JACC: CARDIOVASCULAR IMAGING VOL. 4, NO. 8, 2011

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC. DOI:10.1016/j.jcmg.2011.03.019

Pre-Operative Left Atrial Mechanical Function Predicts Risk of Atrial Fibrillation Following Cardiac Surgery

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OBJECTIVES The purpose of this study was to examine whether left atrial (LA) mechanical function, as measured by LA total emptying fraction (TEF), is a predictor for the development of post-operative atrial fibrillation (POAF) following cardiac surgery.

BACKGROUND POAF is an important and frequent complication of cardiac surgery. LA enlargement has been reported to be a risk factor for POAF, but the relationship between LA mechanical function and POAF is not well understood. We examined the relationship between pre-operative LA function and POAF in patients without a history of atrial fibrillation.

METHODS A total of 101 subjects (mean age 64 ± 13 years) underwent pre-operative transthoracic echocardiograms and were followed for occurrence of POAF during the hospitalization for cardiac surgery. The left atrial maximum volume (LAVmax) and left atrial minimum volume (LAVmin) were measured and indexed to body surface area (LAVmaxI and LAVminI, respectively). LA TEF was calculated as: {[(LAVmax – LAVmin)/LAVmax] × 100%}. Univariate and multivariate analyses examined clinical and echocardiographic predictors of POAF.

RESULTS POAF occurred in 41% of subjects. Mean LA TEF was 49 ± 15%, mean LAVmaxI was 38 ± 15 ml/m^2, and mean LAVminI was 20 ± 13 ml/m^2. Age, LA TEF, and LAVminI were independent predictors of POAF. LA TEF was lower in patients with POAF compared with those without POAF (43 ± 15% vs. 55 ± 13%, $p < 0.001$), and patients with a LA TEF <50% had a high risk of POAF (odds ratio: 7.94, 95% confidence interval: 3.23 to 19.54, $p < 0.001$). Compared with LAVmaxI >32 ml/m^2, LA TEF <50% had higher discriminatory power for POAF, which remained significantly higher when adjusted for age ($p = 0.04$).

CONCLUSIONS LA TEF is an independent predictor of POAF and is a stronger predictor of POAF than LAVmaxI is. Impaired LA mechanical function may help to identify patients who are most likely to benefit from prophylaxis for POAF. (J Am Coll Cardiol Img 2011;4:833–40) © 2011 by the American College of Cardiology Foundation

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Manuscript received November 12, 2010; revised manuscript received March 18, 2011, accepted March 29, 2011.

JACC: CARDIOVASCULAR IMAGING, VOL. 4, NO. 8, 2011
AUGUST 2011:833–40

Post-operative atrial fibrillation (POAF) is an important and frequent complication of cardiac surgery, occurring in up to 40% of patients in the immediate post-operative period (1,2). Although the mechanism for the development of POAF is incompletely understood, it may be due to abnormalities in the underlying substrate (atrial fibrosis and remodeling) combined with perioperative electrophysiologic factors and other peri- and post-operative factors including atrial injury and ischemia, electrolyte imbalances, high sympathetic tone, and inflammation (2). Patients who develop POAF have increased mortality, morbidity, and length of hospital stay (3–5). It has even been reported that patients who develop this complication have increased late mortality up to 4 years after surgery (6). Although multiple risk factors have been identified (1,2,4,5), there is no clear standard for predicting or preventing POAF. Left atrial (LA) size and left atrial maximum volume (LAVmax) have been identified as risk factors for the development of POAF, but the findings have been inconsistent (7–9). In the general population, LA function, determined as LA total emptying fraction (TEF), has been found to be a stronger risk factor for the development of atrial fibrillation than LA volume (10). This study aimed to prospectively examine whether LA mechanical function, as measured by LA TEF, is a predictor for the development of POAF following cardiac surgery.

ABBREVIATIONS AND ACRONYMS

CI = confidence intervals

LA = left atrial

LAVmax = left atrial maximum volume

LAVmaxI = left atrial maximum volume index

LAVmin = left atrial minimum volume

LAVminI = left atrial minimum volume index

LAVp = left atrial volume at onset of atrial systole

OR = odds ratios

POAF = post-operative atrial fibrillation

TEF = total emptying fraction

METHODS

Consecutive subjects who had diagnostic quality pre-operative transthoracic echocardiograms performed at our institution and who underwent cardiac surgery within 3 months following the echocardiogram were prospectively identified and were followed for the occurrence of POAF during the post-operative hospital course. The mean time between echocardiogram and surgery was 14.1 ± 20.4 days. Subjects who were in sinus rhythm without any history of atrial fibrillation were eligible for the study. Patients undergoing Cox-Maze procedures were excluded, but patients undergoing all other types of cardiac surgery were eligible. The study protocol was approved by the Institutional Review Board.

Clinical variables. Baseline clinical data and demographics were obtained by review of the medical records. Clinical variables collected included age, sex, history of atrial fibrillation, history of heart failure, stroke, hypertension (defined if on treatment), diabetes, and renal insufficiency. Pre-operative cardiovascular medications were documented, including beta-blockers, antiarrhythmics, digoxin, and calcium channel blockers.

Echocardiographic variables. Pre-operative echocardiograms were reviewed without knowledge of clinical data, and offline measurements of variables were performed according to established methods (11). Measured variables included: diastolic and systolic ventricular chamber dimensions, interventricular septum and posterior wall thickness, maximum and minimum LA volumes, LA volume at onset of atrial systole (electrocardiographic P-wave), pulmonary venous systolic and diastolic forward flow velocities, pulmonary venous atrial reversal velocity and duration, mitral E-wave and A-wave velocities, mitral E-wave deceleration time, average of tissue Doppler septal and lateral mitral annulus early diastolic velocities (E′), and average of tissue Doppler septal and lateral mitral annulus late diastolic velocities (A′). Left ventricular mass was calculated and indexed to body surface area. Left ventricular ejection fraction was calculated using the modified biplane Simpson method. The degree of mitral regurgitation was numerically graded as none (0), trace/mild (1), moderate (2), or severe (3). Using the area-length method (11), LAVmax, LAV minimum (LAVmin), and LAV at onset of atrial systole (LAVp) were measured at ventricular end systole, ventricular end diastole, and prior to atrial contraction, respectively. LAVmax and LAVmin were indexed to body surface area (LAVmaxI, LAVminI). LA TEF was calculated as (12):

$$\{[(\mathrm{LAVmax} - \mathrm{LAVmin})/\mathrm{LAVmax}] \times 100\%\} \quad (1)$$

Active LA emptying fraction was calculated as: {[(LAVp − LAVmin)/LAVp] × 100%}, and passive LA emptying fraction was calculated as: {[(LAVmax − LAVp)/LAVmax] × 100%}.

Calculation of intraobserver (by the same investigator) and interobserver reproducibility (by a second investigator) for LA TEF was performed in 10 randomly selected subjects. The mean intraobserver difference was 2.5% ($p = 0.707$), and the mean interobserver difference was 2.8% ($p = 0.664$).

Outcome assessment. POAF was defined as an episode of atrial fibrillation of any duration that occurred during the post-operative hospitalization and that required either pharmacologic or

electrical intervention. This definition was chosen in order to identify a clinically significant outcome rather than telemetry-defined occurrences of self-limited atrial fibrillation. Patients were not routinely placed on prophylactic therapy for prevention of POAF. At our institution, there is no standardized protocol for treatment of POAF, although amiodarone is most commonly used as treatment once POAF occurs.

Statistical analysis. LA TEF was designated a priori as the primary variable to be examined. Univariate and multivariate analyses examined clinical and echocardiographic predictors of POAF. Data are presented as the number of observations for categorical variables and as means (± SD) for continuous variables. Clinical and echocardiographic characteristics of patients with and without POAF were compared using Student *t* test for continuous variables and chi-square test or Fisher exact test for categorical variables. Bonferroni correction was performed to adjust for multiple comparisons. Variables that were significantly associated with POAF on univariate logistic regression analysis (using a p value <0.05) were used to construct multivariate logistic regression models. LA TEF, LAVmaxI, and LAVminI were analyzed in separate multivariate regression models, to avoid multicolinearity. Odds ratios (OR) with 95% confidence intervals (CI) were calculated for relevant variables for prediction of POAF. Using previously defined cut points from the literature (7,10,13–16), the discriminatory power (C statistic) of LA TEF <50%, LAVmaxI >32 ml/m^2, and LAVminI <13 ml/m^2 for POAF were compared by chi-square test (17). Net reclassification improvement and integrated discrimination improvement were calculated for pertinent variables (18).

RESULTS

One hundred and one subjects were included in the analysis. Of 111 subjects, 10 were excluded due to inadequate pre-operative transthoracic echocardiograms. The clinical characteristics of the study population are shown in Table 1. The mean age of the subjects was 63.8 ± 13.1 years, and 65% were men. In the total group, 38 (38%) underwent valvular procedures: 9 (9%) mitral valve, 30 (30%) aortic valve, 2 (2%) tricuspid valve; 10 (10%) underwent myectomies; and 51 (50%) underwent coronary artery bypass graft surgery alone. POAF occurred in 41% (n = 41) of subjects. Of these subjects, all received medical treatment (98% with amiodarone), and 8 (20%) required electrical cardioversion in addition to medical therapy. On univariate logistic regression analysis, age ($p < 0.001$) and history of heart failure ($p = 0.025$) were the only clinical variables that were associated with POAF. There was no association between the use of pre-operative cardiovascular medications and risk of POAF.

Comparisons of clinical and echocardiographic variables in patients with and without POAF are shown in Tables 1 and 2. LA TEF was significantly lower in patients with POAF, and a majority of patients in the lower 2 quartiles of LA TEF developed POAF (Fig. 1). On univariate logistic regression analysis, echocardiographic variables

Table 1. Clinical Characteristics of the Study Population

	All Patients (N = 101)	POAF (n = 41)	No POAF (n = 60)	p Value
Age, yrs	63.8 ± 13.1	69.1 ± 10.5	60.2 ± 13.6	<0.001*
Men	66 (65)	25 (61)	41 (68)	0.608
Valvular surgery	38 (38)	18 (44)	20 (33)	0.362
CABG alone	51 (50)	17 (41)	34 (57)	0.169
Other (myectomy, ventriculotomy, aortic root repair)	18 (18)	9 (22)	9 (15)	0.524
History of heart failure	72 (71)	34 (83)	38 (63)	0.051
History of stroke/TIA	9 (9)	4 (10)	5 (8)	1.00
Diabetes mellitus	42 (42)	16 (39)	26 (43)	0.845
Hypertension	71 (70)	31 (76)	40 (68)	0.517
GFR <90 ml/m^2	55 (54)	22 (54)	33 (55)	0.917
Beta-blocker	73 (72)	28 (68)	45 (75)	0.586
Calcium channel blockers	27 (27)	14 (34)	13 (22)	0.268
Digoxin	1 (1)	0 (0)	1 (2)	1.00
Antiarrhythmic drug	2 (2)	1 (2)	1 (2)	1.00

Values are presented as n (%). *The p values are significant at alpha = $p < 0.0016$ (Bonferroni correction for multiple comparisons).
CABG = coronary artery bypass graft surgery; GFR = glomerular filtration rate; POAF = post-operative atrial fibrillation; TIA = transient ischemic attack.

Table 2. Echocardiographic Characteristics of the Study Population

	All Patients (N = 101)	AF (n = 41)	No AF (n = 60)	p Value
LVEF, %	48.4 ± 15.2	49.3 ± 14.3	47.8 ± 15.9	0.895
MR grade				0.206
None or mild	87 (86%)	34 (83%)	53 (88%)	—
Moderate	9 (9%)	4 (10%)	5 (8%)	—
Severe	5 (5%)	3 (7%)	2 (3%)	—
LVMI, gm/m^2	112.6 ± 41.4	126.3 ± 45.4	102.0 ± 38.1	0.661
LVEDD, cm	4.8 ± 1.0	4.6 ± 0.8	4.9 ± 1.0	0.181
LVESD, cm	3.4 ± 1.0	3.2 ± 0.9	3.5 ± 1.1	0.296
LAVmaxI, ml/m^2	37.8 ± 15.3	42.5 ± 17.7	34.5 ± 12.5	0.023
LAVminI, ml/m^2	20.2 ± 12.9	24.3 ± 13.7	17.4 ± 11.6	<0.001*
LA TEF, %	49.0 ± 15.2	43.2 ± 14.6	53.0 ± 14.5	<0.001*
E/A	1.2 ± 0.6	1.2 ± 0.7	1.2 ± 0.5	0.890
DT, ms	198.6 ± 68.4	208.5 ± 77.3	191.6 ± 61.0	0.456
PVs/PVd	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	0.356
PVAr, cm/s	24.1 ± 5.8	23.0 ± 5.0	24.8 ± 6.2	0.313
PVArD, ms	141 ± 29	142 ± 25	141 ± 32	0.615
E′, cm/s	6.2 ± 2.3	5.8 ± 2.0	6.4 ± 2.4	0.252
E/E′	15.8 ± 8.3	18.6 ± 7.9	14.1 ± 8.1	0.003
A′	7.8 ± 2.9	7.6 ± 3.0	8.0 ± 2.8	0.615

*The p values are significant at alpha = p < 0.0016 (Bonferroni correction for multiple comparisons).
A = peak atrial mitral inflow velocity; AF = atrial fibrillation; DT = deceleration time; E = peak early mitral inflow velocity; E′ = early myocardial relaxation; LA TEF = left atrial total emptying fraction; LAVmaxI = left atrial maximum volume index; LAVminI = left atrial minimum volume index; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic dimension; LVMI = left ventricular mass index; MR = mitral regurgitation; PVAr = pulmonary vein atrial reversal wave velocity; PVArD = pulmonary vein atrial reversal duration; PVd = pulmonary vein diastolic velocity; PVs = pulmonary vein systolic velocity.

associated with POAF included %LA TEF (p < 0.001), LAVmaxI (ml/m^2, p = 0.013), LAVminI (ml/m^2, p = 0.003), and mitral E/E′ (p = 0.018). A scatter plot of LA TEF in subjects with and without POAF is shown in Figure 2. On multivariate logistic regression analysis (including age, history of heart failure, LA TEF, and mitral E/E′), only age (OR: 1.11; 95% CI: 1.05 to 1.19, p < 0.001), and %LA TEF (OR: 0.90; 95% CI: 0.85 to 0.96, p < 0.001) were independent predictors of

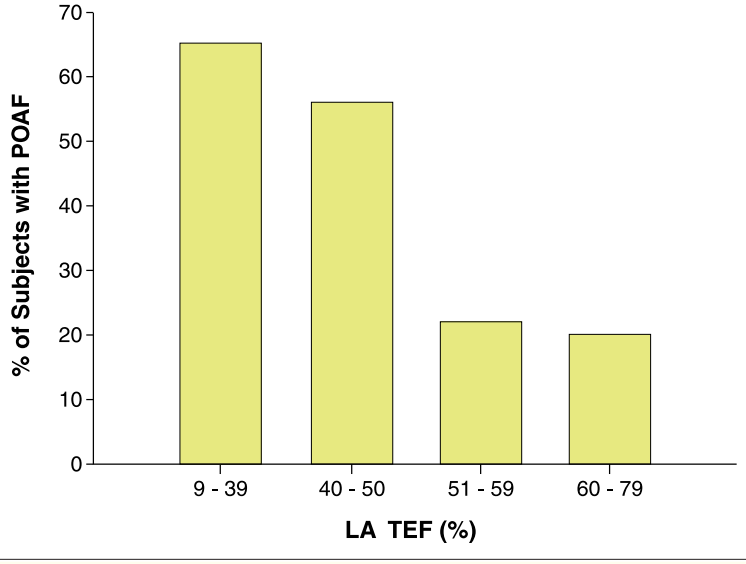

Figure 1. Development of POAF in Increasing Quartiles of LA TEF

The percentage of patients with post-operative atrial fibrillation (POAF) for each quartile of left atrial total emptying fraction (LA TEF) is shown. POAF occurred in the majority of patients in the lower 2 quartiles of LA TEF.

POAF. A separate multivariate model examining LAVminI (ml/m^2) demonstrated that LAVminI also remained a predictor of POAF, after adjusting for age, history of heart failure, and mitral E/E′ (OR: 1.09; 95% CI: 1.02 to 1.17, p = 0.013). The final multivariate regression model (which excluded both LAVminI and LA TEF) examined LAVmaxI and found that this variable was not an independent predictor of POAF in the study population (p = 0.073).

To further examine LA TEF, LAVmaxI, and LAVminI as predictors of POAF, the discriminatory power (C statistic) of previously established cut points of LA TEF <50%, LAVmaxI >32 ml/m^2, and LAVminI >13 ml/m^2 (7,10,13–16) were compared. LA TEF <50% was predictive of POAF with an OR = 7.94 (95% CI: 3.23 to 19.54, p < 0.001). Comparison of C statistics demonstrated that LA TEF <50% had stronger discriminatory power (OR: 0.737, 95% CI: 0.648 to 0.826) for POAF than LAVmaxI (OR: 0.567, 95% CI: 0.469 to 0.669, p = 0.0041) and trended toward higher discrimination than LAVminI (OR: 0.673, 95% CI: 0.587 to 0.759, p = 0.0942). After including age in a multivariable model, LA TEF <50% had an OR = 6.89 (95% CI: 2.64 to 17.97, p < 0.001) for occurrence of POAF and continued to have higher discriminatory power (p = 0.0426) than did LAVmaxI >32 ml/m^2 (Table 3). Net reclassification improvement for LA TEF compared with LAVmaxI was 0.34 (p = 0.0056) and absolute integrated discrimination improvement was 0.34 (p = 0.0041, relative 2.5-fold increase).

In order to further understand the relationship between LA mechanics and POAF, we also examined the association between POAF and active and passive LA emptying fractions. Patients with POAF had lower active LA emptying fraction (22.4 ± 14.4%) than the patients without POAF did (32.0 ± 16.3%, p = 0.041). Passive LA emptying fraction was similar in patients with POAF (30.2 ± 13.0%) and those without POAF (30.6 ± 13.9%, p = 0.904).

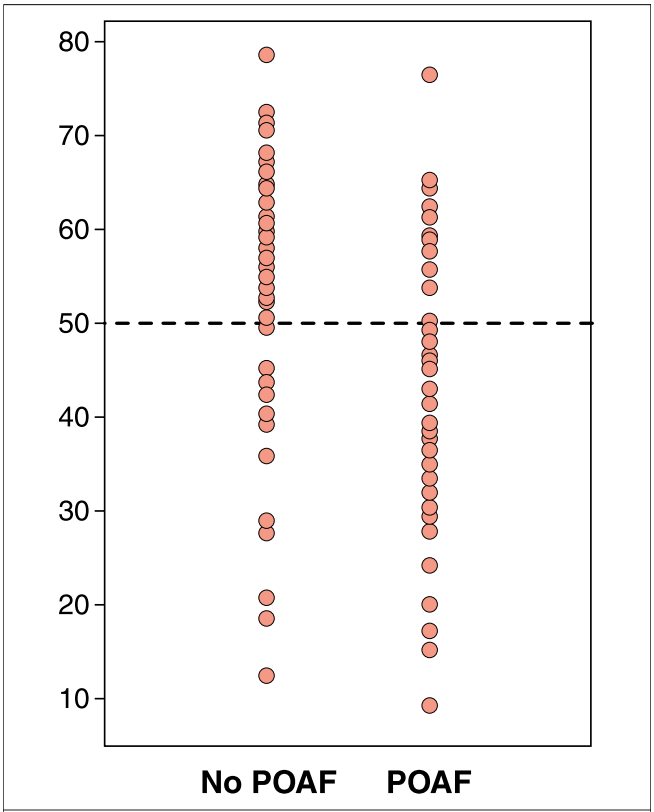

Figure 2. LA TEF and POAF

Scatterplot of LA TEF in patients with POAF and without POAF. In the group of patients with POAF, 71% had a pre-operative LA TEF <50. Among patients without POAF, 72% had a pre-operative LA TEF ≥50%. Abbreviations as in Figure 1.

DISCUSSION

In this study, we found that LA TEF is an independent predictor of POAF and is a stronger predictor of POAF than LAVmax. LA TEF also trended toward a stronger association with POAF than did LAVmin, but this difference was not statistically significant. To our knowledge, this is the first study to examine the relationship between POAF and pre-operative LA TEF derived from volumetric transthoracic echocardiographic methods.

Table 3. C Statistic Comparisons Using Established Cut Points for LA TEF, LAVmaxI, and LAVminI

	Model 1	Model 2	
	LA TEF <50%	LAVmaxI >32 ml/m^2	LAVminI >13 ml/m^2
OR (95% CI, p value)	6.89 (2.64–17.97, p < 0.001)	1.69 (0.70–4.08, p = 0.246)	4.32 (1.57–11.90, p = 0.0047)
C statistic	0.817 (0.725–0.909)	0.734 (0.636–0.833)	0.797 (0.702–0.886)
C statistic comparison	1 vs. 2*	2 vs. 3†	1 vs. 3‡

Multivariable models including age. *p = 0.0426; †p = 0.0573; ‡p = 0.4135.
CI = confidence interval; OR = odds ratio; other abbreviations as in Table 2.

LA size (both LA diameter and LA volume) has been examined in the general population as a predictor of atrial fibrillation (19–21). LA volume, compared with LA diameter, has been shown to provide a more accurate assessment of LA size, given the asymmetric nature of the chamber, nonuniform manner of enlargement, and the limitations of linear measurements obtained from 2-dimensional transthoracic echocardiography (22–24). Furthermore, LA volume index has been demonstrated to be a better predictor than LA diameter for cardiovascular outcomes and atrial fibrillation in the general population (25).

In the cardiac surgery post-operative population, echocardiographic and clinical predictors of POAF have been extensively studied, and older age is still the only consistently reproducible predictor (7–9,26–28). Osranek et al. (7) found that LAVmaxI >32 ml/m^2 was a potent predictor of POAF, but this has not been consistently replicated (8). LA TEF is a measure of LA function and may be more closely associated with LA mechanical and electrical dysfunction. It specifically measures the reservoir, conduit, and systolic booster function of the left atrium and likely reflects a later stage of atrial dysfunction than LA size alone (10,29–30). When the left atrium is chronically exposed to high filling pressures, dilation occurs and interstitial fibrosis develops, leading to electrical and mechanical remodeling that will ultimately affect function (29,31). In the general population, LA TEF has been demonstrated to be a stronger predictor of atrial fibrillation than maximum LA volume (10), and LA TEF may thus add incremental value and information to assessments of LA size. There are also data to suggest that LAVmin may be a stronger predictor than LAVmax for cardiovascular outcomes in both the general population and in patients with myocardial infarction (16,32). LAVmin reflects both the extent of chronically elevated filling pressures and the efficacy of atrial emptying, and in our multivariate analysis, this was a stronger predictor of POAF than LAVmax was. Similar to LA TEF, LAVmin may reflect a later stage of atrial dysfunction when compared with LAVmax, and to our knowledge, LAVmin has not previously been investigated as a predictor for POAF. The data from the current study also indicate that POAF is primarily associated with reduced active LA emptying fraction, rather than reduced passive LA emptying fraction.

Small intraoperative studies have examined LA TEF in the cardiac surgery post-operative population (27,28), but results have been mixed. These studies, however, had limitations including the use of area-based methods of calculating atrial function, the use of intraoperative studies, the use of transesophageal echocardiograms, and the exclusion of patients undergoing valvular procedures. Intraoperative conditions may have affected hemodynamics and echocardiographic parameters, and the left atrium is often difficult to completely visualize on transesophageal echocardiography, potentially leading to underestimation of LA size. The current study is the first to report pre-operative, volume-derived LA TEF as a predictor of POAF, and we found that it was a stronger predictor than LA volume alone.

POAF is a clinically important and common post-operative complication, and prior studies have shown that prophylaxis may be possible with treatments such as beta-blockers, sotalol, amiodarone, and atrial pacing (33–35). Effective protocols such as the amiodarone protocol used in the PAPABEAR (Prophylactic Oral Amiodarone for the Prevention of Arrhythmias Early After Revascularization, Valve Replacement, or Repair) study do require pre-operative initiation and are associated with side effects such as bradycardia and prolongation of QT interval corrected for heart rate (35). It would therefore be ideal to have a simple parameter such as LA TEF that could identify patients at the highest risk for development of POAF, allowing for selective prophylaxis of those who are most likely to benefit.

Study limitations. A limitation of this study is that it included only patients who had adequate quality transthoracic echocardiograms performed at our institution prior to surgery, which could potentially bias the study population. However, the incidence of post-operative atrial fibrillation in this group was similar to the incidence reported in other recent studies of post-operative atrial fibrillation, suggesting that the study group was not biased toward a higher risk population (7). An additional limitation is the relatively small size of the patient population. On the other hand, the study is strengthened by inclusion of patients undergoing all types of cardiac surgery, increasing the generalizability of the findings, and the use of a clinically relevant definition of POAF. Instead of intraoperative transesophageal echocardiography, we used pre-operative transthoracic echocardiography, which is easier to obtain and can give practitioners an opportunity to use the information that is obtained to prophylactically treat patients against POAF.

CONCLUSIONS

LA TEF is an independent predictor of POAF and appears to be a stronger predictor for the development of POAF than LAVmax. LA TEF, which can be easily calculated from 2-dimensional transthoracic echocardiography, may be a useful method for pre-operatively identifying patients with impaired LA mechanical function who are most likely to benefit from prophylaxis for POAF.

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Key Words: atrial fibrillation ■ cardiac imaging ■ echocardiography ■ left atrium.