Atrial fibrillation after non-cardiac surgery: P-wave characteristics and Holter monitoring in risk assessment

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Received 8 November 2006; received in revised form 6 February 2007; accepted 6 February 2007; Available online 6 March 2007

Abstract

Background: We investigated the role of 12-lead ECG P-wave duration and dispersion and of Holter monitoring as predictors of post-thoracic surgery atrial fibrillation. Methods: One hundred and five consecutive patients (88 males—17 females; age 60 ± 9), undergoing thoracic surgery at National Cancer Institute between 2001 and 2003, were enrolled and both standard ECG and Holter monitoring were obtained from each patient. P-wave study was made on a magnified ECG paper copy. Holter monitoring was performed 1—3 days before surgery; patients were divided into three classes according to number and complexity of premature supra ventricular complexes (0: <30/h and no repetitive forms; 1: >30/h or couplets; 2: run of supraventricular tachycardia or atrial fibrillation). Results: Atrial fibrillation was detected in 12 patients (11%) within 96 h from surgery. In univariable logistic model, P-wave duration was not associated with postoperative atrial fibrillation while P-wave dispersion and Holter monitoring demonstrated a statistically significant association with the occurrence of atrial fibrillation (OR of 30 vs 20 ms = 2.06; CI: 1.17—3.64; p = 0.012, OR of class 1—2 vs class 0 = 8.16; CI: 2.04—35.59; p = 0.003, respectively). In the multivariable model, both P-wave dispersion and Holter were shown to be significantly associated with the end-point. Holter monitoring enhanced the predictive ability of P-wave dispersion (area under the ROC curve increased from 0.64 to 0.80). Conclusions: P-wave dispersion, but not duration, was associated with atrial fibrillation after thoracic surgery. Preoperative Holter monitoring adds further information and could be used to enhance the P-wave predictive power.

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Keywords: Post-surgery atrial fibrillation; P-wave duration and dispersion; ECG Holter monitoring

1. Introduction

Atrial fibrillation (AF) is the most common cardiac complication following thoracic surgery, with a prevalence ranging between 10% and 46%, according to the specific surgical procedure [1—3]. Sometimes it results in forms of hemodynamic derangements or discomfort that may lengthen the hospital stay and even affect the mortality rate. In addition, the thromboembolic risk carried by this particular condition and hence the appropriate prophylactic treatment are not well defined. Preoperative identification of patients at risk of developing AF after surgery could be extremely helpful in view of a prevention strategy.

Prior studies demonstrated that a series of epidemiologic, clinical, surgical, electrocardiographic, and echocardiographic parameters are associated with an increased risk of developing AF following coronary artery by-pass graft (CABG) and that some drugs may prevent its occurrence [4—8]. Much less data are available about AF after thoracic surgery. Some authors reported, for patients undergoing lung operations who developed post-operative AF, a worse prognosis, a mortality rate up to 25%, and a longer hospitalization [1,2]. Others did not show any negative impact of early postoperative AF on clinical course of patients operated for lung cancer [10].

However, prospective studies designed to identify major predictors for post-thoracotomy AF have been seldom made and with contradictory results [1,3,9,10]. In particular, the potential role of not strictly epidemiologic or clinical parameters, has been explored few times [1,11].

The purpose of this study was to investigate the association between some simple indicators such as P-wave duration and dispersion from standard 12-lead ECG and the risk of developing AF after thoracic surgery, also evaluating the possible additive role of 24 h Holter monitoring.
2. Methods and materials

2.1. Study population

This study enrolled 105 consecutive patients (88 males and 17 females; mean age 60 ± 9, range 24—80) who underwent surgery for an intrathoracic cancer at our Institute between 2001 and 2003. Exclusion criteria were: history of paroxysmal AF in last 3 months, non-sinus rhythm on admission ECG, and incomplete preoperative or postoperative data.

History, physical examination, laboratory data, chest-X ray, standard 12-lead electrocardiography, dynamic ECG Holter, and pulmonary function test were obtained in all patients. Doppler echocardiographic examination was performed only when clinically requested.

Following institutional policy at the time, verbal informed consent was asked and obtained from all patients. Since the non-invasive nature of the examinations and the fact that the results did not entail a modification of therapeutic strategy, the Institutional Review Board approval was not necessary.

2.1.1. P-wave measurements

A 12-lead ECG at a paper speed of 25 mm/s and size of 10 mV was recorded in each patient at hospital admission. Standard ECG analysis was performed without knowledge of the patients’ clinical status. P-wave duration was measured on a magnified copy in leads II and aVR, from the outer borders of the onset and of the offset. An average among three different beats was made. P-wave dispersion was defined as the difference between the maximal and the minimal P-wave duration in any of the 12 leads.

2.1.2. Holter recording

Preoperative 3 channel 24 h Holter recording was performed 1—3 days before surgery, using a commercially available equipment (Prima Manager, Cardioline).

According to the Holter results, patients were classified into three classes: 0 = premature supraventricular complex (PSVC) <30/h and no repetitive forms; 1: PSVC >30/h or couplets; 2: run of supraventricular tachycardia (SVT) or AF.

2.1.3. Postoperative follow-up

AF was identified by continuous ECG monitoring in the first postoperative hours and thereafter by physicians’ and nurses’ clinical controls, and confirmed by a 12-lead ECG. For practical purpose, atrial flutter was considered as AF. Routinary AF pharmacological treatment included amiodarone i.v. in a bolus of 5 mg/kg over 30—40 min, followed by continuous infusion of 10—15 mg/kg over 24 h; digoxin or verapamil were used to slow ventricular response, when necessary.

2.2. Statistical analysis

To test the association between non-normally distributed continuous variables and dichotomous variables the Kolmogorov—Smirnov test was used; if similar distributions are observed in the subgroups defined by a dichotomous variable, it can be inferred that the variables are not associated. The chi-square test was used for testing the association between discrete variables.

Univariable logistic models were fitted to investigate the association between the occurrence of AF and other covariates such as age, sex, Holter monitoring (classes 1—2 vs 0), P-wave duration, or dispersion. No major deviation from linearity was detected in the shape of the log-odds curve at varying age, P-wave duration, or dispersion values modeled as continuous variables by three-knot restricted cubic splines. Thus, we reported the results of the models including linear terms for all the above covariates. The logistic model results are shown in terms of odds ratio (OR), corresponding 95% confidence interval (CI), and p-value at Wald test. The criterion for assessing the role of the variables in predicting the risk of AF was the non-parametric estimate of the area under the ROC curve, quantified by the c-statistic, bootstrap-corrected for overoptimism. The statistic varies from 0.5, indicating what is expected by chance alone, to a maximum of 1, indicating a perfect prediction. To investigate whether Holter monitoring results could improve P-wave predictivity, the results of the model including both P-wave and Holter as predictors were compared with those of the model including P-wave only. The low number of AF occurrences prevented us to perform reliable multivariable models including other adjustment covariates.

We used SAS™ software (SAS Institute Inc., Cary, North Carolina, 2000) and the S-Plus® (MathSoft, Seattle, WA, 2000) design library to perform the modeling and statistical calculations. We considered two-sided p-values below the 5% conventional threshold as significant.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patients’ preoperative characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No AF (N = 93)</td>
</tr>
<tr>
<td>Males</td>
<td>77 (83%)</td>
</tr>
<tr>
<td>Females</td>
<td>16 (17%)</td>
</tr>
<tr>
<td>Age (in years) (mean ± SD, IQ)</td>
<td>60.5 ± 9.5 (54—67)</td>
</tr>
<tr>
<td>Lobectomy, bilobectomy</td>
<td>49 (53%)</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>10 (11%)</td>
</tr>
<tr>
<td>Other</td>
<td>34 (37%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21 (23%)</td>
</tr>
<tr>
<td>Diabetes in therapy</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Coronary artery disease or heart failure</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Arrhythmias (prev. AF)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Chemotherapy or radiotherapy</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>10 (11%)</td>
</tr>
</tbody>
</table>

SD: standard deviation; IQ: interquartile range.
3. Results

Patients’ preoperative features are shown in Table 1. AF occurred in 12 out of 105 patients (11%) within 96 h from surgery. All the patients returned to sinus rhythm during hospitalization.

There were no differences between patients with or without postoperative AF regarding surgical procedure, prevalence of hypertension, diabetes, and pulmonary and cardiovascular diseases. In the same manner, no differences were found in spirometric tests, transfer lung function for CO, baseline arterial blood gas determinations, and blood sample data (data not shown). The only parameter significantly more represented in the group with postoperative AF was history of AF episodes.

3.1. Association between postoperative AF and age or gender

In the univariable logistic regression model, younger age was associated with a higher AF risk, but this trend was not statistically significant (OR of 54 vs 67 years = 1.23; CI: 0.55—2.74; p = 0.618).

As regard gender, males showed a greater AF risk with respect to females, but also in this case statistical significance was not reached (OR = 2.29; CI: 0.28—18.98; p = 0.444).

3.2. Association between postoperative AF and P-wave duration and dispersion

P-wave duration was similar in patients with and without AF; the median value and the interquartile range (IQ) in the two groups were 95 (92.5—102.5) versus 95 (90–105) ms, respectively. P-wave dispersion showed a tendency to higher values in the AF patients: 32.5 (22.5—45.0) versus 20 (25—30) ms (Table 2). The incidence of AF was 8% (6/80) among patients with P-wave dispersion ≤30 ms, 16% (3/19) in patients with P-wave dispersion >30 and ≤40 ms, and 50% (3/6) in patients with P-wave dispersion more than 40 ms.

P-wave duration did not achieve statistical significance in univariate logistic model (OR of 105 vs 90 ms = 0.99; CI: 0.27—3.60; p = 0.982), whereas P-wave dispersion was significantly associated with AF (OR of 30 vs 20 ms = 2.06; CI: 1.17—3.64; p = 0.012) (Table 2).

3.3. Association between Holter monitoring and P-wave duration and dispersion

Seventy-one patients were classified as class 0 Holter, 10 as class 1, and 24 as class 2.

P-wave duration or dispersion values were similar in the three Holter classes, indicating that there was no association between Holter and P-wave. The median values (IQ) for P-wave duration were 95 (90—105) in class 0, 95 (85–105) in class 1, and 100 (95–102.5) in class 2, respectively (p = 0.305). The corresponding figures for P-wave dispersion were 25 (20–30) in class 0, 20 (20—40) in class 1, and 27 (20–30) in class 2, respectively (p = 0.956).

3.4. Association between postoperative AF and Holter monitoring

AF occurred in 4% (3/71) Holter 0, in 20% (2/10) Holter 1, and 29% (7/24) Holter 2 patients.

In the univariable logistic regression model (Table 2), Holter monitoring was significantly associated with AF (OR of 1—2 vs 0 = 8.16; CI: 2.04—35.59; p = 0.003).

In the multiple model, both P-wave dispersion and Holter were shown to be significantly associated with the end-point: the OR for P-wave of 30 versus 20 ms was 2.25 (CI: 1.20—4.21; p = 0.011); the OR for Holter 1—2 versus 0 was 9.45 (CI: 2.15—41.50; p = 0.003). Holter monitoring increased the predictive ability of P-wave dispersion; indeed, the non-parametric estimate of the area under the ROC curve in the univariable model including P-wave dispersion alone was modest (c = 0.64) and increased to 0.80 in the model including both variables.

4. Discussion

It is well known that patients undergoing thoracic surgery are at risk of developing postoperative atrial fibrillation. Nevertheless, not so many studies focused this issue and even less prospective studies have been so far performed in order to investigate the possibility of a preoperative risk stratification. On the contrary, a great deal of data are available about AF after coronary artery surgery. In this setting, AF has a prevalence ranging from 10% to 40% and is associated with an increased risk of stroke, congestive heart failure, need for a permanent pacemaker, and prolongation of hospital stay[12,13].

Table 2

<table>
<thead>
<tr>
<th></th>
<th>No AF Median (IQ)</th>
<th>AF Median (IQ)</th>
<th>OR (CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-wave duration (ms)</td>
<td>95 (90–105)</td>
<td>95 (92.5—102.5)</td>
<td>0.99 (0.27—3.60)</td>
<td>0.982</td>
</tr>
<tr>
<td>P-wave dispersion (ms)</td>
<td>20 (25—30)</td>
<td>32.5 (22.5—45.0)</td>
<td>2.06 (1.17—3.64)</td>
<td>0.012</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
<th>N (%)</th>
<th>OR (CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holter 0</td>
<td>68 (96)</td>
<td>3 (4)</td>
<td>8.16 (2.04—35.59)</td>
<td>0.003</td>
</tr>
<tr>
<td>Holter 1—2</td>
<td>25 (74)</td>
<td>9 (26)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IQ: interquartile range; OR: odds ratio; CI: 95% confidence interval; p-value at Wald test. For P-wave, OR of 75 vs 25 percentile of the variable distribution; for Holter, OR of 1—2 vs 0.
A series of clinical, anesthetic, surgical, electrocardiographic, and echocardiographic parameters have been shown to be of some value as predictors of post-CABG atrial fibrillation. The factors more commonly associated with an increased risk are older age, male gender, history of AF, systemic hypertension, ejection fraction, left atrial dimension, number and type of graft(s), and withdrawal from β-blocker treatment [4–7].

Much less thick are the data about AF following major non-cardiac thoracic surgery. The reported prevalence ranges from 10% to 20% after lobectomy and up to 46% after extra-pleural pneumonectomy [1−3]. Substantial uncertainty still exists about AF prognostic significance, with some authors describing increased hospital stay, increased 30-day mortality – up to 25% [1,2], whilst others reported a benign course in patients who suffered from this arrhythmia [10]. In a similar way, contradictory results have been reported by studies evaluating factors predisposing to its occurrence. Increasing age and extent of pulmonary resection (pneumonectomy vs lobectomy) are the most consistently reported risk factors. Others that have been variously described included male gender, history of CHF, arrhythmias and peripheral vascular disease, preoperative heart rate, mediastinal lymph node dissection, and need for repeated thoracotomy [1−3,9,10].

In recent years great interest arose from the possibility of predicting AF by P-wave parameters measured on standard 12-lead or signal averaged ECG.

Many investigators demonstrated that prolonged P-wave duration provides significant information on the risk of developing AF [14]. It has been suggested that this parameter could be an acceptable indicator of inter-atrial conduction disturbance. Indeed, prolongation of intra-atrial and inter-atrial conduction time and inhomogeneous propagation of sinus impulse have been recognized as electrophysiologic substrate of atria prone to fibrillation [15]. Moreover, the link between the presence of intra-atrial conduction abnormalities and the induction of paroxysmal AF has been well described [16].

P-wave dispersion is a new ECG parameter that has been associated with the inhomogeneous and discontinuous propagation of sinus impulse; it has already been tested to predict AF in various clinical settings [17,18]. The role of P-wave features in predicting episodes of postoperative AF are less clear because of conflicting results and since they have been almost exclusively used in the context of cardiac surgery. Buxton et al. first described a significantly larger P-wave duration on the standard ECG in patients with post-CABG-AF [19]. Successively, a series of other authors confirmed these results, using 12-lead superficial or signal-averaged ECG. Dagdelen et al. found that patients who developed post-CABF AF, compared to patients who did not, had P-wave duration and dispersion significantly higher on day 4 post-surgery, whereas baseline P-wave parameters did not differ significantly [20].

On the contrary, Chang et al. reported that P-wave dispersion was similar between patients with and without postoperative AF [21]. Weber et al. demonstrated that P-wave duration and dispersion were predictive of postoperative AF at univariate analysis, while P-wave dispersion was no longer significant in logistic regression model [22].

Lately, Chandy et al. found that preoperative P-wave dispersion was significantly shorter (19.6 ± 12.9 ms vs 23.4 ± 12.5 ms, p = 0.0025) and that increased postoperatively to a larger extent (3.1 ± 15.5 ms vs −1.6 ± 14.6 ms, p = 0.028) in the group who subsequently developed post-operative AF compared to the control group [23].

In our study conducted in patients undergoing thoracic surgery, P-wave duration measured preoperatively was not a predictor of postoperative AF, while P-wave dispersion was positively associated with the occurrence of the arrhythmia. These parameters have not yet been extensively used in an analogous scenario and thus our results cannot be adequately compared to others, with the unique exception being represented by the work of Amar et al. They studied 228 patients and found that P-wave duration, both on signal-averaged and on standard 12-lead ECG, was not associated with the risk of new-onset AF after non-cardiac thoracic surgery [11].

Moreover, our study showed that the presence of PSVCs > 30/h or runs of SVT or AF on preoperative Holter monitoring was another independent marker of AF development and that the inclusion of 24-h Holter may enhance the discriminatory value of P-wave dispersion. In a previous work, multiple PSVCs on preoperative Holter records did not translate to an increased incidence of AF or flutter after thoracotomy [3]. The authors reported multiple PSVCs on preoperative Holter monitoring in 16 out of 97 patients (16.5%), but none of these developed postoperative supraventricular dysrhythmias. However, in this study the number of PSVCs was not specified, and thus it seems that the comparison to our work is difficult, in which PSVCs were divided into three classes, according to number and complexity. On the contrary, frequent premature atrial complexes on preoperative electrocardiography have been extensively linked with supraventricular arrhythmias, either after cardiac or after non-cardiac surgery [24].

In our study, the finding that age was not an important factor accounting for postoperative AF was surprising. In the majority of the studies evaluating clinical correlates of postoperative AF for various surgical procedures, age was the dominant risk factor. Indeed, the aging process is associated with atrial myocardial fibrosis and apoptosis with a loss of side-to-side electrical coupling between groups of atrial fibers. Resultant intra-atrial conduction delay and dispersion of refractoriness may represent a substrate for multiple re-entrant wavefront responsible for AF [25].

4.1. Possible mechanism of postoperative AF

The etiopathogenesis of AF after thoracic operation remain poorly understood, given its multifactorial essence. In general, AF is the result of the simultaneous presence of multiple re-entrant wavelets in the atrial myocardium, often triggered or driven by a repetitive focal source within the pulmonary veins. An underlying electrophysiological basis seems to be responsible for the increased vulnerability of certain patients to develop AF. Such vulnerability could be sustained by a variable combination of a critical atrial muscle mass, a shortened refractory period, a dispersion of atrial refractoriness, and a reduction of conduction velocity. After all, postoperative AF could be viewed as a product of pre-existing electrophysiologic substrate and superimposed...
trigger. The factors in the postoperative period, able to influence both the substrate and the trigger, are numerous and include vagal and adrenergic stimuli, hypoxemia, hypovolemia, electrolyte imbalance, atrial trauma and inflammation, pulmonary hypertension, and dilation of right heart chambers.

4.2. Study limitations

Studying larger populations would be necessary to enhance the statistical strength of our findings.

A continuous electrocardiographic monitoring was limited to the first postoperative hours and it is likely that short-lived episodes of AF occurred later but were not diagnosed. However, our end-point was to evaluate clinically relevant AF that represents the reason for patients’ complaints and the target of physicians’ therapeutic intervention.

P-wave characteristics were measured manually on a magnified copy of standard 12-lead ECG. This method could be of limited accuracy, given the well-known difficulties in defining P-wave onset and offset and this could negatively affect the reproducibility of measuring. Dilaveris et al. comparing three different methods for the manual measurement of P-wave parameters — by cursor on high-resolution computer screen, by callipers and a magnifying glass on standard paper-printed ECG, and by a high-resolution digitizing board — found significantly less intra-observer and inter-observer variability using the on-screen measurement. In our study, however, all the calculations were made by a single experienced cardiologist, thus eliminating a possible inter-observer variability.

5. Conclusions

The results of our study suggest that P-wave dispersion, measured on standard 12-lead ECG, was associated with AF after major non-cardiac thoracic surgery, but it showed a moderate predictive ability.

Preoperative Holter monitoring adds further information and could be used to enhance the predictive ability of this basal screening.

Such a finding will require validation on a larger sample size, before it could be extensively used for selecting high-risk patients, who might be appropriate candidates for antiarrhythmic profilaxis.

References