Journal of Cardiology (2010) **55**, 196—204

journal homepage: www.elsevier.com/locate/jjcc

Original article

Factors contributing to left atrial enlargement in adults with normal left ventricular systolic function

Takuji Katayama (MD, PhD)*, Naoki Fujiwara (MD), Yoshio Tsuruya (MD, PhD)

Division of Cardiology, Tokyo-Kita Social Insurance Hospital, 4-17-56 Akabanedai, Kita-Ku, Tokyo 115-0053, Japan

Received 27 July 2009; received in revised form 8 October 2009; accepted 22 October 2009
Available online 1 December 2009

KEYWORDS
Atrial function;
Diastolic dysfunction;
Echocardiography

Abstract
Background: Causes of left atrial (LA) enlargement and its gender difference in patients with normal left ventricular (LV) systolic function have not been clarified. We investigated the factors contributing to LA enlargement in patients with normal LV systolic function, addressing its gender difference.
Methods: We enrolled 380 patients (175 males and 205 females; mean age: 63 ± 15 years) with LV ejection fraction ≥50% who underwent Doppler echocardiography and blood tests at the same time as echocardiography. Patients with arrhythmias, significant valvular heart disease, and LV asynergy were excluded. The LA volume was measured by Simpson's method from apical 2- and 4-chamber views, and LA volume index (LAVI) was calculated as LA volume/body surface area. All patients, male and female were assigned to a group with a low or a high LAVI based on the median LAVI value, respectively.
Results: Age, female gender, hypertension, diabetes, hemoglobin concentration, LV mass index, Doppler parameters of LA contraction, and the ratio of mitral early diastolic velocity to early diastolic velocity of the mitral annulus (E/E') were significantly associated with a high LAVI in all patients. Multivariate analysis showed that LV mass index [odds ratio (OR) 1.05, 95% confidence interval (CI) 1.03—1.06, $P < 0.0001$], hemoglobin concentration (OR 0.76, 95% CI 0.64—0.90, $P < 0.01$), and female gender (OR 1.92, 95% CI 1.12—3.30, $P < 0.05$) independently contributed to a high LAVI in all patients. In addition, LV mass index and hemoglobin concentration independently contributed to a high LAVI in both genders despite the absence of overt LV hypertrophy or anemia.
Conclusion: Increased LV wall thickness and decreased hemoglobin concentration might contribute to LA enlargement in patients with normal LV systolic function irrespective of gender.

Introduction

Because left atrial (LA) enlargement is associated with prognosis and cardiovascular events such as cerebral infarction and heart failure [1,2], the importance of evaluating LA

* Corresponding author. Tel.: +81 3 5963 3311; fax: +81 3 5963 6687.
E-mail address: taku-iku-mm@fa2.so-net.ne.jp (T. Katayama).

0914-5087/$ — see front matter
doi:10.1016/j.jjcc.2009.10.008

size and causes of LA enlargement is increasing in clinical practice. LA volume determined by two-dimensional (2D) echocardiography is superior to the M-mode LA diameter to assess the accurate LA size [3]. LA enlargement is usually induced by pressure and/or volume overload, and various factors and cardiovascular diseases are associated with LA size [4]. As examples, LA volume significantly differs between genders in adults without cardiovascular disease, whereas its gender difference depends on variation in body size [5,6]. In patients with normal left ventricular (LV) systolic function, LA volume is associated with severity of LV diastolic dysfunction and LV mass [7,8]. However, little is known about other causes of LA enlargement and gender difference of those in such patients.

Therefore, we investigated the factors contributing to LA enlargement assessed by LA volume using 2D echocardiography in patients with normal LV systolic function, especially addressing gender difference of those.

Methods

Study population

This cross-sectional study proceeded at Tokyo-Kita Social Insurance Hospital and the institutional Ethics Committee approved the study protocol. Among 2366 patients who underwent echocardiography at our hospital between April 2006 and July 2007, we identified 1326 consecutive patients who underwent echocardiography conducted by the same experienced cardiac sonographer. Of these, patients $\geq$20 years of age, with LV ejection fraction $\geq$50% and who underwent blood tests at the same time as echocardiography were eligible for this study. Patients with a history of arrhythmias including pacemaker implantation, LV asynergy, significant valvular heart disease, cardiomyopathy, congenital heart disease, hemodialysis, and inadequate ultrasonic images for evaluation were excluded. We enrolled 380 adult patients (mean age: 63 ± 15 years; range, 22–91 years) who met all of the inclusion and exclusion criteria. The study population consisted of 205 females (54%), 264 outpatients (69%), and 116 inpatients (31%). All patients underwent echocardiography because of the symptoms of chest pain, dyspnea, palpitation, dizziness and leg edema (30%), electrocardiographic abnormalities (13%), assessment of cardiac function for hypertension (19%), diabetes (4%), coronary heart disease (7%), cerebral vascular disease (4%), non-cardiac surgery (11%), and other reasons (13%).

Clinical data

We investigated whether the patients had a history of hypertension, diabetes, congestive heart failure, coronary heart disease, or taking medications for hypertension and/or heart failure from medical records. Hypertension was defined as systolic blood pressure $\geq$140 mmHg and/or diastolic blood pressure $\geq$90 mmHg, or the use of antihypertensive drugs. Diabetes was defined if the patients had been diagnosed as diabetic, or were receiving antidiabetic treatment. Coronary heart disease was defined as a history of myocardial infarction, effort angina, coronary spastic angina, silent myocardial ischemia, and coronary revascularization such as percutaneous coronary intervention and/or bypass graft surgery. Patients were enrolled if hemoglobin concentrations and serum creatinine levels had been measured within 3 days before or after echocardiography.

Echocardiography

Echocardiography was performed by one experienced cardiac sonographer (H.O.) using the same echocardiographic instrument (Toshiba Aplio SSA-700A, Toshiba, Otawara, Japan) fitted with a 2.5-MHz transducer. The following parameters were examined in M-mode with the parasternal long-axis view: LA diameter, LV diameter in end diastole (LVDd) and LV diameter in end systole (LVDs), fractional shortening, interventricular septal thickness (IVST), posterior wall thickness (PWT), and LV mass [9]. The LV mass index was calculated as LV mass/body surface area. The LV ejection fraction was measured using the Teichholz M-mode method. The infra vena cava diameter was also measured at end expiration in the epigastric view.

Both LV diastolic function and valvular heart disease were assessed by Doppler echocardiography. Transmitral flow velocity curve was recorded using pulsed wave Doppler echocardiography in the apical 3-chamber view. Early diastolic mitral inflow velocity (E), late diastolic mitral inflow velocity (A), the deceleration time of the E wave (DT), the E/A ratio, and duration of A wave (Ad) were measured. Pulmonary venous flow velocity curve was recorded using pulsed wave Doppler echocardiography in the apical 4-chamber view. Systolic forward flow velocity (S), diastolic forward flow velocity (D), atrial reversal flow velocity (AR), and duration of the AR wave (ARd) were measured. The difference between the ARd and Ad (ARd $-$ Ad) was calculated. Tissue Doppler imaging of the septal mitral annulus was recorded in the apical 4-chamber view. The early diastolic velocity (E') and late diastolic velocity (A') were measured, and the ratios of E' to A' (E'/A') and E to E' (E/E') were calculated.

The severity of valvular regurgitation was semiquantitatively evaluated by the distance of the color Doppler jet, and the grade of regurgitation was defined as trace, mild, moderate, and severe. Patients with valvular regurgitation $\geq$ mild grade, valvular stenosis, and prosthetic valves in any valves were excluded from this study due to having clinically significant valvular heart disease. In addition, patients with mitral annulus calcification were excluded if the mitral valve area measured by the pressure half time method using mitral inflow early velocity was $\leq 2\,cm^2$.

A cardiologist unaware of patients' clinical background measured LA volume using the modified Simpson's method [9]. Maximum LA areas except for the confluence of pulmonary veins and the left atrial appendage were traced in apical 2- and 4-chamber views at end systole of the left ventricle. The LA volume index (LAVI) was calculated as LA volume/body surface area. To assess the intraobserver and interobserver variability in measurement of LAVI, 10 patients were randomly selected and measured by main observer at two separate occasions and another independent observer.

Table 1 Clinical characteristics.

	All patients ($n=380$)	Male ($n=175$)	Female ($n=205$)	P-value
Age (years)	63 ± 15	62 ± 15	64 ± 14	NS
Body surface area (m^2)	1.6 ± 0.2	1.7 ± 0.2	1.5 ± 0.1	<0.0001
Body mass index (kg/m^2)	23.5 ± 3.5	23.6 ± 3.3	23.3 ± 3.6	NS
Hypertension (%)	54	53	56	NS
Diabetes (%)	19	20	18	NS
History of CHD (%)	5	8	2	<0.01
History of CHF (%)	1	3	0	<0.05
Medications (%)	41	39	42	NS
ACEI	5	5	5	NS
ARB	22	19	26	NS
ACEI/ARB	27	23	30	NS
CCB	28	27	29	NS
β-Blocker	8	9	8	NS
Diuretics	3	4	3	NS
Serum creatinine (mg/dl)	0.8 ± 0.4	0.9 ± 0.4	0.7 ± 0.2	<0.0001
Hemoglobin (g/dl)	13.4 ± 1.7	14.1 ± 1.8	12.8 ± 1.5	<0.0001

Data are mean ± standard deviation (SD) or percentage of patients. P-values were calculated by comparison between men and women. NS, not significant; CHD, coronary heart disease; CHF, congestive heart failure; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium-channel blocker.

Statistical analysis

Data are expressed as numbers and percentages for categorical variables, and means ± standard deviation for continuous variables. Correlations between continuous variables and LAVI were examined using Spearman's correlation analysis. Patients were assigned based on the median LAVI to either the low or the high ($\leq$ or >median LAVI) group. Two groups were compared using Fisher's exact test or Mann—Whitney's U-test. Independent contributing factors to the LAVI were investigated by multiple logistic regression analysis of significant variables in the univariate analysis. Variables that strongly influenced others were excluded from the multivariate analysis. Male and female were compared using each analysis. A P-value <0.05 was considered significant. All data were analyzed using Stat-View software (version 5.0, SAS Institute Inc., Cary, NC, USA).

Results

Clinical characteristics and echocardiographic measurements

The clinical characteristics of the patients, of whom over half had hypertension and about 40% were administered with anti-hypertensive and/or diuretic drugs, are presented in Table 1. The proportions of coronary heart disease and congestive heart failure, serum creatinine level, and hemoglobin concentration were significantly higher among males than females. Echocardiographic measurements (Table 2) revealed mean LAV and LAVI values of 54 ± 14 ml and 35 ± 9 ml/m^2, respectively. Regarding reproducibility in measurement of LAVI, intraobserver and interobserver variability were 1.0 ± 1.3 ml/m^2 and 3.1 ± 2.2 ml/m^2, respectively. Although the LAV was similar between males and females, the LAVI was significantly higher in females than in males. The LVDd, LVDs and variables regarding LV wall thickness (IVST, PWT, LV mass, and LV mass index) were significantly higher in males than in females. On the other hand, diastolic parameters such as A, ARd − Ad, and E/E' were significantly higher in females than in males.

Correlations of continuous variables with LAVI

As shown in Table 3, age and hemoglobin concentration significantly correlated with LAVI, whereas body mass index and serum creatinine level did not. Echocardiographic findings showed that variables associated with LV wall thickness and LA contraction (peak A velocity, E/A ratio, duration of A wave, and duration of pulmonary venous AR wave) closely correlated with LAVI. Of the tissue Doppler parameters, E'/A' and E/E' ratios were correlated with LAVI because of the negative correlation between E' and LAVI. The results were similar for both genders to those for all patients, but E/E' did not significantly correlate with LAVI in men. We show the scatter plots of LV mass index and hemoglobin concentration for LAVI in all patients (Fig. 1).

Comparison of groups with low and high LAVI

Data from the groups with low and high median LAVI values are presented in Tables 4 and 5. Overall, the patients were older, and the proportions of women, hypertension, diabetes, and history of anti-hypertensive drugs (rennin—angiotensin system inhibitors and calcium-channel blockers) were significantly higher, whereas the hemoglobin concentration was significantly lower in the high, than in the low LAVI group. Body mass index and serum creatinine

Table 2 Echocardiographic measurements.

	All patients ($n = 380$)	Male ($n = 175$)	Female ($n = 205$)	P-value
LA diameter (mm)	40 ± 5	40 ± 5	40 ± 6	NS
LA volume (ml)	54 ± 14	54 ± 13	53 ± 15	NS
LAVI (ml/m^2)	35 ± 9	33 ± 8	37 ± 10	<0.01
LVDd (mm)	47 ± 5	49 ± 4	46 ± 4	<0.0001
LVDs (mm)	31 ± 4	32 ± 4	30 ± 4	<0.0001
LVEF (%)	65 ± 5	64 ± 5	66 ± 5	<0.0001
FS (%)	36 ± 4	35 ± 4	36 ± 4	<0.0001
IVST (mm)	9 ± 2	10 ± 1	9 ± 2	<0.0001
PWT (mm)	9 ± 1	9 ± 1	9 ± 1	<0.0001
LV mass (g)	149 ± 38	164 ± 37	137 ± 36	<0.0001
LV mass index (g/m^2)	96 ± 23	99 ± 22	93 ± 23	<0.01
IVC diameter (mm)	14 ± 3	14 ± 3	14 ± 3	NS
E (cm/s)	74 ± 16	71 ± 15	75 ± 17	NS
A (cm/s)	78 ± 16	75 ± 20	80 ± 22	<0.05
Ad (ms)	151 ± 20	152 ± 21	150 ± 19	NS
E/A	1.0 ± 0.5	1.0 ± 0.4	1.0 ± 0.5	NS
DT (ms)	234 ± 51	237 ± 53	232 ± 50	NS
S (cm/s)	66 ± 14	66 ± 16	66 ± 13	NS
D (cm/s)	44 ± 11	44 ± 11	44 ± 11	NS
S/D	1.6 ± 0.5	1.6 ± 0.5	1.5 ± 0.4	NS
AR (cm/s)	32 ± 10	32 ± 10	32 ± 9	NS
ARd (ms)	137 ± 25	134 ± 23	140 ± 27	NS
ARd − Ad (ms)	−13 ± 28	−18 ± 27	−10 ± 29	<0.05
E' (cm/s)	7 ± 3	7 ± 2	7 ± 3	NS
A' (cm/s)	10 ± 2	10 ± 2	10 ± 2	NS
E'/A'	0.7 ± 0.3	0.7 ± 0.3	0.7 ± 0.3	NS
E/E'	11 ± 3	10 ± 3	11 ± 4	<0.05

Data are mean ± standard deviation (SD). P-values were calculated by comparison between male and female. LA, left atrial; LV, left ventricular; VI, volume index; Dd, diameter in end diastole; Ds, diameter in end systole; EF, ejection fraction; FS, fractional shortening; IVST, interventricular septal thickness; PWT, posterior wall thickness; IVC, inferior vena cava; E, peak early diastolic mitral inflow velocity; A, peak late diastolic mitral inflow velocity; Ad, duration of late diastolic mitral inflow wave; DT, deceleration time; S, peak pulmonary venous systolic forward flow velocity; D, peak pulmonary venous diastolic forward flow velocity; AR, peak pulmonary venous atrial reversal flow velocity; ARd, duration of pulmonary venous atrial reversal flow wave; E', peak early diastolic velocity of the septal annulus; A', peak late diastolic velocity of the septal annulus.

levels were similar between the two groups. These results were similar to those found in females. The proportions of diabetics and those taking medications did not significantly differ among males between the groups (Table 4).

The echocardiographic parameters (Table 5) showed that LVDd and variables regarding LV wall thickness were significantly higher in the high, than in the low LAVI group. In addition, LA contraction (peak A velocity, E/A ratio, duration of A wave, and of pulmonary venous AR wave) and low E' velocity (E'/A' and E/E') significantly differed between the groups. These results were similar for both genders.

Multivariate analysis

The results of multiple logistic regression analysis of the variables with P-values <0.01 in a comparison of the low and high LAVI groups are presented in Table 6. The LV mass index, hemoglobin concentration, and female gender were independently related to high LAVI, whereas age, hypertension, and E/E' were not. The LV mass index and hemoglobin concentration were independently related to a high LAVI for the same variables for each gender.

Discussion

The present study demonstrated that LV mass index, hemoglobin concentration, and female gender were independently associated with LA enlargement assessed by LAVI in patients with normal systolic LV function. In addition, LV mass index and hemoglobin concentration also independently contributed to LA enlargement in both genders.

LV mass index and LAVI

Previous studies already showed the relationship between LV mass index and LAVI [7,8,10,11]; however, the considerable result in the present study was that mean LV mass index was within the normal range even in the high LAVI group. Tsioufis et al. [10] also showed that LV mass index was independently associated with LAVI in hypertensive patients with LV mass index in the normal range. Increased LV mass index is related to increased LV stiffness and elevation of LV filling pressure, which induce LA enlargement [12]. Considering

Table 3 Correlation of clinical and echocardiographic variables with left atrial volume index.

	All patients		Male		Female	
	ρ	*P*-value	ρ	*P*-value	ρ	*P*-value
Age	0.29	<0.0001	0.20	<0.01	0.35	<0.0001
Body surface area	−0.18	<0.01	−0.18	<0.05	−0.04	NS
Body mass index	0.08	NS	0.01	NS	0.17	<0.05
Serum creatinine	−0.05	NS	0.10	0.21	0.05	NS
Hemoglobin	−0.35	<0.0001	−0.28	<0.01	−0.32	<0.0001
LA diameter	0.53	<0.0001	0.35	<0.0001	0.68	<0.0001
LVDd	0.13	<0.05	0.20	<0.05	0.15	<0.05
LVDs	0.06	NS	0.20	<0.01	0.02	NS
LV ejection fraction	0.12	<0.05	−0.07	NS	0.22	<0.05
Fractional shortening	0.13	<0.05	−0.06	NS	0.02	NS
IVST	0.34	<0.0001	0.23	<0.01	0.53	<0.0001
PWT	0.28	<0.0001	0.20	<0.01	0.46	<0.0001
LV mass	0.35	<0.0001	0.35	<0.0001	0.55	<0.0001
LV mass index	0.49	<0.0001	0.45	<0.0001	0.58	<0.0001
IVC diameter	0.03	NS	0.11	NS	0.04	NS
E	0.09	NS	−0.01	NS	0.13	NS
A	0.26	<0.0001	0.10	NS	0.34	<0.0001
E/*A*	−0.17	<0.01	−0.13	NS	−0.18	<0.05
DT	0.02	NS	0.02	NS	0.05	NS
Ad	0.17	<0.01	0.24	<0.01	0.15	<0.05
S	0.03	NS	−0.05	NS	0.09	NS
D	−0.08	NS	−0.01	NS	−0.16	<0.05
S/*D*	0.11	<0.05	0.02	NS	0.19	<0.01
AR	−0.04	NS	−0.01	NS	−0.09	NS
ARd	0.22	<0.0001	0.23	NS	0.18	<0.05
ARd − Ad	0.06	NS	0.03	NS	0.02	NS
E'	−0.30	<0.0001	−0.20	<0.01	−0.36	<0.0001
A'	−0.07	NS	0.01	NS	−0.14	<0.05
E'/A'	−0.21	<0.0001	−0.21	<0.01	−0.21	<0.01
E/E'	0.34	<0.0001	0.14	NS	0.46	<0.0001

LA, left atrial; LV, left ventricular; Dd, diameter in end diastole; Ds, diameter in end systole; IVST, interventricular septal thickness; PWT, posterior wall thickness; IVC, inferior vena cava; *E*, peak early diastolic mitral inflow velocity; *A*, peak late diastolic mitral inflow velocity; DT, deceleration time; Ad, duration of late diastolic mitral inflow wave; *S*, peak pulmonary venous systolic forward flow velocity; *D*, peak pulmonary venous diastolic forward flow velocity; AR, peak pulmonary venous atrial reversal flow velocity; ARd, duration of pulmonary venous atrial reversal flow wave; E', peak early diastolic velocity of the septal annulus; A', peak late diastolic velocity of the septal annulus.

our results and other results, it is suggested that this mechanism is already developed even in the absence of overt LV hypertrophy.

Although hypertension is the most common etiology for an increased LV mass index, it was not an independent contributing factor to a high LAVI in the multivariate analysis. Some studies also showed that LV mass index was the better predictive factor for the increase of LAVI compared with blood pressure levels [10,11]. We postulate that increased LV mass affects more directly left atrium through the elevation of LV filling pressure compared with hypertension.

Hemoglobin concentration and LAVI

A notable finding in the present study is the significant negative correlation between hemoglobin concentration and LAVI irrespective of gender, although mean hemoglobin concentration in each gender was almost within the normal range. Chronic anemia is known to induce cardiac dilatation caused by high cardiac output, and even cardiac hypertrophy in an experimental rat model [13] and humans [14]. Few data are available showing that hemoglobin concentration is directly related to LAVI in patients with hemoglobin concentration within the normal range. However, possible explanations for the result are that lower hematocrit or hemoglobin concentration has been shown to be associated with increased LV mass or diastolic dysfunction, even in the absence of overt anemia [14,15]. Then, both LV mass index and diastolic dysfunction represented by E/E' were related to LAVI as shown in the present study.

Gender difference and LAVI

We found that female gender was independently related to a high LAVI. In contrast, a few studies have shown that LA volume is higher in males than females in adults without cardiovascular diseases [5,6]; however, the difference diminished when LA volume was indexed by body surface

Table 4 Comparison between low and high LAVI groups on clinical characteristics.

	All patients			Male			Female		
	Low LAVI ($n = 190$)	High LAVI ($n = 190$)	*P*-value	Low LAVI ($n = 88$)	High LAVI ($n = 87$)	*P*-value	Low LAVI ($n = 103$)	High LAVI ($n = 102$)	*P*-value
Age (years)	60 ± 15	66 ± 14	<0.0001	59 ± 15	64 ± 15	<0.05	61 ± 15	68 ± 13	<0.01
Gender (female; %)	47	61	<0.01	NA	NA	NA	NA	NA	NA
Body surface area (m^2)	1.6 ± 0.2	1.5 ± 0.2	<0.01	1.7 ± 0.2	1.6 ± 0.2	NS	1.5 ± 0.1	1.5 ± 0.1	NS
Body mass index (kg/m^2)	23.3 ± 3.3	23.7 ± 3.6	NS	23.7 ± 3.2	23.5 ± 3.3	NS	22.8 ± 3.4	24.0 ± 3.8	<0.01
Hypertension (%)	46	63	<0.01	43 62	<0.05	43	69	<0.01	
Diabetes (%)	13	24	<0.01	15	25	NS	8	27	<0.01
History of CHD (%)	6	4	NS	8	8	NS	1	3	NS
History of CHF (%)	1	2	NS	2	3	NS	0	0	NS
Medications (%)	33	48	<0.01	33	45	NS	32	53	<0.01
ACEI	4	6	NS	3	6	NS	5	6	NS
ARB	17	29	<0.01	14	25	NS	17	34	<0.01
ACEI/ARB	20	34	<0.01	9	30	NS	21	39	<0.01
CCB	21	35	<0.01	23	31	NS	18	39	<0.01
Blocker	6	11	NS	7	10	NS	6	11	NS
Diuretics	2	5	NS	2	6	NS	1	5	NS
Serum creatinine (mg/dl)	0.8 ± 0.4	0.8 ± 0.4	NS	0.9 ± 0.5	0.9 ± 0.4	NS	0.6 ± 0.1	0.7 ± 0.3	NS
Hemoglobin (g/dl)	13.9 ± 1.6	12.9 ± 1.7	<0.0001	14.5 ± 1.6	13.6 ± 1.8	<0.01	13.2 ± 1.4	12.5 ± 1.4	<0.01

Data are mean $\pm$ standard deviation (SD) or percentage of patients. *P*-values were calculated by comparison between low and high LAVI groups. LAVI, left atrial volume index; NA, not available; CHD, coronary heart disease; CHF, congestive heart failure; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium-channel blocker.

Table 5 Comparison between low and high LAVI groups on echocardiographic measurements.

	All patients			Male			Female		
	Low LAVI ($n = 190$)	High LAVI ($n = 190$)	*P*-value	Low LAVI ($n = 88$)	High LAVI ($n = 87$)	*P*-value	Low LAVI ($n = 103$)	High LAVI ($n = 102$)	*P*-value
LA diameter (mm)	38 ± 5	42 ± 5	<0.0001	39 ± 4	41 ± 5	<0.01	37 ± 5	44 ± 5	<0.0001
LA volume (ml)	45 ± 7	68 ± 11	<0.0001	45 ± 7	64 ± 11	<0.0001	42 ± 7	65 ± 12	<0.0001
LAVI (ml/m^2)	28 ± 4	42 ± 8	<0.0001	27 ± 4	39 ± 6	<0.0001	29 ± 4	44 ± 9	<0.0001
LVDd (mm)	47 ± 5	48 ± 4	<0.05	48 ± 5	49 ± 4	NS	46 ± 4	47 ± 4	<0.05
LVDs (mm)	31 ± 5	31 ± 4	NS	31 ± 8	33 ± 4	<0.05	30 ± 4	30 ± 4	NS
LVEF (%)	65 ± 5	65 ± 5	NS	64 ± 5	63 ± 5	NS	65 ± 5	66 ± 5	<0.05
FS (%)	35 ± 4	36 ± 4	NS	35 ± 4	34 ± 3	NS	36 ± 4	37 ± 4	<0.05
IVST (mm)	9 ± 1	10 ± 2	<0.0001	9 ± 1	10 ± 2	<0.05	8 ± 1	10 ± 2	<0.0001
PWT (mm)	9 ± 1	9 ± 2	<0.0001	9 ± 1	10 ± 1	<0.05	8 ± 1	9 ± 2	<0.0001
LV mass (g)	138 ± 36	161 ± 37	<0.0001	154 ± 35	174 ± 36	<0.01	121 ± 29	153 ± 35	<0.0001
LV mass index (g/m^2)	87 ± 18	105 ± 23	<0.0001	91 ± 17	107 ± 23	<0.0001	83 ± 18	104 ± 23	<0.0001
IVC diameter (mm)	14 ± 3	14 ± 3	NS	14 ± 3	14 ± 3	NS	13 ± 3	13 ± 3	NS
E (cm/s)	73 ± 15	74 ± 18	NS	72 ± 13	71 ± 17	NS	74 ± 16	77 ± 18	NS
A (cm/s)	73 ± 20	82 ± 21	<0.01	72 ± 19	77 ± 21	NS	74 ± 22	86 ± 21	<0.01
Ad (ms)	148 ± 19	153 ± 20	<0.05	148 ± 20	156 ± 21	<0.01	148 ± 19	151 ± 18	NS
E/*A*	1.1 ± 0.5	1.0 ± 0.4	<0.01	1.1 ± 0.5	1.0 ± 0.4	NS	1.1 ± 0.6	1.0 ± 0.3	<0.05
DT (ms)	233 ± 50	235 ± 53	NS	233 ± 50	241 ± 56	NS	230 ± 49	233 ± 52	NS
S (cm/s)	66 ± 14	66 ± 14	NS	66 ± 16	66 ± 16	NS	65 ± 13	67 ± 13	NS
D (cm/s)	45 ± 11	43 ± 11	NS	44 ± 10	44 ± 12	NS	45 ± 11	43 ± 11	NS
S/*D*	1.6 ± 0.4	1.5 ± 0.5	NS	1.6 ± 0.5	1.6 ± 0.5	NS	1.5 ± 0.5	1.6 ± 0.3	NS
AR (cm/s)	32 ± 11	31 ± 9	NS	31 ± 12	32 ± 9	NS	33 ± 10	31 ± 9	NS
ARd (ms)	134 ± 23	141 ± 27	<0.01	129 ± 18	139 ± 25	<0.01	137 ± 25	142 ± 29	NS
ARd − Ad (ms)	−14 ± 26	−12 ± 30	NS	−19 ± 24	−16 ± 29	NS	−10 ± 28	−9 ± 29	NS
E′ (cm/s)	8 ± 3	7 ± 2	<0.0001	8 ± 2	7 ± 2	<0.05	8 ± 3	7 ± 3	<0.0001
A′ (cm/s)	10 ± 2	10 ± 2	NS	10 ± 2	10 ± 2	NS	10 ± 2	10 ± 2	NS
E′/*A*′	0.8 ± 0.4	0.7 ± 0.3	<0.01	0.8 ± 0.3	0.7 ± 0.3	<0.01	0.8 ± 0.4	0.7 ± 0.3	<0.05
E/*E*′	10 ± 3	12 ± 3	<0.0001	10 ± 3	11 ± 3	NS	10 ± 3	13 ± 4	<0.0001

Data are mean ± standard deviation (SD). *P*-values were calculated by comparison between low and high LAVI groups. LA, left atrial; VI, volume index; LV, left ventricular; Dd, diameter in end diastole; Ds, diameter in end systole; EF, ejection fraction; FS, fractional shortening; IVST, interventricular septal thickness; PWT, posterior wall thickness; IVC, inferior vena cava; *E*, peak early diastolic mitral inflow velocity; *A*, peak late diastolic mitral inflow velocity; Ad, duration of late diastolic mitral inflow wave; DT, deceleration time; *S*, peak pulmonary venous systolic forward flow velocity; *D*, peak pulmonary venous diastolic forward flow velocity; AR, peak pulmonary venous atrial reversal flow velocity; ARd, duration of pulmonary venous atrial reversal flow wave; *E*′, peak early diastolic velocity of the septal annulus; *A*′, peak late diastolic velocity of the septal annulus.

Table 6 Multiple logistic regression analysis to predict high left atrial volume index.

	All patients			Male			Female		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age	0.99	0.98–1.02	NS	0.99	0.97–1.03	NS	0.99	0.96–1.02	NS
Gender (female)	1.92	1.12–3.30	<0.05	NA	NA	NA	NA	NA	NA
Hypertension	0.95	0.56–1.62	NS	1.15	0.53–2.49	NS	0.87	0.41–1.85	NS
Diabetes	1.13	0.59–2.15	NS	0.76	0.31–1.85	NS	1.99	0.71–5.61	NS
Hemoglobin	0.76	0.64–0.90	<0.01	0.74	0.59–0.95	<0.05	0.77	0.60–0.99	<0.05
LV mass index	1.05	1.03–1.06	<0.0001	1.04	1.02–1.06	<0.01	1.06	1.03–1.08	<0.0001
E/E'	1.08	0.99–1.18	NS	1.01	0.88–1.16	NS	1.14	0.99–1.29	NS

OR, odds ratio; CI, confidence interval; LV, left ventricular; NS, not significant; NA, not available; E, peak early diastolic mitral inflow velocity; E', peak early diastolic velocity of the septal annulus.

area [4,6]. The difference between the studies is that our study population included patients with cardiovascular diseases, whereas we could not sufficiently explain the relationship between female gender and a high LAVI.

Diastolic function and LAVI

E/E' is more closely correlated than conventional diastolic parameters with mean LV diastolic pressure [16]. Two studies showed that LV diastolic dysfunction was associated with LAVI [7,8]; whereas Pritchett et al. reported that LAVI is not a robust marker of mild or moderate diastolic dysfunction [8]. Here, E' and E/E' were significantly correlated with LAVI among LV diastolic parameters in the univariate, but not in the multivariate analysis. This finding indicated that some factors such as LV mass index, hemoglobin concentration, and gender difference were more strongly associated with LA enlargement than diastolic function represented by E/E' in the present study. In addition, several patients with mild to moderate diastolic dysfunction might have been included in the present study, because E/A was negatively correlated with LAVI.

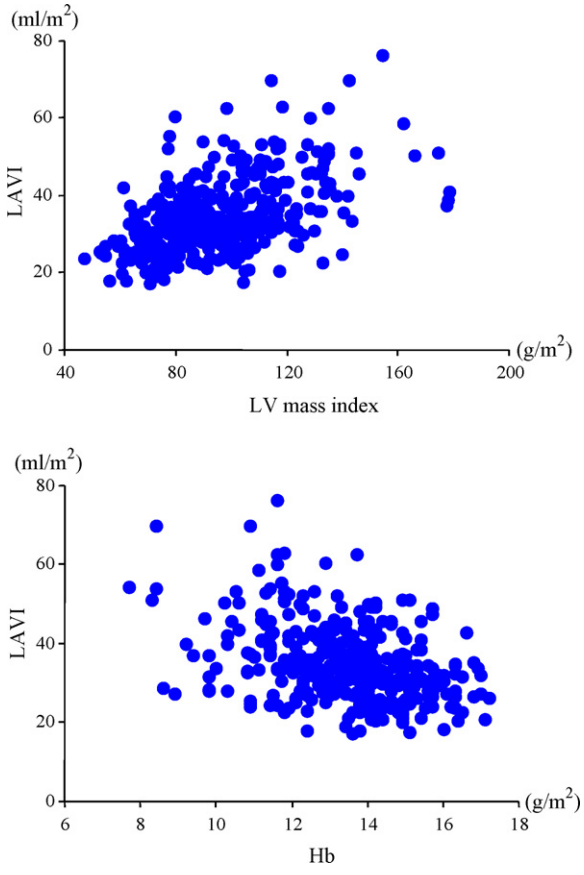

Figure 1 Scatter plots of left ventricular mass index (left panel) and hemoglobin concentration (right panel) for left atrial volume index in all patients. LAVI, left atrial volume index; LV, left ventricular; Hb, hemoglobin.

Study limitations

Although associations were demonstrated between LAVI and a few factors, we could not prove any cause-and-effect relationships using this cross-sectional design.

Moreover, the mean LAVI of 35 ml/m^2 in the present study was considerably higher than that in other studies [8,17]. Yamaguchi et al. [17] reported that mean LAVI measured by the biplane Simpson's method is 22 ml/m^2 and that mean LAVI + 2SD is 30 ml/m^2 in normal Japanese adults with a mean age of 39 years. The discrepancy in LAVI values is partly explained by the inclusion of elderly patients with cardiovascular diseases in the present study. The accuracy of LA area planimetry might be limited because the left atrium was located in the far field of the apical view [9].

Finally, selection bias might have affected our results because we enrolled only patients who underwent blood tests at the same time as echocardiography.

Conclusions

Increased LV wall thickness and decreased hemoglobin concentration may contribute to LA enlargement in patients with normal LV systolic function irrespective of gender. Moreover, it is suggested that these parameters affect LA size even in the absence of overt LV hypertrophy or anemia.

Acknowledgments

We sincerely appreciate Hisae Okawa and Yumi Shimizu for their technical assistance with the echocardiography,

and are grateful to Dr Takanori Yasu for helpful discussions regarding the study findings.

References

[1] Benjamin EJ, D'Agostino RB, Belanger AJ, Wolf PA, Levy D. Left atrial size and the risk of stroke and death. The Framingham Heart Study. Circulation 1995;92:835—41.
[2] Kizer JR, Bella JN, Palmieri V, Liu JE, Best LG, Lee ET, Roman MJ, Devereux RB. Left atrial diameter as an independent predictor of first clinical cardiovascular events in middle-aged and elderly adults: Strong Heart Study (SHS). Am Heart J 2006;151:412—8.
[3] Lester SJ, Ryan EW, Schiller NB, Foster E. Best method in clinical practice and in research studies to determine left atrial size. Am J Cardiol 1999;84:829—32.
[4] Abhayaratna WP, Seward JB, Appleton CP, Douglas PS, Oh JK, Tajik AJ, Tsang TS. Left atrial size: physiologic determinants and clinical applications. J Am Coll Cardiol 2006;47:2357—63.
[5] Wang Y, Gutman JM, Heilbron D, Wahr D, Schiller NB. Atrial volume in a normal adult population by two-dimensional echocardiography. Chest 1984;86:595—601.
[6] Pritchett AM, Jacobsen SJ, Mahoney DW, Rodeheffer RJ, Bailey KR, Redfield MM. Left atrial volume as an index of left atrial size: a population based study. J Am Coll Cardiol 2003;41:1036—43.
[7] Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. Am J Cardiol 2002;90:1284—9.
[8] Pritchett AM, Mahoney DW, Jacobsen SJ, Rodeheffer RJ, Karon BL, Redfield MM. Diastolic dysfunction and left atrial volume: a population-based study. J Am Coll Cardiol 2005;45:87—92.
[9] Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ, Chamber Quantification Writing Group. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440—63.
[10] Tsioufis C, Stougiannos P, Taxiarchou E, Skiadas I, Chatzis D, Thomopoulos C, Lalos S, Stefanadis C, Kallikazaros I. The interplay between haemodynamic load, brain natriuretic peptide and left atrial size in the early stages of essential hypertention. J Hypertens 2006;24:965—72.
[11] Milan A, Caserta MA, Dematteis A, Naso D, Pertusio A, Magnino C, Puglisi E, Rabbia F, Pandian NG, Mulatero P, Veglio F. Blood pressure levels, left ventricular mass and function are correlated with left atrial volume in mild to moderate hypertension patients. J Hum Hypertens 2009;23:743—50.
[12] Appleton CP, Galloway JM, Gonzalez MS, Gaballa M, Basnight MA. Estimation of left ventricular filling pressure using two-dimensional and Doppler echocardiography in adult patients with cardiac disease. Additional value of analyzing left atrial size, left atrial ejection fraction and the difference in duration of pulmonary venous and mitral flow velocity at atrial contraction. J Am Coll Cardiol 1993;22:1972—82.
[13] Rakusan K, Cicutti N, Kolar F. Effect of anemia on cardiac function, microvascular structure, and capillary hematocrit in rat hearts. Am J Physiol Heart Circ Physiol 2001;280:H1407—14.
[14] Amin MG, Tighiouart H, Weiner DE, Stark PC, Griffith JL, MacLeod B, Salem DN, Sarnak MJ. Hematocrit and left ventricular mass: the Framingham Heart study. J Am Coll Cardiol 2004;43:1276—82.
[15] Srivastava PM, Thomas MC, Calafiore P, MacIsaac RJ, Jerums G, Burrell LM. Diastolic dysfunction is associated with anaemia in patients with Type II diabetes. Clin Sci 2006;110:109—16.
[16] Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM, Tajik AJ. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: a comparative simultaneous Doppler catheterization study. Circulation 2000;102:1788—94.
[17] Yamaguchi K, Tanabe K, Tani T, Yagi T, Fujii Y, Konda T, Kawai J, Sumida T, Morioka S, Kihara Y. Left atrial volume in normal Japanese adults. Circ J 2006;70:285—8.