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Research Article

Simultaneous Analysis of Global and Regional Left Atrial Function Using Three-Dimensional Speckle-Tracking Echocardiography

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Abstract

Background

Accurate and reliable quantitative evaluation of LA size and function are necessary for the diagnosis and treatment of heart disease and prediction of prognosis.

Method sand results

Randomly selected 188 patients (male: 65%, 64 ± 16 years) visiting the laboratory for routine echocardiographic examination and 30 healthy subjects underwent three dimensional speckle tracking analysis (3DSTA) of the left atrium. Left atrial maximal and minimal volume, emptying fraction (LAEmpF), active ejection fraction (LAEjF), area change (AC) at peak (ACmax) and before atrial kick (ACpreA) were determined. Regional ACs in 16 segments of the left atrium were also calculated. Left atrial volumes and functional indices and global AC had excellent reliability (intraclass correlation: 0.84–0.99). Left atrial functional indices using 3D volumes and global ACs that represent left atrial reservoir (LAEmpF and ACmax) and active pump function (LAEjF and ACpreA) showed excellent exponential correlation (r^2 = 0.79 and r^2 = 0.78). Both LAEmpF and ACmax correlated significantly with E/e' (r^2 = 0.28 and r^2 = 0.25) and E/A in patients with LVEF <50% (r^2 = 0.41 and r^2 = 0.25). Regional AC showed significant variation among segments even in healthy subjects.

Conclusions

3DSTA enables quick, reliable, and simultaneous measurement of left atrial global and regional function. The indices calculated using 3DSTA have potential roles in the evaluation of left ventricular diastolic function.

Keywords: Left atrium; Left atrial function; Three-dimensional speckle-tracking analysis; Left ventricular filling pressure.

Introduction

Measurement of left atrial (LA) volume and function has become an essential issue because the number of patients with atrial fibrillation and/or heart failure has continued to grow [1]. Both LA size and functional indices have critical roles in determining the prognosis and risk stratification for various cardiovascular diseases [2, 3] because they are representative of the magnitude and duration of left ventricular (LV) diastolic dysfunction. Three-dimensional echocardiography (3DE) is a promising method of volume measurement with better accuracy and reproducibility than two-dimensional echocardiography (2DE) [4–7]. Volumetric indices calculated by 3DE have been reported to be better prognostic biomarkers in patients with various cardiovascular diseases [8–10], although studies using 3DE are limited compared with those using 2DE. However, LA functional parameters obtained by tissue Doppler and 2DE, including 2D speckle-tracking analysis (2DSTA), have been introduced as good predictors of worsening heart failure [11,12], atrial fibrillation [13–15], and cardiac events after myocardial infarction [16–18]. However, measurements of multiple indices for LA volume and wall deformation by 2DE and/or 2DSTA require time, sophisticated techniques, and complicated processes. Quick, easy, and accurate methods are required for clinical use.

The three primary objectives of this study were to assess the availability of LA volume and indices for global and regional atrial function using three-dimensional speckle-tracking analysis (3DSTA); to study the reliability of these parameters for the clinical use; and to assess the interrelationship between LA functional indices determined using 3DSTA and standard indices used to estimate LV-filling pressure.

Methods

Patients and healthy subjects

A total of 300 randomly selected patients (all the patients visiting the laboratory room 1 in the morning of regular two days a week) for the routine echocardiographic examination from July 2010 to June 2011 were enrolled in this study. Patients with atrial fibrillation (n = 8), frequent PVC and PACs (n = 7), moderate to severe mitral or aortic regurgitation (n = 20), mitral stenosis and mitral valve replacement (n = 12), and/or who had the history of

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pulmonary vein isolation (PVI) (n = 42) were excluded from the study. Furthermore, 21 patients with poor imaging results in the 3D data sets and two patients who refused the 3D data acquisition were also excluded. Therefore, a total of 188 patients were enrolled in the study. Thirty healthy subjects were selected for the study to determine normal reference values using 3DSTA. The healthy subjects satisfied the following criteria: no history of cardiac symptoms, hypertension, or diabetes; no use of medication; and normal results of physical examination, electrocardiogram, and echocardiogram. All subjects gave informed consent, and the local ethics committee approved the protocol.

Echocardiographic imaging

3DSTA imaging was performed from an apical position using a commercial scanner (Artida 4D, Toshiba Medical Systems, Nasu, Tochigi, Japan) with a fully sampled matrix array transducer (PST-25SX). Entire LA images were recorded. They consisted of four wedge-shaped sub volumes that were acquired over four consecutive cardiac cycles during a single breath hold. Sector width and depth were controlled to improve the temporal and spatial resolution of the images, resulting in a mean temporal resolution of 28 ± 6 volumes per s.

A standard 2DE examination was performed in all patients. 3DSTA was performed using an offline analysis system (Ultra Extend).

Global and regional LA function

Analysis of the LA volume and internal area change (AC) using three-dimensional speckle tracking echocardiographic images required the examiners to set several markers consecutively on two orthogonal apical views from the septal to lateral and posterior to anterior edges of the mitral valve ring. The LA endocardial border was then automatically detected by the 3D-tracking software (Toshiba Medical Systems) [19,20], after which the examiner could manually adjust the endocardial border. The software then automatically performed the global volume and segmental AC analyses through the entire cardiac cycle. The continuous values of global volume and internal surface AC for all 16 segments were simultaneously calculated and represented on graphic images (Fig. 1a) [21,22]. As the indices of LA function (Fig. 1b), left atrial emptying fraction (LAEmpF), ejection fraction (LAEjF), and distensibility index (DI) were calculated. Global AC (global AC: mean of AC in 16 segments) was also calculated and the maximum AC (ACmax) and AC before atrial kick (ACpreA) were compared with volume indices. Global longitudinal and circumferential changes of the LA wall were also calculated from the same data sets.

Intra- and inter-observer variability

Intra and inter-observer variability of global and regional surface AC was assessed in 40 randomly selected patients and 20 randomly selected healthy subjects. Intra-observer measures were performed 1 week apart, on average, in a random order.

To assess the inter-observer variability (test–retest reliability), a complete dataset was acquired by a second examiner within 10 min after the dataset acquired by the first examiner. These datasets were each subsequently analyzed without knowing the results of the other examination. The inter-observer variability was calculated using these two datasets.

Bland–Altman plots of three volumes (LAVmax, LAVmin, LAVpreA) and two area ACmax and ACpreA parameters were drawn.

Statistical Analysis

Data were analyzed using SPSS version 19.0 software (SPSS, Inc., Chicago, IL). Continuous data are presented as mean ± SD. Statistical significance was defined as $P < 0.05$. Correlation between each index was assessed using Pearson's correlation coefficient.

Intra- and inter-observer variability of the LA volumes and AC parameters, as continuous variables, were assessed using intraclass correlation (ICC) with a variance components procedure (restricted maximum likelihood method of estimation), where the observer and subject (or segment) were entered as random effects. The clinical significance of ICC was interpreted as follows: excellent: >0.80; good: 0.60–0.80, moderate: 0.40–0.60, poor: <0.40. Biases and limits of agreement (LOA) were also calculated to check the agreement between the two datasets of indices.

Table 1. Left atrial volume and area indices in healthy subjects

Number	30
Age	38.2 ± 18.5
Male sex (%)	17 (57%)
Body surface area (m^2)	1.72 ± 0.21
Heart rate (beats/min)	67 ± 11
2DE and Doppler indices	
LVEF(%)	62.3 ± 5.4
LAVImax(ml/m^2)	22.3 ± 3.8
E/A ratio	1.5 ± 0.28
E/e' ratio	6.5 ± 2.1
Three-dimensional speckle tracking echocardiography	
LAV Imax (ml/m^2)	26.4 ± 5.5
LAVI min (ml/m^2)	11.8 ± 2.5
LAVI preA (ml/m^2)	15.4 ± 3.8
LAEmpF(%)	54.9 ± 5.0
LAEjF (%)	24.6 ± 6.1
DI (%)	123 ± 27
DIpreA(%)	30.1 ± 10.2
ACmax (%)	75.8 ± 15.4
ACpreA (%)	24.4 ± 4.9

Values are means ± SD.

2DE:2-dimentional echocardiography; LVEF: left ventricular ejection fraction LAVImax:maximal left atrial volume index; LAVImin:minimal left atrial volume index; LAVIpreA: left atrial volume before atrial ejection; LAEmpF:left atrial emptying fraction;LAEjF:left atrial ejection fraction; DI:distensibilityindex; DIpreA:DI before atrialejection; ACmax:maximal area change;ACpreA:area change before atrial ejection.

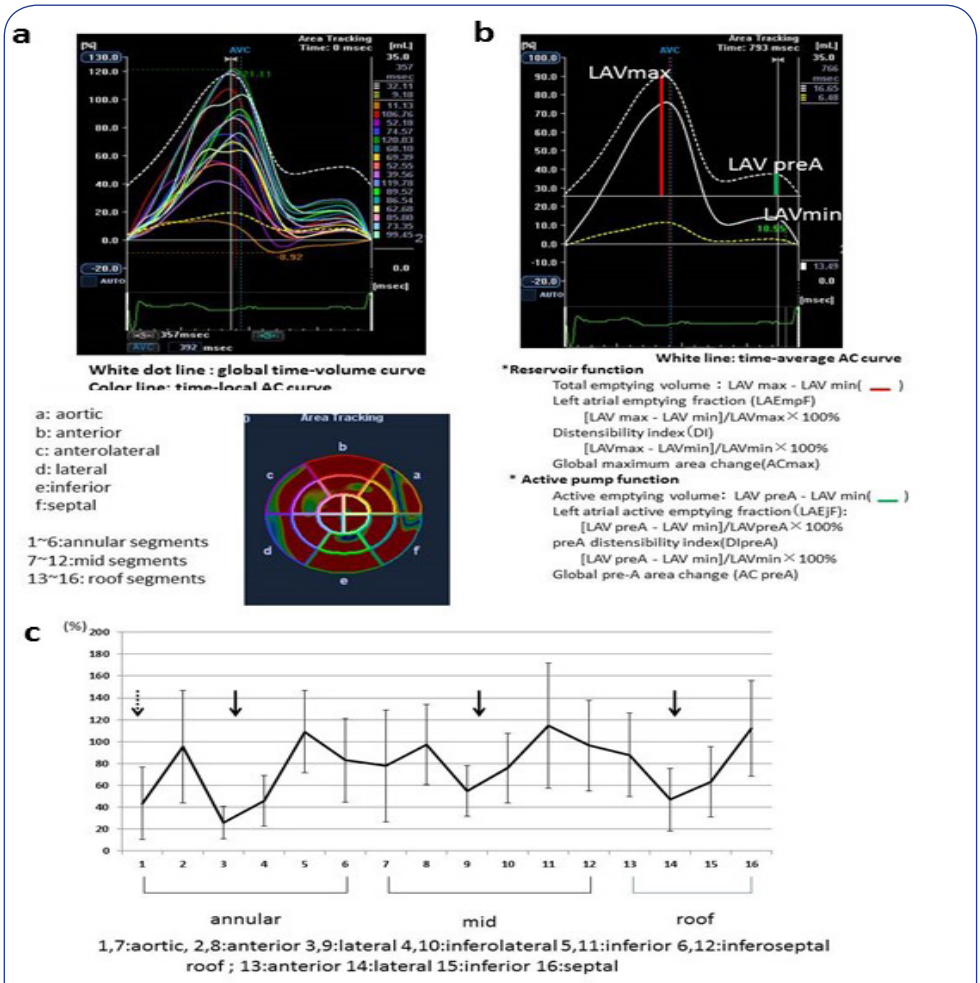

Figure 1: Three-dimensional speckle-tracking analysis of the left atrium

a. Time–volume graph and time–local area change graph calculated using three-dimensional speckle-tracking analysis (3DSTA) of the left atrium. Bull's eye shows the color-coded local peak area strain.

b. Time–global left atrial volume (white dot line) and time–global area change graph (white line) are shown with global left atrial indices.

LAVmax: maximum left atrial volume; LAVmin: minimum left atrial volume; LAVpreA: left atrial volume before atrial kick.

c. Differences in area change of left atrial local segments in healthy subjects

Results

Normal reference values

In the population of healthy subjects, the global LA volume and AC demonstrated normal distributions and small SDs, indicating relatively tight normal ranges (Table 1). However, AC tended to be lower in the area behind the aorta and the lateral wall (annular and roof) compared with the other segments (Fig. 1C). They were significantly lower than the highest AC, observed in the mid inferior segment.

Intra and inter-observer variability

Both intra- and inter-observer variability in the volumetric and area parameters of healthy and study patients had excellent ICCs (Tables 2). ICCs for volume indices LAEmpF, DI, and ACmax were >0.9, and those for LAEjF, DIpreA, and ACpreA were >0.8. For inter-observer variability, Bland–Altman plots of three volume and two area indices are shown in Fig. 2. No additive or relative errors were found in any of the indices. LOA for the volume indices were within 10 ml. LOA of ACmax and ACpreA were 13% and 11.2%, respectively.

Clinical characteristics and echocardiographic findings of study patients

The clinical characteristics and echocardiographic findings of study patients are shown in Table 3. Hypertension and dyslipidemia were

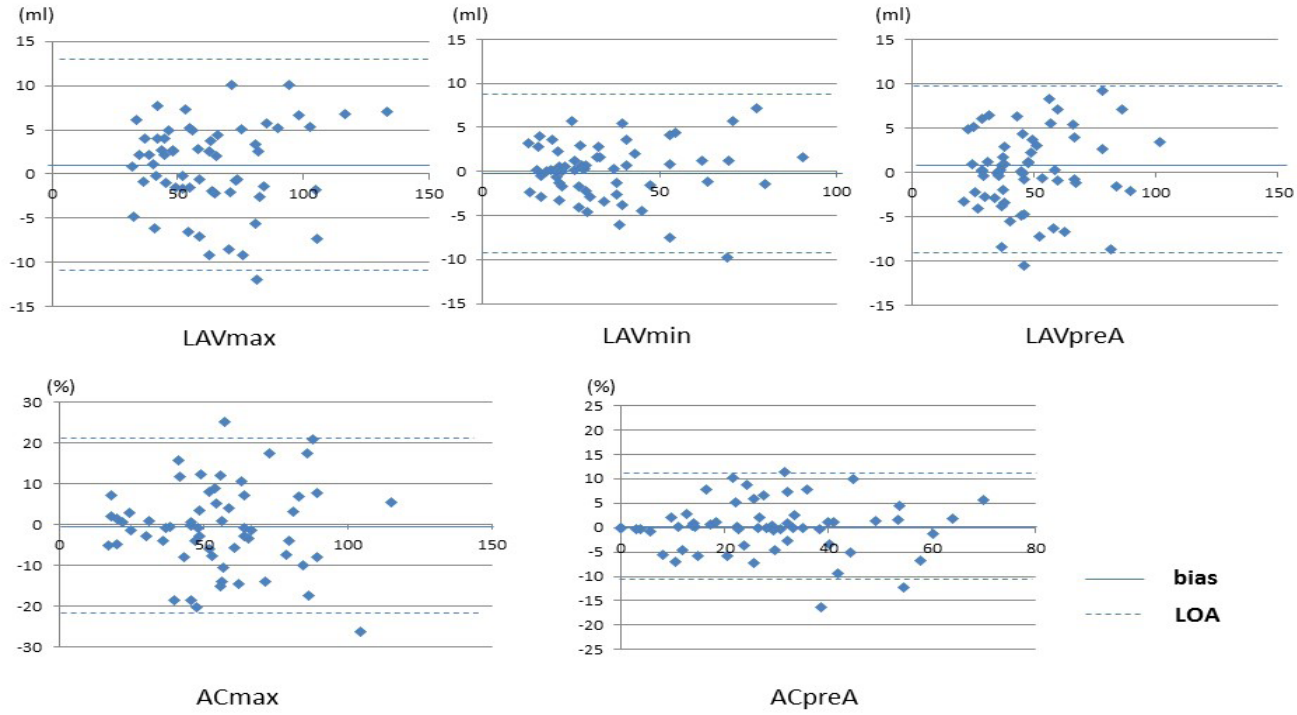

Figure 2: Bland–Altman plots of volume and area indices (inter-observer variability)

Table 2. Intra and Inter--observer variability of study patients

	Intra-observer variability			**inter-observer variability (test-retest variability)**		
	bias ± SD	ICC	SEM	bias ± SD	ICC	SEM
LAV max (ml)	−0.64 ± 4.12	0.988 (0.962–0.989)	2.95	0.62 ± 6.26	0.964 (0.926–0.983)	4.35
LAV min (ml)	−0.02 ± 3.13	0.984 (0.970–0.992)	2.21	0.23 ± 4.68	0.980 (0.959–0.990)	3.2
LAV preA (ml)	−0.08 ± 3.21	0.974 (0.953–0.987)	2.27	0.57 ± 4.46	0.958 (0.958–0.980)	3.12
LVEmpF (%)	0.49 ± 3.47	0.912 (0.895–0.934)	2.42	0.89 ± 3.91	0.912 (0.895–0.934)	2.75
DI (%)	−1.1 ± 13.7	0.913 (0.895–0.934)	9.7	0.22 ± 15.9	0.913 (0.895–0.934)	10.9
LAEjF (%)	0.32 ± 7.52	0.854 (0.832–0.874)	2.94	0.97 ± 5.7	0.854 (0.832–0.874)	2.94
DIpreA (%)	0.70 ± 9.81	0.843 (0.831–0.873)	6.88	0.94 ± 8.71	0.843 (0.831–0.873)	6.07
ACmax (%)	−1.1 ± 8.78	0.9 (0.89–0.935)	6.2	−1.24 ± 13.0	0.911 (0.89–0.935)	9.08
ACpreA (%)	−0.24 ± 3.70	0.853 (0.83–0.873)	2.64	−0.19 ± 5.6	0.853 (0.83–0.873)	3.94

ICC: intraclass correlation coefficient;SEM: standard error of measurement; LAVmax: maximum left atrial volume;

LAVmin: minimum left atrial volume; LAVpreA: left atrial volume before atrial ejection;

LAEmpF: left atrial emptying fraction; DI: distensibility index; LAEjF: left atrial ejection fraction;

DIpreA: distensibility index before atrial ejection; ACmax: maximum area change; ACpreA: area change before atrial ejection

frequent in their medical histories and over 50% had coronary artery disease. The maximum 3DLA volume index (3DLAVImax) was significantly larger [4 ml (10%); $P < 0.01$] than the maximum 2D LA volume index (2DLAVImax).

Correlation of global AC to global volume parameters of the left atrium

The shapes of the global time–AC curves were similar to those of the time–volume curves. ACmax had a significant, strong exponential correlation with LAEmpF ($r^2 = 0.89$, $p<0.001$) and a

Table 3. Clincial characteristics and echocardiographic findings of study patient

Number	188
Age	64 ± 16 (16–88)
Male sex(%)	123 (65)
BSA (m^2)	1.64 ± 0.19
Heart rate (beats/min)	66 ± 12
Medical history	
Hypertension	84 (45)
Diabetes mellitus	34 (18)
Dyslipidemia	62 (33)
Smoking	32 (17)
Medical diagnosis	
Coronary artery disease	58 (31)
Previous myocardial infarction	34 (18)
Hypertensive heart disease	28 (15)
Aortic valve disease (>moderate)	24 (13)
Dilated cardiomyopathy	16 (9)
Hypertrophic cardiomyopathy	18 (10)
Echocardiographic findings	
2D LVEDVI (ml/m^2)	53 ± 28
2D LVEF (%)	55 ± 16
2DLAVImax (ml/m^2)	37 ± 15
3DLAVImax (ml/m^2)	41 ± 14
3DLAVImin (ml/m^2)	23 ± 15
3DLAVI preA (ml/m^2	34±13
LAEmp F (%)	39 ± 13
DI (%)	69 ± 37
LAEjF (%)	25 ± 11
DIpreA (%)	36 ± 21
ACmax (%)	41 ± 24
ACpreA (%)	20 ± 13
E (cm/s)	73 ± 24
A (cm/s)	75 ± 61
E/A ratio	1.23 ± 0.83
Deceleration time(ms)	292 ± 63
E' average (cm/s)	5.9 ± 2.5
E/E' average	12.8 ± 5.5

Values are mean ± SDLVEDVI: left ventricular end-diastolic volume index;
LVEF: left ventricular ejection fraction; LAVImax: maximal left atrial volume index;
LAVImin: minimal left atrial volume index; LAVIpreA: left atrial volume index before atrial ejection
LAEmpF: left atrial emptying fraction; DI: distensibilityindex LAEjF: l eft atrial ejection fraction
DIpreA: DI before atrialejection; ACmax:maximal area changeACpreA: area change before atrial ejection

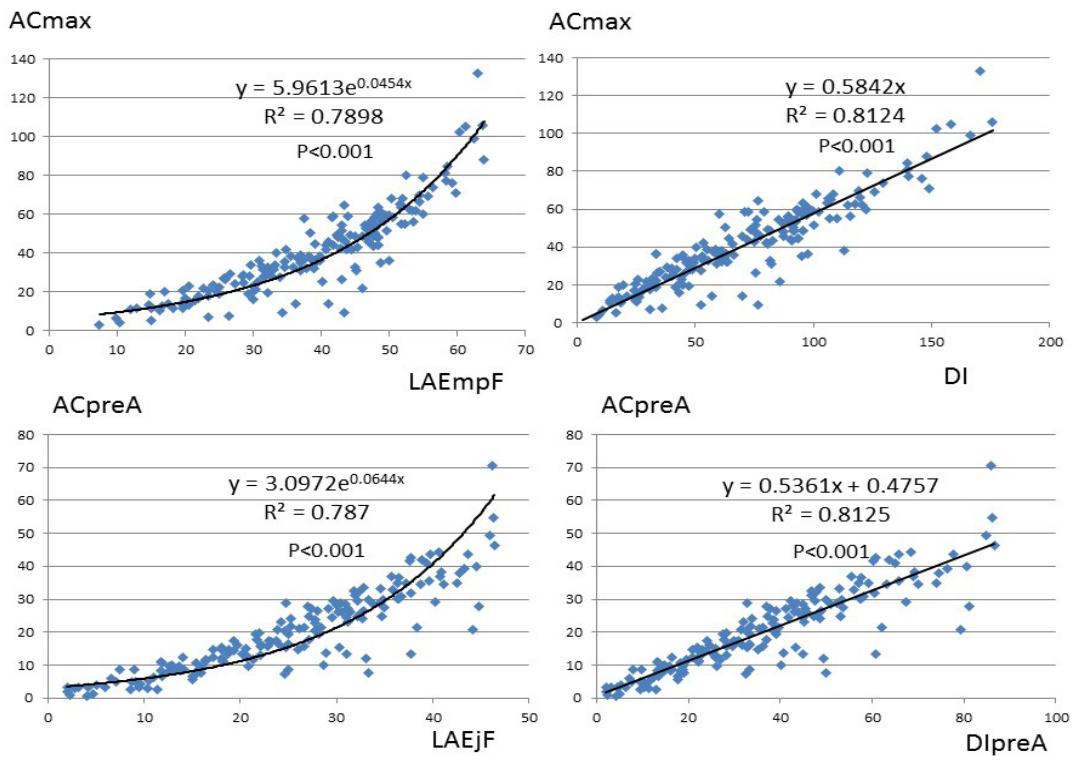

Figure 3: Correlations between global area change and global volume indices

Global ACmax and ACpreA showed excellent exponential correlations with LAEmpF and LAEjF, and linear correlations with DI and DIpreA.

ACmax: maximum area change; ACpreA: area change before atrial kick; LAEmpF: left atrial emptying fraction; LAEjF: left atrial ejection fraction; DI: distensibility index; DIpreA: distensibility index before atrial kick.

significant strong linear correlation with DI (r^2 = 0.91, p<0.001) (Fig. 3a). ACpreA also had a significant exponential correlation with LAEjF (r^2 = 0.89, p<0.001) and a significant linear correlation with DIpreA (r^2 = 0.90, p<0.001) (Fig. 3b).

Correlation of global volume and area indices with other LV diastolic indices

LA time–volume and time–AC curves and 3 dimensional color coded area change at different timing in representative cases according to the degree of diastolic dysfunction are shown in Fig 4. Both time–volume and global time–AC curves represented preserved reservoir function with compensated active pump function in patients with ASE (American Society of Echocardiography) grade I diastolic dysfunction (abnormal relaxation pattern). LAEmpF, LAEjF, global maximum AC, and ACpreA decreased in patients with grade II (pseudnormal pattern) and III (restrictive pattern) diastolic dysfunction. LAEmpF had a significant linear correlation (r^2 = 0.28, p<0.001) and ACmax had a significant exponential correlation (r^2 = 0.25, p<0.001) with E/e' (Fig. 4, upper panel). In the 50 patients with EF <50%, LAEmpF had a significant linear correlation (r^2 = 0.4, p<0.001) and ACmax had a significant exponential correlation (r^2 = 0.25, p<0.01) with E/A (Fig. 5, lower panel).

Discussion

Measurement of LA volume and function by 3DSTA

Calculation of the LA volume by ellipsoid approximation and disc summation using orthogonal 2D images is sometimes inaccurate in cases with left atrium that are compressed by a nearby obstacle, such as a vertebra, descending aorta or the lung. Measuring LA volume using 3DSTA or a direct method is considered ideal even for irregularly shaped atria [1,4,5].

There are several advantages to 3D acquisition of the left atrium, compared with LV. A narrower image angle allowed the scanning of the entire left atrium, which produced a higher volume rate and better time resolution. Identification of the internal surface area is easier in the left atrium than in LV, which overcomes the decrease in spatial resolution caused by the distance between the 3D probe and LA. Finally, adequate 3D images for analysis were obtained from 85% of the study patients. Both indices of LA global volume and internal AC had good reproducibility and reliability. Image acquisition time for one 3D image was only 1–2 min, and the time required for offline analysis to calculate the various indices was <5 min. In addition, the 3D data showed simultaneous multiplane orthogonal views. Therefore, no sophisticated technique to obtain orthogonal planes for calculating LA volumes using 2DE

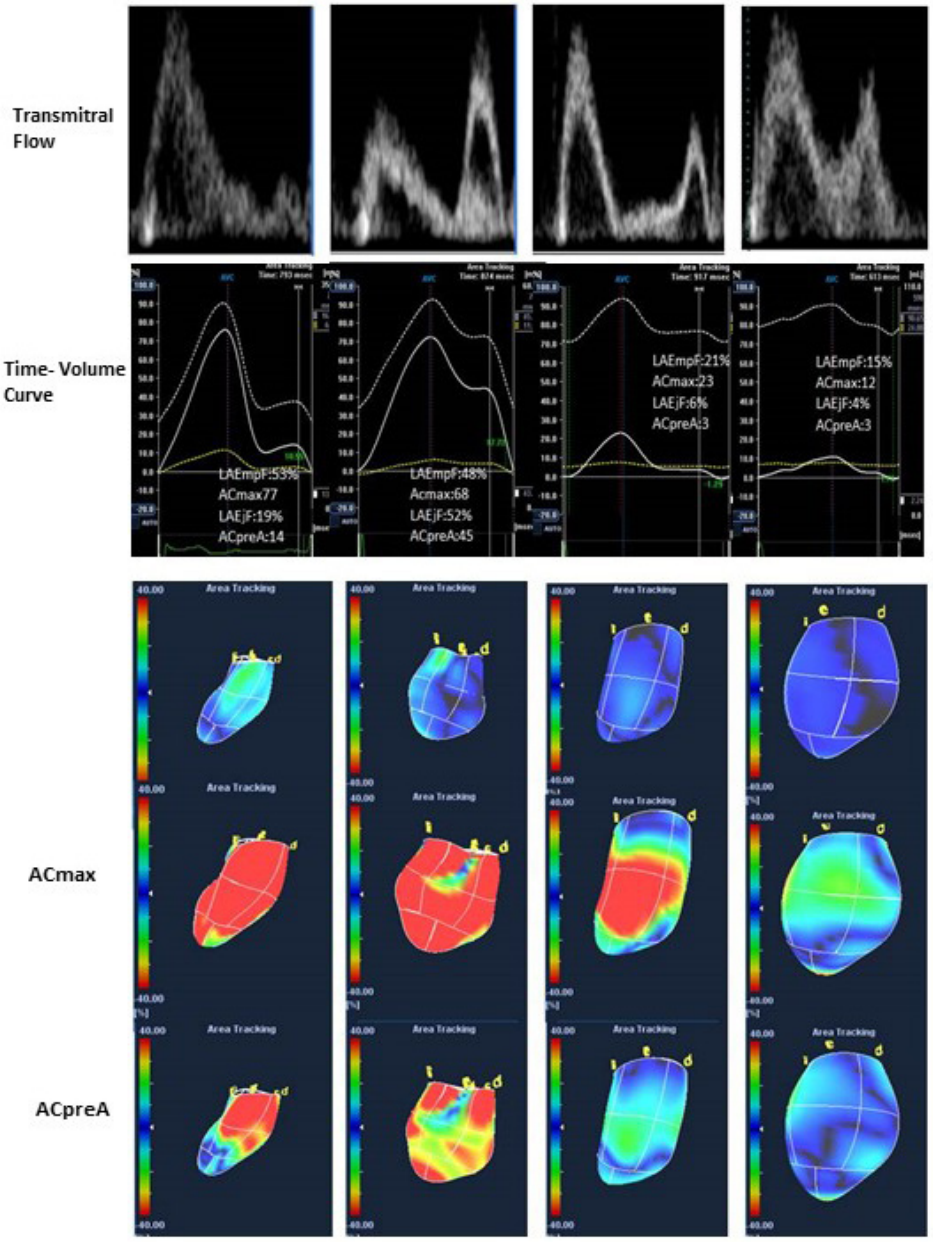

Figure 4: Representative left atrial three-dimensional speckle-tracking analysis from each grade of diastolic dysfunction

Preserved left atrial emptying fraction (LAEmpF) and atrial compensation are clearly shown in the case with grade I diastolic dysfunction, whereas a decrease in LAEmpF is evident in the cases with grade II and III diastolic dysfunction. Difference in regional AC at different timings in each patient is shown with color coding in lower panel.

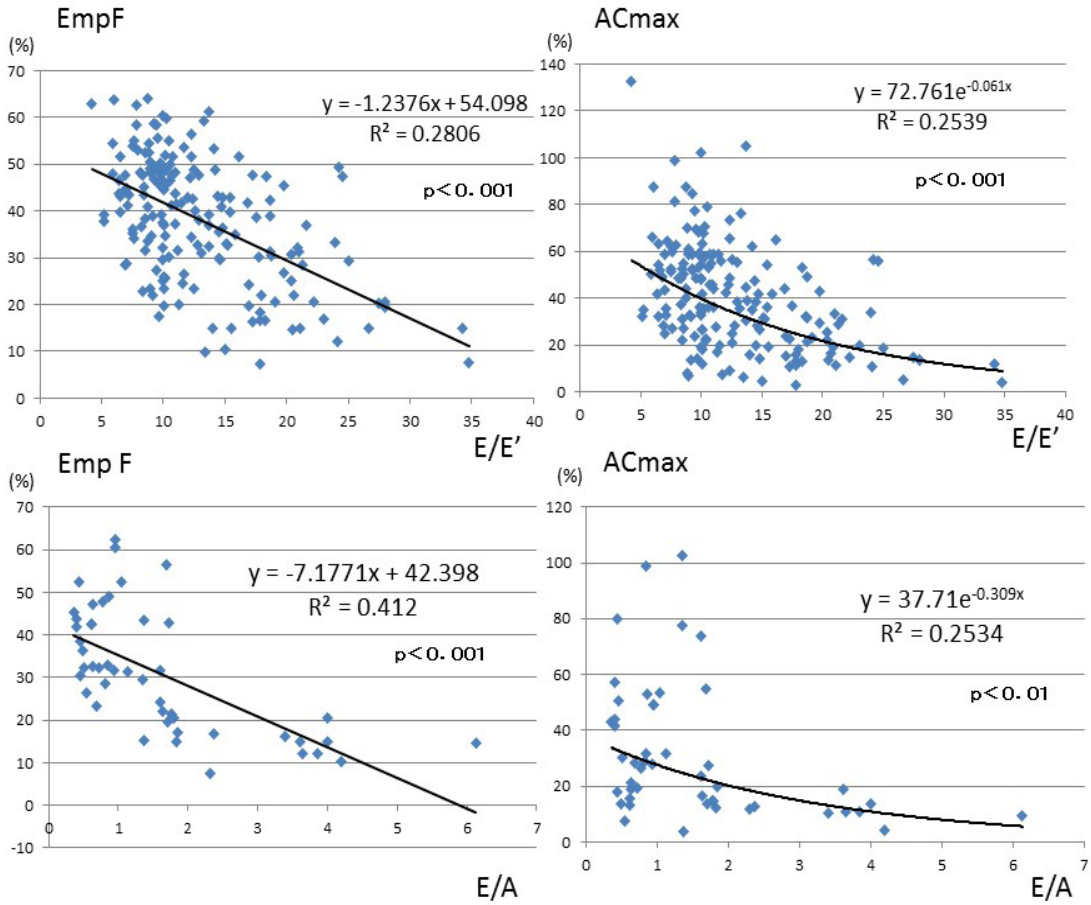

Figure 5: Correlations of global volume and area indices with other left ventricular diastolic indices

The correlation of left atrial emptying fraction with E/e' is shown in upper panel. The correlation of E/A in patients with left ventricular ejection fraction <50% is shown in lower panel.

was necessary. Both LA maximum and minimum volume have been reported to be strong predictors for the prognosis of future cardiovascular disease and events [23, 24]. 3DSTA enabled easy and quick measurement of these important parameters. In addition, it was possible to calculate several important functional parameters semi-automatically using one image at a time. All these advantages support the clinical use of 3DSTA for measuring LA volume and function.

Three dimensional indices for global reservoir and the left atrium active pump function using LA volume indices and AC

3D indices for the global reservoir and the left atrium active pump function are expected to reflect LA compliance and contraction more accurately than 2D LA longitudinal strain.

Considering the excellent correlation between LAEmpF and ACmax, as well as between LAEjF and ACpreA (Fig. 3), both LA volume and AC represented the LA reservoir and active pump function. LOAs were greater for ACmax, ACpreA, DImax, and DIpreA than for LAEmpF and LAEjF (Fig.2), as the denominator and numerator are reversed in indices of expansion. Future studies are necessary to evaluate which indices are better as predictors for various cardiac events.

Comparison to other parameters, which represent LV-filling pressure

The correlation coefficient between LAEmpF, DI and E/e' was not very high (Fig.5), but it was statistically significant ($p<0.001$). Although E/e' is an easily recordable index with much evidence that it can be used to predict LV-filling pressure [25, 26], the rates of intermediate values are high, and there are several limitations for the clinical use of this index [27–30]. Clearly, LA pressure and compliance of the LA wall are two strong factors determining LA expansion. In addition to these parameters, LV longitudinal shortening and distension may influence the longitudinal wall motion of the left atrium. In cases with stable LA wall compliance, DI may be a good indicator of the elevation of LA pressure. Hisao has already reported the superiority of the LA DI to the E/e' for the prediction of LV-filling pressure using 2D echocardiography [31]. However, the compliance of the LA local wall is influenced by several other factors, such as primary changes in the LA tissue, right atrial pressure, and compression by other organs, and/or pericardial effusion. The power of LA functional indices calculated

using the direct method and 3DSTA should be evaluated in the future.

Evaluation of regional atrial function using 3DSTA

Differences in local wall strain have also been reported using tissue Doppler and 2DSTA [32, 33]. 3DSTA clearly showed regional differences in compliance and contraction of LA wall through the 3D AC (Fig.1, Fig.4) with a shorter analysis time. It is not surprising that adjoining structures, such as the ascending aorta, bilateral lungs, and atrial septum, easily influenced area deformation. The inferior and anterior segments of LA had higher compliance and greater sensitivity to the change in the LA volume and pressure than other segments because there were no anatomical obstacles. The annular segment and part of the mid-anterior segments were open for the LA appendage and AC, including the change in tangent area of the LA appendage. The LA roof is open for four pulmonary veins and AC determined using 3DSTA also includes the sectional AC of these veins.

Even with these limitations, information about local LA wall deformation has potential clinical value. The left atrial wall is divided into three parts (appendage, anterior, and venous segments) that have different embryological origin [34]. The tissue of each segment has unique characteristics, and their extensibility is also considered different. Among these three segments, transthoracic 3DE does not have the ability to evaluate the volume and ACs of the LA appendage. However, the difference between the anterior and venous left atrium can be evaluated by AC calculated using 3DSTA. ACs excluding venous segments may be more important for the estimation of LA pressure because it would be the area most distensible and sensitive to pressure change. The evaluation of dyssynchrony and/or discoordination of the LA wall are also easily available using 3DSTA. Further clinical applications are expected, including right to left atrial interaction and the change in regional function after catheterization or surgical intervention for atrial fibrillation.

Limitations

In this study, we used the 16 atrial segments because the software was originally designed for the LV wall motion analysis. More ideal segmentation of the left atrium should be established from an embryological point of view, as previously described. Compared with 2DSTA, a complete 3DSTA dataset was only available for those patients who could regulate respiration and were without frequent atrial and/or ventricular premature beats because four stable sequential beats were necessary for combining images. However, we could acquire adequate images in almost 85% of study patients, which is enough numeral data for the clinical use of 3DSTA for LA analysis.

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