Journal of Cardiology (2012) 59, 329–336

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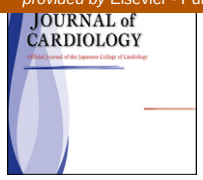

Original article

Left atrial appendage emptying fraction assessed by a feature-tracking echocardiographic method is a determinant of thrombus in patients with nonvalvular atrial fibrillation

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Received 29 July 2011; received in revised form 10 December 2011; accepted 2 January 2012
Available online 17 February 2012

KEYWORDS
Atrial fibrillation;
Atrial function;
Transesophageal echocardiography;
Thrombosis

Summary
Background: Left atrial appendage (LAA) thrombus increases the risk of thromboembolism in atrial fibrillation (AF), and LAA contractile function like emptying fraction (EF) should have physiological importance in thrombus formation. The aim of this study was to validate a velocity vector imaging (VVI) method for quantification of the LAA function and to elucidate echocardiographic parameters that are related to the presence of LAA thrombus in patients with nonvalvular AF.
Methods: We measured left atrial (LA) dimension and LAEF by VVI using transthoracic echocardiography, and LAA emptying velocity, spontaneous echo contrast (SEC), and LAAEF by VVI using transesophageal echocardiography (TEE) in 142 consecutive patients with nonvalvular AF. The patients were divided into two groups according to the presence ($n = 38$) or absence ($n = 104$) of LAA thrombus.
Results: There was a good correlation between the VVI method and manual-tracing method for LAAEF and LAEF of patients with AF ($r = 0.97$, $r = 0.96$, respectively, $p < 0.001$). LAAEF in AF with thrombus was significantly reduced compared with AF without thrombus ($16.9 \pm 3.1\%$ and

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0914-5087/$ – see front matter
doi:10.1016/j.jjcc.2012.01.002

29.0 ± 9.7%, $p < 0.001$). In multivariate logistic regression analysis, LAAEF, SEC, and prior stroke were independent determinants of LAA thrombus. Using 20% of LAAEF as a cutoff value, the sensitivity was 92% and specificity was 88% for LAA thrombus.
Conclusion: The VVI method was reliable in the measurement of LAAEF and LAEF compared with the manual-tracing method. LAAEF assessed by the VVI method using TEE was related to the presence of LAA thrombus.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia associated with increased mortality and morbidity [1—4]. Left atrial appendage (LAA) thrombus in patients with AF is a high risk factor for cardiogenic cerebral infarction. Echocardiographic parameters such as LAA peak emptying velocity (LAAPV) and spontaneous echo contrast (SEC) are proposed as important factors that are related to the presence of LAA thrombus in clinical practice [5—9]. LAA contractile function like LAA emptying fraction (EF) and LAA mean emptying velocity (LAAMV) should have a physiological importance in LAA thrombus formation [9]. Recently, a feature-tracking echocardiographic method has been developed based on speckle tracking in which ultrasound speckles within the image are tracked and strain is determined from the displacement of speckles in relation to each other, therefore providing an angle-independent parameter of cardiac function [10—12]. Using this method, time—LAA volume curve can be automatically and promptly provided. Thus, the evaluation of LAA and LA function by velocity vector imaging (VVI) method is thought to be useful in clinical practice. The aim of this study was to validate the LAA function parameter obtained with the VVI-method by comparison with the conventional manual tracing method and to elucidate echocardiographic parameters that were related to the presence of LAA thrombus in patients with nonvalvular AF.

Methods

Study protocol

We performed transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) in 171 consecutive patients with Holter electrocardiographically documented chronic AF for more than one month. There were 29 AF patients excluded from the present study because of the existence of mitral stenosis or mild-to-severe mitral regurgitation. We studied 142 patients with nonvalvular AF dividing them into two groups according to the presence ($n = 38$) or absence ($n = 104$) of LAA thrombus. There were 123 patients who received an anticoagulant drug (warfarin) to avoid thromboembolism according to CHADS2 score (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and prior stroke or transient ischemic attack) [13], when TTE and TEE were performed. LAA thrombus was defined as an echo-dense mass of more than 2 mm in diameter attached to the LAA wall. In addition, we studied 36 patients with sinus rhythm to validate the feasibility and reliability of the feature-tracking echocardiographic method for the quantification of LAA and LA function. The experimental protocol was approved by the ethics committee of our institution and informed consent was obtained from all patients.

Echocardiography

TTE and TEE were performed using an ACUSON sequoia 512 (Siemens, Mountain View, CA, USA) ultrasound system to validate VVI in the quantification of LAA and LA function. Echocardiographic parameters were obtained according to the standards of the American Society of Echocardiography [14]. For TEE, a 4—7 MHz multi-plane transducer with a 7.4-mm diameter pediatric probe was used to diminish patient discomfort: local oropharyngeal anesthesia with lidocaine was the only premedication as previously described [15]. Echocardiographic images were stored and transferred to a computer for off-line analysis. LAA and LA volumes in patients with sinus rhythm were measured at the end of atrial diastole just before mitral valve opening (maximal volume) and at the end of atrial systole at the onset of the R-wave in the electrocardiogram (ECG) just after mitral valve closure (minimal volume). The frame rate of the TTE imaging was 55—60/min and that of the TEE was 60—70/min. We measured LAA volume by two-dimensional TEE three times at three different angles from 70°, 80°, and 90° and used average values for further analysis to improve the accuracy of the LAA volume determined by VVI. LAA and LA volumes in patients with AF were measured during an identical cardiac cycle by the conventional manual-tracing method and by the VVI method with the feature-tracking echocardiography using off-line software (Syngo Velocity Vector Imaging, Siemens). The LAAEF and LAEF were calculated from the measured volumes and compared between the two methods. With the VVI method, the endocardial border of LAA and LA is visually identified by the user and manually outlined at first. The manual placement of an endocardial tracing over one frame is then automatically tracked throughout the cardiac cycle. The software allows editing of the initial trace and the endocardial velocity is derived as the ratio between frame-to-frame displacement and the time interval [10—12]. The velocity vectors in the two-dimensional plane are displayed throughout the cardiac cycle, representing displacement of the speckles in relation to each other along the endocardial contour of the LAA and LA (Fig. 1). The time—LA volume curves plotted by the speckle-tracking imaging method exhibited good agreement with those determined using the manual method [12]. LAAEF and LAEF were defined as (maximal volume − minimal volume)/maximal volume × 100% during a cardiac cycle using Simpson's method. In addition, LAAPV, LAAMV, SEC score (grade 0—4), LA dimension (LAD), and left ventricular (LV) ejection fraction were measured by the same methods as previously reported [5,9,16]. LAAMV profiles were obtained

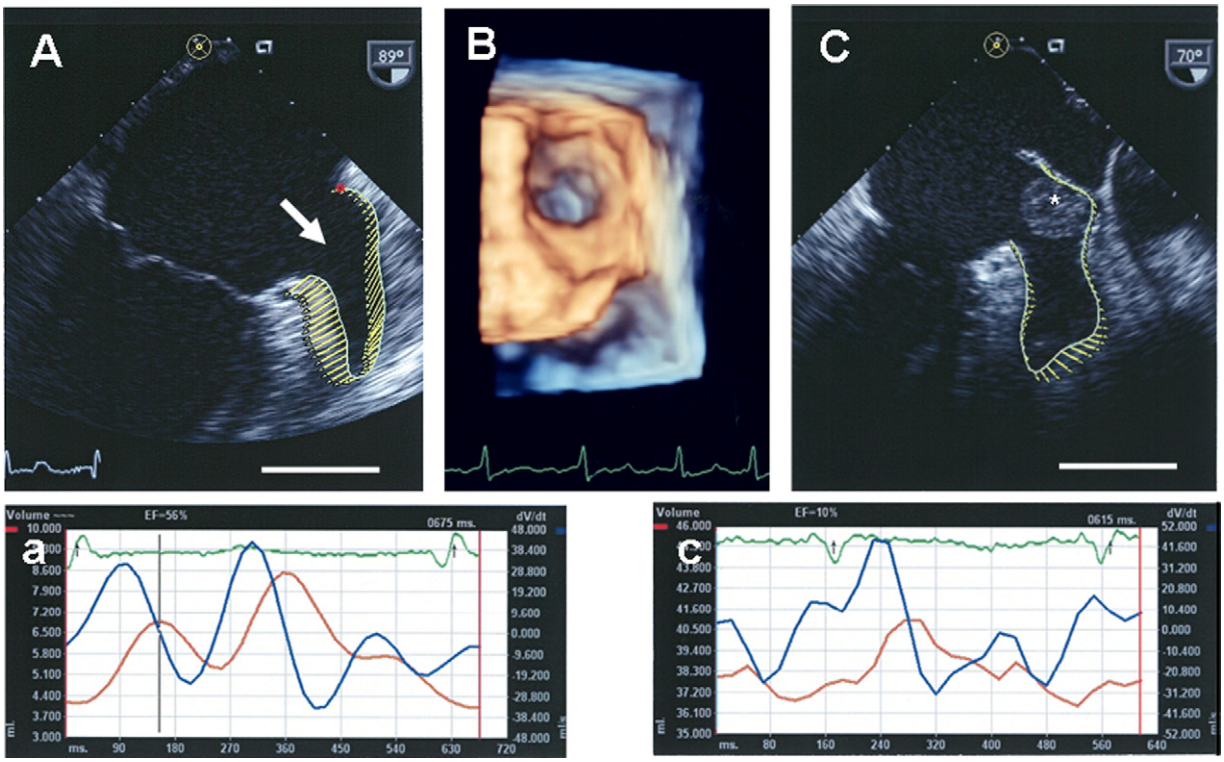

Figure 1 Representative image of left atrial appendage (LAA) and time—volume curve constructed by velocity vector imaging in patients with atrial fibrillation. (A) LAA of a patient without thrombus. Bar = 1 cm. (a) Time—volume curve is shown (Lower), time-*dv*/*dt* curve is shown (Middle), and electrocardiography is shown (Upper). (B) Three-dimensional view from a site indicated by white arrow in (A). Note that LAA was in the shape of a round. (C) LAA of a patient with thrombus. *: thrombus. Bar = 1 cm. (c) Time—volume curve is shown (Lower), time-*dv*/*dt* curve is shown (Middle), and electrocardiography is shown (Upper).

by pulsed wave Doppler at the medial, mid, and lateral portions of the orifice and at the deep mid portion of LAA. LAAPV was measured at the mid portion of the orifice of LAA. Average values of three cardiac cycles were analyzed in AF.

Reproducibility and reliability of LAAEF and LAEF by VVI method

We determined interobserver variability of LAAEF and LAEF in 30 randomly selected recordings that were measured by two observers in a blinded way in patients with sinus rhythm and 31 randomly selected recordings that were measured by two observers in patients with AF. Likewise, we determined intraobserver variability of LAAFE and LAEF in 30 randomly selected recordings that were measured two times by one observer in patients with sinus rhythm, and in 31 randomly selected recordings measured twice by one observer with a 7-day interval between the two measurements in patients with AF.

Statistical analyses

Data are expressed as the mean ± one standard deviation. The relationship between VVI method and manual tracing method in LAAEF and LAEF, and the relationship between LAAEF and LAEF by VVI method were tested by linear regression analysis. Categorical data were summarized as percentages and compared using a Chi-square test. Comparisons of echocardiographic parameters between the two groups were performed by an unpaired Student's *t*-test. Comparisons of SEC between the two groups were performed by Mann—Whitney U test. Comparisons of LAAMV among the four portions of the LAA were performed by analysis of variance followed by post hoc testing with the Fisher's least significant difference test. The optimal cutoff values for the determination of sensitivity and specificity for LAA thrombus in echocardiographic parameters were obtained from receiver operating characteristic (ROC) curve analysis. Multivariate logistic regression analysis was performed to identify the independent determinants of LAA thrombus. A p-value < 0.05 was considered to be significant. Statistical analyses were performed using Stat View version 5.0 (SAS Institute Inc, Cary, NC, USA).

Results

Reproducibility and reliability of LAAEF and LAEF by VVI method

The interobserver variability of LAAEF and LAEF by the VVI method was 1.8 ± 5.4% and 0.6 ± 5.4% in sinus rhythm and 1.1 ± 5.7% and 1.9 ± 4.9% in AF, respectively. The interobserver correlation coefficient was 0.96 for LAAEF and 0.95

for LAEF in sinus rhythm and 0.96 for LAAEF and 0.97 for LAEF in AF. The intraobserver variability of LAAEF and LAEF by the VVI method was $1.6 \pm 4.2\%$ and $0.6 \pm 3.7\%$ in sinus rhythm and $1.0 \pm 3.7\%$ and $1.9 \pm 3.9\%$ in AF, respectively. The intraobserver correlation coefficient was 0.98 for LAAEF and 0.98 for LAEF in sinus rhythm and 0.98 for LAAEF and 0.97 for LAEF in AF. It takes approximately 1 min (50 ± 13 s) to obtain LAAEF and LAEF by VVI method.

Patients' characteristics

The patients' clinical characteristics are listed in Table 1. There were no significant differences in gender, history of smoking, history of diabetes mellitus, history of hypertension, warfarin therapy, and prothrombin-international normalized ratio (PT-INR) between the AF group with and without thrombus. The averages of PT-INR in the two groups were within 1.6—2.6 that was recommended in elderly patients ≥70 years old by the Japanese Circulation Society. Significant differences were observed in age, duration of AF, CHADS2 score, and prior stroke. LAA thrombus was detected in 38 patients and 19 thrombi were located deep in the LAA, 18 were located at the lateral wall of the LAA and 4 were located at the medial wall of the LAA.

Echocardiographic parameters

There was a good correlation between the VVI method and manual-tracing method for LAAEF and LAEF of patients with AF ($r = 0.97$, $r = 0.96$, respectively, $p < 0.001$) (Fig. 2). LAAEF and LAEF by the VVI method for the AF patients were significantly reduced compared with those in sinus rhythm ($25.8 \pm 10.0\%$ and $55.9 \pm 12.1\%$, $24.7 \pm 7.9\%$ and $49.6 \pm 11.1\%$, respectively, $p < 0.001$). LAAEF and LAEF assessed by the VVI method in AF patients with thrombus were significantly reduced compared with those in AF without thrombus ($16.9 \pm 3.1\%$ and $29.0 \pm 9.7\%$, $18.4 \pm 4.3\%$ and $27.0 \pm 8.0\%$, respectively, $p < 0.001$) (Table 2).

LAAMV in 142 patients with AF varied significantly among the medial, mid, lateral, and deep mid portions of LAA (26.2 ± 12.3, 21.5 ± 9.8, 15.9 ± 8.4, 19.0 ± 9.2 cm/s, respectively, between deep and mid: $p = 0.045$; except between deep and mid: $p < 0.001$)

Determinants of LAA thrombus

Age, LAEF, SEC, LAAPV, LAAEF, CHADS2 score, and AF duration were tested in multivariate logistic regression analysis as confounding factors (Fig. 3). Multivariate logistic regression analysis was performed to identify the independent determinants of LAA thrombus. All variables with a p-value < 0.05 in an unpaired Student's t-test comparing LAA thrombus-positive with LAA thrombus-negative were included in multivariate logistic regression analysis. However, LAAMV was excluded because there was a strong correlation between LAAMV and LAAPV ($r = 0.90$, $p < 0.001$). In multivariate logistic regression analysis, LAAEF ($p < 0.001$), SEC ($p = 0.044$), and prior stroke ($p = 0.038$) were the independent determinants of LAA thrombus among the echocardiographic parameters (Table 3). The sensitivity, specificity, positive predictive values, and negative predictive values at the optimal cutoff values are listed in Table 4.

Discussion

The present study demonstrated that LAA and LA function could be assessed by a VVI based on a feature-tracking echocardiographic method compared with the traditional manual-tracing method. We also showed that LAAEF assessed by the VVI method has the feasible utility among the echocardiographic parameters for thromboembolic risk stratification. In multivariate logistic regression analysis, LAAEF was an independent determinant for LAA thrombus among the clinical and echocardiographic parameters.

Clinical implications of predicting LAA thrombus

AF is the most common sustained cardiac arrhythmia encountered in clinical practice with an overall prevalence of 0.4% in the general population, and increases with age [17,18]. Although guidelines for the management of patients with AF were established by the committee of the American College of Cardiology, American Heart Association, and the European Society of Cardiology, thromboembolic events related to AF result in significant morbidity and mortality [18—21]. It is common knowledge that anticoagulant therapy can reduce thromboembolic risk in patients with AF [22]. However, a large proportion of patients with AF, who will not develop thromboembolism may be exposed to the risks associated with warfarin therapy [23]. On the other hand, some patients with AF who have already had warfarin therapy suffered from cerebral embolism because of insufficiency of the effect of warfarin. The CHADS2 score was proposed as a method for thromboembolic risk stratification in routine clinical practice [13]. However, current risk stratification schemes used to predict thromboembolism in patients with nonvalvular AF have similar discriminatory ability, but the predictive ability is relatively poor [24,25]. Promising risk stratification is crucially needed to improve selection of AF patients who require strict anticoagulant therapy [26].

Thrombotic material associated with AF arises most frequently in the LAA. Thrombus formation begins with Virchow's triad of stasis, endothelial dysfunction, and a hypercoagulable state. TEE has been thought to be a sensitive and specific method to assess LAA function and detect thrombus formation [9,10,16,27]. We validated the VVI method for the quantification of LAAEF and LAEF and established the value of these parameters for LAA thrombus using VVI.

Velocity vector imaging for the detection of LAA thrombus

Currently, regional myocardial function of the LA and LAA in AF has been assessed by strain rate imaging and tissue Doppler [28,29]. It was reported that the mean LAAEF (percent area change) in 11 AF patients without thrombus was 18%, and also reported that the percent area change during a cardiac cycle of LAA in AF patients was reduced compared with those in sinus rhythm [29]. LAA contractile

Table 1 Patient clinical characteristics.

Number	AF without LAA thrombus ($n = 104$)	AF with LAA thrombus ($n = 38$)	p-value
Age (year)	64.7 ± 11.6	69.1 ± 9.9	0.004
Male, n (%)	80 (77)	30 (79)	0.80
Smoking, n (%)	33 (34)	13 (34)	0.87
Diabetes mellitus, n (%)	18 (18)	10 (26)	0.29
Hypertension, n (%)	51 (49)	23 (61)	0.22
Prior stroke, n (%)	4 (4)	10 (26)	<0.001
AF duration, n (year)	5.4 ± 6.1	8.4 ± 7.3	0.015
Warfarin therapy, n (%)	89 (86)	34 (89)	0.54
CHADS2 score	0.97 ± 1.02	1.68 ± 1.45	0.011
PT-INR*	2.0 ± 0.4	2.0 ± 0.4	>0.99

Age, AF duration, and PT-INR are expressed as the mean ± one standard deviation. AF, atrial fibrillation; LAA, left atrial appendage; PT-INR, prothrombin-international normalized ratio.

* Including patients who did not take warfarin.

Table 2 Echocardiographic parameters.

Number	AF without LAA thrombus ($n = 104$)	AF with LAA thrombus ($n = 38$)	p-value
LVEF (%)	56.6 ± 9.7	52.4 ± 7.0	0.004
LAD (mm)	47.4 ± 8.0	51.9 ± 7.7	0.015
Max LAV (mL)	121.7 ± 48.1	134.4 ± 52.4	0.17
LAEF (%)	27.0 ± 8.0	18.4 ± 4.3	<0.001
SEC score (0—4 grade)	1.2 ± 0.8	1.8 ± 1.0	<0.001
LAAPV (cm/s)	29.9 ± 12.4	20.4 ± 8.0	<0.001
LAAMV (cm/s)	23.7 ± 9.6	14.4 ± 6.5	<0.001
LAAEF (%)	29.0 ± 9.7	16.9 ± 3.1	<0.001

Numerical data are expressed as the mean ± one standard deviation. AF, atrial fibrillation; LAA, left atrial appendage; LAD, left atrial dimension; Max LAV, maximum left atrial volume; LVEF, left ventricular ejection fraction; LAEF, left atrial emptying fraction; SEC, spontaneous echo contrast; LAAPV, left atrial appendage peak velocity; LAAMV, left atrial appendage mean velocity; LAAEF, left atrial appendage emptying fraction.

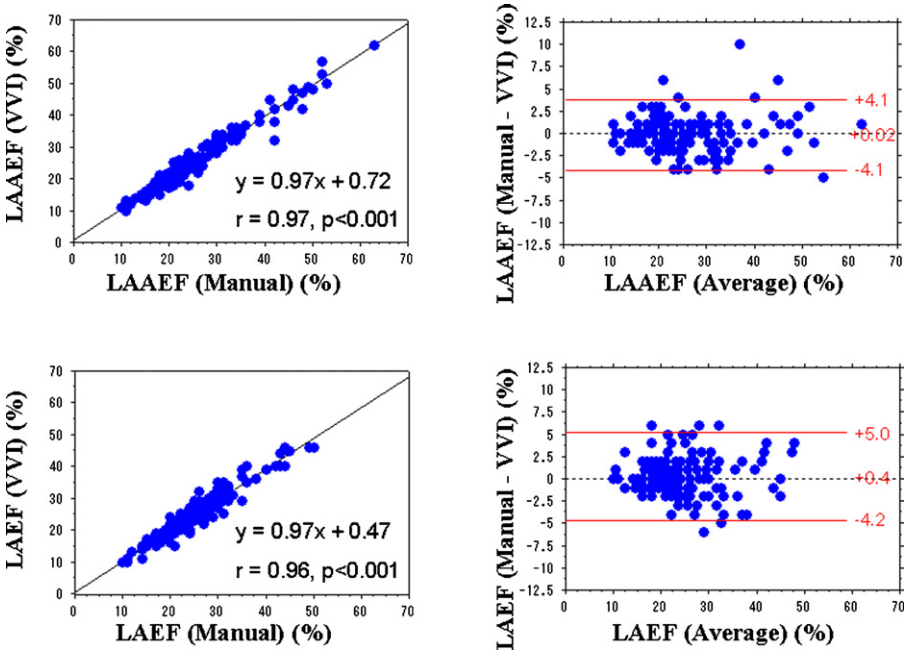

Figure 2 Comparison between manual-tracing and velocity vector imaging (VVI) method. Left: comparison of the left atrial appendage emptying fraction (LAAEF) and left atrium emptying fraction (LAEF) between VVI and the manual-tracing method in atrial fibrillation. Right: Bland and Altman plot.

Table 3 Multivariate logistic regression analysis for LAA thrombus.

Variables	Odds ratio	95% confidence interval	*p*-value
Clinical parameters			
Age	1.049	0.971–1.121	0.21
Prior stroke	21.14	1.187–376.5	0.038
CHADS2 Score	1.332	0.829–2.140	0.24
AF duration	1.004	0.920–1.096	0.61
Echocardiographic parameters			
LVEF	0.966	0.895–1.042	0.37
LAD	1.042	0.964–1.127	0.30
LAEF	0.942	0.805–1.102	0.45
SEC score	2.303	1.040–5.098	0.040
LAAPV	0.998	0.923–1.076	0.96
LAAEF	0.631	0.499–0.800	<0.001

LAA, left atrial appendage; LAD, left atrial dimension; LVEF, left ventricular ejection fraction; LAEF, left atrial emptying fraction; SEC, spontaneous echo contrast; LAAPV, left atrial appendage peak velocity; LAAEF, left atrial appendage emptying fraction.

Table 4 Accuracy of ultrasound parameters for the determinants of LAA thrombus.

Cutoff values	Sensitivity	Specificity	PPV	NPV
LAAEF (≤20%)	92 (88–96)	88 (83–93)	74 (67–81)	97 (95–99)
SEC (≥grade 2)	53 (45–61)	72 (65–79)	41 (34–49)	81 (75–87)

Data are percentages. Numbers in parentheses are 95% confidence intervals. LAA, left atrial appendage; PPV, positive predictive value; NPV, negative predictive value; LAAEF, left atrial appendage emptying fraction; SEC, spontaneous echo contrast.

function, like LAA emptying fraction, should have physiological importance in thrombus formation as well as filling and emptying dynamics. However, LAA contractile function has not yet been elucidated because it is time-consuming to measure LAAEF by the manual-tracing method [9]. It takes less than one minute to obtain LAAEF and LAEF by VVI method but more than twenty minutes by manual tracing method. In the present study, excellent correlations were observed between the VVI and manual-tracing methods for LAA and LA emptying fraction. The parameters measured by VVI were significantly different between the AF patients with and without LAA thrombus.

Study limitations

There are several limitations in the present study. First, LAA volume assessed by the VVI method using two-dimensional TEE might be different from the real LAA volume. It is not always easy to analyze the morphology of the LAA by

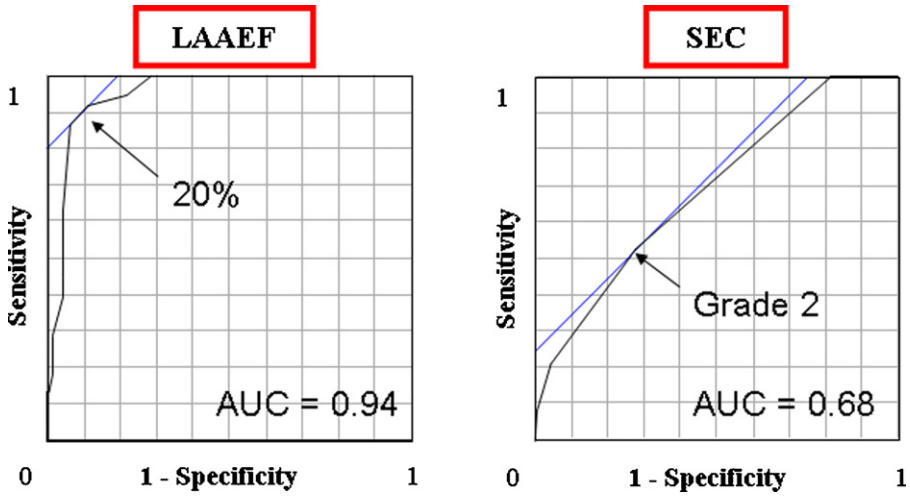

Figure 3 Receiver operating characteristic curves for the determination of left atrial appendage thrombus. LAAEF, left atrial appendage emptying fraction; SEC, spontaneous echo contrast; AUC, area under the curve.

two-dimensional TEE, because it was reported that the LAA is usually a multilobed structure in an autopsy study [30]. However, three-dimensional TEE revealed that LAA was in the shape of a round in a living body [31]. In addition, we measured LAA volume by two-dimensional TEE three times at three different angles from 70° to 90° and used average values for further analysis to improve the accuracy of the LAA volume determined by VVI. Furthermore, we determined LAAEF since this parameter is independent of the absolute LAA volume. Second, our findings are based on observations in a relatively small number of patients, particularly in the patients with both AF and thrombus. Third, we cannot draw conclusions regarding long-term outcomes, because the present study was a cross-sectional study without any additional follow-up of patients. A prospective study in a larger patient population on long-term outcomes is needed to elucidate which echocardiographic parameter is the most useful to predict LAA thrombus. The predictive accuracy of the selected cut-off value for LAAEF needs to be tested prospectively in an independent population to assess its clinical value to predict LAA thrombosis.

Conclusions

The VVI method was accurate and reliable in the measurement of LAAEF and LAEF compared with the manual-tracing method. LAAEF assessed by the VVI method using TEE was a useful determinant of LAA thrombus. AF patients with LAAEF less than 20% by TEE may require a strict regimen of warfarin therapy to avoid thromboembolic events.

Acknowledgments

The authors acknowledge the help of Mr Noriyuki Oonishi and Ms Ayaka Yamashita for ultrasound investigation, and Ms Ritsuko Tanaka and Mr Keisuke Moriya for preparation of the manuscript.

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