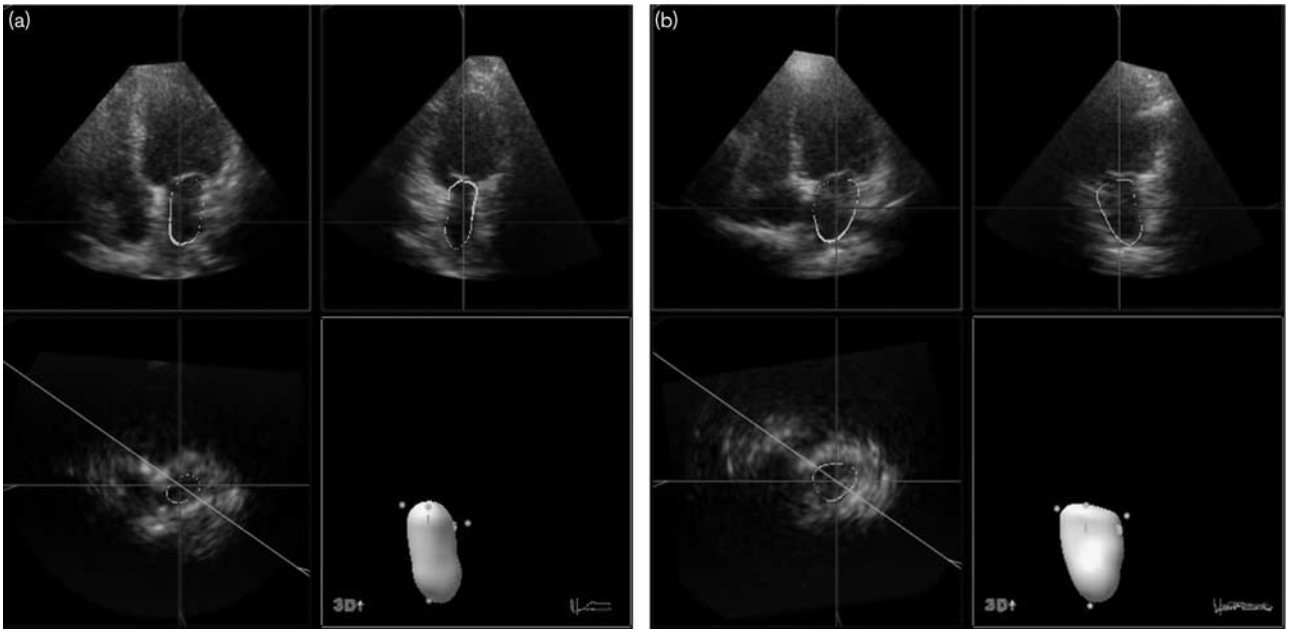
were performed offline using commercially available software (QLab-Philips, version 7.1; Philips Medical Systems). Two independent observers blinded to the clinical data analyzed all the stored digital data. The parameters of LA size and function included in our analyses were (i) LA maximum volume (V_{max}; Fig. 1a): at end systole, the time at which the atrial volume was the largest just before the mitral valve opening, (ii) LA minimum volume (V_{min}; Fig. 1b): at end diastole, the time at which the atrial volume at its base before mitral valve closure, and (iii) before atrial contraction volume ($V_{pre\ A}$): the last frame before mitral valve reopening or at time of the P wave on ECG (Fig. 2). Using three volumes, the other calculations were carried out and considered indices of LA function according to previous studies [18,20–22].

Detailed three-dimensional echocardiographic measurements and abbreviations

LA total stroke volume (TSV): $V_{max} - V_{min}$.
LA total emptying fraction: $TSV/V_{max} \times 100$.
LA active stroke volume: $V_{pre\ A} - V_{min}$.
LA active emptying fraction: $ASV/V_{pre\ A} \times 100$.
LA expansion index: $TSV/V_{min} \times 100$.
LA passive emptying fraction: $(V_{max} - V_{pre\ A})/V_{max} \times 100$.

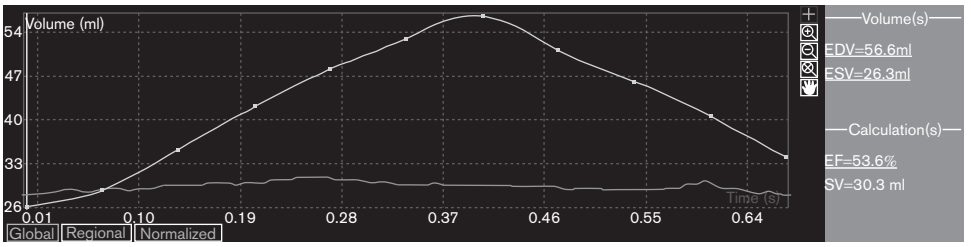
The LV ejection fraction was also assessed by RT3DE through evaluation of apical four-chamber and two-chamber views using the pyramidal 3D data set [23]. Interobserver variability was assessed by analysis of the RT3DE data from 20 randomly selected individuals from each group by two independent observers, each blinded to the measurement obtained by the other. Interobserver

Fig. 1



(a) Analysis of maximal LA volumes using RT3DE with QLAB software. (b) Analysis of minimal LA volume using RT3DE with QLAB software. LA, left atrial; RT3DE, real-time three-dimensional echocardiography.

Fig. 2



Time–volume curve with left atrial end-diastolic (EDV) and left atrial end-systolic (ESV) volume. EF, ejection fraction, SV, stroke volume.

variability was 5.5% for LA V_{max}, 7.3% for LA V_{min}, and 5.5% for LA $V_{pre\ A}$, respectively.

Statistical analysis

SPSS was used for all statistical analyses (SPSS for Windows, version 17.0 software; SPSS Inc., Chicago, Illinois, USA). All continuous variables were expressed as mean ± SD and categorical variables were defined as percentages. Differences among the groups were assessed using the χ^2-test for categorical variables. Continuous variables were compared between the groups using Student's *t*-test or the Mann–Whitney *U*-test depending on whether they were distributed normally or not as tested by Shapiro–Wilk's test. Pearson's correlation analysis was carried out to estimate the relationship between the test parameters. A *P*-value of 0.05 was considered to be statistically significant.

Results

Baseline clinical and laboratory characteristics of 37 WCH patients (17 women, 20 men) and 30 healthy (18 women, 20 men) individuals are listed in Table 1. The mean age of the patients was 48.4 ± 5.7 years in the WCH group and 47.9 ± 7.5 years in the normotensive group. There were no significant differences between WCH and the control participants in terms of age, sex, BMI, blood glucose, total cholesterol, LDL cholesterol, and HDL cholesterol. LA diameter, IVRT and EDT were significantly higher in the patients with WCH than in the controls (37 ± 2.8 vs. 35 ± 3.1 mm, $P = 0.017$; 95.4 ± 12.5 vs. 88.2 ± 12.8 ms, $P = 0.021$ and 212.1 ± 34.3 vs. 193.4 ± 3 7.8 ms, $P = 0.03$), although all the other 2DE measurements of both groups were similar (Table 2). Also, there were no significant differences between WCH and the control individuals in the ambulatory BP monitoring average, day time, and night-time measurements (Table 3).

RT3DE results are shown in Table 4. LA total systolic volume and LA maximal volume were significantly higher in the patients with WCH than in the controls (41.1 ± 6.9 vs. 35.5 ± 3.7 ml, $P = 0.0001$; 25.8 ± 5.4 vs. 21.3 ± 3.3 ml, $P = 0.0001$, respectively). LA volume before LA contraction and LA active stroke volume were significantly higher in the patients with WCH than in the normotensives (24.4 ± 6.3 vs. 20.9 ± 2.7 ml, $P = 0.002$; 9.1 ± 4.8 vs. 6.7 ± 2.5 ml, $P = 0.007$, respectively). Moreover, the LA expansion index was significantly higher in the patients with WCH than in the normotensives (178.7 ± 53.6 vs. 155.3 ± 36.3, $P = 0.037$).

Discussion

The LA has three important functions in a normal cardiac cycle: 'a reservoir' for pulmonary venous blood during the ventricular systole phase, 'a conduit' for this blood during the early diastole phase, and 'a muscular pump' to complete the process of LV filling [20,23]. Blood flow hemodynamic across the mitral valve is the leading factor that determines these LA functions. To the best of our knowledge, this is first study to assess LA volumes and LA mechanical functions using 3D echocardiography in patients with WCH. We observed that V_{max}, TSV, ASV, $V_{pre\ A}$, and the LA expansion index were significantly higher in the patients with WCH than in the controls. In addition, LA diameters were significantly higher in the patients with WCH than in the controls. These results indicate that LA passive-active functions and volumes significantly increased in WCH.

Increase in BP is the leading cause of myocyte growth, impaired LV diastolic functions, and ventricular stiffness [1]. It is well known that blood flow from the LA toward the LV deteriorates when LV stiffness increases and LV enlargement capacity decreases and in turn, LA volumes and LA reservoir function increase [23–25]. In early diastole, passive emptying volume reduces because of increased LV stiffness and deteriorated diastolic relaxation [26]. The impairment in LA passive emptying volume also contributes toward a larger residual LA volume before its active contraction. As is known, an increase in presystolic LA volume and fiber length occurs with augmented LA contraction forces (Frank–Starling mechanism [20]). LA systolic functions play a pivotal role during LV filling as suggested by the increased LA active emptying volume in patients with WCH. The LA

Table 1 Clinical characteristics and laboratory data of the study participants

	White-coat hypertension ($n = 37$)	Normotensive controls ($n = 38$)	*P* value
Age (years)	48.4 ± 5.7	47.9 ± 7.5	NS
Sex (male/female)	17/20	18/20	NS
BMI (kg/m^2)	25.3 ± 3.0	26.5 ± 3.7	NS
Blood glucose (mg/dl)	90.1 ± 12.4	88.4 ± 11.7	NS
Creatinine (mg/dl)	0.95 ± 0.1	0.93 ± 0.2	NS
Total cholesterol (mg/dl)	203.1 ± 37.4	203.2 ± 36.9	NS
LDL-cholesterol (mg/dl)	130.4 ± 28.5	122.2 ± 27.7	NS
Triglyceride (mg/dl)	185.5 ± 25.0	195.6 ± 21.8	NS
HDL-cholesterol (mg/dl)	38.2 ± 6.9	38.7 ± 10.3	NS
Office systolic blood pressure (mmHg)	147.1 ± 7.2	112.2 ± 9.3	< 0.001
Office diastolic pressure (mmHg)	93.2 ± 4.4	72.8 ± 5.9	< 0.001
Heart rate (beats/min)	78.5 ± 12.5	76.5 ± 8.9	NS
Hs-CRP (mg/l)	1.9 ± 1.1	1.6 ± 1.2	NS

Hs-CRP, high-sensitivity C-reactive protein; NS, not significant.

Table 2 Two-dimensional echocardiographic and Doppler parameters of the study population

	White-coat hypertension ($n=37$)	Normotensive controls ($n=38$)	P value
LVEDD	46.2±3.9	45.7±3.1	NS
LVESD	29.2±3.3	30.2± 2.3	NS
Ejection fraction	67.7±2.9	65.8±2.8	NS
Left atrial diameter	37±2.8	35.1±3.1	0.017
Aortic diameter	31.5	30.9	NS
IVST	10.4±1.4	9.8±1.1	NS
Posterior wall thickness	9.5±0.11	9.1±0.07	NS
LVMI (g/m^2)	90.4±14.4	88.1±13.5	NS
E/*A*	1.13±0.1	1.11±0.57	NS
EDT (ms)	212.1±34.3	193.4±37.8	0.03
IVRT (ms)	95.4±12.5	88.2±12.8	0.021
S_m (cm/s)	12.4±2.4	13.1±1.9	NS
E_m/A_m	0.92±0.26	1.03±0.26	NS
E/E_m	7.7±3.1	8.3±3.6	NS
Peak *E*′ velocity	9.5±1.9	9.1±2.3	NS
Peak *A*′ velocity	8.4±3.1	8.2±2.1	NS

A′, late mitral annulus velocity; DT, deceleration time; *E*′, early mitral annulus velocity; *E*/*A*, peak velocity of early diastolic flow/peak velocity of late diastolic flow; E/E_m, peak velocity of early diastolic flow across mitral valve/myocardial peak velocity of early diastole; E_m/A_m, myocardial peak early diastolic velocity/myocardial peak late diastolic velocity; IVRT, isovolumetric relaxation time; IVST, interventricular septal thickness; LVEDD, Left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVMI, left ventricular mass index; NS, not significant; Sm, myocardial systolic peak velocity.

expansion index reflects both LA stretch ability and LV filling status [27]. LA function shows a significant independent correlation with LV diastolic dysfunction, cardiac arrhythmias, and arterial stiffness in most categories of patients compared with LA volume [28]. Recent studies showed that the LA expansion index, which accurately reflects instantaneous LV filling pressure in many patients, is useful for predicting atrial fibrillation after coronary artery bypass graft surgery [29,30]. It can be assumed that LA dysfunction is more sensitive than morphologic measurements. Being significantly higher in patients with WCH in the current study, the LA expansion index may predict cardiac arrhythmias in these patients. In addition, this finding indicates impaired LA reservoir function, which occurs with deterioration of contraction and relaxation of the LA myocardium [31,32].

A number of studies have shown that increased LV mass index, impaired diastolic function, and higher diastolic LV filling pressure in a variety of disorders are closely related to LA volume and functions [13–17,31–34]. Although we did not observe a clear-cut difference between the two study groups in terms of all echocardiographic LV diastolic function parameters, except for IVRT and EDT, identification of LA function and volume abnormalities before obvious LV diastolic dysfunction suggests that early LA function and volume alterations may be observed first in patients with WCH. In addition, traditional pulsed wave and tissue Doppler imaging have some limitations when used in the assessment of diastolic functions such as the flow dependence of the mitral valve. As measurements are derived from different phases of the cardiac cycle, we believe that the evaluation of LA functions by RT3DE may be more sensitive and reliable. Our previous study [20] found that LA volume and LA systolic functions were significantly higher in prehypertensive patients and we assumed that these changes were because of hemodynamic and structural changes caused by levels of BP in prehypertensive in cardiac tissue.

2DE linear measurements and calculations are routinely used for the calculation of LA size and function in many laboratories and clinical studies. However, these may lead to errors because their calculation method is based on geometric assumptions such as cube or spherical models in 2DE. Because of the oblique position of the interatrial septum, shape of the LA appendage, and asymmetric LA enlargement, calculations may result in errors [35]. Although MRI is accepted as the gold standard method for measuring LA size, RT3DE enables more precise determination of LA endocardial borders than 2DE and the correlation of RT3DE with MRI for defining LA volume is very good [36].

There is more evidence that worsening health outcomes, such as target organ damage, are related to WCH. Erdogan *et al.* [7] reported that WCH may alter left ventricular diastolic function and aortic elastic properties, which are markers of target organ damage in hypertension; however, these were not as severe as those caused by sustained hypertension. Meanwhile, WCH often progresses to sustained hypertension. In the Pressioni Arteriose Monitorate E Loro Associazioni study, which included 1412 patients, 42.6% of patients with WCH developed sustained hypertension at their 10-year follow-up [37]. This may lead to an increase in negative health outcomes over time. A recent meta-analysis of 10 studies reported that carotid atherosclerosis was significantly increased in patients with WCH compared with

Table 3 Data indicating ambulatory blood pressure measurements of the study participants

mmHg	White-coat hypertension ($n=37$)	Normotensive controls ($n=38$)	P value
Average 24 h systolic blood pressure	114.1±11.9	111.6±7.2	NS
Average 24 diastolic blood preesure	71.4±10.5	69.0±7.1	NS
Average day time systolic blood pressure	118.9±9.4	115.7±8.6	NS
Average day time diastolic blood pressure	74.7±9.8	72.9±8.1	NS
Average night time systolic blood pressure	110.2±10.1	108.1±7.5	NS
Average night time diastolic blood pressure	68.8±10.7	66.9±7.5	NS

NS, not significant.

Table 4 Three-dimensional echocardiographic data of the study population

	White-coat hypertension ($n=37$)	Normotensive controls ($n=38$)	P value
LA maximal volume	41.1±6.9	35.5±3.7	<0.0001
LA minimal volume	15.3±4.2	14.2±2.6	NS
LA volume before LA contraction (ml)	24.4±6.3	20.9±2.7	0.002
LA total systolic volume	25.8±5.4	21.3±3.3	<0.0001
LA total emptying fraction	62.6±7.5	60±6.5	NS
LA active stroke volume	9.1±4.8	6.7±2.5	0.007
LA active emptying fraction	35±14.7	31.8±9.9	NS
LA expansion index	178.7±53.6	155.3±36.3	0.037
LA passsive emptying fraction	40.1±12.8	41±6.9	NS

LA, left atrium, NS, not significant.

normotensive individuals [38]. In addition, although we did not detect a significant difference, one meta-analysis reported a significant increase in LV mass in patients with WCH compared with those with normal BP [1].

Study limitations

This study had several limitations. The major limitation of our study is the limited number of patients. Because of the small sample size, the actual differences may have been concealed for defining target organ damage among the study groups. This study has a cross-sectional design and long-term follow-up of the patients was not performed. Thus, large-scale prospective studies with long-term follow-up are needed to determine the predictive value of LA volumes and mechanical functions in patients with WCH. Another limitation is that all the echocardiographic measurements were performed at only a single institution.

Conclusion

In the present study, we showed that LA mechanical functions and volume are impaired in WCH. Impairments in LA parameters may be indicative of subclinical cardiac involvement, irrespective of whether there is clinical evidence of cardiovascular disease or not. Therefore, we believe that atrial arrhythmias may develop in these patients because of impaired LA functions; further studies are needed to determine the independent prognostic power of the atrial measurement as a predictor of future cardiovascular events in WCH patients.

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Conflicts of interest

There are no conflicts of interest.

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