

Preoperative left atrial dysfunction and risk of postoperative atrial fibrillation complicating thoracic surgery

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Objective: Postoperative atrial fibrillation complicating general thoracic surgery increases morbidity and stroke risk. We aimed to determine whether preoperative atrial dysfunction or other echocardiographic markers are associated with postoperative atrial fibrillation.

Methods: In 191 patients who had undergone anatomic lung or esophageal resection, preoperative clinical and echocardiographic data were compared between patients with and without postoperative atrial fibrillation. Presence of postoperative atrial fibrillation lasting more than 5 minutes during hospitalization was detected using continuous telemetry or 12-lead electrocardiography. Maximal left atrial volume and indices of left atrial function were assessed.

Results: Patients with postoperative atrial fibrillation (33/191, 17%) were older (71 ± 5 years vs 64 ± 12 years, $P < .0001$), were taking β -blockers more often, had greater left atrial volume, had decreased left atrial emptying fraction, and had lower E' and A' septal velocities compared with patients without postoperative atrial fibrillation. The incidence of postoperative atrial fibrillation in patients with left atrial volume 32 mL/m^2 or greater was 37% (11/30) and greater than in those with left atrial volume less than 32 mL/m^2 (14%, 22/160, $P = .002$). Length of hospital stay was significantly increased in patients with postoperative atrial fibrillation compared with patients without ($P = .04$). Older age was significantly associated with greater β -blocker use and left atrial volume and lower left atrial emptying fraction. On multivariate analysis, lower left atrial emptying fraction (odds ratio, 1.03 per unit decrement; 95% confidence interval, 1.002–1.065; $P = .04$) and preoperative use of β -blockers (odds ratio, 2.82; 95% confidence interval, 1.18–6.77; $P = .02$) were the only independent risk factors associated with postoperative atrial fibrillation.

Conclusions: These data show that an echocardiogram before major thoracic surgery, increased use of preoperative β -blockers, and decreased left atrial emptying fraction were associated with postoperative atrial fibrillation. Echocardiographic predictors of left atrial mechanical dysfunction may prove clinically useful in risk stratifying patients in whom postoperative atrial fibrillation is more likely to develop and to benefit from prevention strategies aimed at mitigating atrial function before surgery. (J Thorac Cardiovasc Surg 2012;143:482-7)

Atrial fibrillation (AF) occurs in 3% to 30% of patients after noncardiac thoracic surgery depending on the patient's age and whether an anatomic surgical resection is performed.¹⁻³ The clinical symptoms, time of AF onset, and natural course of the arrhythmia are similar whether a patient has cardiac, thoracic, or other surgery.¹⁻³ In virtually all studies of postoperative atrial fibrillation (POAF), increasing age has consistently been shown to be

an independent preoperative risk factor regardless of type of surgery.¹⁻⁵ Some studies have demonstrated that pre-existing conditions, such as congestive heart failure and valvular heart disease, increase the risk for POAF in patients who do not undergo cardiac surgery.¹ The mechanism responsible for POAF is not entirely clear but may represent a combination of the effects of altered sympathovagal balance, intraoperative trauma to autonomic fibers, and oxidative and inflammatory changes contributing to an enhanced susceptibility to reentrant arrhythmias after surgery. Identification of preoperative risk factors would allow for more targeted intervention in selected patients for whom preventive, preoperative antiarrhythmic therapy might be beneficial, while also reducing the exposure of those at a lower risk for POAF to potential drug-related toxicity and costs.

Recent literature has illustrated the predictive value of maximal left atrial volume (LAV) with regard to POAF, supporting the idea that left atrial enlargement reflects

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Abbreviations and Acronyms

AF	= atrial fibrillation
AUC	= area under the receiver operating characteristic curve
BNP	= brain natriuretic peptide
CI	= confidence interval
LAEF	= left atrial emptying fraction
LAV	= left atrial volume
OR	= odds ratio
POAF	= postoperative atrial fibrillation

increased left ventricular filling pressure and diastolic dysfunction.^{6,7} Controversy remains, however, as to which preoperative markers of atrial function will distinguish patients in whom POAF is most likely to develop. Thus, our goal was to focus on indices of left atrial function and POAF in a cohort of patients undergoing noncardiac thoracic surgery.

MATERIALS AND METHODS

With institutional review board approval, we retrospectively reviewed the charts of patients who had anatomic lung or esophageal resection of cancer with more than 80% ($n = 706$) of the operations performed between June 2008 and August 2009. Patients who had preoperative echocardiography as part of their routine preoperative evaluation ($n = 191$) are the subjects of this study. Although there were no specific criteria applied to determine which patients had an echocardiogram before surgery, which was generally obtained by the surgeon or medical consultant, we compared patient characteristics (age, race, operation, smoking, hypertension, coronary artery disease, diabetes, and POAF rate) of the groups with or without an echocardiogram and found no significant differences. The primary end point of the study was the new onset of POAF lasting more than 5 minutes during hospitalization and detected by continuous telemetry or 12-lead electrocardiogram. Excluded were patients who were not in sinus rhythm before surgery or those with a history of paroxysmal AF, patients taking antiarrhythmic drugs, and patients who only had an exploratory thoracotomy or limited nonanatomic resection (eg, wedge), and therefore were at low risk for AF. Patients for whom echocardiographic images were not suitable for measurements of interest were also excluded ($n = 3$). Complete transthoracic echocardiograms and Doppler echocardiograms obtained for the 191 patients within 3 months before thoracic surgery were analyzed. Maximal LAV was calculated using the biplane area-length method, per the American Society of Echocardiography recommendation.⁸ On the basis of published data, a “gender neutral” cutoff of LAV 32 mL/m² or less was used as normal/mildly abnormal.^{6,7} To determine interobserver variability, LAV measurements were obtained by 2 independent investigators in 10% of the study population or 19 randomly selected cases. An estimated excellent intraclass correlation coefficient of 0.93 (95% confidence interval [CI], 0.83–0.97) was obtained. Left atrial emptying fraction (LAEF) was calculated as follows: (maximal LAV–minimal LAV)/maximal LAV.

Postoperative pain relief was provided to all patients by continuous administration of epidural opioid (usually hydromorphone and bupivacaine). After an overnight stay in the postanesthesia care unit, patients were transferred to the thoracic surgical floor on postoperative day 1. Major postoperative cardiac or pulmonary complications were recorded throughout the hospital stay. An end point of the study was the new onset of AF for more

than 5 minutes during hospital stay, detected by continuous telemetry (72–96 hours) or AF episodes requiring intervention because of symptoms or hemodynamic compromise. AF was defined by an irregularly irregular cardiac rhythm without clear P waves that was confirmed by 12-lead electrocardiogram.

The intraclass correlation coefficient and CI of LAV measurements between 2 observers was calculated on the basis of 1-way analysis of variance. To determine the difference of clinical characteristics and echocardiographic parameters between patients with and without POAF, univariate analysis was conducted using Student *t* or chi-square test. Data are presented as mean value \pm standard deviation unless otherwise indicated. *P* values were computed for each variable for all available data. Left atrial systolic volume, E-wave velocity, E/A ratio, E/E' septal ratio, and E/E' lateral ratio required log transformation to reduce skewness of the distributions. Multivariate logistic regression analysis was used to identify independent risk factors of POAF. Results were confirmed to agree with both forward and backward stepwise selection. This analysis was done first for echocardiographic parameters, and then clinical variables were added to the significant echocardiographic parameters. Variables with *P* value of .05 or less by univariate analysis were included in the initial models (echocardiographic $n = 4$ and clinical $n = 2$). The area under the receiver operating characteristic curve (AUC) was calculated to measure the predictive power of identified parameters. Correlation between age and indices of atrial function was computed using Spearman correlation analysis. Cochran-Armitage trend test was used to assess the relationship between categories of LAEF and status of POAF. Statistical analysis was performed with SAS version 9.2 (SAS Institute Inc, Cary, NC).

RESULTS

The mean age for the 191 patients included in the study was 65.4 ± 11.2 years, and 53% were male. Patient characteristics and surgical data are presented in Table 1. POAF occurred in 33 of 191 patients (17%) a median of 2 days (range, 0–6) after surgery. On univariate analysis, patients with POAF (70.5 ± 5.3 years) were on average 6.2 years older (95% CI, 3.6–8.8 years) than those without POAF (64.4 ± 11.8 years) ($P < .0001$) and proportionally taking more β -blockers before surgery ($P = .007$, Table 1). The mean length of hospital stay was increased in patients with POAF (9.1 ± 5.0 days) compared with those without POAF (7.9 ± 7.4 days). The average length of hospital stay in patients with POAF was 1.29 times longer than those without POAF (95% CI, 1.02–1.65) by *t* test based on logarithm-transformed data ($P = .04$).

Patients with POAF had greater maximal LAV, decreased LAEF, and lower E' and A' septal velocities compared with patients without POAF by univariate analyses ($P < .05$; Table 2 and Figure 1). By using a gender-neutral cutoff,⁸ the incidence of POAF in patients with LAV 32 mL/m² or greater was 37% (11/30) and significantly greater than in those with LAV less than 32 mL/m² (14%, 22/160, $P = .002$). There was a trend of greater minimal LAV and left ventricular diastolic filling pressure (as estimated by the E/E' septal ratio) in patients with POAF (Table 2). The groups did not differ in left ventricular ejection fraction. Consideration of 4 echocardiographic parameters with a *P* value of .05 or less by univariate analysis in the

TABLE 1. Patient and operative characteristics

Variable	Patients with POAF (n = 33)	Patients without POAF (n = 158)	P value
Preoperative			
Age (y)	70.5 ± 5.3	64.4 ± 11.8	<.0001
Male gender, n (%)	21 (64)	78 (49)	.14
White race	29 (88)	144 (91)	.52
Weight (kg)	79.6 ± 16.2	75.8 ± 17.3	.25
Height (cm)	168.6 ± 10.0	167.5 ± 10.1	.56
Body surface area (m ²)	1.9 ± 0.2	1.8 ± 0.2	.24
Preoperative heart rate (beats/min)	74.0 ± 15.2	71.1 ± 13.0	.27
Preoperative white blood cell count (k/ μ L)	7.0 ± 1.8	6.9 ± 2.2	.82
Diabetes, n (%)	6 (18)	17 (11)	.23
Coronary artery disease, n (%)	11 (33)	39 (25)	.30
Hypertension, n (%)	19 (42)	61 (39)	.68
Mitral valve prolapse, n (%)	0 (0)	3 (2)	1.00
Congestive heart failure, n (%)	2 (6)	2 (1)	.14
Chronic obstructive pulmonary disease, n (%)	4 (12)	6 (4)	.07
Ex/current smoker, n (%)	26 (79)	110 (70)	.29
Statin, n (%)	13 (39)	61 (39)	1.00
β -blocker, n (%)	14 (42)	32 (20)	.007
Renin-angiotensin-aldosterone-system blocker, n (%)	10 (30)	38 (24)	.51
Calcium channel blocker, n (%)	9 (27)	22 (14)	.06
Operative			
Total fluid input (mL)	2088 ± 1642	1872 ± 1705	.19
Estimated blood loss	286 ± 192	307 ± 367	.74
Duration of operation (min)	241 ± 128	218 ± 106	.32
Surgical procedure			
Esophagectomy, n (%)	8 (24)	38 (24)	.82
Lobectomy, n (%)	20 (61)	99 (63)	
Pneumonectomy, n (%)	1 (3)	9 (6)	
Segmentectomy	4 (12)	12 (8)	
Operation laterality (lung only)			
Left, n (%)	14 (56)	50 (42)	.19
Right, n (%)	11 (44)	70 (58)	

POAF, Postoperative atrial fibrillation.

initial multivariate logistic regression analysis showed that lower LAEF (odds ratio [OR], 1.04 per unit decrement; 95% CI, 1.01–1.07; $P = .005$; AUC = 0.59) was the only echocardiographic parameter significantly associated with POAF. Further multivariate logistic regression by adding 2 clinical characteristics with a P value of .05 or less on univariate analysis showed that lower LAEF (OR, 1.03 per unit decrement; 95% CI, 1.001–0.064; $P = .04$) and preoperative use of β -blockers (OR, 2.82; 95% CI, 1.18–6.77; $P = .02$) were the only independent risk factors associated with POAF (Table 3). The AUC for this final model was 0.67 and moderately predictive of POAF and the Hosmer–Lemeshow statistic ($P = .09$). Preoperative use of β -blockers was significantly associated with older age ($P = .0002$ by t test). With LAEF and preoperative use of β -blockers in the model, age did not add further significant prognostic information ($P = .09$). By Spearman correlation analysis, greater age was significantly associated with

higher LAV ($\rho = 0.24$, $P = .001$), lower E' septal velocity ($\rho = -0.25$, $P = .008$), and decreased LAEF ($\rho = -0.26$, $P = .001$).

DISCUSSION

The main finding is that greater preoperative use of β -blockers and decreased LAEF were important risk factors for POAF in patients who had an echocardiogram before anatomic lung or esophageal resection. Older age was significantly associated with greater β -blocker use and LAV and lower LAEF. It is likely that greater preoperative use of β -blockers in this cohort was a surrogate marker of a trend in many institutions at the time these patients underwent operation to prophylactically administer these medications to reduce perioperative cardiovascular morbidity, rather than a cause and effect. For these reasons, we believe that older age, a known predictor of POAF,^{1–5} dropped out of the final multivariate model. Our patients had no clinical signs of

TABLE 2. Echocardiographic parameters

Parameter	Patients with POAF (n = 33)	Patients without POAF (n = 158)	P value
LV IDs (cm)	3.2 ± 0.9	3.0 ± 0.6	.46
LV wall mass (g/m ²)	85.4 ± 29.5	76.6 ± 20.3	.11
LV ejection fraction (%)	61.6 ± 12.6	64.9 ± 7.9	.16
LA diastolic volume (mL/m ²)	29.2 ± 9.8	25.5 ± 7.5	.048
LA systolic volume (mL/m ²)	14.9 ± 10.4	10.6 ± 5.1	.053
E-wave velocity (cm/s)	81.1 ± 31.5	74.7 ± 17.5	.53
A-wave velocity (cm/s)	77.6 ± 23.1	81.5 ± 22.2	.37
E' septal velocity (cm/s)	6.6 ± 1.4	7.6 ± 2.6	.004
E' lateral velocity (cm/s)	8.7 ± 3.0	9.5 ± 3.3	.2
A' septal velocity (cm/s)	7.9 ± 3.0	8.9 ± 2.4	.04
A' lateral velocity (cm/s)	9.3 ± 4.2	10.3 ± 3.8	.22
E/A ratio	1.2 ± 0.8	1.0 ± 0.4	.43
E/E' septal ratio	13.1 ± 6.6	11.3 ± 7.5	.06
E/E' lateral ratio	11.1 ± 8.8	8.9 ± 5.1	.1
DT (ms)	230 ± 64.3	227 ± 47.8	.8
LA emptying fraction	52.1 ± 18.6	59.6 ± 11.0	.04
TR jet	23.8 ± 8.7	23.2 ± 7.3	.73
Estimated PA systolic pressure	29.8 ± 10.1	28.2 ± 8.2	.42

DT, Deceleration time; IDs, internal dimension during systole; LA, left atrium; LV, left ventricle; PA, pulmonary artery; POAF, postoperative atrial fibrillation; TR, tricuspid regurgitation.

congestive heart failure or evidence of significant valvular heart disease as a group but did show subtle or “subclinical” signs of left atrial distension (using LAV ≥ 32 mL/m²) and mechanical dysfunction as risk factors for POAF. In our first prospective study examining the value of serial echocardiographic changes in 100 patients undergoing major pulmonary resection, only a mild to moderate increase in postoperative tricuspid regurgitation jet velocity was shown to significantly correlate with supraventricular tachydysrhythmias consisting mostly of

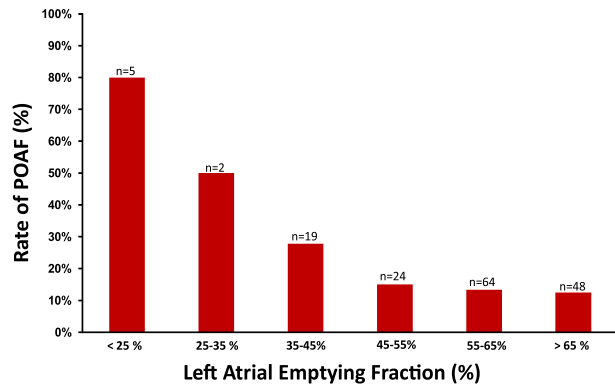


FIGURE 1. Relationship between left atrial emptying fraction and rate of POAF. Stratification of left atrial emptying fraction values into 6 groups ranging from an left atrial emptying fraction less than 25% to more than 65% indicated that the event rate of atrial fibrillation increased as left atrial emptying fraction decreased ($P = .005$). POAF, Postoperative atrial fibrillation.

TABLE 3. Multivariate analysis of risk factors for postoperative atrial fibrillation

	OR	95% CI	P value
β -blocker use	2.82	1.18–6.77	.02
LAEF, per unit decrement	1.03	1.002–1.07	.04

LAEF, Left atrial emptying fraction.

POAF.² This suggested that increased right heart pressure could be a contributing mechanism for POAF. However, none of the preoperative parameters, including left atrial size, by standard 2-dimensional measurements were predictive in that study. In contrast, newer echocardiographic methods (eg, integrated LAV and LAEF) have allowed us to better examine left atrial function in the current study. We have no clear explanation as to why patients with POAF were taking β -blockers more often than those without POAF and paradoxically had a higher incidence of POAF. Because the incidence of other comorbidities (eg, hypertension or coronary artery disease) did not differ between these groups, it is plausible that patients selected for this study may have had more preoperative testing (eg, baseline echocardiograms) in comparison with younger patients and perhaps as a result were given prophylactic β -blockers more often for perioperative cardiac protection.

Vaporciyan and colleagues⁹ showed that preoperative risk factors, such as increased age, male gender, and a history of congestive heart failure, arrhythmias, or peripheral vascular disease were all correlated with the development of POAF in a large database of patients undergoing noncardiac thoracic surgery. In a similar study of patients undergoing lung resection, Roselli and colleagues¹⁰ found that older age, male gender, paroxysmal AF, heart failure, clamshell incision, and right pneumonectomy were correlated with POAF. They also found that the majority of patients with POAF had concurrent cardiovascular, respiratory, or infectious complications, possibly reflecting an inflammatory role in the pathophysiology of POAF. Such variations in study outcomes are common among large epidemiologic studies and may reflect differences in patient characteristics, demographics surveyed, study sample size, and types of procedures. In previous work, we devised a clinical prediction rule and point score for POAF risk using the easily available preoperative clinical characteristics of age more than 55 years, male gender, and preoperative heart rate greater than 72 beats/min, with age as the most important risk factor.¹¹ We examined whether inflammation contributed to POAF but could not demonstrate greater levels of C-reactive protein among patients with POAF by using serial measurements.¹² However, we did find in another study that patients with POAF were more likely to have a higher white blood cell count on postoperative day 1 than those without POAF.¹³ In the search for serum marker correlates of POAF, it has been shown that subjects who had AF after

esophageal or pulmonary resection had increased atrial production of brain natriuretic peptide (BNP).^{14,15} Cardinale and colleagues¹⁶ evaluated more than 400 patients undergoing thoracic surgery for lung cancer and showed that in patients with POAF, the pre- and postoperative N-terminal-proBNP values were significantly higher than in those patients without POAF.¹⁶ Taken together, these and our results suggest that the presence of subclinical left atrial dysfunction before surgery as measured by echocardiography or elevated BNP contribute to the electrical substrate necessary to initiate POAF in older patients undergoing major thoracic surgery.¹⁴⁻¹⁶

Unrelated to surgery, LAV has been shown to linearly correlate with increased left ventricular end-diastolic pressure and thus can be an indication of diastolic dysfunction.¹⁷ One of the original studies looking at patients with preexisting mitral valve disease showed that a left atrial dimension greater than 40 mm was significantly associated with the onset of AF.¹⁸ Chronic exposure to increased ventricular filling pressures can cause increased atrial wall tension and stretch.^{19,20} Various mechanisms have been proposed to explain this phenomenon, including an increase in atrial effective refractory period because of myocyte stretch and myocardial fibrosis.²¹ In the cardiac surgical population, Roshanali and colleagues²² showed that patients with POAF had significantly decreased preoperative A-wave transmitral flow velocity, increased LAV, and a prolongation of the interval from the onset of the P wave to the beginning of atrial systole, as measured at the lateral side of the left atrium. Benedetto and colleagues²³ demonstrated that a larger left atrial area and peak atrial systolic mitral annular velocity (A velocity) 9 cm/s or less were independent predictors of POAF in this population.²³ Recent work by Nojiri and colleagues²⁴ showed that higher early transmitral velocity/mitral annular early diastolic activity was found to be significantly associated with POAF in patients who had undergone lobectomy for lung cancer resection. We found that patients undergoing noncardiac thoracic surgery who had POAF had significantly decreased mitral annular velocities (E'), although we did not find any difference between the 2 groups with respect to the transmitral early peak velocity (E). Although the study by Nojiri and colleagues²⁴ complements our work, they excluded patients undergoing segmentectomy, bilobectomy, or pneumonectomy and did not evaluate LAV or left atrial ejection or emptying fraction, which we found as more significant discriminators for POAF risk.

Study Limitations

Although this analysis was retrospective, this population represents a cohort of patients whose clinical data were collected and recorded at regular intervals. Manual measurement of LAV is dependent on accurate circumferential

tracing of the left atrial chamber and computation of the long axis. This is subject to some level of variability based on the observer. However, we did find a high level of agreement in left atrial measurements between 2 independent investigators in a subset of randomly selected studies. The current study with 191 patients and 33 events (POAF) was of adequate sample size to identify several predictors that were significant on univariate analysis. However, the overall predictive accuracy is moderate (AUC = 0.67), and some of the potential predictor variables are correlated with each other. Thus, only the strongest predictors remained in the final multivariable model. The model was not overfitted. A larger study would have to be done to confirm or rule out any additive predictive value from variables that in this study were only moderately significant on univariate analysis or to explore other clinical risk factors, such as race or cancer stage.²⁵

CONCLUSIONS

In a cohort of patients undergoing thoracic surgery who also had preoperative echocardiography, we found that greater use of preoperative β -blockers and indices of left atrial mechanical dysfunction were jointly associated with POAF occurrence. It is likely that greater preoperative use of β -blockers in this cohort was a surrogate marker of a trend in many institutions at the time these patients underwent operation to prophylactically administer these medications to reduce perioperative cardiovascular morbidity, rather than a cause and effect. Our echocardiographic findings are important in our efforts to better understand the pathophysiology of POAF. The use of these parameters may help in identifying a subset of patients with the highest risk of POAF. We speculate that these patients would most benefit from prophylactic interventions aimed at reducing LAV or improving LAEF in addition to conventional antiarrhythmics other than β -blockers. The goal would be to decrease the incidence of POAF and the length of stay and related costs in patients undergoing thoracic surgery.

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