Original Article

Noninvasive Assessment of Left Atrial Function by Strain Rate Imaging in Patients with Hypertension: A Possible Beneficial Effect of Renin-Angiotensin System Inhibition on Left Atrial Function

Nobuaki KOKUBU¹⁾, Satoshi YUDA²⁾, Kazufumi TSUCHIHASHI¹⁾, Akiyoshi HASHIMOTO¹⁾, Tomoaki NAKATA¹⁾, Tetsuji MIURA¹⁾, Nobuyuki URA¹⁾, Kazuhiko NAGAO³⁾, Masahiro TSUZUKI³⁾, Chikashi WAKABAYASHI³⁾, and Kazuaki SHIMAMOTO¹⁾

Renin-angiotensin system (RAS) inhibitors are likely to reduce the development of atrial fibrillation by preventing atrial fibrosis. Strain rate (SR) imaging is a novel echocardiographic technique to quantify left atrial (LA) function. However, it has not been determined whether SR imaging is applicable for detection of LA dysfunction in hypertensive (HT) patients. We used SR imaging to assess alteration in LA function in HT patients and its modification by RAS inhibitors. SR imaging was performed in 80 HT patients and 50 age-matched normotensive (NT) subjects. HT patients were divided into two groups according to left ventricular hypertrophy (LVH) and LA dilatation. Peak SR was measured at each LA segment (septal, lateral, posterior, anterior, and inferior) and mean peak systolic SR (SR-LAs) was calculated by averaging data in each segment. Mean SR-LAs levels in the dilated LA group ($1.97 \pm 0.45 \text{ s}^{-1}$, $n=25$) and non-dilated LA group ($2.15 \pm 0.57 \text{ s}^{-1}$, $n=55$) were significantly ($p<0.05$) lower than that in NT subjects ($2.53 \pm 0.71 \text{ s}^{-1}$). Irrespective of the presence or absence of LVH, mean SR-LAs in HT patients was lower than that in NT subjects. When RAS inhibitors were used, the mean SR-LAs level in the non-dilated LA group was equivalent to that in NT subjects. In HT patients, mean SR-LAs, an index of LA reservoir function, decreases before development of LA enlargement and LVH. Treatment with RAS inhibitors appears to preserve LA reservoir function in HT patients without dilated LA. SR imaging can detect LA dysfunction in HT patients and is useful for evaluation of the therapeutic benefit on LA reservoir function. (*Hypertens Res* 2007; 30: 13–21)

Key Words: strain rate imaging, left atrium, hypertension, renin-angiotensin system inhibitors

Introduction

Left atrial (LA) structural and functional changes occur in patients with hypertension (HT). LA enlargement is commonly found by echocardiography in patients with HT (1, 2) and is associated with increased risks for atrial fibrillation

(AF) and diastolic heart failure (3, 4). Recently, Goette *et al.* (5) have shown that AF is associated with an increased expression of angiotensin-converting enzyme in atrial tissue, leading to development of fibrosis. In an animal model, renin-angiotensin system (RAS) inhibitors have been shown to prevent LA dilatation, atrial fibrosis and intra-atrial conduction slowing, and these changes are associated with a lower rate of

From the ¹⁾Second Department of Internal Medicine and ²⁾Department of Diagnostic Ultrasound and Medical Electronics, Sapporo Medical University School of Medicine, Sapporo, Japan; and ³⁾Division of Cardiology, Sapporo Cardiovascular Hospital, Sapporo, Japan.

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Address for Reprints: Satoshi Yuda, M.D., Ph.D., Department of Diagnostic Ultrasound and Medical Electronics, Sapporo Medical University School of Medicine, South-1, West-16, Chuo-ku, Sapporo 060-0061, Japan. E-mail: yuda@sapmed.ac.jp

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AF induction with atrial pacing (6, 7). Several secondary analyses of large randomized trials have revealed that RAS inhibitors prevent the development of AF (8). Thus, inhibition of the RAS could be a novel treatment for AF, and a prospective human study is required to determine whether RAS inhibitors can modify structural and functional alterations of the atrium, such as atrial remodeling. However, conventional methods for the assessment of LA function have not been established.

Strain rate (SR) imaging has been proposed as a novel non-invasive echocardiographic technique to quantify regional myocardial function independent of cardiac rotational motion and a tethering effect (9–14). SR imaging enables quantitative assessment of LA function in patients with paroxysmal or persistent AF, atrial septal defect and cardiac amyloidosis (9–13). The efficacy of SR imaging, however, has not been determined in patients with HT. Inaba *et al.* (9) have recently demonstrated that LA systolic SR is significantly reduced in correlation with aging and LA dilation and that patients with persistent AF have significantly lower LA systolic SR than age-matched controls. These findings suggest that SR imaging can assess LA function and detect structural or functional changes of LA in HT patients. The purposes of this study were to determine whether SR imaging enables detection of LA dysfunction in HT patients and evaluation of the effects of RAS inhibition on LA function.

Methods

Patient Population

Echocardiographic evaluation, including SR imaging, was performed in 80 patients with essential HT (HT group; 40 males, mean age of 64 ± 9 years) without a history of cardiovascular disease, and evidence of cardiovascular disease by ECG and conventional echocardiography. Stress ECG ($n=26$), stress myocardial perfusion imaging ($n=4$) or coronary angiography ($n=9$) were performed in 39 patients, and no evidence of myocardial ischemia or significant coronary stenosis was found in these patients. Fifty age-matched normotensive (NT) subjects (18 males, mean age of 61 ± 8 years) who did not have cardiovascular disease, HT or diabetes mellitus were enrolled in this study. No abnormal findings were found in the NT subjects on physical examinations, ECG and conventional echocardiography, and none of the NT subjects were receiving cardio-active medication. Seven of the 80 HT patients had paroxysmal AF that was diagnosed at least 3 months before the start of this study. Neither left ventricular (LV) systolic dysfunction defined as an ejection fraction $<50\%$, LV dilatation defined as an end-diastolic diameter >55 mm, or significant valvular disease was found in the HT patients and NT subjects. All patients were in sinus rhythm when the echocardiographic examination was performed. HT was defined as a systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, or current use of antihy-

Table 1. Clinical Characteristics and Conventional Echocardiographic Parameters of NT Group and HT Group

	NT group ($n=50$)	HT group ($n=80$)
Age (years)	61 ± 8.3	64 ± 9.2
Male	18 (36%)	40 (50%)
Body mass index (kg/m^2)	23.6 ± 3.4	$25.2 \pm 3.4^*$
Heart rate (beats/min)	67 ± 11	66 ± 13
Systolic BP (mmHg)	127 ± 14	$140 \pm 16^\dagger$
Diastolic BP (mmHg)	75 ± 10	$81 \pm 10^\dagger$
Risk factors		
Paroxysmal AF	0	7 (9%)*
Diabetes mellitus	0	15 (19%) [†]
Hypercholesterolemia	8 (16%)	26 (33%)*
Current smoker	11 (22%)	21 (26%)
Medication		
Calcium antagonists	0	43 (54%) [†]
ACE-inhibitors	0	7 (9%)*
ARBs	0	30 (38%) [†]
β -Blockers	0	20 (25%) [†]
Echocardiographic parameters		
LA dimension (mm)	33.6 ± 3.9	$37.9 \pm 4.3^\dagger$
Septal wall thickness (mm)	9.6 ± 1.4	$11.6 \pm 2.4^\dagger$
Posterior wall thickness (mm)	9.5 ± 1.4	$11.2 \pm 1.7^\dagger$
LV end-diastolic diameter (mm)	46.5 ± 3.3	$48.7 \pm 4.3^\dagger$
LV mass index (g/m^2)	97.3 ± 20.6	$128.5 \pm 33.0^\dagger$
LV ejection fraction (%)	65.9 ± 6.5	66.1 ± 5.2
Doppler parameters		
Mitral <i>E</i> (m/s)	0.65 ± 0.12	$0.60 \pm 0.13^*$
Mitral <i>A</i> (m/s)	0.71 ± 0.13	0.74 ± 0.13
<i>E/A</i> ratio	0.94 ± 0.25	$0.83 \pm 0.22^\dagger$
Deceleration time of <i>E</i> (ms)	205 ± 47	$223 \pm 56^*$
Pulmonary <i>A</i> (m/s)	0.34 ± 0.08	0.32 ± 0.08
Pulmonary <i>S</i> (m/s)	0.67 ± 0.12	0.63 ± 0.11
Pulmonary <i>D</i> (m/s)	0.49 ± 0.11	0.48 ± 0.10

Data are presented as mean value $\pm$ SD or number (%) of patients. *A*, peak velocity during late diastolic filling; ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARBs, angiotensin II receptor blockers; BP, blood pressure; *D*, peak velocity during early diastolic filling; *E*, peak velocity during early filling; HT, hypertensive; LA, left atrial; LV, left ventricular; NT, normotensive; *S*, peak velocity during systole. * $p < 0.05$ vs. NT group, $^\dagger p < 0.01$ vs. NT group.

pertensive drugs. Diabetes mellitus and hypercholesterolemia were defined according to a previous report (14). The clinical characteristics of the study population are summarized in Table 1. Informed consent to participate in this study was obtained from all subjects.

Echocardiographic Study

A commercially available ultrasound machine (Vivid 7; Gen-

Fig. 1. A representative strain rate (SR) curve of left atrium (LA) and measurements of peak systolic strain rate of left atrium (SR-LAs) and peak late diastolic strain rate of left atrium (SR-LAa) in a normotensive subject. SR can be calculated from 2 velocity measurements ($V(r)$, $V(r + \Delta r)$) of tissue Doppler imaging whose sample volume distance is Δr . LV, left ventricle.

eral Electric Medical Systems, Milwaukee, USA) equipped with a 2.5-MHz variable frequency transducer was used for all of the echocardiographic evaluations. Standard echocardiographic views, including parasternal long-axis and apical four-, three- and two-chamber views, with the subjects in the left lateral decubitus position were obtained in two-dimensional and color tissue Doppler modes. The septal and posterior wall thicknesses at end-diastole (mm), and LV end-diastolic and end-systolic dimensions (mm) were determined from M-mode echocardiogram. LV ejection fraction (%) was calculated using a Teichholz formula. LV mass was calculated using the formula proposed by Levy *et al.* (15) and normalized for body surface area (LV mass index, g/m²). LV hypertrophy (LVH) was defined as an LV mass index of >131 g/m² for men and >100 g/m² for women (14, 15). LA dimension was measured by M-mode echocardiography and dilated LA was defined as an LA dimension >40 mm (9, 16). Each parameter was obtained from an average of three to five measurements.

Transmitral flow velocities were obtained by pulsed-wave Doppler echocardiography, positioning a sample volume at a mitral tip level in an apical four-chamber view. Mitral flow parameters including peak velocities during early diastole (*E*), late diastole (*A*), and *E* wave deceleration time were measured and the *E/A* ratio was calculated. Pulsed-wave Doppler signals were obtained at a sweep speed of 100 mm/s. All examinations were performed using second harmonic imaging.

Measurements of SR Imaging in LA

Gray-scale and color tissue Doppler images from apical

four-, three- and two-chamber views were recorded, with frame rates between 80 and 120 frames/s automatically changed by the sector width. Data of single cardiac cycle loops triggered to the QRS complex were saved on a magneto-optical disk (MO-4.8GB; IMATION Inc., Tokyo, Japan) and were analyzed offline using a commercial software package (Echopac version PC; General Electric Medical Systems).

SR was measured from tissue Doppler image data on the basis of instantaneous differences in myocardial velocities (corrected for a distance of 6 mm in this study). A 2 × 6 mm region of interest was positioned on each mid segment of the LA walls in four-, three- and two-chamber views and was manually tracked frame-by-frame to maintain its position within the LA walls. Peak systolic SR (SR-LAs) and late diastolic SR (SR-LAa) were measured from SR curves in each of the five mid LA segments (septal, lateral, posterior, anterior, and inferior walls) (Fig. 1). Mean SR-LAs and mean SR-LAa were calculated by averaging the results for each segment. Data were excluded when a smooth SR curve was not obtained or when an angle between the scan line and LA wall was >30 degrees in order to preclude angle-dependency of these parameters. Data were taken from three consecutive heart cycles and averaged using a compound function to eliminate noise.

Statistical Analysis

All numeric data are expressed as the means ± SD. Differences in continuous variables between two groups were assessed by unpaired Student's *t*-test, and comparison among multiple groups was performed by analysis of variance with Scheffé's post hoc test. Categorical variables were analyzed

Fig. 2. Comparison of mean SR-LAs (left) and mean SR-LAa (right) among normotensive (NT) subjects and hypertensive (HT) patients with and without left ventricular hypertrophy (LVH). White bars, NT subjects; gray bars, HT patients without LVH; black bars, HT patients with LVH. * $p < 0.05$ vs. NT subjects, † $p < 0.01$ vs. NT subjects.

by the χ^2 test, and Fisher's exact test was used when appropriate. The correlation between two variables was tested by linear regression analysis. Variables with a p value of less than 0.10 in univariate analysis were entered into the multivariate model with a stepwise regression analysis. All data analysis was performed by using the commercially available statistical analysis software package Statview version 4.1 (Abacus Concepts, Inc., Berkeley, USA) or SPSS version 9.0 (SPSS Inc., Chicago, USA). We considered results significant when the p value was < 0.05 .

Sample size calculations were performed using a single end point variable of mean SR-LAs. Based on the initial 20 HT patients, we calculated the sample size for a two-sided Student's t -test using an SD of 0.50 s^{-1} , $\alpha = 0.05$ and a desired power of 80% to be 16 patients per each group. The expected difference in means for this calculation was 0.50 s^{-1} .

Results

Reproducibility and Feasibility Data and Segmental Variation of SR Parameters

Of the 250 segments in the NT subjects, 245 (99%) had adequate waveforms for assessment of SR. Of the 400 analyzed segments in HT patients, 396 (99%) had adequate waveforms for the assessment of SR. Inter- and intra-observer variabilities of the mean SR-LAs and SR-LAa were evaluated in randomly selected controls ($n = 10$). For the assessment of inter- and intra-observer variabilities of SR variables, we repeated the entire processes from the initial two-dimensional tissue Doppler image. Mean absolute differences and coefficients of variance (CV, %) of the inter-observer variability for mean SR-LAs and SR-LAa were $0.18 \pm 0.16 \text{ s}^{-1}$ (CV: 7.5%) and $0.21 \pm 0.14 \text{ s}^{-1}$ (CV: 7.2%), respectively. Mean absolute differences and CV of the intra-observer variability for mean SR-LAs and SR-LAa were $0.26 \pm 0.20 \text{ s}^{-1}$ (CV: 11.7%) and $0.24 \pm 0.18 \text{ s}^{-1}$ (CV: 7.4%), respectively.

Clinical Characteristics and Echocardiographic Findings

The clinical characteristics and echocardiographic parameters of the NT subjects and HT patients are summarized in Table 1. All HT patients were treated with calcium antagonists, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and/or β -blockers, but none of these agents were used in NT subjects. Both systolic and diastolic blood pressures in HT patients were greater than those in NT subjects. The prevalences of diabetes mellitus, hypercholesterolemia, and paroxysmal AF in HT patients were significantly greater than those in NT subjects. HT patients had greater septal and posterior wall thicknesses, larger LA and LV end-diastolic dimensions, smaller peak velocity of E wave and E/A ratio and longer E wave deceleration time than did NT subjects. There was no difference between the two groups in age, gender, heart rate, LV ejection fraction, peak velocities of A waves, or Doppler parameters of pulmonary venous flow.

Effects of LV Hypertrophy and LA Size on SR Parameters of LA

Mean SR-LAs, which was considered to be an indicator of LA reservoir function, was significantly lower in HT patients than NT subjects (2.10 ± 0.54 vs. $2.53 \pm 0.71 \text{ s}^{-1}$, $p < 0.01$). However, mean SR-LAa, which was considered to be an indicator of LA booster function, was similar in the two groups (-2.89 ± 0.97 vs. $-2.94 \pm 1.06 \text{ s}^{-1}$, NS, respectively). Independent of the presence of LVH, mean SR-LAs in HT patients was significantly lower than that in NT subjects (Fig. 2, left), although there was no significant difference in mean SR-LAa among the three groups (Fig. 2, right). Mean SR-LAs was significantly lower in both HT patients with and without dilated LA than in NT subjects (Fig. 3, left). However, there was no significant difference in mean SR-LAa among the three groups (Fig. 3, right).

Fig. 3. Comparison of mean SR-LAs (left) and mean SR-LAa (right) among NT subjects and HT patients with and without dilated left atrium (LA). White bars, NT subjects; gray bars, HT patients without dilated LA; black bars, HT patients with dilated LA. [†] $p < 0.01$ vs. NT subjects.

Fig. 4. Comparison of mean SR-LAs among NT subjects and HT patients subgrouped according to dilated LA and treatment with RAS inhibitors. White bar, NT subjects; light gray bar, HT patients without dilated LA who were treated with RAS inhibitors; dark gray bar, HT patients without dilated LA who did not receive treatment with RAS inhibitors; hatched bar, HT patients with dilated LA who were treated with RAS inhibitors; black bar, HT patients with dilated LA who did not receive treatment with RAS inhibitors. * $p < 0.05$ vs. NT subjects.

Effects of RAS Inhibitors on SR Parameters of LA

RAS inhibitors consisted of valsartan ($n=13$), candesartan ($n=12$), losartan ($n=5$), imidapril ($n=3$), enalapril ($n=2$), temocapril ($n=1$) and trandolapril ($n=1$), all of which had been used for at least 2 weeks before echocardiographic examinations (mean, 30 ± 25 months; range, 0.5 to 85 months) in this study. Of these, 11 patients were treated with RAS inhibitor alone. Mean SR-LAs was significantly lower not only in the HT patients treated with RAS inhibitors (2.16 ± 0.59 s⁻¹, $p < 0.05$) but also in those not treated with RAS inhibitors (2.04 ± 0.49 s⁻¹, $p < 0.01$) compared with that in the NT subjects (2.53 ± 0.71 s⁻¹). The mean SR-LAs in patients treated with RAS inhibitors alone was comparable to that in NT subjects (2.28 ± 0.71 vs. 2.53 ± 0.71 s⁻¹, NS, respectively). Both HT patients treated with and without RAS inhibitors were subdivided into two subgroups, according to the

presence or absence of dilated LA. In the non-dilated LA group, the mean SR-LAs in patients treated with RAS inhibitors was comparable to that in NT subjects (2.35 ± 0.66 and 2.51 ± 0.73 s⁻¹, NS, respectively) but was different from that in patients who did not receive treatment with RAS inhibitors (Fig. 4). In the non-dilated LA group, there was no significant difference in clinical or echocardiographic variables between patients treated with and without RAS inhibitors (Table 2). Figure 4 showed that HT patients treated with RAS inhibitors in the dilated LA group had a significantly lower mean SR-LAs than did NT subjects. The patients treated with calcium antagonists in both the non-dilated LA and non-LVH groups had a significantly lower mean SR-LAs than did NT subjects. The patients treated with calcium antagonists alone (2.03 ± 0.65 s⁻¹, $n=14$) also had a significantly lower mean SR-LAs than did NT subjects. There was no significant correlation ($r = -0.12$, NS) between mean SR-LAs and

Table 2. Clinical Characteristics and Echocardiographic Parameters of NT and HT Patients Grouped According to Dilated LA and Treated with RAS Inhibitors

	NT (<i>n</i> =50)	Dilated LA (–) RAS inhibitors (+) (<i>n</i> =20)	Dilated LA (–) RAS inhibitors (–) (<i>n</i> =35)	Dilated LA (+) RAS inhibitors (+) (<i>n</i> =17)	Dilated LA (+) RAS inhibitors (–) (<i>n</i> =8)
Age (years)	61±8.3	59±11.4	65±7.7	67±7.4	66±10.5
Body mass index (kg/m ²)	23.6±3.4	25.0±3.5	24.4±3.0	26.2±2.9	26.8±5.1
Heart rate (beats/min)	67±11	71±10	67±9	57±7* [‡]	70±8 [§]
Systolic BP (mmHg)	127±14	139±15*	139±16*	139±14*	145±24*
Diastolic BP (mmHg)	75±10	83±10*	80±9	78±11	82±9
Echocardiographic parameters					
LA dimension (mm)	33.6±3.9	35.9±2.9	35.6±2.9	42.7±2.8* [‡]	42.7±2.9* [‡]
Septal wall thickness (mm)	9.7±1.4	11.2±1.0*	10.9±1.5	13.5±3.9* [‡]	11.9±1.8*
Posterior wall thickness (mm)	9.5±1.4	10.9±1.4*	10.9±1.6*	11.8±2.3*	11.9±1.6*
LV end-diastolic diameter (mm)	46.5±3.3	48.3±4.3	47.6±3.9	51.0±5.2* [‡]	49.6±2.8
LV mass index (g/m ²)	97.3±20.6	120.0±27.1*	118.9±24.8*	151.8±44.2* [‡]	142.4±25.4*
LV ejection fraction (%)	65.9±6.5	66.6±4.8	66.1±5.2	65.7±5.4	66.3±6.1
Doppler parameters					
Mitral <i>E</i> (m/s)	0.66±0.15	0.65±0.19	0.60±0.14	0.59±0.11	0.62±0.15
Mitral <i>A</i> (m/s)	0.70±0.14	0.73±0.17	0.76±0.12	0.71±0.12	0.74±0.12
<i>E/A</i> ratio	1.01±0.53	0.98±0.69	0.81±0.24	0.84±0.21	0.85±0.23
Deceleration time of <i>E</i> (ms)	205±47	213±52	219±41	221±32*	269±122*
Pulmonary <i>A</i> (m/s)	0.34±0.08	0.31±0.07	0.35±0.10	0.30±0.06	0.28±0.07 [†]
Pulmonary <i>S</i> (m/s)	0.67±0.12	0.61±0.09	0.69±0.11	0.59±0.11	0.61±0.10
Pulmonary <i>D</i> (m/s)	0.49±0.11	0.49±0.11	0.50±0.13	0.46±0.07	0.45±0.08

Data are presented as mean value±SD. Abbreviations are shown in the Table 1. **p*<0.05 vs. NT, [‡]*p*<0.05 vs. non-dilated LA without RAS inhibitors, [†]*p*<0.05 vs. non-dilated LA without RAS inhibitors, [§]*p*<0.05 vs. dilated LA without RAS inhibitors.

duration of RAS inhibitor treatment in HT patients. No significant difference in mean SR-LAa was found among NT subjects and HT patients treated with and without RAS inhibitors (−2.89±0.97, −2.99±1.04, −2.90±1.09 s^{−1}, NS, respectively).

Relationships between SR Parameters of LA and Clinical and Echocardiographic Variables in HT Patients

Mean SR-LAs correlated inversely with age (*r*=−0.29, *p*<0.05) and deceleration time of *E* wave (*r*=−0.28, *p*<0.05) and positively with heart rate (*r*=0.31, *p*<0.01) and peak velocity of pulmonary venous flow during atrial contraction (*r*=0.43, *p*<0.01). Age (*p*=0.04) and deceleration time of *E* wave (*p*=0.03) were independent determinants of mean SR-LAs in the multivariate model. Mean SR-LAa correlated inversely with heart rate (*r*=−0.25, *p*<0.05), peak velocity of mitral *A* wave (*r*=−0.27, *p*<0.05) and peak velocity of pulmonary venous flow during atrial contraction (*r*=−0.36, *p*<0.05). Heart rate (*p*=0.03) was an independent determinant of mean SR-LAa in the multivariate model. There was a significant inverse correlation between mean SR-LAs and mean SR-LAa (*r*=−0.60, *p*<0.001). However, body mass index, systolic and diastolic blood pressures, LA dimension,

LV mass index, LV ejection fraction and *E/A* ratio showed no correlation with mean SR-LAs or mean SR-LAa.

Discussion

This is the first study to evaluate LA function in HT patients using SR imaging. The major findings in this study are as follows: 1) SR imaging enables detection of LA dysfunction (*i.e.*, decreased LA reservoir function) in HT patients before manifestation of LA enlargement and LVH; and 2) SR imaging enables evaluation of the effects of RAS inhibitors on LA reservoir function in HT patients without LA geometric change.

Alterations of LA structure (*i.e.*, enlargement of LA) and function (*i.e.*, increased LA pump and reservoir functions) are frequently observed in HT patients by using conventional two-dimensional and Doppler echocardiography (1, 2, 17–19). However, it has not been determined whether LA dysfunction precedes manifestation of LA structural and functional changes. The present study showed that mean SR-LAs was lower in HT patients than in NT subjects independently of LA dilatation and LVH. Inaba *et al.* (9) have reported that LA systolic SR is significantly reduced in correlation with aging and LA dilation. Furthermore, Di Salvo *et al.* (10) have shown that LA systolic SR is correlated with peak velocity of

systolic pulmonary venous flow. Thus, mean SR-LAs, which is LA deformation at systole, could be used as an index of LA reservoir function. A decrease in mean SR-LAs in HT patients may reflect not only impairment of LA wall stretching but also histological change (e.g., fibrosis), which is found in atrial tissue in animal models of HT (20). Mean SR-LAs in HT patients was significantly lower than that in NT subjects, although the peak velocity of systolic pulmonary venous flow in the two groups was similar. The discrepant results of SR imaging and conventional Doppler imaging could be explained as follows. LA reservoir function assessed by SR imaging represents LA myocardial changes, while Doppler data represent only blood flow at systole but not necessarily LA reservoir function *per se*. This is supported by results showing that LA systolic SR, but neither LA size nor LA reservoir index, can differentiate patients with and those without maintenance of sinus rhythm after cardioversion (10).

SR-LAa was negative during late diastole (Fig. 1), indicating shortening of the LA wall. Furthermore, in HT patients, mean SR-LAa correlated inversely with the peak velocity of mitral A wave and pulmonary venous flow during atrial contraction, which are parameters of LA booster function. These findings support the idea that SR-LAa has value as an index of LA booster function. In contrast to the results of previous studies (17–19) that showed augmented LA booster pump parameters in HT patients, mean SR-LAa in HT patients was comparable to that in NT subjects in this study. This may be attributable to differences in the studied populations. In most patients in this study, HT was relatively mild and well controlled by treatment, and the Doppler parameters of the booster pump in HT patients were comparable to those in NT subjects.

The results of a preliminary study showed that SR during LA contraction in patients who had both pseudonormal and restrictive filling patterns was lower than that in patients with a normal filling pattern (21). Modesto *et al.* (11) have reported that SR imaging enables detection of LA contractile dysfunction in patients with cardiac amyloidosis. Interestingly, SR during LA contraction in non-cardiac amyloidosis patients was lower than that in controls, suggesting LA involvement of amyloidosis before manifestation of echocardiographic features of cardiac amyloidosis (11). SR imaging could detect those subtle changes in the LA wall that cannot be recognized by conventional echocardiographic parameters.

The present study also demonstrates that SR imaging can evaluate LA function with a high feasibility (9, 10). Using the compound function, the intra- and interobserver variabilities of mean SR-LAs and mean SR-LAa were improved in this study compared to our previous data (9). The variabilities of mean SR-LAs and mean SR-LAa were comparable to those reported in other studies (10, 11, 13), showing good reproducibility of LA SR parameters.

Beneficial effects of RAS inhibitors on LV myocardium (e.g., regression of fibrosis), LV function and arterial elasticity have been demonstrated in both experimental (22) and

clinical studies (23, 24). Although a number of animal studies (5–7, 25) have examined the effects of RAS inhibitors on LA myocardium and LA function, there have been few clinical studies on the effects of RAS inhibitors on LA function (26, 27). Furthermore, in these studies (26, 27), LA function has not been assessed directly, but rather as a change in LA volume using conventional Doppler and two-dimensional echocardiography. The present study applied an SR imaging technique in LA walls and demonstrated beneficial effects of RAS inhibitors on LA reservoir function in HT patients without LA geometric abnormality. Although the mechanisms of these effects on LA function remain to be investigated, there are several possible explanations. Reduction in preload and afterload seems unlikely to explain these findings, because LA dimension, LV end-diastolic diameter and blood pressure were comparable in patients treated with and without RAS inhibitors in the non-LVH group. Shi *et al.* (7) have demonstrated in a heart failure model that atrial fibrosis correlated with a decrease in LA fractional area shortening and that enalapril reduced atrial fibrosis and preserved LA fractional area shortening. In addition, Díez *et al.* (23) have shown in HT patients that losartan-dependent regression of LV fibrosis is associated with reduction in LV stiffness. Thus, we speculate that RAS inhibitors inhibit or regress LA fibrosis, contributing to preservation or improvement of LA reservoir function when HT induced LA remodeling has not been advanced. In patients with LA remodeling, however, RAS inhibitors may be less effective at improving LA function due to the advanced levels of fibrosis and/or myocyte hypertrophy.

SR imaging enables quantitative and noninvasive measurement of LA function and detection of LA dysfunction before manifestation of functional or morphological abnormalities on conventional echocardiographic imaging. Experimental studies have shown that RAS inhibitors can prevent atrial remodeling (5–7) and AF (8). Therefore, early detection of LA dysfunction may help in the choice of therapy for prevention of AF and in prediction of the efficacy of therapeutic strategies against AF, including defibrillation (10). It is also possible that assessment of LA dysfunction would be useful for stratifying the risk for stroke and thromboembolism, because LA dysfunction induces thrombogenesis and intra-arterial stasis. Furthermore, SR imaging may be useful for assessment of the beneficial effects of statins on arrhythmias and LA function (28).

There were several limitations to this study. The possibility that myocardial ischemia influenced the LA function cannot be excluded. However, there were no significant differences between mean SR-LAs (2.11 ± 0.52 vs. 2.08 ± 0.56 s⁻¹, NS, respectively) or mean SR-LAa (-3.00 ± 1.14 vs. -2.88 ± 0.99 s⁻¹, NS, respectively) in patients with and those without stress ECG, myocardial perfusion imaging or coronary angiography. It was not determined in this study whether systolic LV function affects SR parameters of LA. There was no significant difference in LV ejection fraction between any groups in this study. Furthermore, a recent study (10) has shown no sig-

nificant correlations of peak systolic displacement of the mitral ring, which is a parameter of longitudinal LV function, and peak LA systolic SR. The association between mean SR-LAs and mean SR-LAa and histological alterations of LA myocardium (e.g., fibrosis) is still speculative, but histological study in HT patients is unlikely to be ethically acceptable. Measurement of serum levels of collagen markers (29) and assessment of LA myocardium reflectivity using ultrasonic integrated backscatter, which can assess myocardial fibrosis non-invasively (14, 30), may contribute to correlating LA fibrosis with the LA dysfunction identified by SR imaging. The HT patients in this study were relatively mild and well controlled and the results in this study cannot be applied to patients with severe HT. The retrospective study and small numbers of patients in the subgroups may have limited the strength of the effects of RAS inhibitors on LA function. A large-scale prospective and longitudinal study is needed to determine whether RAS inhibitors have beneficial effects on LA function in patients with not only mild HT, but also severe HT who have a high risk of development of AF.

In conclusion, in HT patients, mean SR-LAs, which is an index for LA reservoir function, decreases before manifestation of LA enlargement and LVH. Treatment with RAS inhibitors appears to preserve LA reservoir function in HT patients without dilated LA. SR imaging enables detection of LA dysfunction in HT patients and evaluation of the effects of RAS inhibitors on LA reservoir function in HT patients.

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