Determinants of Left Atrial Size in Uncomplicated Hypertensive Patients

Hwang, Hye Jin

Department of Medicine

The Graduate School, Yonsei University

Determinants of Left Atrial Size in Uncomplicated Hypertensive Patients

Directed by Professor Namsik Chung

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Hwang, Hye Jin

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Thesis Supervisor: Namsik Chung

Kyung Jong Yoo

Jong-Won Ha

The Graduate School Yonsei University

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Finally I dedicate this master's thesis to my shepherd, the
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ABSTRACT

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Hwang, Hye Jin

Department of Medicine

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Introduction: Left atrium (LA) has been proposed as a good marker of the severity and duration of diastolic dysfunction and a predictor of various cardiovascular outcomes. Hypertension can lead to left ventricular(LV) hypertrophy, diastolic dysfunction, consequentially and LA enlargement. The aim of this study is to define the echocardiographic determinants of LA size in patients with uncomplicated hypertension.

Methods: We analyzed 818 of 1333 hypertensive patients with preserved LV systolic function, referred to the Severance hospital, Yonsei University Medical Center. All patients underwent a complete echocardiographic examination with assessment of LV diastolic function, including pulsed-wave Doppler and tissue Doppler imaging. LA volume index, LV systolic and diastolic volume, stroke volume, and LV ejection fraction were measured and cardiac index and LV mass

index calculated from these parameters

Results: In univarite analyses, LA volume index was significantly correlated with age, LV

diastolic volume index, LV systolic volume index, pulse pressure, LV mass index, stroke

volume index, cardiac index, and E/E'(all p < 0.05). It also showed inverse correlations with

heart rate, diastolic blood pressure, S', and E'(all p<0.05). The pseudonormal pattern showed

larger LA volume index than normal filling (25.9 \pm 6.2 vs. 21.4 \pm 5.2 ml/m2, p<0.001) or

abnormal relaxation (25.9 \pm 6.2 vs. 22.1 \pm 6.0 ml/m2, p<0.001), whereas there was no difference

between normal filling and abnormal relaxation(p>0.05). In multivariate analysis, age, gender,

heart rate, pulse pressure, stroke volume index, LV mass index, and E/E' were independent

predictors of LA size(overall model fit, r =0.58, p <0.001).

Conclusions: This study suggests that LA size is affected by diastolic dysfunction, and it is

concomitantly dependent on volume load in hypertensive patients. LA size should be carefully

interpreted considering the current volume status in hypertensive patients.

Key words: left atrium, hypertension, diastolic dysfunction

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I. INTRODUCTION

Left atrium (LA) has been proposed as a good marker of diastolic burden to reflect the chronic expression of elevated left ventricular (LV) pressure and diastolic dysfunction ¹⁻³, and a predictor of various cardiovascular outcomes such as atrial fibrillation, stroke, congestive heart failure, cardiovascular death ³⁻⁷. Previous studies have also reported an association between atrial enlargement and hypertension ⁸. Hypertension leads to ventricular hypertrophy, sequentially LV end-systolic stiffness and diastolic dysfunction, as imposing more pulsatile and late-systolic loads on the LV chamber. With increased stiffness or noncompliance of the LV, LA pressure rises to maintain adequate LV filling ³, and the increased atrial wall tension leads to chamber dilatation and stretch of the atrial myocardium. However, these sequential processes may be attenuated in hypertensive patients who have been on treatment with various blood pressure

(BP) lowing agents. Thus, we sought to define the echocardiographic determinants of LA size in patients with uncomplicated, well-treated hypertension.

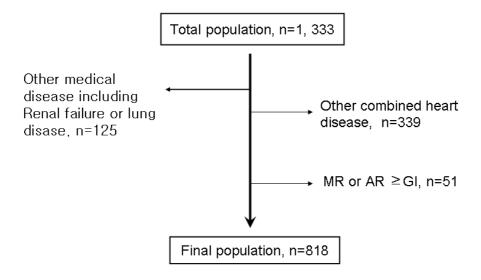
II. MATERIALS AND METHODS

1. Study population

We studied retrospectively 1,333 hypertensive patients referred to the Department of Cardiology at the Severance hospital, Yonsei University Medical Center between Nov. 1, 2005 and Dec 30, 2007 for routine evaluation. Eligible patients were 40 to 75 years old, preserved left ventricular ejection fraction(EF) ≥50%. Exclusion criteria were symptomatic heart failure of New York Heart functional class II-IV, other combined heart diseases including valvular heart disease, mitral regurgitation≥G I, aortic regurgitation≥GI, coronary disease, and cardiomyopathy, prior history of atrial fibrillation, cardiac surgery, and other medical disease such as renal failure, or lung problem. Each subject's medical record was reviewed and then total 818 of 1,333 subjects were finally included in the present study (Figure 1).

Figure 1. Study population.

Hypertensive patients with preserved LV systolic fuction (age 40-75)



2. Echocardiographic study

A complete echocardiographic examination was performed in all patients and its imaging data was stored in digital format. LV volume and ejection fraction were measured by manually tracing the LV cavity in both the apical four- and two-chamber views using the biplane modified Simpson's method. LA volume index was measured by the prolate ellipsoidal method ⁹. Stroke volume (SV) was measured by pulse wave Doppler echocardiography. Cardiac index was calculated from SV and heart rate. LV mass index(LAMI) was calculated by dividing the LV mass by the body surface area ¹⁰, with an cutoff of 105g/m2 in men and 91g/m2 in women ¹¹. Relative wall thickness was calculated as two times the posterior wall thickness/left ventricular

diastolic diameter ratio. Cutoff values of this index was 0.429. Overall stage for LV geometry was defined as normal(LVMI <105 g/m2 in men, 91g/m2 in women, and RWT<0.42), concentric remodeling (LVMI<105 g/m2 in men, 91 < g/m2 in women, and RWT>0.42), concentric hypertrophy(LVMI>105g/m2 in men, 91> in women, and RWT>0.42), and eccentric hypertrophy(LVMI>105g/m2 in men, 91> in women, and RWT<0.42). Diastolic indexes were acquired over 10 consecutive beats using sweep speeds of 50 and 100 cm/s. With pulsed-wave Doppler, we acquired transmitral flow using a 1 to 2 mm sample volume placed at the mitral leaflet tips in the apical four-chamber view. The transmitral peak E and A velocities and early deceleration time (DT) were measured from pulsed-wave Doppler. Tissue Doppler imaging was acquired with standard presets optimized to eliminate background noise and enhance tissue signals and using a 5 to 10 mm sample volume placed at the septal mitral annular margins in the four-chamber view. The peak systolic (S'), early (E'), and late diastolic (A') velocities were measured from tissue Doppler ¹². Overall diastolic stage, determined from the pattern of transmitral flows, was defined as normal pattern (transmitral E:A ratio >1, DT 220 to 150ms), abnormal relaxation (transmitral E:A ratio <1, DT >220 ms), pseudonormal (E:A ratio 1 to 2, DT 150 to 220 ms, E:A ratio <1 in valsalva), or restrictive (E:A ratio >2, DT <150 ms). Rest systolic BP and diastolic BP were determined by cuff sphygmomanometry immediately before the echocardiographic examination. Pulse pressure was calculated as the difference between

systolic BP and diastolic BP.

3. Statistics

All continuous data were presented as the mean \pm SD, and categorical variables were presented as proportions. Student t- test or the one way ANOVA for continuous variables were used to compare differences in LA size between subjects grouped according to pattern of gender, diastolic pattern, and LV geometry. The associations of LA volume index and clinical and echocardiogrpahic parameters were assessed by Pearson's correlation coefficient. And then, we performed stepwise multiple linear regression analysis to assess the determinants of LA volume index. The univariate correlation coefficients for these variables were determined, and they were also entered into a multivariate model for predicting LA volume index by use of the SPSS 15.0 statistical package (SPSS Inc., Chicago, Illinois). A value of p < 0.05 was considered significant.

III. RESULTS

1. Baseline characteristics

Demographic and clinical data for 818 patients were shown in Table 1. Mean age was 57 ± 9 (range: 40-75) and 44.8 % of the patients were male. ACE inhibitors or AT1 blockers were taken in 377(47%) patients, β blockers in 338(42%), calcium channel blocker in 113(14%), and diuretics in 143(18%). The echocardiographic data of all patients were presented in Table 2.

Mean LA volume index was 22±6 ml/m2. The pattern of diastolic filling showed normal filling in 139(17%), abnormal relaxation in 606(74.1%), and pseudonormal in 73(8.9%). There was no restrictive pattern in this study. 175 (21.4%) subjects had concentric remodeling, 151 (18.5%) concentric hypertrophy, and 109(13.3%) eccentric hypertrophy.

Table 1. Clinical chacracteristics of the study population (n=813)

Age, years	57±9
Gender(M:F)	367/436
Body surface area, mm2	1.7±0.2
Diabetes(%)	42(5)
Receiving ACE inhibitor/AT1 receptor blocker (%)	377(47)
Receiving beta-blocker (%)	338(42)
Receiving calcium channel blocker(%)	113(14)
Receiving diuretics(%)	143(18)
Heart rate, bpm	68±11
Systolic blood pressure, mmHg	136±16
Diastolic blood pressure,mmHg	87±12

Data are expressed as mean ±SD or number (%). ACE, angiotensin converting enzyme; AT, angiotensinogen.

Table 2. Echocardiographic parameters in the study population (n=813)

LVEDVI, ml/m2	37±9
LVESVI, ml/m2	12±4
Stroke volume index, ml/m2	25±6
Ejection fraction, %	67±5
LA AP diamter,mm	36±7
LA volume index	22±6
LV mass index, g/m2	93±20
E, cm/s	0.61±0.15
A, cm/s	0.69±0.15
Deceleration time, ms	204±37
S, cm/s	6.9±1.4
E', cm/s	6.1±1.8
A', cm/s	8.7±1.7
E/E'	10.5±3.4
Diastolic stage(%)	
Normal pattern	137(17)
Abnormal relaxation	593(74)
Pseudonormal pattern	73(9)
Restrictive pattern	0
LV geometry pattern(%)	
Normal	373(47)
Concentric remodeling	174(22)

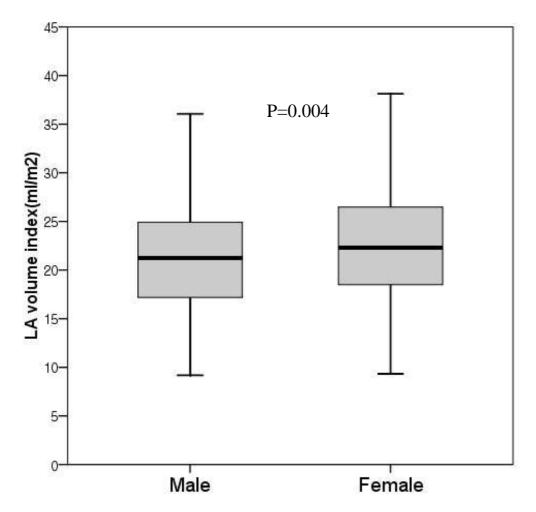
Concentric hypertrophy	149(19)
Eccentric hypertrophy	107(13)

Data are expressed as mean ±SD or number (%). LVESVI, left ventricular end-systolic volume index; LVEVI left ventricular end-diastolic volume index; LA, left atrial; LV, left ventricular.

2. The relation between LA size and gender, diastolic pattern, and LV hypertrophy

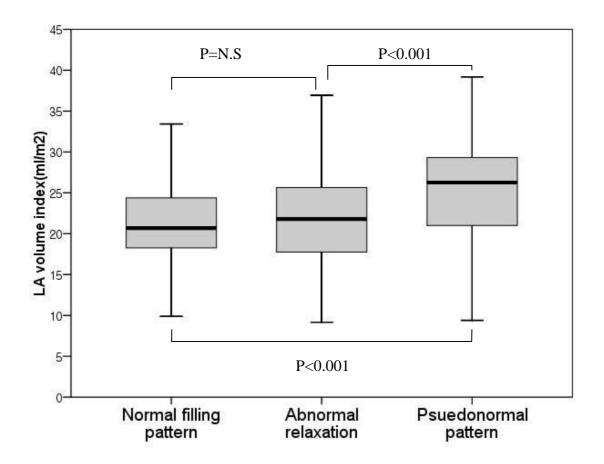
LA volume index was larger in female than in male(22.9 ± 6.4 vs. 21.5 ± 5.8 ml/m2, p=0.001)(Fig.2). In diastolic pattern, the subjects with pseudonormal pattern had a larger LA volume index than those with normal filling(25.9 ± 6.2 vs. 21.4 ± 5.2 ml/m2, p<0.001) and abnormal relaxation (25.9 ± 6.2 vs. 22.1 ± 6.0 ml/m2, p<0.001)(Fig.3). However, there was no statistical difference between normal filling pattern and abnormal relaxation in LA volume index (21.4 ± 5.2 ml/m2 vs. 22.1 ± 6.0 ml/m2, p>0.05). The subjects with concentric LV hypertrophy had a lager LA volume index than those with concentric remodeling (25.2 ± 6.7 vs. 21.1 ± 5.9 ml/m2, p<0.001) or normal geometry of LV(25.9 ± 6.2 vs. 22.1 ± 6.0 ml/m2, p<0.001). However, LA volume index showed no difference in normal geometry of LV and concentric remodeling (p>0.05)(Fig.3). And, LA volume index also showed no difference between concentric hypertrophy and eccentric hypertrophy(p>0.05).





The bold bar indicated median value.

Figure 3. LA volume index according to LV filling pattern



The bold bar indicated median value.

45 P<0.001 P=N.S40 P=N.S35 LA volume index(ml/m2) -02 15-10-P<0.001 5 P<0.001 Normal LV Concentric Concentric Eccentric geometry remodling hypertrophy hypertrophy

Figure 4. LA volume index according to LV geometry

The bold bar indicated median value.

3. The correlation between LA size and other variables

The relation of clinical and echocardiographic parameters to LA volume index was presented in Table 3. LA volume index was significantly correlated with age(r=0.16, p< 0.001), $LVEDVI(r=0.31, p<0.001), LVESVI(r=0.21, p<0.001), pulse pressure(r=0.2, p<0.001), LV \\ mass index(r=0.44, p<0.001), SV index(r=0.32, p<0.001), cardiac index(r=0.09, p=0.001), \\$

E/E'(r=0.26, p<0.001), and pulse pressure(r=0.07, p=0.04). It also showed inverse correlations with heart rate (r=-0.31, p<0.001), diastolic blood pressure (r=-0.12, p<0.001), S'(r=-0.13, p<0.001), and E'(r=-0.12, p=0.001). However, it did not showed statistically significant correlations with EF, DT, and A (all p value>0.05).

4. Determinants of LA size

In a multiple linear regression analysis adjusted by age, gender, heart rate, pulse pressure, LVEDVI, stroke volume index, cardiac index, LV mass index, S', E', E/E', BP medication such as calcium channel blockers, ACE/ARB, diuretics, and β -blocker, independent predictors of LA volume index were age, gender, heart rate, pulse pressure, SV index, LV mass index, diastolic pattern, and E/E'(overall model fit, r =0.58, p <0.001)(Table 4).

Table 3. Univariate and multivariate relationships of clinical and echocardiographic indexes to LA volume index

	Pearson's	Standazied		
	correlation	P	β	P
	coefficients		regression	
Age	0.16	< 0.001	0.09	0.005
Body surface area	-0.04	0.31		
Heart rate	-0.31	< 0.001	-0.14	< 0.001
Systolic blood pressure	0.06	0.08		

Diastolic blood pressure	-0.12	< 0.001		
Pulse pressure	0.2	< 0.001	0.1	0.004
LVESVI	0.21	< 0.001		
LVEDVI	0.31	< 0.001		
IVSd				
PWd				
Stroke volume index	0.32	< 0.001	0.22	< 0.001
Ejection fraction	0.04	0.22		
Cardiac index	0.09	0.01		
LV mass index	0.44	< 0.001	0.33	< 0.001
Е	0.17	< 0.001		
A	0.06	0.08		
DT	-0.04	0.27		
S'	-0.13	< 0.001		
E'	-0.12	0.001		
A'	-0.09	0.01		
E/E'	0.26	< 0.001	0.09	0.004
Gender			0.1	0.003
Diastolic pattern			0.08	0.009

Abbreviations as in Table 1 and 2. IVSd, interventricular septum thickness at end-diastole; IVSd, interventricular septum thickness at end-diastole; PWd, posterior wall thicknessat end-diastole

IV. DISCUSSION

Many investigators have demonstrated that LA volume reflects average effect of LV filling pressure over time ^{3,13} and provide prognostic information for cardiovascular diseases beyond that of diastolic dysfunction grade ^{14,15}. It has been traditionally thought that ventricular stiffness and impaired diastolic dysfunction lead to an increase of LA size. As stiffness of the LV increase, LA pressure rises to maintain adequate LV filling, and the increased atrial wall tension leads to chamber dilatation and stretch of the atrial myocardium. To better understand the determinants of LA size, we performed careful assessment of cardiac function and noninvasive hemodynamic parameters with comprehensive echocardiography in uncomplicated hypertensive subjects presenting no symptoms or NYHA I. The results of our study show that 1) there are significant relationships between LA size and LV diastolic function, and 2) LA size may reflect concomitantly the current volume status.

Dilatation of LA responses to two broad conditions; pressure overload and volume overload.

LA enlargement by pressure overload is usually due to an increase of LA afterload such as LV diastolic dysfunction or mitral valve stenosis. Because LA during diastole is exposed by LV filling pressure, LA is known to express the chronicity of LV diastolic function 13, in contrast that mitral inflow pattern and tissue Doppler parameters reflect acute hemodynamic change. Our data showed that LA size was strongly associated with LV mass index which was regarded as

good marker of chronic exposure of abnormal filling pressure, as demonstrated by prior studies^{1,16}. Concurrently, LA size shows positive correlations with stroke volume, LV diastolic volume, and cardiac index and inverse correlation with heart rate, which is related to the current volume status. Although LA enlargement by volume overload could be associated with pathologic conditions such as valvular insufficiency or high output state including anemia¹⁷, our results suggest that LA size, at least in uncomplicated hypertensive patients without HF or with mild symptom, can reflect considerably acute volume change within physiologic range, as well as chronic diastolic burden. In our study, there was no difference in LA size between normal filling and abnormal relaxation of diastolic pattern, in contrast the pseudonormal pattern showed enlarged LA compared with them. In patients with preserved systolic function and with mild to moderate diastolic dysfunction, those factors may be insufficient to induce abnormal LA enlargement. Instead, preload change within physiologic range may mainly determine LA size. Pritchett. et al³. reported that LA volume index added no incremental prognostic value beyond that provided by diastolic filling pattern in population based study. In present study, the subjects with enlarged LA and normal geometry of LV in our study population was 69(8.4%); normal sized LA with hypertrophy of LV 177(21.6%); enlarged LA with normal diastolic filling 16(2%); and normal sized LA with abnormal diastolic filling 543 (66.4%), using cutoff values of 27 ml/m2 in LA volume index⁹. Interestingly, in current study, there was no statistical

been traditionally thought to be more advanced than concentric hypertrophy. These results are in agreement with prior other study¹⁶. Eccentric LV hypertrophy defined through 2D echocardiography in our study may not necessarily represent one of sequential pathologic progress of heart failure. Eccentric hypertrophy in hypertensive patients may suggest simply an increase of preload but not advanced form of concentric form. We identified that subjects with eccentric hypertrophy had more increased cardiac index and stroke volume index, though these data not shown. From this point of view, LV mass index, a value mathematically derived from LV end-diastolic dimension and LV wall thickness can be the most powerful predictor of LA size, as reflecting concomitantly LV volume load status and diastolic burden, in patients with mild to moderate diastolic dysfuction.

The present study has some limitations. These data are cross-sectional and cannot establish causal relationships between clinical and echocardiographic variables and LA size. Furthermore, the number of subjects with severe diastolic dysfunction in our study was so small that we could not identify precisely the relation of severe diastolic dysfunction and LA size.

IV. CONCLUSIONS

Our study provides a framework for interpreting LA size in patients with mild to moderate diastolic dysfunction. This study suggests there are significant relationships between LA size

and LV diastolic function, and LA size may reflect concomitantly the current volume status.	

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ABSTRACT (IN KOREAN)

고혈압 환자에 있어서 좌심방 크기에 미치는 인자

<지도교수 정남식>

연세대학교 대학원 의학과

황혜진

좌심방은 좌심실 이완의 심각도와 기간을 잘 반영할 뿐만 아니라 여러 심혈관 질환의 예후를 설명하는 표지자로 제안되고 있다. 고혈압은 좌심실비대, 좌심실 이완기능에 장애를 주어 좌심방의 크기에 영향을 미친다. 본 연구는 고혈압 환자에서 심초음파를 통해 좌심방에 미치는 여러 인자들을 알아보고자 하였다. 1333명의 고혈압 환자 중 좌심실 기능이 보존되어 있고, 약물치료를 통해 잘혈압이 잘 조절되고 있는 환자 818명을 대상으로 연구하였다. 모든 환자에게서 병원 기록을 통해 임상적 특징에 대한 테이터를 수집하였으며, 심초음파 기록을 통해 좌심실 이완기능, 좌심실 심방 및 심실 용적, 좌심실 구출율, 심박출량을 구하였다. 좌심방 용적지수는 나이, 맥압, 좌심실 이완기 및 수축기 용적 지수, 심박출량 지수, 좌심실 질량 지수 EE'과 양의 상관관계를 보였으며, 심박동수, 이완기 혈압, S', E'과 역 상관관계를 보였다. 또한 여자는 남자보다 좌심방 크기가 증가되어 있는 소견을 보였다. 다중선형회귀 분석 결과, 나이, 성별, 심박동수, 맥압, 심박출량 지수, 좌심실 질량 지수, E/E'가 통계적으로 의미 있는 인자로 밝혀졌다. 결론적으로, 고혈압 환자에 있어서 좌심방 용적은 좌심실이완기능을 잘 나타낼

뿐만 아니라, 동시에 전부하를 반영하기도 한다.

핵심 단어; 고혈압, 좌심방, 좌심실이완장애