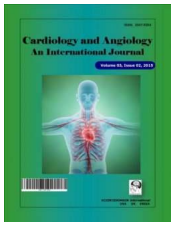

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Early Detection of Abnormal Left Atrial and Left Ventricular Coupling, Using Two-dimensional Speckle Tracking Echocardiography in Patients with Preserved Left Ventricular Ejection Fraction

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aims: The aim of this study was to detect the abnormalities of left atrial (LA)-left ventricular (LV) coupling using two-dimensional speckle tracking echocardiography in patient with preserved LV ejection fraction.
Methods: A total of 177 asymptomatic patients with preserved LV ejection fraction were studied. Global LV longitudinal peak strain (GLS) and peak LA longitudinal strain during systole (PALS) were measured. The ratio of E/Ea to PALS was used as an index of LA stiffness.
Results: The patients were classified into 2 groups according to the GLS: impaired group (n=81; GLS>-18%) and normal group (n=96; GLS≤-18%). Both GLS and PALS were reduced in the impaired group (p<0.001). LA stiffness was increased in the impaired group (p<0.05). In the normal group, there was no significant correlation between GLS and LA volume index. There was no significant correlation between GLS and LA stiffness. In the impaired group, GLS significantly correlated with correlated with the LA stiffness (r=0.50, p<0.001). Similarly, GLS significantly correlated with LA volume index (r=0.36, p<0.001).

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Conclusions: In patients with preserved longitudinal LV systolic function, LA structure and function are preserved. However, LA structure and function are rapidly impaired in patients with reduced longitudinal LV systolic function. LV longitudinal systolic dysfunction may cause the LA wall to become stiffer rapidly.

Keywords: Left atrial stiffness; myocardial fibrosis; myocardial strain; left ventricular dysfunction.

1. INTRODUCTION

Left atrial (LA) dilatation is well recognized as a prognostic marker in diverse conditions, such as heart failure, myocardial infarction, and atrial fibrillation [1-3]. Moreover, LA function has also described as a prognostic indicator [4]. The LA is directly exposed to left ventricular (LV) diastolic pressure through then mitral valve, the size of the LA reflects the duration and severity of increased LA pressure following increased LV diastolic pressure [5]. LA function plays a central role in maintaining optimal cardiac output despite impaired LV relaxation and reduced LV compliance. Therefore, assessments of LA and LV function have a clinical impact, because an abnormal LA-LV coupling is a mechanism responsible for production congestion symptom. The recent development of two-dimensional (2D) speckle-tracking echocardiography has facilitated the early detection of LA and LV dysfunction in patents with cardiovascular risk factors [6-8]. The aim of this study was to detect the abnormalities of LA-LV coupling using 2D speckle tracking echocardiography in patient with preserved LV ejection fraction.

2. METHODS

2.1 Study Population

Our study population consisted of consecutive 200 asymptomatic patients who visited our laboratory between March 2010 and November 2010. No abnormal findings were found in all subjects on physical examinations and electrocardiogram. Twenty-two of the 200 patients were excluded for the following reasons: history of heart failure, poor image quality, atrial fibrillation, clinically significant valvular heart disease, coronary artery disease, previous valve replacement, and reduced LV ejection fraction (<50%). The remaining 177 patients were enrolled. Informed consent to participate in this study was obtained from all subjects.

2.2 Echocardiography

Echocardiographic studies were performed using a standard commercial ultrasound machine (Vivid e9, General Electric, Horten, Norway) with a phased-array transducer. Single cine loops were recorded from 2 standard apical planes consisting of 4-chamber and 2-chamber views. LV end-diastolic volume, LV end-systolic volume and ejection fraction were determined from apical 2-chamber and 4-chamber views using the modified Simpson's method. LA volume was measured using the biplane area-length method, and was indexed to the body surface area. The tracing of all the endocardial borders was performed manually 3 times, and the measurements were averaged. LV mass was calculated using the formula proposed by Devereux et al. and corrected by the body surface areas to derive LV mass index [9]. Conventional echocardiographic parameters were measured according to the recommendations of the American Society of Echocardiography [10]. The early diastolic transmitral velocity (E) and late diastolic transmitral velocity (A) were recorded in the apical 4-chamber view with the sample volume (5 mm) positioned in the direction of antegrade flow at the level of the mitral valve tips in diastole. The early diastolic velocity (Ea) and late diastolic velocity (Aa) of the mitral annulus in the 4-chamber view were measured. Ea and Aa were obtained at the septal and lateral sites of the annulus, and average values of these measurements were calculated for each patient.

2.3 Strain Analysis with Speckle-tracking Imaging

2.3.1 LV and LA strain analysis

Two-dimensional B-mode grayscale images were captured with a frame rate of 60 to 90 frames per second, and performed on 3 apical views (long-axis, 4-chamber, and 2-chamber). Image analysis was performed offline on a remote workstation using custom analysis software (EchoPAC version 112.0.1; GE Vingmed Ultrasound AS). LV longitudinal function was assessed by global LV longitudinal peak strain (GLS) using a semiautomatic algorithm (Automated Function Imaging, GE, Horten, Norway) (Fig. 1). Briefly, 3 points (2 annular and

1 apical) were positioned in each of the 3 apical projections enabling the software to track the myocardium semiautomatically throughout the heart cycle. The region of interest was adjusted to cover the thickness of the myocardium. Aortic valve closure was identified on continuous wave Doppler recording through the aortic valve. The tracking was carefully inspected and corrected manually when required. In case of unsatisfactory tracking, the segment would be excluded from the analysis. The Automated Function Imaging algorithm allowed GLS to be calculated for each of the 3 apical projections, if at least 5 out of 6 segments were sufficiently tracked. The algorithm then calculated overall GLS as the average value of all 3 projections. If GLS could only be assessed in 2 of 3 apical projections, we calculated overall GLS as the average of these 2. If GLS could not be assessed in ≥2 of the apical projections, the patient examination was classified as having image quality insufficient for LV strain measurements.

Two-dimensional grayscale images of the septal and lateral LA walls were acquired in the standard apical 4-chamber view. The LA endocardial border was traced manually and adjusted to cover the thickness of the LA walls, resulting in strain curves from a total of 6 atrial segments. From the average of all 6 resulting strain curves, we assessed peak atrial longitudinal strain during systole (PALS) as the maximum positive strain value during LV systole (Fig. 1). LA stiffness index was calculated as E/Ea/PALS, as described by Kurt et al. [11]. The patients were classified into 2 groups according to the GLS, as described by Marwick et al. [12]: impaired LV group (n=81; GLS>-18%) and normal LV group (n=96; GLS≤-18%).

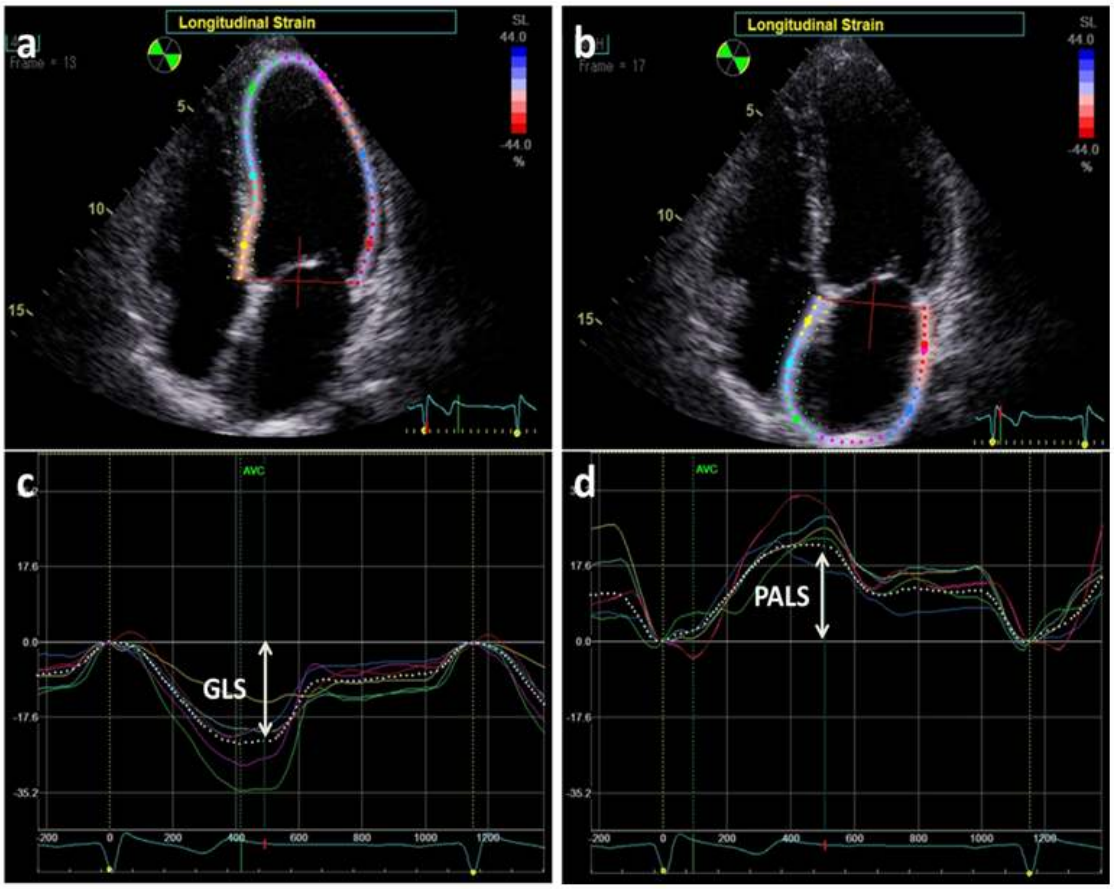

Fig. 1. Example of two-dimensional speckle-tracking of the left ventricle (a) ant the left atrium (b). The resulting strain curves for the left ventricle (c) and left atrium (d) are shown with markings corresponding to global left ventricular longitudinal peak strain (GLS) and peak left atrial longitudinal strain (PALS)

2.4 Statistical Analysis

Data are expressed as mean ± standard deviation (SD). Comparisons between the two groups were performed using the Student's t-test for continuous variables, or chi-square test for categorical variables. The correlation between LA strain, LA volume and LV strain were assessed by simple liner regression analysis. We assessed the interobserver and intraobserver variability for strain measurements from 15 randomly selected patients. For all analyses, a P value <0.05 was considered significant.

3. RESULTS

3.1 Baseline Characteristics and Echocardiographic Measurements

Table 1 lists the baseline clinical characteristics. There were no significant differences in age, sex, history of diabetes, and smoking between the 2 groups. Hypertension and hyperlipidemia were significantly greater in the impaired LV group than in the normal LV group (p<0.05, and p<0.05, respectively). Table 2 lists the echocardiographic characteristics of the 2 groups. As shown in Table 2, there were no significant differences in LVEF, LV end-diastolic volume and E/Ea between the 2 groups. Furthermore, LV end-systolic volume and LA volume index were significantly greater in the impaired LV group as compared to the normal LV group (p<0.05, and p<0.05, respectively).

3.2 Strain Measurements

Table 3 shows strain measurements in the 2 groups. GLS and PALS were significantly decreased in the impaired LV group compared with that in the normal LV group (GLA: -15.2±2.1 vs. -20.9±2.2, p<0.001; PALS: 21.0±7.2 vs. 25.5±7.4, p<0.001). Similarly, LA stiffness was significantly increased in the impaired LV group compared with that in the normal LV group (0.585±0.329 vs. 0.779±0.523, p<0.05). Intraobserver variability of LA strain and LV strain were 4.2 ± 3.1%, and 5.6 ± 4.9%, respectively. Interobserver variability of LA strain and LV strain were 5.3 ± 4.7%, and 7.1± 5.9%, respectively.

Table 1. Clinical characteristics

	Impaired LV group (n=81)	Normal LV group (n=96)
Age (yrs)	67 ± 11	68 ± 10
Male	48 (59%)	62 (66%)
Body surface area (m^2)	1.61 ± 0.14	1.72 ± 0.16
Systolic blood pressure (mmHg)	143 ± 14	127 ± 11*
Diastolic blood pressure (mmHg)	80 ± 8	79 ± 6
Heart rate (beat per minute)	75 ± 13	79 ± 6
Diabetes mellitus	14 (17%)	15 (15%)
Hypertension	45 (55%)	31 (32%)*
Dyslipidemia	29 (36%)	9 (9%)*
Current smoker	8 (10%)	8 (8%)

*$p<0.05$

Table 2. Echocardiographic characteristics

	Impaired LV group (n=81)	Normal LV group (n=96)
LV end-diastolic volume (ml)	76 ± 21	67 ± 19
LV end-systolic volume (ml)	28 ± 11	21 ± 8 *
LV ejection fraction (%)	63 ± 7	68 ± 20
LV mass index (g/m^2)	127 ± 38	112 ± 31
LA volume index (ml/m^2)	39 ± 13	34 ± 11*
E/A	0.9 ± 0.6	0.9 ± 0.3
Deceleration time of E(msec)	255 ± 66	229 ± 61
Ea (cm/s)	5.4 ± 1.6	9.2 ± 1.9
Aa (cm/s)	8.1 ±2.2	8.3±1.6
E/Ea	13.9 ± 5.5	13.4 ± 5.6

*$p<0.05$;
LV: Left Ventricular, LA: Left Atrial

Table 3. Strain measurements

	Impaired LV group (n=81)	Normal LV group (n=96)	*P* value
Global LV longitudinal peak strain (%)	-15.2 ± 2.1	-20.9 ± 2.2 ‡	<0.001
Global LA longitudinal strain (%)	21.0 ± 7.2	25.5 ± 7.4 †	<0.001
LA stiffness	0.779 ± 0.523	0.585 ± 0.329*	<0.05

3.3 Relationship between LA Strain, LA Volume, and LV Strain

In the normal LV group, there was no significant correlation between GLS and LA volume index (Fig. 2). Moreover, there were no significant correlations between GLS and LA stiffness and PALS (Figs. 3 and 4). On the other hands, in the impaired LV group, GLS significantly correlated with correlated with the LA stiffness and PALS (r=0.50, p<0.001; r=-0.37, p<0.001, respectively; Figs. 3 and 4). Similarly, GLS significantly correlated with LA volume index (r=0.36, p<0.001; Fig. 2).

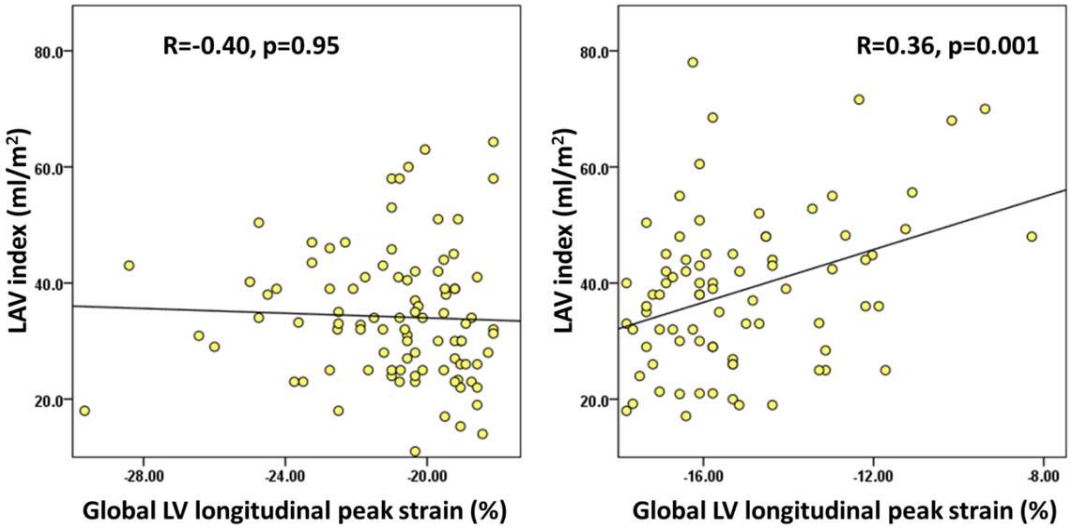

Fig. 2. Correlation between the global left ventricular longitudinal peak strain and left atrial volume index. Global left ventricular longitudinal peak strain in the normal LV group was not significantly correlated with the left atrial volume index (left). Global left ventricular longitudinal peak strain in impaired LV group was significantly correlated with the left atrial volume index (Right)

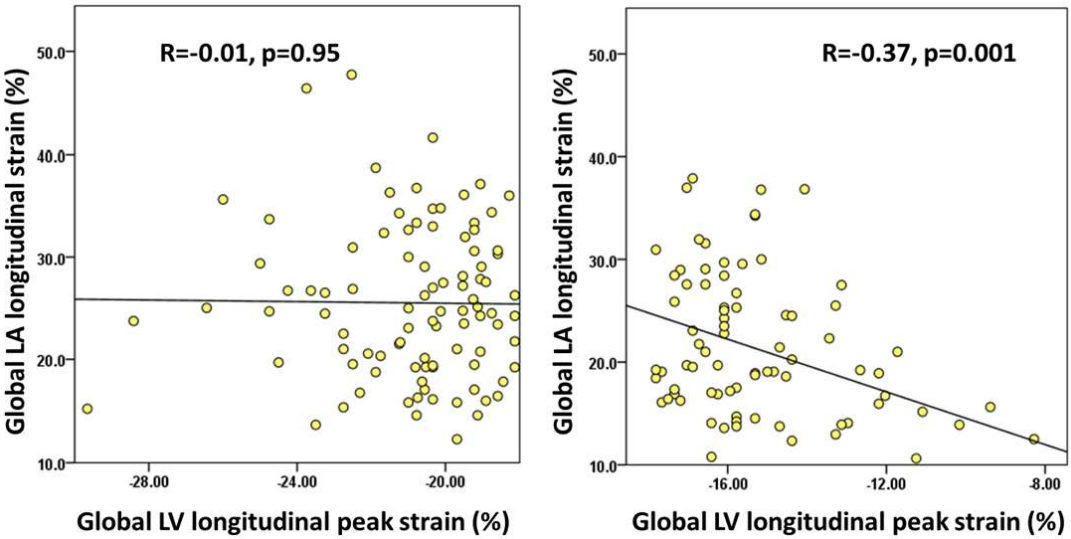

Fig. 3. Correlation between the global left ventricular longitudinal peak strain and peak left atrial longitudinal strain. Global left ventricular longitudinal peak strain in the normal LV group was not significantly correlated with the peak left atrial longitudinal strain (left). Global left ventricular longitudinal peak strain in impaired LV group was significantly correlated with the peak left atrial longitudinal strain (Right)

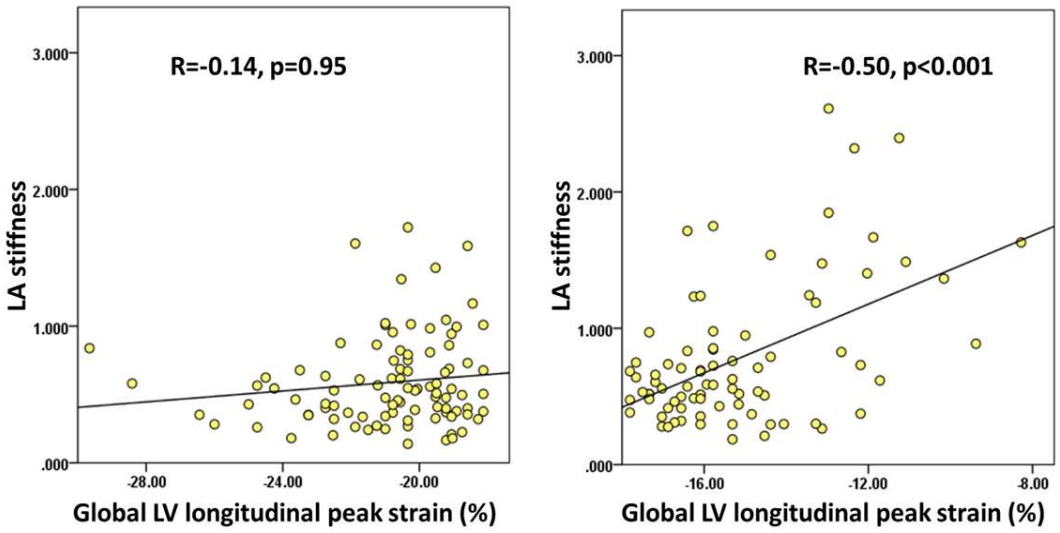

Fig. 4. Correlation between the global left ventricular longitudinal peak strain and left atrial stiffness. Global left ventricular longitudinal peak strain in the normal LV group was not significantly correlated with the left atrial stiffness (left). Global left ventricular longitudinal peak strain in impaired LV group was significantly correlated with the left atrial stiffness (Right)

4. DISCUSSION

The major findings of the present study were follows: (1) In patients with preserved longitudinal LV systolic function, LA structure and function are preserved; (2) LA structure and function are rapidly impaired in patients with reduced longitudinal LV systolic function.

Recent studies using speckle tracking echocardiography have reported that LV contraction is first impaired in the longitudinal direction in patients with cardiovascular risk factors [13,14]. Moreover, previous studies have shown that PALS, as a measure of LA reservoir function, exhibits distinct abnormalities in a number of conditions, including cardiovascular risk factors and heart failure with preserved LVEF [6,7,15]. LA is directly exposed to LV diastolic pressure through the mitral valve, the size of the LA reflects the duration and severity of increased LA pressure following increased LV diastolic pressure. LA function plays an important role in maintaining optimal cardiac output despite impaired LV relaxation and reduced LV compliance. Based on this, PALS has been proposed as a measure of LA intrinsic functional properties reflecting earlier stages of diseases processes. However, little has been reported whether LA reservoir function diminish in parallel to the decrease in LV longitudinal strain in patients with preserved LVEF. Barbier et al. [16] demonstrated that LA reservoir function is determined by the longitudinal descent of the cardiac base and LA chamber stiffness. However, in the present study, there was no significant correlation between GLS and PALS in patients with preserved longitudinal LV strain. We demonstrated that LA reservoir function (PALS and LA stiffness) did not diminish in parallel to the decrease in LV longitudinal strain in patients with normal longitudinal LV strain. On the other hands, we reported that LA reservoir function diminished in parallel to the decrease in LV longitudinal strain in patients with impaired longitudinal LV strain. The myoarchitecture of the LA is complex, with fibers predominantly arranged in two layers, the subendocardial layer (frequently composed of longitudinal fibers) and the subepicardial layer (mostly composed of circumferential fibers) [17]. Morris et al. [18] reported that LA subendocardial systolic and diastolic dysfunction was associated with the same fibrosis processes that affect the LV subendocardial fibers and to a lesser extent with LV filling pressure in patients with heart failure with preserved ejection fraction. We hypothesis that LV fibrosis causes progressive stiffening of the LV wall, resulting in ventricular longitudinal dysfunction. Similarly, the increase in interstitial fibrosis compromises the elastic properties of the atrial myocardium and promotes to impairment of atrial compliance and thus to a reduction of LA reservoir function, as assessed by PALS and LA

stiffness. Cameli et al. [19] reported that PALS showed the best diagnostic accuracy to detect LA fibrosis, and has an inverse correlation to LA endocardial thickness. In the present study, GLS significantly correlated with the LA stiffness, and PALS in LV longitudinal dysfunction patients. We speculate that LA fibrosis has not occurred at the stage of preserved LV systolic function. Moreover, at this stage, the decrease of longitudinal systolic strain depends on the descent of the cardiac base, not LV fibrosis. However, if once LA and LV fibrosis occur, LV longitudinal systolic dysfunction may cause the LA wall to become stiffer rapidly, deteriorating LA relaxation and stiffness.

4.1 Clinical Implications

In animal model, renin-angiotensin system inhibitors have been shown to prevent LA dilatation, atrial fibrosis and intra-atrial conduction slowing [20,21]. Some studies reported that renin-angiotensin system inhibitors prevent LA functional and structural dysfunction [22,23]. Recent studies have shown that fibrotic changes of the LA can be reversed with antifibrotic therapies, such as spironolactone, with a consequent improvement of the remodeling and function of LA [24,25]. The findings of this study suggest that LA and LV longitudinal strain might be considered a useful tool to detect early impairment in LA-LV coupling in patients with preserved LVEF. Thus strain measurements can be considered a promising method for the better quantification of LA function in patients with preserved LV function, allowing the potential identification of LA impairment, useful for deciding the timing of medication.

5. STUDY LIMITATIONS

Several limitations should be addressed in the present study. First, the number of patients was relatively small. Second, the study population was heterogeneous including subjects with and without cardiovascular risk factors. Similarly, the study population was heterogeneous including subjects with or without coronary artery disease. Although we excluded patients with evidence of coronary artery disease as indicated by electrocardiography and conventional echocardiography, and none of the study subjects complained of typical symptoms, the possibility that a small number of subjects with silent myocardial ischemia were included cannot be ruled out because of the lack of confirmation by stress testing or coronary angiography. Third, LA deformation was assessed as global LA strain in the apical 4-chamber view because the septal and lateral walls of LA were consistently imaged without significant dropout. Fourth, no histological data of LA and LV myocardium was available in the present study. The association between LA strain and histological alterations of LA myocardium is still speculative. In addition, histological study in asymptomatic patients from routine health checkups and outpatient facilities is likely to be considered unethical. Finally, no data was available for medical therapy and hemodynamic measurement of LA and LV function, because we used asymptomatic patients visited for routine checkup and from outpatient facilities. Therefore, future studies are needed to validate the findings of our study.

6. CONCLUSIONS

In patients with preserved longitudinal LV systolic function, LA structure and function are also preserved. However, LA structure and function are rapidly impaired in patients with reduced longitudinal LV systolic function. LV longitudinal systolic dysfunction may cause the LA wall to become stiffer rapidly, deteriorating LA relaxation and then causing increase of LA volume.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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