Signal-averaged P-wave Duration Does Not Predict Atrial Fibrillation after Thoracic Surgery

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Background: Atrial fibrillation (AF) is the most common dysrhythmia seen early after major thoracic surgery but occurs infrequently after minor thoracic or other operations. A prolonged signal-averaged P-wave duration (SAPWD) has been shown to be an independent predictor of AF after cardiac surgery. The authors sought to determine whether a prolonged SAPWD alone or in combination with clinical or echocardiographic correlates predicts AF after elective noncardiac thoracic surgery.

Methods: Of the 250 patients enrolled, 228 were included in the final analysis. Preoperative SAPWD was obtained in 155 patients who had major thoracic surgery and in 73 patients undergoing minor thoracic or other operations who served as comparison control subjects. The SAPWD was recorded from three orthogonal leads using a sinus P-wave template. The filtered vector composite was used to measure total P-wave duration. Clinical, surgical, and echocardiographic parameters were collected and patients followed for 30 days after surgery for the development of symptomatic AF.

Results: Symptomatic AF developed in 18 of 155 (12%) patients undergoing major thoracic surgery and in 1 of 73 (1%) patients having minor thoracic or abdominal surgery, most commonly 2 or 3 days after surgery. In comparison with similar patients undergoing major thoracic surgery without AF, those who developed AF were older (66 ± 8 yr, 62 ± 10 yr; P = 0.04) but did not differ in SAPWD (145 ± 17 ms vs. 147 ± 16, ms) in standard electrocardiographic P-wave duration (105 ± 7 ms vs. 107 ± 10 ms), incidence of left-ventricular hypertrophy on 12-lead electrocardiography, male sex, history of hypertension, diabetes, or coronary heart disease. Thoracic-surgery patients at risk for postoperative AF did not differ from all other patients at low risk for AF in clinical or SAPWD parameters.

Conclusions: Under the conditions of this study, SAPWD did not differentiate patients who did or did not develop AF after noncardiac thoracic surgery, and therefore its measurement cannot be recommended for the routine evaluation of these patients. Older age continues to be a risk factor for AF after thoracic surgery. (Key word: Signal-averaged electrocardiogram.)

ATRIAL arrhythmias develop in 10-40% of patients 2-3 days after cardiac1 or noncardiac thoracic surgery.2-4 The predominant arrhythmia is atrial fibrillation (AF). AF is more common after pneumonectomy or lobectomy as well as after esophagogastrectomy but is rare after exploratory thoracotomy or minor wedge resection.2-4 Although usually well tolerated in younger patients, new-onset AF after thoracic surgery can be associated with disabling symptoms and have life-threatening consequences in the elderly population. Patients with postoperative AF spend nearly twice as many days in the intensive care unit as patients without AF, and their total hospital stay is extended by 3-4 days with accompanying increased costs.1-4 The thromboembolic potential develops early (<3 days) after the onset of AF.1 To try to reduce significant injury caused by AF after surgery, it would be advantageous to identify patients who are at high risk before surgery so that prolonged monitoring and early treatment could be initiated for these patients. However, currently we are unable to identify those patients who are at risk with usual preoperative diagnostic testing.

Recently, the value of P-wave signal-averaged electrocardiography (ECG) has been demonstrated in patients undergoing cardiovascular surgery.5-8 In addition to known risk factors such as older age, valvular surgery,
and less frequent use of postoperative beta-blockers, a prolonged P-wave duration by signal-averaged ECG was shown to be a strong and independent predictor of postoperative AF.5,6 It has been postulated that a prolonged signal-averaged P-wave may identify delayed atrial conduction that may predispose to postoperative AF. Signal-averaged ECG is a technique that allows recording of signals with low electrical noise so that low-level cardiac signals that may be important in a number of disease processes can be identified. One such application of signal-averaged ECG has been to detect ventricular late potentials in patients after myocardial infarction as a risk for ventricular tachycardia or fibrillation.7 This technique has been expanded to the evaluation of the P-wave duration for prediction of the occurrence of paroxysmal8,9 or chronic10 AF in susceptible populations. In particular, those patients with a prolonged signal-averaged P-wave duration (SAPWD) have been shown to have an increased risk of developing AF.10,12 This prospective study was designed to determine whether a preoperative prolonged SAPWD alone or in combination with clinical or echocardiographic data predicts AF occurrence in patients scheduled to undergo major noncardiac thoracic surgery.

Methods

Patients

After institutional review board approval and provision of written informed consent, we prospectively enrolled 250 patients in sinus rhythm scheduled for elective thoracic and nonthoracic surgery. Patients having a lobectomy, pneumonectomy, pleurectomy, or esophagegastrectomy were grouped as at high risk for developing AF,10,11 or chronic12 AF in susceptible populations. In particular, those patients with a prolonged signal-averaged P-wave duration (SAPWD) have been shown to have an increased risk of developing AF.10,12 This prospective study was designed to determine whether a preoperative prolonged SAPWD alone or in combination with clinical or echocardiographic data predicts AF occurrence in patients scheduled to undergo major noncardiac thoracic surgery.

Data Acquisition

In men, chest hair was shaved as needed for proper electrode attachment. After thorough cleansing and mild abrasion of the skin, silver/silver chloride adhesive electrodes were applied as X leads in the right and left axilla, Y leads at the manubrium sterni and the left upper abdomen, and Z leads at the fifth intercostal space in the midclavicular line and the opposite point in the posterior chest. ECG data were recorded on a commercially available system (Predictor I, Arrhythmia Research Technology, Austin, TX) via the X, Y, and Z leads at a sampling frequency of 1,000 Hz and stored on disk for subsequent analysis. All recordings were made for 15–20 min.

P-wave Signal-averaged ECG Analysis

The acquired data were analyzed using previously described techniques.5 The QRS complex was used as the trigger for the signal-averaging process; however, the fiducial point was shifted to the extreme right side of the 300-ms window to expose the P-wave and the PR segment. A sinus P-wave template was selected by the operator for averaging. By a cross-correlation algorithm, a 99% correlation coefficient with the template was required for inclusion in the average. Ectopic atrial beats and sinus beats with excessive noise were excluded by this method. The correlation window width was 25 ms, and the number of correlations to achieve a fit was 10. All the beats in the recording were averaged with a goal to achieve a minimal noise level of 0.3 μV. The individual X, Y, and Z leads were combined into a vector sum \((X^2 + Y^2 + Z^2)^{1/2}\). The averaged P-waves were filtered using a least-squares fit filter with a window width of 100 ms (giving a high-pass cutoff of 29 Hz). This type of filter causes less signal distortion and ringing of the P-wave. The P-wave duration (in ms) has become a standard criterion by which the P-wave signal-averaged ECG is evaluated.5–8 The P-wave onset was defined above baseline noise level in the TP segment (fig. 1). The offset was defined as the return of the atrial signal to the baseline level or the onset of the QRS complex, whichever was earlier.

Standard ECG

All patients had a 12-lead ECG performed before surgery. Left-ventricular hypertrophy was defined by Romhilt-Estes criteria.13 P-wave duration was measured from simultaneous recording of the 12 standard leads by the MATRIX program software (Marquette Electronics, Milwaukee, WI). The MATRIX program simultaneously

Anesthesiology, V 91, No 1, Jul 1999
Fig. 1. An example of a measured P-wave from the vector combination of filtered orthogonal leads (X, Y, Z). The signal-averaged electrocardiogram P-wave duration was 138 ms in this patient. The saturating deflection on the right is the QRS complex.

aligns the P-wave onset of all 12 leads. The computer-derived P-wave duration was then visually verified by two investigators, blinded to clinical endpoints or signal-averaging data, by using the standard ECG recorded at a paper speed of 50 mm/s, at amplification of 20 mm/mV, and with filtration 100 Hz. The frequency of agreement or disagreement between the investigator’s assessment and the computer-derived data was recorded. The longest P-wave duration in any of the 12 standard leads was then used as representative of the total P-wave duration. This analysis could be done in all but eight patients who had their preoperative routine 12-lead ECG done elsewhere; of these, one developed AF, two were at high risk without AF, and five were low-risk patients.

Pulmonary Function Studies
Most patients scheduled for thoracic surgery had pulmonary function studies ordered by their primary physician before surgery. A standard nomogram adjusting for sex, age, and height was used to calculate the percentage of predicted values of the forced expired volume in 1 s.14

Echocardiography
Transthoracic echocardiograms were performed while patients were awake and in the supine position on postoperative day 2–4 using a 2.5/2.0-MHz transducer for imaging and Doppler echocardiography (SONOS 1500, Hewlett Packard, Waltham, MA) in a subset of patients after major thoracic surgery (74 of 155) and in 8 of 40 patients undergoing minor thoracic operations. All patients were in sinus rhythm at the time echocardiography was performed. Any evidence of pericardial disease was recorded. Left-ventricular ejection fraction was measured by established methods from M-mode parasternal views.15 Right- and left-atrial superior-to-inferior diameters were measured in the apical four-chamber view at end-systole from still frames. The apical four-chamber, parasternal, and subxiphoid views were used to access the maximum tricuspid regurgitation jet Doppler velocity. The regurgitant jet was localized in the pulse mode and then maximized and measured in the continuous-wave mode at a sweep speed of 100 mm/s. This Doppler velocity was used to estimate right-ventricular systolic pressure (RVSP) by a modification of the Bernoulli formula: Right-ventricular systolic pressure = right-atrial pressure + (peak TRJ velocity)² × 4. Right-atrial pressure (RAP,) was estimated at rest in the supine position by assessing the response of the inferior vena cava to normal and deep inspiration in the subcostal view. A RAP, of 3 mmHg was recorded if the inferior vena caval diameter was small (<15 mm) and collapsed during spontaneous respiration. A RAP, of 7 mmHg was recorded if the inferior vena caval diameter was of normal size (<20 mm) and collapsed more than 50% only with deep inspiration. A RAP, of 17 mmHg was recorded if the inferior vena caval diameter did not collapse more than 50% during deep inspiration.16 All analyses were later made from videotape by one investigator blinded to patient endpoints.

Anesthesia, Surgery, and Postoperative Care
All patients were premedicated with midazolam and glycopyrrolate and received routine anesthetic management that consisted of isoflurane and nitrous oxide supplemented by intravenous fentanyl and morphine as needed. Postoperative pain relief was provided to all patients by either continuous administration of epidural fentanyl or patient-controlled administration of intravenous morphine. After an overnight stay in the postanesthesia care unit patients were transferred to the nursing floor. Intraoperative blood loss and fluid intake and output were recorded. Postoperative complications were recorded throughout the hospital stay, and patients were monitored for complications as outpatients for 30 days.
**Data Analysis**

A power analysis was done to evaluate the ability to detect a >13-ms difference in SAPWD between patients who develop postoperative AF and those who do not within the high-risk group of patients undergoing major thoracic surgery, using previously published data.\(^3\) With a predicted overall AF incidence of 10%, we estimated that a sample size of 300 patients would be adequate to detect this difference with 80% power at a significance level of 0.05. An interim analysis was performed after 250 patients were enrolled, with evaluable data in 236 patients. A clinically meaningful difference in SAPWD would have been >10 ms between patients with AF and those without AF within the high-risk group. The 95% confidence interval for our data excluded such a difference. Even a 99.5% confidence interval still excludes a true difference >10 ms. It was our opinion that further accrual of large numbers of patients would not alter the fact that this was a "negative study." Thus, we decided to stop the study.

Patients were grouped on the basis of the operation performed and by those who did or did not develop AF (one or more episodes vs. no episodes). Data are mean value ± SD unless otherwise indicated. Continuous variables were analyzed by the Student t test and discrete variables by the Fisher exact test; all tests were two-tailed, and P < 0.05 was considered significant.

**Results**

**Patient Population and Occurrence of Atrial Fibrillation**

Of the 250 patients enrolled, 236 had adequate data for analysis. Twenty-two patients were excluded from final data analysis because of postponement of surgery (n = 6), inadequate data (n = 9), protocol violation (n = 3), or equipment failure (n = 4). Included in the final analysis were 228 patients whose mean age was 62 ± 10 yr. Symptomatic AF occurred in 18 of 155 (12%) patients undergoing major thoracic surgery compared with 1 of 73 (1%) patients undergoing minor thoracic or abdominal surgery (P = 0.009). Early (≤14 days) postoperative AF occurred in 18 of 19 patients a median of 3 days after the operation (3.4 ± 2.5 days, range 0–9 days). Late (>14 days) AF occurred in one patient on postoperative day 24 in the setting of septic shock.

**Clinical and Echocardiographic Correlates and AF Occurrence**

The clinical, surgical, and echocardiographic characteristics of patients with and without AF after major thoracic surgery are described in table 1. Patients who developed AF were on the average older than those who did not develop AF (P = 0.04). Although AF patients had a statistically lower predicted forced expiratory volume in 1 s (table 1) than those without AF, the values were only slightly abnormal. The incidence of AF according to operation type is shown in table 2. AF occurrence was more prevalent after pneumonectomy than lobectomy (P = 0.02) but not after esophagectomy (P = 0.76) or pleurectomy (P = 1). Echocardiographic data in high-risk patients are shown in table 3. High-risk patients with and those without AF did not differ in estimated operative blood loss or in the combined sum of crystalloid, colloid, and red blood cell transfusion fluid volume given during surgery. No other clinical, surgical, or echocardiographic parameter differentiated patients who did or did not develop AF. Within high-risk patients, the rate of intensive care unit admission for any reason was greater in AF versus non-AF patients, 5 of 18 versus 6 of 137, P < 0.01. The median hospital stay was 14 days for patients who developed AF compared with 7 days for high-risk patients without AF, P < 0.01.

**SAPWD and Incidence of Atrial Fibrillation**

The SAPWD and the incidence of SAPWD > 140 ms did not predict AF after major thoracic surgery (table 1). The SAPWD did not differ between patients in the high- and low-risk groups for postoperative AF. Within the highest-risk group undergoing pneumonectomy, a separate analysis showed that those patients developing AF (n = 7) had a significantly shorter SAPWD than those (n = 27) who did not, 133 ± 6 ms versus 144 ± 11 ms, P = 0.014, respectively. Baseline heart rate was similar among the groups (table 1). There were no differences among the groups in P-wave duration measured by the computerized 12-lead ECG analysis. This measurement correlated poorly with the SAPWD (r = 0.36). Maximum P-wave duration was determined to occur in lead II both by the computer and by visual inspection by the cardiologist in 198 of 220 (90%) of cases followed by lead I in 14 of 220 (6%) of cases. Disagreement between the investigators and the computer-generated P-wave duration occurred in 26 of 220 (12%) cases and was resolved by accepting the manual interpretation.
Table 1. Patient Characteristics According to Risk for Development of Postoperative Atrial Fibrillation

<table>
<thead>
<tr>
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<th>High Risk (n = 18)</th>
<th>Low Risk (n = 73)</th>
<th>No AF (n = 137)</th>
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<tr>
<td>Clinical characteristics</td>
<td></td>
<td></td>
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<tr>
<td>Age (yr)</td>
<td>66 ± 8*</td>
<td>62 ± 10</td>
<td>63 ± 12</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76 ± 16</td>
<td>76 ± 15</td>
<td>77 ± 17</td>
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<tr>
<td>Male (%)</td>
<td>78</td>
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<tr>
<td>Hypertension (%)</td>
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<td>Diabetes (%)</td>
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<td>14</td>
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<tr>
<td>Coronary heart disease (%)</td>
<td>11</td>
<td>8</td>
<td>5</td>
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<tr>
<td>FEV, % predicted†</td>
<td>71 ± 17†</td>
<td>89 ± 24</td>
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<td>Preoperative treatment (%)</td>
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<td>Beta-blockers</td>
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<tr>
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<td>β-Agonist inhalers</td>
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<td>Chemotherapy</td>
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<td>ECG findings</td>
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<tr>
<td>Average heart rate (bpm)</td>
<td>76 ± 19</td>
<td>75 ± 13</td>
<td>75 ± 14</td>
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<tr>
<td>LVH by ECG (%)</td>
<td>0</td>
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<td>1</td>
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<tr>
<td>P-wave duration on ECG (ms)</td>
<td>105 ± 7</td>
<td>107 ± 10</td>
<td>106 ± 10</td>
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<tr>
<td>P-wave duration on SAECG (ms)</td>
<td>145 ± 17</td>
<td>147 ± 16</td>
<td>145 ± 15</td>
</tr>
<tr>
<td>Range (ms)</td>
<td>125–206</td>
<td>118–217</td>
<td>102–185</td>
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<tr>
<td>P-wave duration on SAECG &gt; 140 ms (%)</td>
<td>50</td>
<td>64</td>
<td>62</td>
</tr>
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</table>

SAECG = signal-averaged electrocardiogram; high risk = major thoracic surgery; low risk = minor thoracic and other operations.

* AF versus no AF groups, P = 0.04.
† Pulmonary function studies were obtained in 12/18 AF patients, 115/137 no AF patients, and only in 26/73 low-risk patients.
‡ AF versus no AF groups, P < 0.01.

**Discussion**

In contrast to cardiac surgery,5-8 the presence of a prolonged SAPWD was not associated with the risk of new-onset AF after major thoracic surgery. This may be caused by a number of important differences between these two patient populations. First, baseline SAPWD may differ between the two groups or perhaps vary significantly in response to different surgical stresses. Second, noncardiac thoracic surgery does not involve cardiopulmonary bypass, atrial cannulation, and exposure to myocardial ischemia, hypothermia, or cardioplegia. Third, patients undergoing cardiac surgery are likely to have more severe coronary or valvular disease and hence, to require β-adrenergic blockers, nitrates, and other cardiotonic medications in comparison with patients having thoracic surgery. Finally, catecholamine and other vasoactive agents are more frequently required for cardiopulmonary bypass support after cardiovascular surgery. A recent study examining the effects of varying degrees of autonomic tone and their influences on the SAPWD has shown in healthy volunteers that this measurement is not fixed but varies with different autonomic stimuli.17 Specifically, epinephrine and proprano-
olol administration caused a prolongation of the SAPWD, whereas isoproterenol and atropine administration decreased this measurement. It is interesting that beta-blockers on the one hand may in theory help decrease the incidence of adrenergically mediated AF after surgery but on the other hand cause an increase in the SAPWD, which may indicate prolonged atrial conduction, a known pathologic substrate for AF generation.

The beneficial role of the SAPWD as a predictor of AF after elective cardiac surgery, however, has not been uniformly demonstrated. Although most of the reports suggest that a prolonged SAPWD is predictive of AF occurrence, one investigation of 189 consecutive patients scheduled for coronary artery bypass surgery found that SAPWD did not provide significant information for risk stratification in the 42 patients who developed AF or flutter. Moreover, these investigators found a significantly longer P-wave duration in AF patients on the standard ECG using the total P-wave duration method previously described. The same group of investigators also demonstrated limited reproducibility of the signal-averaged P-wave in patients with coronary artery disease and that a normal or abnormal signal-averaged P-wave can be predicted from the conventional ECG with high accuracy. In contrast to the total P-wave duration method described by Buxton and Josephson, our automated technique was simple, quick, and easily available at no additional cost to users of this system. The use of SAPWD for predicting AF after cardiac surgery is not widely accepted as standard, and concerns regarding its cost have been raised. Future studies in larger groups of patients would be important to resolve this controversy.

It is known that both adrenergic or vagal stimuli can shorten the atrial effective refractory period and cause reentry or promote triggered activity to produce AF in patients who are not undergoing surgery. Tachycardia can facilitate reentry by shortening the atrial effective refractory period, by altering spatial dispersion of refractoriness, and by slowing atrial conduction velocity. Many, if not most, forms of AF are believed to result from the simultaneous presence of multiple reentrant wavelets in the atrial myocardium. The number of simultaneous reentrant wavelets that can be sustained in the atria is a function of the atrial muscle mass and the wavelength of the atrial impulse (i.e., the product of conduction velocity and refractory period). The underlying mechanisms of postoperative AF and the role of the autonomic nervous system in its generation are unknown. However, biochemical studies done in our laboratory have shown a persistent down-regulation and desensitization of the lymphocyte β-adrenergic receptor-adenyl cyclase system throughout the first postoperative week in response to abdominal or thoracic surgery, which correlated to significant and persistent decrements in heart-rate variability. These data indirectly suggest persistent activation of autonomic regulatory mechanisms during this critical period. Because the incidence of AF appears to be directly related to the extent of surgical resection (i.e., lobectomy 10–15% vs. pneumonectomy 20–30%), it is tempting to speculate that intraoperative trauma to cardiac plexus nerves may lead to areas in the atria with less homogenous autonomic innervation, which in conjunction with autonomic mechanisms after operative stress may provide the setting for AF generation by a “denervation supersensitivity” phenomenon. In clinical investigations designed to characterize echocardiographic correlates of atrial dysrhythmias after thoracic surgery, we could not demonstrate a mechanical substrate for postoperative AF, such as atrial distension or right-heart overload.

Our results confirm that, as in AF unrelated to surgery, older age is consistently the only independent preoperative risk factor associated with postoperative AF. A likely explanation for this may be that aging causes a significant amount of atrial myocardial fibrosis. Although the pathogenesis of AF in patients not undergoing surgery is complex and different from postoperative AF, it is likely to follow the concept that “AF begets AF.” That is, the longer the duration of the paroxysm of AF, the harder it will be to restore sinus rhythm. Because thromboembolic potential develops early (<3 days) after the onset of AF, early arrhythmia detection and an aggressive approach to restore sinus rhythm within 24–48 h are probably warranted in high-risk individuals. Although patients who developed AF had a lower predicted forced expiratory volume in 1 s than those who did not, the values were mildly abnormal and were obtained only in two thirds of this subset of patients.

Limitations

The rationale for stopping the study early are described in the Methods sections. We do not know whether the application of other alignment algorithms or filter settings might change our results. Because SAPWD interpretation is subjective, it is possible that in some individuals the interpretation of data might vary among investigators. Signal averaging of the P-wave using the QRS as a trigger is somewhat limited by the inability to separate the end of the P-wave and the
beginning of the QRS in 15 of 236 (6%) patients, of whom 9 were at high risk and 6 were at low risk for postoperative AF. Despite these limitations, the SAPWD was shown to be highly reproducible if evaluated at immediate and short-term reacquisition regardless of age, sex, cardiac disease, or history of previous AF. Because the primary endpoint of the study was the occurrence of symptomatic AF and Holter monitors were not used, it is probable that short-lived episodes of AF occurred but were not diagnosed. However, our study was designed to evaluate clinically significant dysrhythmias that are the focus of patients' complaints and physicians' therapeutic interventions. Our conclusions, therefore, do not apply to the occurrence of asymptomatic episodes of AF and SAPWD.

Conclusions

Under the conditions of this study, SAPWD did not differentiate patients who did or did not develop AF after major thoracic surgery, and its measurement cannot be recommended to preoperatively risk-stratify these patients. Older age continues to be a risk factor for AF after thoracic surgery. Therefore, extended monitoring in elderly patients (>60 yr of age) undergoing major thoracic surgery and early therapeutic intervention may be indicated for the diagnosis and prevention of important sequelae of AF.

The authors thank Howard Thaler, Ph.D., for expert statistical advice; David H. Fogel, M.D., for help with data collection; and G. Clark for the preparation of this manuscript.

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