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ORIGINAL ARTICLE

Atrial fibrillation after thoracic surgery for lung cancer: use of a single cut-off value of N-terminal pro-B type natriuretic peptide to identify patients at risk

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Abstract
Postoperative atrial fibrillation (AF) is a well-known complication occurring after thoracic surgery. B-type natriuretic peptide has recently been investigated as a predictive marker of postoperative AF after cardiac surgery. The aim of this study was to evaluate a definite cut-off for N-terminal pro-B type natriuretic peptide (NT-proBNP) in predicting postoperative AF in lung cancer patients. NT-proBNP was determined before and after surgery in 400 patients. Cardiac function was monitored by continuous postoperative ECG and clinical cardiological evaluation. AF occurred in 18% of the patients. Receiver operating characteristic curve analyses identified a cut-off of 182.3 ng l^{-1} as the one with the highest sensitivity and specificity. Perioperative increased levels of NT-proBNP seem to predict postoperative AF in patients undergoing thoracic surgery, and a single cut-off of 182.3 ng l^{-1} can be used to select high-risk patients who could receive preventive therapy, leading to a considerable decrease in the total costs associated with the management of this complication.

Keywords: *Atrial fibrillation; NT-proBNP; natriuretic peptides; thoracic surgery; lung cancer disease*

Introduction

Natriuretic peptides are cardiac hormones synthesized in the atria and ventricles in response to ventricular dysfunction and wall stress. They modulate plasma volume homeostasis and systemic blood pressure through their action as diuretic, renin–angiotensin–aldosterone system antagonists, and inhibitors of sympathetic outflow and vasoconstrictor production (Goetze 2004, Struthers 1994).

In particular, several studies have demonstrated the importance of brain natriuretic peptide (BNP) and N-terminal pro-B type natriuretic peptide (NT-proBNP) as markers of cardiac impairment; they are elevated in patients with cardiac disorders such as congestive heart failure (CHF), with levels correlating with the severity of the disease (Hunt et al. 1997, Dao et al. 2001, Cowie et al. 1997, Seino et al. 2004), and are useful in the risk stratification of patients with acute coronary syndromes and in the clinical assessment of left ventricular dysfunction (Yamamoto et al. 1996, Lubien et al. 2002, Mueller et al. 2004).

Atrial fibrillation (AF) represents one of the most frequent postoperative cardiac complications occurring after surgery, especially in patients undergoing cardiothoracic surgery, with an incidence ranging from 10 to 40% (Ommen et al. 1997, Brathwaite & Weissman 1998, Cardinale et al. 1999). Although AF is often transient and benign, it may lead to important complications resulting in a longer hospital stay, increased morbidity and postoperative mortality

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(Cardinale et al. 1999, Ascione et al. 2000, Amar 2002, De Decker et al. 2003, Roselli et al. 2005).

Strategies directed toward an early identification of patients who might be at risk of postoperative arrhythmias and who might benefit from prophylactic therapy were based on the evaluation of various clinical risk factors and on the development of scoring systems to estimate the likelihood of postoperative AF (Asamura et al. 1993, Vaporciyan et al. 2004, Amar et al. 2004, Passman et al. 2005, Auer et al. 2005).

However, there is not yet a reliable method to evaluate the risk of postoperative AF. Recently the association between BNP and AF both in patients with lone AF and in patients undergoing cardiac surgery has been evaluated (McKie & Burnett 2005, Ellinor et al. 2005, Lee et al. 2006, Wazni et al. 2004, Patton et al 2009), and the results suggest a significant correlation between BNP levels and the risk of development of AF.

We recently investigated the role of NT-proBNP in the prediction of AF after major thoracic surgery for lung cancer and showed that elevated perioperative NT-proBNP levels were significantly associated with the development of postoperative AF (Cardinale et al. 2007). In this study stratification of the patients took into account six different cut-off points, according to the age and gender of the subjects. This may be difficult to implement in routine clinical practice. Therefore, the aim of the present study was to look for a single definitive cut-off point to be used by clinicians in order to evaluate the risk of postoperative AF, also in the light of a study in which a preventive therapy could be given to patients to avoid this cardiac complication.

Methods

Study population

The study population included 441 consecutive patients undergoing major thoracic surgery for lung cancer disease in our Institute, from October 2004 to December 2005. The study was approved by the Institutional Review Board and written consent from the patients was obtained. Patients with a history of heart failure ($n=4$), a left ventricular ejection fraction (LVEF) value <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 beta-blockers or calcium channel blockers for reasons other than cardiac arrhythmia. Finally, there were 400 eligible patients.

Study protocol

The study protocol was the same as described previously and this study represents a further analysis of the data, undertaken to find a single definitive cut-off level for NT-proBNP (Cardinale et al. 2007). Briefly, a clinical cardiological evaluation, electrocardiogram, echocardiogram, chest X-ray and pulmonary function tests were part of the preoperative assessment. Plasma for NT-proBNP determination was taken the day before surgery and immediately after (within 1 h). All patients remained under continuous electrocardiographic monitoring for at least 72 h after surgery, then underwent daily clinical cardiological evaluation until discharge. Any documented episode of AF lasting at least 5 min or requiring intervention because of symptoms or haemodynamic impairment was considered. Treatment of AF was left to the discretion of the referring cardiologist, as directed by the international guidelines (ACC/AHA/ESC 2001).

Laboratory methods

Blood samples were centrifuged at 1000 *g* for 10 min and stored at –30°C until analysis was performed. NT-proBNP was assayed using an electrochemiluminescence immunoassay (Elecsys NT-proBNP Test; Roche Diagnostics, Mannheim, Germany) on a semiautomated analyser (Elecsys-1010; Roche Diagnostics).

The analytical sensitivity of the assay is <5 ng l^{-1} NT-proBNP with a maximum of the master calibration curve of 35 000 ng l^{-1}.

Statistical analysis

Numerical variables with a nearly normal distribution were summarized as means and SD, those with skewed distributions as medians and interquartile range (IQR), and categorical variables as frequency and percentage. Pre- and postoperative NT-proBNP levels were compared between groups using the Wilcoxon rank-sum test. In order to identify the best NT-proBNP measure in predicting the development of postoperative AF, receiver operating characteristic (ROC) curve analysis was used. This approach allows both sensitivity and specificity to be accounted for and it is preferred to computing overall accuracy, which is affected by the prevalence of events within the studied population. ROC curves were computed using postoperative AF as a dependent variable and considering four measures of NT-proBNP: (1) preoperative values; (2) postoperative values; (3) mean value between pre- and postoperative determinations; and (4) the maximum value between pre- and postoperative NT-proBNP.

Stratified analysis was performed according to gender and age of patients, two variables known to be associated with NT-proBNP levels. A sample size of 400 patients allowed us to estimate the area under the curve (AUC) with a standard error of 3%, with an established incidence of postoperative AF of 18%. The optimal cut-off value was identified using the 'closest-to-(0.1)' criterion, i.e. the value corresponding to the point on the ROC curve closest to the upper-left corner of the total area (the point with coordinates 0.1 on the plane) (Coffin & Sukhatme 1997).

All analyses were performed using SAS statistical package v. 9.13 (SAS Institute Inc., Cary, NC, USA).

Results

The clinical characteristics of the study population are shown in Table 1. NT-proBNP values were available for 271 males (67.7%) and 129 women (32.3%) (mean age 62 ± 10 years) who underwent thoracic surgery (pneumonectomy $n = 49$ (12%), lobectomy $n = 297$ (74%), bilobectomy $n = 6$ (2%), single or multiple resections $n = 48$ (12%)). All had good performance status, defined according to the Eastern Cooperative Oncology Group scale as a performance status <2 (Oken et al. 1982, Mohamed et al. 2005), and had been free from acute major clinical events for at least 2 months.

Postoperative AF occurred in 72 patients (18%), with a peak of incidence (33% of the cases) on the second postoperative day for a total of 81% of the events during the first 3 days.

NT-proBNP concentrations were significantly higher in patients who developed postoperative AF (preoperative evaluation 231 ng l^{-1}, IQR 98–348; postoperative evaluation 202 ng l^{-1}, IQR 83–437) versus patients with no postoperative AF (preoperative evaluation 55 ng l^{-1}, IQR 31–107; postoperative evaluation 58 ng l^{-1}, IQR 34–107) ($p < 0.001$ for both pre- and postoperative comparisons).

The ROC curve analysis indicated for preoperative and postoperative samples two cut-off points with similar sensitivity and specificity, and comparable AUC (Figure 1). In the case of the preoperative sample a cut-off value of 128.7 ng l^{-1} emerged as the most appropriate, with a sensitivity of 69.4% and a specificity of 82.6%. A similar cut-off was found for the postoperative sample (120 ng l^{-1}) with identical sensitivity and slightly lower specificity (79%). We also evaluated the possibility of combining the results of the two tests for the same patients. Using the mean value between pre- and postoperative determinations, we found a cut-off level of 117.5 ng l^{-1} with increased sensitivity (77.8%) but a slight decrease in specificity (77.7%), compared with the two previous analyses. Finally, when the maximum value between the two measures was considered, an AUC of 0.82 (95% confidence interval (CI) 0.76–0.88) was found, with a good sensitivity (72.2%) and the best specificity (86.9%), at a cut-off value of 182.3 ng l^{-1}.

Given that age and gender have a great impact on NT-proBNP concentration, two subgroup analyses were performed by subdividing the study population according to age (≤60 years vs >60 years) or gender. The results are shown in Tables 2 and 3. In all strata, the best AUC was achieved when the maximum value was considered. In Table 2, similar AUC and sensitivity were found both for mean and maximum values when women were considered; however, specificity was considerably better in the case of maximum value (89.3%) compared with the mean value (76.8%), and also the cut-off levels were substantially different. In men, all the AUC were comparable for all the samples, and the best combination of sensitivity and specificity was found again for the maximum value. Table 3 shows the different value of sensitivity and specificity dividing the population into two age groups, ≤60 years and >60 years. In younger patients we found similar AUC for all the samples, apart from the preoperative samples, with different cut-off values and quite different sensitivity and specificity. In older subjects the AUC were comparable (0.80, 95% CI 0.73–0.87) for all the samples, with different cut-off values, apart from the postoperative sample, for which a slightly lower AUC (0.76, 95% CI 0.69–0.84) corresponded to a lower value of sensitivity and specificity.

Table 1. Baseline characteristics of the patients.

Eligible patients, *n*	400
Age (years), mean ± SD	62 ± 10
Men, *n* (%)	271 (67.7)
Hypertension, *n* (%)	141 (35.2)
Creatinine clearance <60 ml min^{-1}, *n* (%)	7 (1.75)
Preoperative LVEF (%)	62 (± 4)
Atrial fibrillation, *n* (%)	72 (18)
Medication, n (%)	
β-Blockers	34 (8.5)
ACE inhibitors	86 (21.5)
Calcium channel blockers	49 (12.25)
Statins	33 (8.25)

LVEF, left ventricular ejection fraction.

Discussion

A number of multifactorial risk indexes have been evaluated in an attempt to predict postoperative AF in patients undergoing major thoracic surgery. Although these indexes have been extensively studied, their reliability in predicting postoperative cardiac complications is uncertain and no gold standard currently exists. Recent studies evaluated the performance of natriuretic peptides in this setting (Karthikeyan et al. 2009), analysing patients undergoing cardiac surgery: significant correlation between preoperative levels of these molecules and patients' outcome has been suggested (Hutfless et al. 2004, Kerbaul et al. 2004, Dernellis & Panaretou 2006). In particular, Wazni et al. (2004) reported that elevated preoperative BNP levels predict the onset of postoperative AF

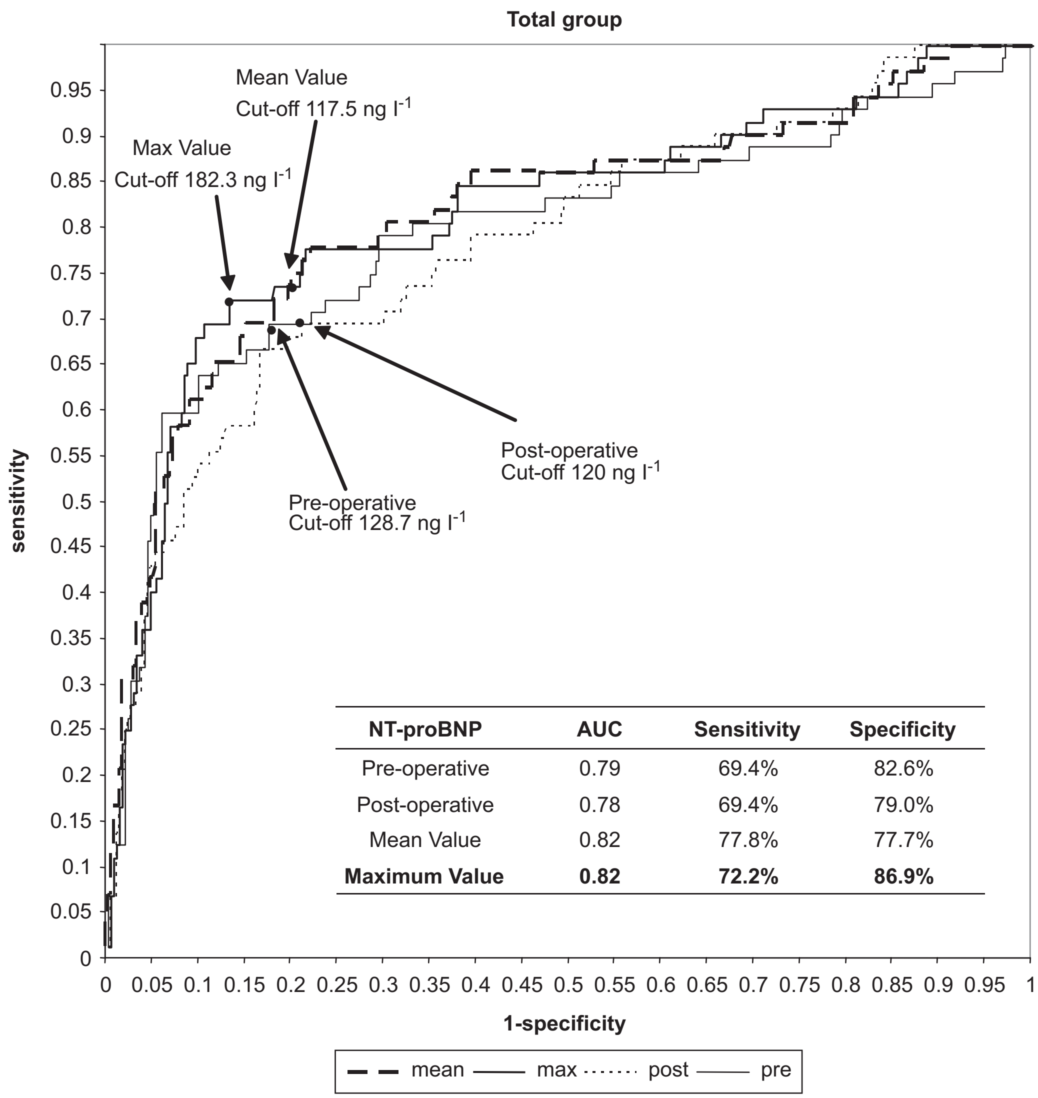

Figure 1. Receiver operating characteristic (ROC) curves for N-terminal pro-B type natriuretic peptide (NT-proBNP) as a predictor of postoperative atrial fibrillation. The arrows indicate cut-off concentrations of NT-proBNP taking into account the pre- and postoperative evaluation, and the mean and maximum value between the two NT-proBNP determinations. AUC, area under the curve.

Table 2. Sensitivity and specificity for N-terminal pro-B type natriuretic peptide (NT-proBNP) in predicting atrial fibrillation according to gender.

	Women (*n* = 129, 32.3%)				Men (*n* = 271, 67.7%)			
NT-proBNP	Cut-off (ng l^{-1})	AUC	Sensitivity (%)	Specificity (%)	Cut-off (ng l^{-1})	AUC	Sensitivity (%)	Specificity (%)
Preoperative	182.5	0.81	76.5	87.5	94.7	0.80	78.2	72.7
Postoperative	150.4	0.84	76.5	82.1	126.7	0.78	65.5	81.9
Mean value	117.5	0.88	88.2	76.8	119.7	0.80	74.5	79.6
Maximum value	205.7	0.88	88.2	89.3	143.0	0.81	74.5	78.7

AUC, area under the curve.

in patients undergoing cardiac surgery, and concluded that BNP levels could be used to identify the underling susceptibility to develop postoperative AF. Other studies evaluated the usefulness of BNP determinations in patients with lone AF. Lee et al. (2006) compared plasma levels of BNP between subjects with sinus rhythm and subjects with lone AF, and found that markedly elevated BNP value was associated with lone AF. In spite of the results, these molecules are presently not included as part of the assessment tools routinely used in the preoperative evaluation of the patients undergoing surgical procedures.

We previously showed (Cardinale et al. 2007) that in patients undergoing thoracic surgery NT-proBNP

Table 3. Sensitivity and specificity for N-terminal pro-B type natriuretic peptide (NT-proBNP) in predicting atrial fibrillation according to age.

	Age ≤60 years (n = 157, 39.3%)				Age >60 years (n=243, 60.7%)			
NT-proBNP	Cut-off (ng l^{-1})	AUC	Sensitivity (%)	Specificity (%)	Cut-off (ng l^{-1})	AUC	Sensitivity (%)	Specificity (%)
Preoperative	101.1	0.69	63.6	84.4	170.4	0.80	70.5	83.4
Postoperative	140.7	0.78	63.6	93.3	140.4	0.76	67.2	76.7
Mean value	80.7	0.81	81.8	77.8	157.6	0.80	70.5	82.9
Maximum value	101.1	0.81	81.8	79.3	199.0	0.80	73.8	86.5

AUC, area under the curve.

measurement before or immediately after the surgical procedures was a strong independent predictor of AF occurrence, potentially allowing the implementation of prophylactic therapy in high-risk patients. Our population was stratified using six different cut-off points, suggested by the manufacturer, depending on age and sex. This further analysis was undertaken in order to find a single cut-off value, easy to implement in clinical practice, allowing a good discrimination between subjects who will or will not develop AF after thoracic surgery.

To the best of our knowledge there is no substantial consensus on the NT-proBNP threshold to be used in different clinical conditions. In particular, no data have been reported until now defining the cut-off value for NT-proBNP in the prediction of AF associated with lung surgery.

ROC curve analysis was performed to evaluate the sensitivity and the specificity of NT-proBNP throughout a wide range of concentrations both considering the preoperative samples alone, the postoperative samples alone, and the mean and maximum value between the two determinations.

A threshold of 182.3 ng l^{-1}, calculated by considering the maximum value between the two determinations, emerged as the best cut-off value with a sensitivity of 72.2% and a specificity of 86.9%. Using this cut-off value we obtained the correct classification of 337 patients (84.3%, 95% CI 80.3–87.7%). Comparing the performance of this single cut-off value with the performance when using age and gender specific cut-off values, we observed that the best performance of the NT-proBNP was found when the maximum value between the pre- and the postoperative samples was considered, although substantially different cut-off values for male and female (143 ng l^{-1} and 205.7 ng l^{-1}, respectively) and for old (>60 years) or young (≤ 60 years) patients (199 ng l^{-1} and 101.1 ng l^{-1}, respectively) were found. However, the improvement in the performance of different NT-proBNP thresholds, compared with the use of the single cut-off value, was limited, and only in the female subgroup were the AUC, the sensitivity and the specificity higher. We further explored whether the use of this single cut-off value was comparable with the performance obtained using the cut-off points proposed by the manufacturer, and used in our previous study (Cardinale et al 2007). Using this approach, which implies the use of six different cut-off points specific for the two genders and three age strata, we obtained a sensitivity of 75% and specificity of 87.2% which allowed the identification of 54 true positive patients and of 286 true negative patients. Forty-two subjects did not develop postoperative AF, although their NT-proBNP level was above the cut-off point, while 18 developed postoperative AF with low levels of NT-proBNP. Using the newly proposed single cut-off value of 182.3 ng l^{-1}, we obtained substantially the same classification: 52 true positive, 285 true negative, 43 false positive and 20 false negative. Therefore, compared with the use of the six specific cut-off levels, the single cut-off approach yielded one more false positive result and 2 more false negatives. Lastly, we also compared this new single cut-off level with the one previously estimated of 204 ng l^{-1} (Cardinale et al. 2007). It is true that the percentage of correct classification (87.7%) was higher compared with what we found in the present evaluation (84.3%). However, that result was attained at the price of an inadequate sensitivity (58%) thus confirming that, when the prevalence of events is low, the approach based on ROC curve analysis is more reliable than that based on the correct classification. Moreover, our previous result was calculated taking into consideration only the preoperative value, while our new more advanced analysis showed the higher performance of maximum value between pre- and postoperative samples.

Few data are available in the literature with which to compare our results. The only report we can consider is by Wazni et al. (2004); we share with this study the same endpoint, i.e. the prediction of postoperative AF, but substantial differences are represented by the clinical situation, as they evaluated patients after coronary artery bypass and/or valve surgery, and the use of BNP. They reported that patients with BNP concentration above the 50th percentile have a higher risk of AF development in the postoperative period. However they do not specify a definite cut-off to be used in the clinical practice.

Historically, postoperative AF has often been considered to be a ‘benign,’ self-limiting complication. However, the accumulated evidence, suggests that AF is often associated with other serious complications (resulting in increased utilization of hospital resources and lengthened postoperative hospital stay), and may be a persistent or recurrent problem for affected patients even after hospital discharge. Given the large number of patients undergoing thoracic surgery each year, the aggregate economic costs associated with this complication are enormous. We previously demonstrated (Cardinale et al. 2007) that patients presenting AF had a longer postoperative hospital length of stay compared with those in whom this complication did not present (9 ± 8 vs 6 ± 5 days; $p = 0.003$). Therefore it is clear that this complication leads to a substantial increase in costs both due to the lengthening of hospital stay and to the cardioversion procedure. Identifying patients at risk of AF earlier through the evaluation of NT-proBNP before and after surgery, and targeting these patients with preventive therapy, when needed, may result in a much more cost-effective strategy. We estimated that, at our institution, additional hospital charges plus cardioversion technique were associated with a mean charge of 2200€ per patient treated, versus a cost of about 65€, which includes two NTproBNP determinations and the administration of prophylactic therapy. Therefore, it seems that any decrease in the rate of occurrence of AF could potentially result in a large decrease in the total cost associated with the management of this complication. Also assuming that only ~50% of the patients will benefit from the preventive therapy, we could obtain a significant reduction of the hospital costs. We also have to consider that the preventive therapy is usually well tolerated, it is given for only a few days (until discharge) and it prevents the patients from the discomfort of an AF complication.

We are aware that our study may have some limitations. First, we do not know whether our results can be transferred to different clinical settings, as only patients with lung cancer undergoing thoracic surgery were analysed. Second, the gender unbalance in our population may have had an impact in the determination of the cut-off value, due to the potential effect of gender on NT-proBNP concentration. However, our results reflect the gender distribution actually found in this malignancy.

In conclusion, our analysis demonstrated that a single and definitive cut-off value of NT-proBNP can be used to select patients at high risk of developing postoperative AF. This marker could be included as a predictive index in the evaluation of the patients, providing the clinician with useful information in the management of the patients, who may possibly undergo prophylactic therapy.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients with Atrial Fibrillation). (2001). *J Am Coll Cardiol* 38:1231–65.

Amar D. (2002). Post-operative atrial fibrillation. *Heart Dis* 4:117–23.

Amar D, Shi W, Hogue CW Jr, Zhang H, Passman RS, Thomas B, Bach PB, Damiano R, Thaler HT. (2004). Clinical prediction rule for atrial fibrillation after coronary artery bypass grafting. *J Am Coll* 44:1248–53.

Asamura H, Naruke T, Tsuchiya R, Goya T, Kondo H, Suemasu K. (1993). What are the risk factors for arrhythmias after thoracic operations? A retrospective multivariate analysis of 267 consecutive thoracic operations. *J Thorac Cardiovasc Surg* 106:1104–10.

Ascione R, Caputo M, Calori G, Lloyd CT, Underwood MJ, Angelini GD. (2000). Predictors of atrial fibrillation after conventional and beating heart coronary surgery: a prospective, randomized study. *Circulation* 102:1530–5.

Auer J, Weber T, Berent R, Ng CK, Lamm G, Eber B. (2005). Risk factors of postoperative atrial fibrillation after cardiac surgery. *J Card Surg* 20:425–31.

Brathwaite D, Weissman C. (1998). The new onset of atrial arrhythmias following major non-cardiothoracic surgery is associated with increased mortality. *Chest* 114:462–8.

Cardinale D, Martinoni A, Cipolla CM, Civelli M, Lamantia G, Fiorentini C, Mezzetti M. (1999). Atrial fibrillation after operation for lung cancer: clinical and prognostic significance. *Ann Thorac Surg* 68:1827–31.

Cardinale D, Colombo A, Sandri MT, Lamantia G, Colombo N, Civelli M, Salvatici M, Veronesi G, Veglia F, Fiorentini C, Spaggiari L, Cipolla CM. (2007). Increased perioperative N-terminal pro-B-type natriuretic peptide levels predict atrial fibrillation after thoracic surgery for lung cancer. *Circulation* 115:1339–44 .

Cowie MR, Struthers AD, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Sutton GC. (1997). Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet* 350:1349–53.

Coffin M, Sukhatme S. (1997). Receiver operating characteristic studies and measurement errors. *Biometrics* 53:823–37.

Dao Q, Krishnaswamy P, Kazanegra R, Harrison A, Amirnovin R, Lenert L, Clopton P, Alberto J, Hlavin P, Maisel AS. (2001). Utility of B-type natriuretic peptide (BNP) in the diagnosis of CHF in an urgent care setting. *J Am Coll Cardiol* 37:379–85.

De Decker K, Jorens PG, Van Schil P. (2003). Cardiac complications after noncardiac thoracic surgery: an evidence-based current [Review]. *Ann Thorac Surg* 75:1340–8.

Dernellis J, Panaretou M. (2006). Assessment of cardiac risk before non-cardiac surgery: brain natriuretic peptide in 1590 patients. *Heart* 92:1645–50.

Ellinor PT, Low AF, Patton KK, Shea MA, MacRae CA. (2005). Discordant atrial natriuretic peptide and brain natriuretic levels in lone atrial fibrillation. *J Am Coll Cardiol* 45:82–8.

Goetze JP. (2004). Biochemistry of pro-B-type natriuretic peptide-derived peptides: the endocrine heart revisited [Minireview]. *Clin Chem* 50:1503–10.

Hunt PJ, Richards AM, Nicholls NG, Yandle TG, Doughty RN, Espiner EA. (1997). Immunoreactive amino-terminal pro-brain natriuretic peptide (NT-proBNP): a new marker of cardiac impairment. *Clin Endocrinol* 47:287–96.

Hutfless R, Kazanegra R, Madani M, Bhalla MA, Tulua-Tata A, Chen A, Clopton P, James C, Chiu A, Maisel AS. (2004). Utility of B-type natriuretic peptide in predicting postoperative complications and outcomes in patients undergoing heart surgery. *J Am Coll Cardiol* 43:1873–9.

Karthikeyan G, Moncur RA, Levine O, Heels-Ansdell D, Chan MT, Alonso-Coello P, Yusuf S, Sessler D, Villar JC, Berwanger O, McQueen M, Mathew A, Hill S, Gibson S, Berry C, Yeh HM, Devereaux PJ. (2009). Is a pre-operative brain natriuretic peptide or N-terminal pro-B-type natriuretic peptide measurement an independent predictor of adverse cardiovascular outcomes within 30 days of noncardiac surgery? A systematic review and meta-analysis of observational studies. *J Am Coll Cardiol* 54:1599–606.

Kerbaul F, Collart F, Giorgi R, Oddoze C, Lejeune PJ, Guidon C, Caus T, Bellezza M, Gouin F. (2004). Increased plasma levels of pro-brain natriuretic peptide in patients with cardiovascular complications following off-pump coronary artery surgery. *Intensive Care Med* 30:1799–806.

Lee SH, Jung JH, Choi SH, Lee N, Park WJ, Oh DJ, Rhim CY, Lee KH. (2006). Determinants of brain natriuretic peptide levels in patients with lone atrial fibrillation. *Circ J* 70:100–4.

Lubien E, DeMaria A, Krishnaswamy P, Clopton P, Koon J, Kazanegra R, Gardetto N, Wanner E, Maisel AS. (2002). Utility of B-natriuretic peptide in detecting diastolic dysfunction: comparison with Doppler velocity recordings. *Circulation* 105:595–601.

McKie PM, Burnett JC. (2005). B-type natriuretic peptide as a biomarker beyond heart failure: speculations and opportunities. *Mayo Clinic Proc* 80:1029–36.

Mohamed MK, Ramalingam S, Lin Y, Gooding W, Belani CP. (2005). Skin rash and good performance status predict improved survival with gefitinib in patients with advanced non-small cell lung cancer. *Ann Oncol* 16:780–5.

Mueller C, Scholer A, Laule-Kilian K, Martina B, Schindler C, Buser P, Pfisterer M, Perruchoud AP. (2004). Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. *N Engl J Med* 350:647–54.

Ommen SR, Odell JA, Stanton MS. (1997). Atrial arrhythmias after cardiothoracic surgery [Review]. *N Engl J Med* 336:1429–34.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. (1982). Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 5:649–55.

Passman RS, Gingold DS, Amar D, Lloyd-Jones D, Bennett CL, Zhang H, Rusch VW. (2005). Prediction rule for atrial fibrillation after major noncardiac thoracic surgery. *Ann Thorac Surg* 79:1698–703.

Patton KK, Ellinor PT, Heckbert SR, Christenson RH, DeFilippi C, Gottdiener JS, Kronmal RA.(2009). N-Terminal pro-B-type natriuretic peptide is a major predictor of the development of atrial fibrillation. *Circulation* 120:1768–74.

Roselli EE, Murthy SC, Rice TW, Houghtaling PL, Pierce CD, Karchmer DP, Blackstone EH. (2005). Atrial fibrillation complicating lung cancer resection. *J Thorac Cardiovasc Surg* 130:438–44.

Seino Y, Ogawa A, Yamashita T, Fukushima M, Ogata K, Fukumoto H, Takano T. (2004). Application of NT-proBNP and BNP measurements in cardiac care: a more discerning marker for detection and evaluation of heart failure. *Eur J Heart Fail* 15:295–300.

Struthers AD. (1994). Ten years of natriuretic peptide research: a new dawn for their diagnostic and therapeutic use? [Review]. *BMJ* 308:1615–19.

Vaporciyan AA, Correa AM, Rice DC, Roth JA, Smythe WR, Swisher SG, Walsh GL, Putnam JB Jr. (2004). Risk factors associated with atrial fibrillation after noncardiac thoracic surgery: analysis of 2588 patients. *J Thorac Cardiovasc Surg* 127:779–86.

Wazni OM, Martin DO, Marrouche NF, Latif AA, Ziada K, Shaaraoui M, Almahameed S, Schweikert RA, Saliba WI, Gillinov AM, Tang WH, Mills RM, Francis GS, Young JB, Natale A. (2004). Plasma B-type natriuretic peptide levels predict postoperative atrial fibrillation in patients undergoing cardiac surgery. *Circulation* 110:124–7.

Yamamoto K, Burnett JC Jr, Jougasaki M, Nishimura RA, Bailey KR, Saito Y, Nakao K, Redfield MM. (1996). Superiority of brain natriuretic as a hormonal marker of ventricular systolic and diastolic dysfunction and ventricular hypertrophy. *Hypertension* 28:988–94.