Predictive value of preoperative tissue Doppler echocardiographic analysis for postoperative atrial fibrillation after pulmonary resection for lung cancer

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Objective: The objective of the present study was to evaluate the utility of tissue Doppler imaging for predicting the development of postoperative atrial fibrillation.

Methods: In this prospective observational study, we evaluated 126 patients with lung cancer who underwent a lobectomy during the 18-month period from August 2007 to January 2009. Preoperative evaluations for all patients included tissue Doppler imaging in addition to conventional echocardiographic analysis. The study end point was the development of postoperative atrial fibrillation.

Results: Postoperative atrial fibrillation was identified in 29 (23%) patients, in whom significantly higher early transmitral velocity/tissue Doppler mitral annular early diastolic velocity values were noted compared with those seen in patients without atrial fibrillation (9.76 ± 2.3 vs 7.14 ± 1.7 , $P < .0001$). The area under the receiver operating characteristic curve for early transmitral velocity/tissue Doppler mitral annular early diastolic velocity to predict postoperative atrial fibrillation after pulmonary resection for lung cancer was 0.83 (95% confidence interval, 0.74–0.92; $P < .001$). An early transmitral velocity/tissue Doppler mitral annular early diastolic velocity value of greater than 8 had a sensitivity of 90% and a specificity of 73% for predicting postoperative atrial fibrillation.

Conclusions: Postoperative atrial fibrillation after pulmonary resection might be associated with left ventricular diastolic dysfunction before surgical intervention revealed by using tissue Doppler imaging. Additional studies to establish the significance of tissue Doppler imaging as a tool to predict postoperative atrial fibrillation could contribute to improvements in lung cancer treatments. (*J Thorac Cardiovasc Surg* 2010;140:764-8)

Atrial fibrillation (AF) is the most common cardiac arrhythmia during the early postoperative period of pulmonary resection.¹⁻⁴ Although AF after pulmonary resection is transient in most cases, it sometimes results in a serious outcome, including thromboembolic events and hemodynamic deterioration, which finally leads to increased mortality.^{5,6} Therefore it is desirable to identify patients with a high risk for AF and prevent the condition with the use of targeted pharmacologic strategies. Older age,^{1,2} male sex,² extended resection,^{2,3} induction therapy,³ chronic obstructive pulmonary disease (COPD),⁴ and mediastinal lymph node dissection¹ have been reported as risk factors for postoperative

AF after the procedure. However, conventional methods provide only a limited ability to predict the development of postoperative AF, and thus it is important to elucidate more specific and sensitive markers.

Because left ventricular (LV) diastolic dysfunction has been reported to be a risk factor for AF,^{7,8} we speculated that LV diastolic dysfunction before surgical intervention might be associated with the development of postoperative AF after a pulmonary resection procedure.

Conventional echocardiographic assessment of LV diastolic function has been dependent on the evaluation of the pulsed-wave Doppler flow-velocity waveform recorded with the sample volume positioned at the mitral valve leaflet tips. The mitral inflow in subjects with sinus rhythm represents flow-velocity curves at early diastolic filling and atrial contraction, and a ratio of peak early diastolic mitral flow velocity (E) to peak mitral flow velocity at atrial contraction (A), the E/A ratio, has been used as an index for diastolic function. The E/A ratio should decrease with the development of diastolic dysfunction; however, it increases with an increase in LV diastolic pressure caused by progressive diastolic dysfunction. This phenomenon is termed pseudonormalization.⁹ In addition, the E/A ratio does not reflect diastolic dysfunction in patients with normal LV ejection

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Abbreviations and Acronyms

AF	= atrial fibrillation
COPD	= chronic obstructive pulmonary disease
E/A	= peak early diastolic mitral flow velocity to peak mitral flow velocity at atrial contraction
E/Ea	= early transmitral velocity/tissue Doppler mitral annular early diastolic velocity
FEV ₁	= forced expiratory volume in 1 second
FVC	= forced vital capacity
LV	= left ventricular
RV	= right ventricular
TDI	= tissue Doppler imaging

fraction.¹⁰ Thus the reliability of the mitral inflow in the detection of diastolic dysfunction is insufficient. Tissue Doppler imaging (TDI) is a noninvasive imaging modality that directly interrogates myocardial velocity with high temporal and spatial resolution. The TDI recording of the mitral annular movement during diastole represents velocity curves at early diastole and atrial contraction. In the past decade, several studies have demonstrated that a ratio of early transmitral velocity (E)/tissue Doppler mitral annular early diastolic velocity (Ea), the E/Ea ratio (the normal value of E/Ea is ≤ 8), increases with the increase in LV diastolic pressure caused by diastolic dysfunction independently of LV ejection fraction.¹¹⁻¹³ Based on these previous studies, the E/Ea ratio is proposed as a first-line diagnostic index for heart failure with normal LV ejection fraction and diastolic dysfunction in the consensus statement published by the Heart Failure and Echocardiography Associations of the European Society of Cardiology.¹⁴

We have hypothesized that the presence of LV diastolic dysfunction is a risk for the development of AF after pulmonary resection and that the E/Ea ratio is a useful predictive index. The objective of the present study was to evaluate the utility of TDI in patients undergoing pulmonary resection for lung cancer for predicting the development of postoperative AF.

MATERIALS AND METHODS**Study Population**

After approval by the appropriate institutional review board and waiver of informed consent, we prospectively evaluated 150 consecutive patients who underwent elective pulmonary resection procedures for non-small cell lung cancer at Toneyama National Hospital from August 2007 to January 2009. Exclusion criteria were rhythm other than sinus, dysthyroidism, renal failure requiring hemodialysis, current use of antiarrhythmic drugs, repeated pulmonary resection, moderate or severe valvular heart disease, and recent angina pectoris or myocardial infarction (<1 month). Also excluded were patients who underwent a lesser resection (wedge resection or segmentectomy) or a more extensive operation (bilobectomy, pneumonectomy, chest wall resection, or major vascular resection). Finally, 126 patients (84 male and 42 female patients; mean

age, 66 ± 9 years) who underwent a lobectomy were selected for the present study.

All patients received preoperative epidural anesthesia for pain management, which usually remained in place for 2 to 4 days or until the chest drainage tubes were removed, after which they were switched to oral analgesia. Other postoperative management methods included early ambulation and low-flow nasal oxygen supplementation, as necessary.

Preoperative evaluations included a detailed history, physical examination, blood gas analysis, 12-lead electrocardiogram, spirometry, and TDI in addition to conventional transthoracic echocardiographic analysis. The study end point was the development of postoperative AF.

Pulmonary Functional Examinations

A spirometric test was performed before surgical intervention by using an Autospirometer System 9 (Minato Medical Science, Osaka, Japan), and vital capacity and percentage of forced vital capacity expired in 1 second (forced expiratory volume in 1 second [FEV₁]/forced vital capacity [FVC] ratio) were calculated. Predicted postoperative pulmonary function was calculated by using a previously reported formula.¹⁵

Echocardiographic Examinations

Two-dimensional measurements were obtained based on the recommendations of the American Society of Echocardiography by using an ultrasonic device (SONOS 7500; Philips, Andover, Mass). Images were obtained from parasternal views and an apical 4-chamber view. The patient was placed in a left lateral decubitus position for the parasternal views and the supine position for the apical 4-chamber view. The results were analyzed by an echocardiologist blinded to all clinical, hemodynamic, and laboratory findings. LV end-systolic and end-diastolic diameters were measured with M-mode echocardiographic analysis from the left parasternal short- and long-axis views. LV mass was calculated by using the Devereux formula¹⁶ and was indexed to body surface area. LV ejection fraction was determined by using the Teicholz formula. Systolic pulmonary artery pressure was predicted from tricuspid regurgitation by using the method of Currie and coworkers.¹⁷ Pulsed Doppler transmitral flows were obtained from the apical 4-chamber view. Doppler velocity curves were recorded at 100 mm/s. Mitral inflow measurements included E, A, E/A ratio, and acceleration and deceleration time of early diastolic mitral flow velocity. Ea at the septal annular site was obtained by using TDI.

Postoperative AF

In the 3-day period after surgical intervention, continuous electrocardiographic monitoring was done for all patients to detect postoperative AF, with additional electrocardiographic examinations performed when an irregular pulse was recognized by a physician or the nursing staff or when the patient complained of palpitations. AF was defined by an irregular rhythm with absent P waves confirmed by means of 12-lead electrocardiographic analysis.

Statistical Analysis

Data are reported as the means $\pm$ standard deviations or as proportions. All data were analyzed with SPSS version 11.0 software (SPSS, Inc, Chicago, Ill). The comparison of all parameters was analyzed by using 1-way analysis of variance. Comparisons of 2 groups were made with the Mann-Whitney test, and χ^2 testing was used for categorical variables. Logistic regression analyses were used to explore risk factors for postoperative AF. Receiver operating characteristic curves were constructed to determine optimal sensitivity and specificity.

RESULTS

The clinical and surgical characteristics of patients with and without postoperative AF are summarized in Table 1.

TABLE 1. Patients' characteristics*

Variables	Without AF (n = 97)	With AF (n = 29)	P value
Age (y)	65 ± 9	71 ± 8	.002
Male	67 (69)	17 (59)	.48
Body mass index (kg/m ²)	22.4 ± 2.5	22.2 ± 3.0	.78
Hypertension	40 (41)	16 (55)	.09
Hypercholesterolemia	27 (28)	8 (28)	.98
Diabetes mellitus	16 (17)	6 (21)	.61
Ischemic heart disease	2 (2)	3 (10)	.08
VATS procedure	63 (65)	14 (48)	.11
Operating time (min)	273 ± 73	253 ± 61	.19
Blood loss (mL)	118 ± 150	148 ± 185	.38
Mediastinal lymph node dissection	84 (87)	23 (80)	.22
Lung cancer staging			
IA, IB	74 (76)	19 (66)	.25
IIA, IIB	11 (11)	6 (21)	.20
IIIA, IIIB, IV	12 (12)	4 (14)	.84

AF, Atrial fibrillation; VATS, video-assisted thoracic surgery. *Values are shown as numbers (percentages) or means ± standard deviations, unless otherwise indicated.

Postoperative AF was identified in 29 (23%) of the 126 pulmonary resection cases analyzed. Of 29 patients with postoperative AF, 4 had transient AF, and 25 required class II or III antiarrhythmic drugs. Sinus rhythm was restored in all patients. Operative mortality occurred in 1 (1%) patient, who died of acute heart failure caused by prolonged sepsis after 14 days.

Patients with postoperative AF were significantly older than those without AF. In contrast, there were no statistical differences between patients with and without postoperative AF with respect to sex, body mass index, comorbidity, video-assisted thoracic surgery procedure, operating time, intraoperative blood loss, mediastinal lymph node dissection, or pathologic stage. In a comparison of the results of pulmonary function parameters between the 2 groups, patients with

TABLE 2. Preoperative pulmonary function variables*

Variables	Without AF (n = 97)	With AF (n = 29)	P value
VC (% predicted)	109 ± 16	105 ± 16	.17
FEV ₁ (% predicted)	92.6 ± 16	88.1 ± 20	.15
FEV ₁ /FVC ratio (%)	76.7 ± 8.5	72.2 ± 11	.03
DLco (% predicted)	97.2 ± 22	92.5 ± 27	.34
RV/TLC	37.8 ± 6.8	40.4 ± 7.8	.09
ppo VC (%)	86.9 ± 15	80.9 ± 15	.07
ppo FEV ₁ (%)	74.1 ± 14	67.0 ± 17	.04
ppo DLco (%)	76.7 ± 19	70.7 ± 24	.19
pH	7.41 ± 0.02	7.41 ± 0.02	.54
Pao ₂ (mm Hg)	87.3 ± 11	86.0 ± 10	.58
Paco ₂ (mm Hg)	40.3 ± 3.5	39.9 ± 3.8	.56

AF, Atrial fibrillation; VC, vital capacity; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; DLco, carbon monoxide diffusing capacity; RV/TLC, ratio of residual volume to total lung capacity; ppo, predicted postoperative; Paco₂, carbon dioxide blood partial pressure; Pao₂, arterial oxygen blood partial pressure. *Values are shown as means ± standard deviations.

FIGURE 1. Preoperative early transmitral velocity/tissue Doppler mitral annular early diastolic velocity (E/Ea) ratios in patients with and without postoperative atrial fibrillation (AF). Patients with postoperative AF had significantly higher E/Ea values compared with values seen in those without AF ($P < .0001$).

postoperative AF had significantly impaired FEV₁/FVC ratios and predicted postoperative FEV₁ (as a percentage) compared with values seen in those without postoperative AF (Table 2). As for echocardiographic parameters, patients with postoperative AF had significantly lower Ea and higher E/Ea ratio values (Figure 1), as well as relatively impaired LV ejection fraction (Table 3), and therefore LV ejection fraction was important, although Ea and E/Ea ratio values were more important for postoperative AF.

In receiver operating characteristic analysis the areas under the curve for age, FEV₁/FVC, and E/Ea ratio to predict postoperative AF after pulmonary resection for lung cancer

TABLE 3. Preoperative echocardiographic variables*

Variables	Without AF (n = 97)	With AF (n = 29)	P value
LVDd (mm)	43.8 ± 3.9	43.2 ± 3.5	.45
LVDs (mm)	26.9 ± 3.3	27.9 ± 3.7	.15
Ejection fraction (%)	68.3 ± 5.2	65.5 ± 5.4	.06
LV mass index (g/m ²)	110.8 ± 25.4	116.8 ± 41.2	.27
PAP (mm Hg)	33.6 ± 5.5	34.9 ± 4.0	.34
E/A ratio	0.87 ± 0.3	0.87 ± 0.3	.83
DcT (ms)	219 ± 44	220 ± 49	.92
AcT (ms)	134 ± 20	133 ± 23	.86
Ea (cm/s)	8.46 ± 2.0	7.39 ± 1.7	.008
E/Ea	7.14 ± 1.7	9.76 ± 2.3	<.0001

AF, Atrial fibrillation; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LV, left ventricular; PAP, pulmonary artery pressure; E/A, peak early diastolic mitral flow velocity to peak mitral flow velocity at atrial contraction; DcT, deceleration time of peak early diastolic mitral flow velocity; AcT, acceleration time of peak early diastolic mitral flow velocity; PAP, pulmonary artery pressure; Ea, tissue Doppler mitral annular early diastolic velocity; E/Ea , early transmitral velocity/tissue Doppler mitral annular early diastolic velocity. *Values are shown as means ± standard deviations.

TABLE 4. Univariate and multivariate analyses of factors for prediction of postoperative AF

Variables	Univariate analysis		Multivariate analysis	
	Relative risk (95% CI)	P value	Relative risk (95% CI)	P value
Age	1.094 (1.031–1.162)	.003	1.058 (0.983–1.138)	.13
FEV ₁ /FVC	0.947 (0.903–0.994)	.03	1.010 (0.946–1.078)	.77
ppo FEV ₁ , %	1.033 (1.001–1.065)	.04	0.978 (0.935–1.023)	.33
E/Ea	1.982 (1.487–2.640)	.0001	1.810 (1.356–2.417)	.0001

AF, Atrial fibrillation; CI, confidence interval; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ppo, predicted postoperative; E/Ea, early transmitral velocity/tissue Doppler mitral annular early diastolic velocity.

were 0.71, 0.40, and 0.83, respectively (95% confidence interval, 0.61–0.82, 0.28–0.52, and 0.74–0.92, respectively). An E/Ea ratio of 8 or greater had a sensitivity of 90%, a specificity of 73%, a positive predictive value of 51%, and a negative predictive value of 96% for predicting postoperative AF. Univariate and multivariate analyses (Table 4) revealed that the preoperative E/Ea ratio was the most significant predictor of postoperative AF.

DISCUSSION

The present results indicate that patients with postoperative AF have higher preoperative E/Ea ratios compared with those seen in patients without postoperative AF, and thus patients with LV diastolic dysfunction before surgical intervention might have an increased risk for postoperative AF. TDI is a promising and appropriate diagnostic tool to predict the development of postoperative AF after pulmonary resection for lung cancer.

The presence and severity of LV diastolic dysfunction are associated with an increased risk for first-time AF in patients with sinus rhythm.^{7,8} Older age, hypertension, female sex, diabetes and obesity, and LV hypertrophy have been reported as risk factors for diastolic heart failure.¹⁸ In addition, LV diastolic dysfunction has been frequently reported in patients with COPD.^{19,20} Some recent studies found that patients with right ventricular (RV) pressure or volume overload had a leftward shift of the ventricular septum toward the center of the LV cavity,²¹ resulting in a geometric distortion of the left ventricle. Leftward ventricular septal shift in patients with RV overload can explain LV filling abnormalities. Furthermore, Funk and colleagues²² reported that LV diastolic dysfunction was present in patients with COPD with normal pulmonary artery pressure. COPD with lung hyperinflation and distension leads to increased stiffness of the parietal pleura and thus of the walls of the cardiac fossa.²³ Such a condition might contribute to LV diastolic dysfunction in patients with COPD independent of pulmonary hypertension, although that has not been established.

LV diastolic dysfunction in patients with lung cancer is caused by older age, essential hypertension, and COPD. Interestingly, patients with postoperative AF in the present study were significantly older ($P = .002$) and had impaired FEV₁/FVC ratios ($P = .03$) compared with those without AF. In addition, hypertension was associated in 55% of

our patients with postoperative AF, whereas it was seen in 41% of those without AF.

Because of the absence of pseudonormalization, TDI has been proposed to be a valuable diagnostic tool for evaluating first-time LV diastolic dysfunction.^{11,14} Notably, E/Ea ratios were closely correlated with LV filling pressures. E is dependent on left atrial driving pressure, LV relaxation kinetics, and age, whereas Ea is mostly dependent on LV relaxation kinetics and age. Therefore for the E/Ea ratio, the effects of LV relaxation kinetics and age are eliminated, and the value becomes a measure of left atrial driving pressure and LV filling pressure. Using the lateral mitral annulus for measurement, Nagueh and associates¹² first demonstrated that E/Ea ratio was correlated well with pulmonary capillary wedge pressure. In addition, Ommen and co-workers¹³ used the mitral septal annulus and demonstrated that E/Ea ratio had a reasonable correlation ($r = 0.64$, $P < .001$) with mean LV diastolic pressure in patients referred for left heart catheterization. Mitral E/Ea ratio measurement has since been used in multiple patient populations with cardiac disease to noninvasively estimate LV filling pressure and LV diastolic dysfunction. Recently, TDI was recommended as a first-line diagnostic approach for LV diastolic dysfunction by the European Society of Cardiology.¹⁴

Açıl and colleagues²⁴ reported that LV diastolic dysfunction assessed with TDI was not significantly associated with postoperative AF after coronary artery bypass grafting. The mechanisms of postoperative AF might be different between patients undergoing pulmonary resection surgery and those undergoing cardiac surgery, which could have various factors, such as extent of valvular heart disease, myocardial ischemia, and cardiac mechanical injury. However, in our patient population RV overload caused by pulmonary resection was considered to be measured without other complicating factors. However, an E/Ea ratio had no higher negative predictive value, and therefore we could not predict clearly the development of postoperative AF by using the E/Ea ratio only.

To the best of our knowledge, this is the first study to evaluate LV diastolic function with TDI as a possible predictor for the development of postoperative AF in patients undergoing pulmonary resection for lung cancer. Our study provides a new prospective in terms of prophylactic strategies for postoperative AF. We can speculate that the patients with preoperative higher E/Ea ratios might be able to prevent

postoperative AF with β -blockers or statins before surgical intervention. In Japan the cost of echocardiographic analysis is only 8,800 yen (about 95 dollars), and the recording of TDI during an echocardiographic study does not require an additional fee. Thus preoperative TDI recording is likely cost-effective for patients who have risk factors of LV systolic and diastolic dysfunction.

Study Limitations

This study was a single-institution clinical study, which restricted our ability to generalize the results. In addition, the number of patients in the study cohort was relatively small, and thus additional investigations are necessary to define the utility of TDI for predicting postoperative AF in patients undergoing pulmonary resection for lung cancer. Finally, echocardiographic examinations were not performed after the operation, and therefore there are no data regarding the presence of RV overload or LV diastolic dysfunction after surgical intervention. Nevertheless, the present method can be applied to assess the development of postoperative AF in all non-cardiac surgery patients.

CONCLUSIONS

LV diastolic dysfunction before surgical intervention revealed by TDI might be associated with the development of postoperative AF after pulmonary resection for lung cancer. Additional studies to establish the significance of TDI as a tool to predict postoperative AF might contribute to improvements in lung cancer treatments.

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