

Increased Perioperative N-Terminal Pro-B-Type Natriuretic Peptide Levels Predict Atrial Fibrillation After Thoracic Surgery for Lung Cancer

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Background—Postoperative atrial fibrillation (AF) is a complication of thoracic surgery for lung cancer, with a reported incidence that can run as high as 42%. Recently, it has been observed retrospectively that B-type natriuretic peptide predicts AF after cardiac surgery. We performed a prospective study to evaluate the role of N-terminal pro-B-type natriuretic peptide (NT-proBNP) as a marker for risk stratification of postoperative AF in patients undergoing thoracic surgery for lung cancer.

Methods and Results—We measured NT-proBNP levels in 400 patients (mean age, 62±10 years; 271 men) 24 hours before and 1 hour after surgery. The primary end point of the study was the incidence of postoperative AF. Overall, postoperative AF occurred in 72 patients (18%). Eighty-eight patients (22%) showed an elevated perioperative NT-proBNP value. When patients with either preoperatively or postoperatively elevated NT-proBNP were pooled, a greater incidence of AF was observed compared with patients with normal values (64% versus 5%; $P<0.001$). At multivariable analysis, adjusted for age, gender, major comorbidities, echocardiography parameters, pneumonectomy, and medications, both preoperative and postoperative NT-proBNP values were independent predictors of AF (relative risk, 27.9; 95% CI, 13.2 to 58.9; $P<0.001$ for preoperative NT-proBNP elevation; relative risk, 20.1; 95% CI, 5.8 to 69.4; $P<0.001$ for postoperative NT-proBNP elevation).

Conclusions—Elevation of perioperative NT-proBNP is a strong independent predictor of postoperative AF in patients undergoing thoracic surgery for lung cancer. This finding should facilitate studies of therapies to reduce AF in selected high-risk patients. (*Circulation*. 2007;115:1339-1344.)

Key Words: atrial fibrillation ■ natriuretic peptides ■ thoracic surgery

Atrial fibrillation (AF) is a common complication during the early postoperative period in various clinical settings.¹⁻⁸ Its incidence after thoracic surgery for lung cancer has been reported to range from 8% to 42%.⁵ The clinical relevance of postoperative AF is still controversial. In some studies, AF has been found to be benign and transient, although it is associated with a prolonged length of hospitalization and high related costs,⁹⁻¹² whereas, in others, it has been related to significantly increased morbidity and mortality.¹³⁻¹⁶

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Several pharmacological strategies have been proposed for the prevention of postoperative AF with various degrees of success.¹⁶⁻¹⁸ However, their use involves some risks related to side effects and increased costs. Therefore,

the identification of high-risk patients, which would allow us a more targeted and hence more cost-effective and successful application of these prophylactic measures, represents a clear need. Many of the risk factors for postoperative AF that have been indicated (male gender, major extent of lung resection, right side of procedure, history of diabetes mellitus, hypertension, chronic obstructive pulmonary disease [COPD], and coronary artery disease [CAD]) have not been confirmed in other studies.^{9,11,16} Actually, the most robust risk factor for an increased incidence of postoperative AF is advanced age.¹⁸ Hence, our ability to accurately identify patients at high risk for AF is limited^{9,16,17}; consequently, a targeted prophylactic treatment cannot easily be settled on.

Cardiac natriuretic peptides such as brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP)

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have recently emerged as potentially useful biomarkers in the diagnosis and prognostic stratification of heart failure patients and in patients in other clinical settings.^{19,20} More recently, it has been reported that the increase in these biomarkers may indicate the underlying subclinical predisposition to AF both in patients undergoing cardiac surgery²¹ and in patients without a history of cardiac disease.²² However, the capability of NT-proBNP to predict postoperative AF has never been evaluated prospectively; therefore, its clinical applicability remains unclear, as does its transferability to other clinical settings. We performed a prospective clinical study to evaluate the role of NT-proBNP as a possible marker for risk stratification of postoperative AF in patients undergoing thoracic surgery for lung cancer.

Methods

Study Sample

We prospectively evaluated 441 consecutive patients undergoing elective thoracic surgery for lung cancer in our Institute from October 1, 2004, to December 31, 2005. Patients with a history of heart failure (n=4); a left ventricular ejection fraction <50% (n=13); paroxysmal, persistent, or chronic AF (n=15); and antiarrhythmic drug use (n=9) were excluded from the study. Patients were not excluded if they were taking β -blockers or calcium channel blockers for reasons other than cardiac arrhythmia. Four hundred patients (mean age, 62 \pm 10 years; 271 men) fulfilled the inclusion criteria and were enrolled in the study. All eligible patients underwent elective thoracic surgery and had been free from acute major clinical events for at least 2 months. All had good performance status, defined according to the Eastern Cooperative Oncology Group scale as a performance status <2.^{23,24}

Study Protocol

Clinical cardiologic evaluation, ECG, echocardiogram, chest x-ray, and pulmonary function tests were part of the preoperative assessment. Plasma NT-proBNP concentration was measured 24 hours before surgery and soon (within 1 hour) after surgery. All patients remained under continuous ECG monitoring for at least 72 hours after surgery and then underwent daily clinical cardiologic evaluation until discharge.

The primary end point of the study was the incidence of postoperative AF. Any documented episodes of AF lasting at least 5 minutes or requiring intervention because of symptoms or hemodynamic compromise were considered. Treatment of AF was left to the discretion of the referring cardiologist as directed by international guidelines.² The investigation conformed to the principles of the Declaration of Helsinki. The local ethics committee approved the protocol, and written informed consent was obtained from all patients.

NT-proBNP Measurements

For determination of the serum NT-proBNP levels, blood samples were centrifuged at 1000g for 10 minutes and stored at -30°C until analysis. NT-proBNP was assayed with an electrochemiluminescence immunoassay (Elecys NT-proBNP Test, Roche Diagnostics, Mannheim, Germany) on a semiautomated analyzer (Elecys-1010, Roche Diagnostics, Germany). As cutoff levels, we used those suggested by the manufacturer: 64 and 125 ng/L for men and women \leq 49 years of age, 125 and 186 ng/L for men and

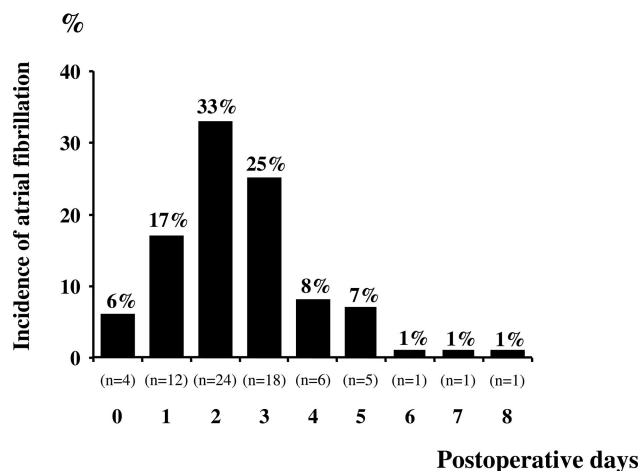


Figure 1. Daily distribution of postoperative AF.

women 50 to 59 years of age, and 194 and 204 ng/L for men and women \geq 60 years of age, respectively.

Statistical Analysis

All statistical tests were 2 sided, and significance was assumed at $P<0.05$. Student *t* test was used for normally distributed continuous variables (expressed as mean \pm SD), and the χ^2 or Fisher exact test, as appropriate, was used for categorical variables.

The association of NT-proBNP levels with the occurrence of postoperative AF was tested by a multivariable logistic regression analysis adjusting for factors presumably associated with AF risk: advanced age, male gender, hypertension, pneumonectomy, CAD, and COPD. NT-proBNP levels were entered as both a continuous and a dichotomous variable using the above mentioned cutoff values. Adjusted relative risk (RR) and 95% confidence intervals were computed. Sensitivity, specificity, and predictive values of NT-proBNP levels with respect to postoperative AF were estimated by use of 2 \times 2 tables. The significance of sensitivity increase using different models was assessed by the McNemar test. All analyses were performed with the SAS statistical package (version 8, SAS Institute Inc, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Postoperative AF occurred in 72 of the 400 patients (18%) who underwent thoracic surgery. All episodes required antiarrhythmic treatment (flecainide in most cases) for their termination. The distribution of AF onset showed a peak on the second postoperative day (mean time, 2.5 \pm 1.5 days), with a cumulative 81% of events occurring during the first 3 days (Figure 1). Postoperative hospital stay was significantly longer in patients with AF compared with those without AF (9 \pm 8 versus 6 \pm 5 days; $P=0.003$). Three patients died during the in-hospital postoperative period; none of them had experienced AF.

Eighty-eight patients (22%) showed an elevated value of NT-proBNP above the predefined gender- and age-adjusted cutoff level in the perioperative period. Seventy-one of them (80%) had elevated NT-proBNP levels detect-

Clinical and Demographic Characteristics of the 2 Study Groups

	Elevated NT-proBNP (n=88)	Normal NT-proBNP (n=312)	<i>P</i>
Age, y	66±10	61±10	<0.001
Men, n (%)	61 (69)	210 (67)	0.82
Hypertension, n (%)	38 (43)	103 (33)	0.10
CAD, n (%)	11 (13)	10 (3)	0.001
COPD, n (%)	17 (19)	37 (12)	0.01
Creatinine clearance, mL/min	92±31	103±29	0.004
Creatinine clearance <60 mL/min, n (%)	7 (8)	0 (0)	<0.001*
Medication, n (%)			
β-Blockers	17 (19)	27 (9)	0.009
ACE inhibitors	22 (25)	64 (21)	0.44
Calcium channel blockers	17 (19)	32 (10)	0.02
Statins	10 (11)	23 (7)	0.32
LVEF, %	61±5	62±4	0.18
Left atrial diameter, mm	38±6	37±5	0.17
FEV ₁ , % predicted	80±20	86±20	0.01
VC, % predicted	77±17	82±16	0.04
DLCO, % predicted	68±19	78±18	<0.001
Type of operation, n (%)			
Pneumonectomy	16 (18)	18 (11)	0.08
Lobectomy	61 (69)	236 (76)	0.28
Bilobectomy	2 (2)	4 (1)	0.39 *
Single wedge resection	5 (6)	26 (8)	0.55
Multiple wedge resections	4 (5)	13 (5)	0.88
Laterality (right)	48 (55)	188 (60)	0.40
NT-proBNP, ng/L			
Before surgery	309±220	63±47	
After surgery	409±491	65±46	

ACE indicates angiotensin-converting enzyme; LVEF, left ventricular ejection fraction; FEV₁, forced expiratory ventilation in 1 second; VC, vital capacity; and DLCO, diffusion capacity of the lung for carbon monoxide. Data are expressed as mean±SD when appropriate.

*By Fisher exact test.

able before surgery, whereas in 17 patients (20%), NT-proBNP increased soon after surgery. In the remaining 312 patients (78%), the NT-proBNP value remained within the normal limits at both the preoperative and postoperative evaluations. Among the 71 patients with a positive preoperative NT-proBNP value, NT-proBNP remained elevated also at the postsurgery evaluation in 54 (76%).

For patients in whom AF occurred, the NT-proBNP mean value was significantly higher than in patients not experiencing AF at both the preoperative (270±242 versus 84±93 ng/L; *P*<0.001) and postoperative (351±523 versus 94±140 ng/L; *P*<0.001) evaluations.

The clinical and demographic characteristics of patients with elevated and normal perioperative (preoperative and postoperative) NT-proBNP values are shown in the Table.

Patients with elevated NT-proBNP values were older, more likely to have had a history of CAD and COPD and/or moderate (stage 3) renal insufficiency,²⁵ and had more compromised baseline pulmonary function tests. Furthermore, they had, on average, a lower calculated creatinine clearance.²⁶

The incidence of AF was 68% in patients with a preoperative positive and 7% in those with a preoperative negative NT-proBNP value (*P*<0.001). Among patients with a preoperative negative NT-proBNP value, 17 patients (5%) showed a postoperative NT-proBNP first increase. In this subgroup of patients, the incidence of AF was higher than that of patients showing always-normal NT-proBNP values (47% versus 5%; *P*<0.001) (Figure 2, left). When both the preoperative and postoperative NT-proBNP values were considered, the incidence of AF was significantly higher in patients with elevated NT-proBNP values (64% versus 5%; *P*<0.001) (Figure 2, right).

At multivariable analysis, after adjustment for confounding parameters such as age, gender, hypertension, pneumonectomy, left atrial size, left ventricular ejection fraction, CAD, COPD, and treatment with β-blockers, both preoperative and postoperative NT-proBNP values were independent predictors of postoperative AF. The RR for AF occurrence in patients with elevated NT-proBNP before surgery was 27.9 (95% confidence interval [CI], 13.2 to 58.9; *P*<0.001). The RR for AF in patients with only postoperative elevated NT-proBNP was 20.1 (95% CI, 5.8 to 69.4; *P*<0.001). When the NT-proBNP positivity was considered, regardless of the time point of detection (either preoperative or postoperative evaluation), the RR for AF was 35.8 (95% CI, 16.7 to 76.7; *P*<0.001). When preoperative NT-proBNP was included in the regression model as a continuous rather than a dichotomous variable, the linear trend was still very significant (*P*<0.0001), with an estimated RR of 1.52 (95% CI, 1.32 to 1.74) for each 50-ng/L increment. The estimated RR for postoperative NT-proBNP for each 50-ng/L increment was 1.26 (95% CI, 1.14 to 1.38; *P*<0.0001). To calculate the positive and negative predictive values of NT-proBNP, we defined a true positive test as AF occurrence in patients with elevated NT-proBNP value and a true negative test as the absence of AF in patients with both preoperative and postoperative NT-proBNP normal values. When only the preoperative NT-proBNP value was considered, the positive predictive value was 68%, and the negative predictive value was 93% (sensitivity, 67%; specificity, 93%). When patients with elevated preoperative and postoperative NT-proBNP values were pooled, the positive predictive value was 64%, and the negative predictive value was 95% (sensitivity, 78%; specificity, 90%). In the end, we estimated, using logistic regression analysis, the single best cutoff for preoperative NT-proBNP to predict AF development. The resulting cutoff (204 ng/L) had a slightly worse performance (87.7% correct classification) than the age- and gender-specific multiple cutoff (88.5% correct classification).

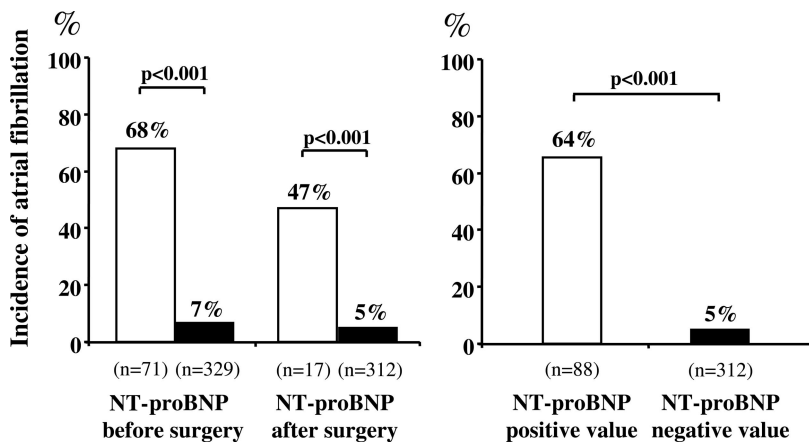


Figure 2. Left, Percentage of postoperative AF considering either preoperative or postoperative NT-proBNP values in patients with elevated (open bar) and normal (solid bar) NT-proBNP values. Right, Percentage of patients with elevated (preoperative and postoperative positivities pooled; open bar) and normal (solid bar) NT-proBNP who develop AF.

Discussion

AF is a frequently occurring arrhythmia after thoracic surgery for lung cancer, with reported incidences ranging from 8% to 20% after lobectomy and up to 42% after pneumonectomy.^{5,9} Although postoperative AF is self-limited in most cases, its treatment requires additional costs for care and prolonged hospital stay, even when not complicated.⁹⁻¹²

Even if prior studies have identified several possible risk factors,^{9,11,16} a clear link between them and the occurrence of AF has not yet been established. Indeed, most of the recognized risk factors are associated with low odds ratios, so no single variable can be used to appropriately stratify a patient's risk.¹⁷ On the other hand, the complexity of the proposed risk scores, resulting from the many variables included, has made their clinical application impractical.^{7,15,17,27-29} At present, a well-targeted prophylactic strategy for AF is still a challenge, and even if preventive therapies such as β -blockers and other antiarrhythmic agents have been shown to reduce the occurrence of AF, their widespread use has been limited by concern over potential side effects.¹⁷

Cardiac natriuretic peptides have been demonstrated to be useful markers of left ventricular dysfunction in both asymptomatic and symptomatic patients. High levels of plasma natriuretic peptides have been reported not only in patients with advanced heart failure or acute myocardial infarction but also in other clinical settings.¹⁹⁻²⁰ Wazni et al²¹ reported that an elevated preoperative BNP value may indicate the underlying predisposition to AF in patients undergoing cardiac surgery. However, this study was retrospective, and the timing and indication for BNP determination were unknown and possibly related to the preexisting cardiac disease. Notably, in this study, many patients had a reduced left ventricular ejection fraction before surgical intervention. The present study is the first to evaluate prospectively the role of NT-proBNP in predicting postoperative AF in patients undergoing thoracic surgery for lung cancer. Our data clearly show that an elevated level of plasma NT-proBNP before or soon after thoracic surgery for lung cancer is a strong independent predictor of AF occurrence. This information may allow us to accurately stratify patients according to their risk and

has important clinical implications. First, a targeted prophylactic therapy may be planned only in selected high-risk patients, namely those with an elevated NT-proBNP value that started either before or immediately after surgery to prevent the occurrence of this frequent arrhythmic complication. Second, given the high negative predictive value of NT-proBNP (95%), low-risk patients, who represent the majority of our population (78%), may be safely excluded from a prophylactic strategy, thus minimizing costs and risks to those patients who are unlikely to derive benefit from such interventions.

In our population, an elevated NT-proBNP value was associated with advanced age, more frequent history of CAD and COPD, and reduced renal function, all well-recognized risk factors for postoperative AF.^{9,11,16,17} Given the high relative risk associated with this marker, it is possible that, either as an independent predictor or when adjusted for the other recognized risk factors, NT-proBNP summarizes in a single parameter the cumulative preoperative risk represented by several factors, so its increase may identify subjects more prone to develop AF. Wang et al³⁰ found that, in a sample of general population without heart failure, the increase in BNP levels significantly correlated with an increased risk of future cardiovascular events, which included AF. All these observations seem to confirm that elevated NT-proBNP levels represent a final common pathway for many subclinical cardiovascular pathological states.^{30,31}

In addition to the preoperative evaluation, we also measured NT-proBNP soon after surgery to investigate whether a late increase in this marker may reflect the influence of intraoperative risk factors on the occurrence of AF.^{5,16,28} Indeed, this additional sample was able to identify patients at increased risk of AF. When the 2 results (preoperative and postoperative) were pooled, the sensitivity of NT-proBNP increased significantly (from 67% to 78%; $P=0.005$). These findings suggest that both preoperative elevation and postoperative elevation of NT-proBNP are involved in the prediction of AF in patients undergoing thoracic surgery for lung cancer, possibly reflecting the influence of baseline patient-related characteristics and intraoperative risk factors, respectively.

Our study provides a new prospective in terms of prophylactic strategies for postoperative AF. We can speculate that, in addition to drugs with antiarrhythmic properties, treatment with agents able to lower baseline NT-proBNP and to prevent NT-proBNP rise after surgery could protect against AF. However, further studies are needed to demonstrate that a reduction in this marker before surgery is paralleled by a consequent reduction in the risk of AF occurrence. Nonetheless, it has previously been demonstrated that a BNP- or NT-proBNP-tailored therapy reduces the occurrence of cardiovascular events in patients with heart failure.³²

Our study has some limitations. First, although it benefited from a sizeable number of patients, it included a population admitted to a single center. Second, we performed only 1 NT-proBNP determination after thoracic surgery. Presumably, further postoperative determinations might be required in NT-proBNP negative patients to improve sensitivity and positive predictive value.

Conclusions

Elevation of perioperative NT-proBNP value is a strong independent predictor of AF occurrence in patients undergoing thoracic surgery for lung cancer. This finding allows us to stratify perioperative risk for AF in such a population and to plan prophylactic strategies in selected high-risk patients.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Atrial fibrillation (AF) is a frequent complication of thoracic surgery for lung cancer that prolongs hospital stay and increases costs. Moreover, AF has been related to increased morbidity and mortality. Several pharmacological strategies have been proposed for its prevention, with various degrees of success. Several possible risk factors for AF have been identified, but a clear link between them and AF has not yet been established. Our study shows that elevated perioperative levels of plasma N-terminal pro-B-type natriuretic peptide are strong independent predictors of AF occurrence. Our study suggests a new perspective on prophylactic strategies for postoperative AF and has relevant clinical implications that warrant further study. First, it offers the opportunity to implement prophylactic therapy only in selected high-risk patients with an elevated N-terminal pro-B-type natriuretic peptide value. Second, given the high negative predictive value of N-terminal pro-B-type natriuretic peptide (95%), low-risk patients, representing the majority (78%) of our population, can be excluded from a preventive antiarrhythmic strategy, minimizing the costs and the risks to those patients who are unlikely to derive benefit from such interventions. In addition, we speculate that preoperative treatment of high-risk patients to attempt to reduce elevated baseline N-terminal pro-B-type natriuretic peptide and to prevent its rise after surgery might be explored to determine whether this strategy would reduce postoperative AF.