Increased N-terminal pro-brain natriuretic peptide level predicts atrial fibrillation after surgery for esophageal carcinoma

Jiang-Long Hou, Ke Gao, Mei Li, Jian-Yang Ma, Ying-Kang Shi, Yun Wang, Yong-Fan Zhao

Jiang-Long Hou, Ke Gao, Jian-Yang Ma, Ying-Kang Shi, Yun Wang, Yong-Fan Zhao, Department of Thoracic and Cardiovascular Surgery, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China Mei Li, Department of Thoracic Cancer, Cancer Center, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China

Author contributions: Hou JL and Gao K contributed equally to this work; Hou JL, Gao K, Li M, Ma JY, Shi YK, Wang Y and Zhao YF designed the research; Hou JL, Gao K and Ma JY performed the research; Hou JL, Gao K and Li M analyzed the data; Hou JL, Gao K and Li M wrote the paper.

Correspondence to: Yun Wang, Department of Thoracic and Cardiovascular Surgery, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China. yunwangcd@yahoo.com.cn Telephone: +86-28-85422501 Fax: +86-28-85422493 Received: October 11, 2007 Revised: March 4, 2008

Abstract

AIM: To evaluate the value of plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) level for predicting postoperative atrial fibrillation (AF) in patients undergoing surgery for esophageal carcinoma.

METHODS: NT-proBNP levels were measured in 142 patients 24 h before and 1 h after surgery for esophageal carcinoma. All patients having a preoperative cardiac diagnosis by electrocardiogram (ECG), remained under continuous monitoring for at least 48 h after surgery, and then underwent clinical cardiac evaluation until discharge.

RESULTS: Postoperative AF occurred in 11 patients (7.7%). AF patients were significantly older (69.6 ± 12.2 years vs 63.4 ± 13.3 years, P = 0.031) than non-AF patients. There were no significant differences in history of diabetes mellitus, sex distribution, surgical approach, anastomosis site, intraoperative hypotension and postoperative fever. The preoperative plasma NT-proBNP level was significantly higher in patients who developed postoperative AF (121.3 ± 18.3 pg/mL vs 396.1 ± 42.6 pg/mL, P = 0.016). After adjustment for age, gender, chronic obstructive pulmonary disease (COPD), history of cardiac diseases, hypertension, postoperative hypoxia and thoracic-gastric dilation, NT-proBNP levels were found to be associated with the highest risk factor for postoperative AF (odds ratio = 4.711, 95% CI = 1.212 to 7.644, P = 0.008).

CONCLUSION: An elevated perioperative plasma BNP level is a strong and independent predictor of postoperative AF in patients undergoing surgery for esophageal carcinoma. This finding has important implications for identifying patients at higher risk of postoperative AF who should be considered for preventive antiarrhythmic therapy.

Introduction

Postoperative infections and cardiac events are the major complications after surgery for esophageal carcinoma and the dominating causes of death. Atrial fibrillation (AF) is a frequent arrhythmia after esophageal procedures and is associated with an increased morbidity and mortality and a longer, more expensive hospital stay[1-5].

In a previous study, we retrospectively studied 63 patients with AF after surgery for esophageal carcinoma in comparison with 126 patients without AF after esophagectomy during the same time. We identified some risk factors as predictors of AF after surgery for esophageal carcinoma, such as postoperative hypoxia, history of obstructive pulmonary disease (COPD), thoracic-gastric dilatation, age older than 65 years, male gender, and history of cardiac disease[6]. However, our ability to accurately identify patients at high risk for AF is still limited. No accurate assessment tool or biomarker has
been identified that could predict the occurrence of AF early after esophageal procedures so far. Since a targeted preventive treatment cannot be performed easily, a sensitive blood biomarker that can predict the occurrence of AF in patients after surgery for esophageal carcinoma with a high specificity is desirable.

Brain natriuretic peptide (BNP) is a neurohormone which is stored mainly in myocytes of the cardiac ventricles and released as a result of volume and pressure overload or myocardial damage[7, 10]. N-terminal pro BNP (NT-proBNP) has a longer half life than brain natriuretic peptide and is less influenced by acute therapeutic regimens and clinical deteriorations, making it available for predicting cardiac functions[11-14]. NT-proBNP has been proved useful for diagnostic and prognostic purposes in patients with congestive heart failure and other cardiac conditions[15-18]. It was recently reported that increased NT-proBNP can indicate the underlying subclinical predisposition to AF both in patients undergoing cardiac surgery[19] and in patients without a history of cardiac disease[20]. To our knowledge, the ability of NT-proBNP to predict AF after esophageal procedures has not been evaluated.

We speculate that an elevated level of NT-proBNP could predict the occurrence of AF early after esophageal procedures. The aim of this study is to determine whether NT-proBNP levels are associated with AF after surgery for esophageal carcinoma.

**MATERIALS AND METHODS**

**Patients**

One hundred and fifty consecutive patients undergoing elective surgery for esophageal cancer were identified in our hospital from December 2006 to May 2007. Patients with a history of heart failure (n = 3), chronic AF (n = 2), severe renal dysfunction (n = 1), and antiarrhythmic drug use (n = 2) were excluded from the study. One hundred and forty-two patients (113 males and 29 females with an average age of 66.5 years, range 49-86 years) accordant with the inclusion criteria were enrolled in the study.

All patients having a preoperative cardiac diagnosis by electrocardiogram (ECG) remained under continuous monitoring for at least 48 h after surgery and then underwent clinical cardiac evaluation until discharge. AF was defined as absent P wave before the QRS complex with irregular ventricular rhythm on the rhythm strips.

Plasma NT-proBNP concentration was measured 24 h before and soon (within 1 h) after surgery. Blood samples were collected into tubes containing potassium EDTA, centrifuged for 5 min at 1500 r/min and kept at 4 °C. The separated plasma was kept at -30 °C until analysis. NT-proBNP analyses were done with Elecsys Roche Diagnostics commercial kits on a semiautomatic analyzer (Elecsys-2010, Roche Diagnostics, Germany). The test is self-processing and produces a result within 15 min. The precision, analytic sensitivity and stability characteristics of this system have been described elsewhere[21].

**Statistical analysis**

Continuous variables are expressed as mean ± SD or median (range) and were compared by Student’s t-test.

Chi square test or Fisher’s exact test was used to compare groups of categorical data. The relationship between the occurrence of postoperative AF and baseline predictors was assessed with multivariable logistic regression model adjusted for factors presumably associated with AF risk, including advanced age, male gender, COPD, cardiac diseases, hypertension and diabetes mellitus, site of anastomosis, postoperative hypoxia, thoracic–gastric dilatation and plasma NT-proBNP[12, 22-25]. P < 0.05 was considered statistically significant. Statistical analysis was performed using the SPSS 11.0 statistical software package (SPSS, Inc).

**RESULTS**

The baseline characteristics of the 142 patients are listed in Table 1. The patients were divided into 2 groups according to whether they developed postoperative AF. Postoperative AF occurred in 11 patients (7.7%). Postoperative AF patients were significantly older (69.6 ± 12.2 years vs 63.4 ± 13.3 years, P = 0.031) than non-postoperative AF patients. Patients in the postoperative AF group had a history of COPD (45.5% vs 12.2%, P = 0.021) and cardiac disease more frequently (6.9% vs 27.3%, P = 0.046). Postoperative AF patients had a significantly higher incidence of postoperative hypoxia (36.4% vs 8.4%, P = 0.018) and thoracic–gastric dilatation (45.5% vs 12.2%, P = 0.021) than non-postoperative AF patients. There were no significant differences in gender, history of hypertension, diabetes mellitus, surgical approach, anastomosis site, intraoperative hypotension and postoperative fever between the two groups. Preoperative plasma NT-proBNP level was significantly higher in patients who developed postoperative AF (121.3 ± 18.3 pg/mL vs 396.1 ± 42.6 pg/mL, P = 0.016).

In a multivariable logistic regression model adjusted for age, gender, COPD, history of cardiac disease, hypertension, diabetes mellitus, site of anastomosis, postoperative hypoxia, thoracic–gastric dilatation and plasma NT-proBNP, NT-proBNP levels were associated with the highest risk factor for postoperative AF (odds ratio = 4.711, 95% CI = 1.212 to 7.644, P = 0.008) (Table 2).

**DISCUSSION**

AF after esophagectomy remains one of the most frequently encountered complications. The incidence of AF in this study was 7.7%, lower than the reported data ranging from 11.3% to 22%[26-27]. Although the causes for postoperative AF after esophagectomy have not been completely disclosed, we speculate that AF after esophagectomy is precipitated by the resolution of inflammatory response following blunt or sharp surgical trauma to sympathovagal nerve fibers supplying the heart, which alters the autonomic modulation of atrial myocardial cells to endogenous catecholamines. Although postoperative AF is self-limited in most cases, it can increase the risk of postoperative stroke[28]. The treatment of postoperative AF requires a prolonged hospital stay and additional costs. Although previous studies[6, 22-27] have shown different risk factors for postoperative AF,
A definite relation between these factors and occurrence of AF has not been well established. A proper preventive treatment of AF is still a challenge. Even if preventive therapies with antiarrhythmic agents can reduce the occurrence of postoperative AF, their use has been limited because of potential side effects[29].

BNP and NT-proBNP are members of the natriuretic peptide family synthesized and secreted by the ventricular myocardiun. The natriuretic peptide family plays a role in regulation of the cardiovascular system[34]. Moreover, it was reported that an elevated NT-proBNP level can be used as a diagnostic and prognostic marker in patients with congestive heart failure, myocardial infarction, unstable angina and left ventricular hypertrophy[15-18].

The present study evaluated the role of NT-proBNP in predicting postoperative AF in patients undergoing surgery for esophageal carcinoma. The results showed that an elevated level of plasma NT-proBNP obtained before or soon after surgery for esophageal carcinoma was a strong and independent predictor of the occurrence of postoperative AF, suggesting that patients can be stratified according to their risk of postoperative AF. A targeted preventive therapy may be performed only for high risk patients with an elevated NT-proBNP level before or soon after esophageal surgery to prevent the occurrence of operative AF. Low-risk patients with a high negative predictive value of NT-proBNP should not receive any preventive treatment.

Our study provided a new prospective in terms of preventive strategies against postoperative AF. It was reported that NT-proBNP-tailored therapy reduces the occurrence of cardiovascular events in patients with heart failure[21,12]. Further studies are needed to demonstrate that reduction in this marker before esophageal surgery is paralleled to a consequent reduction in the risk of AF occurrence. Our study has some limitations, such as a small number of patients, NT-proBNP determined only once after esophagectomy.

In conclusion, an elevated level of perioperative NT-proBNP is a strong and independent predictor of AF occurrence in patients undergoing surgery for esophageal carcinoma.

**Table 1 Characteristics of study subjects, n (%)**

| Characteristic                  | No postoperative AF | Postoperative AF | P    |
|--------------------------------|---------------------|-----------------|------|
| Age (yr)                       | 63.4 ± 13.3         | 69.6 ± 12.2     | 0.031|
| Male                           | 109 (83.2)          | 9 (81.8)        | 0.971|
| COPD                           | 16 (12.2)           | 5 (45.5)        | 0.021|
| History of cardiac diseases    | 9 (6.9)             | 3 (27.3)        | 0.046|
| History of hypertension        | 8 (6.1)             | 1 (9.1)         | 0.717|
| Diabetes mellitus              | 7 (5.3)             | 1 (9.1)         | 0.63 |
| Site of anastomosis            |                     |                 |      |
| Neck                           | 28 (21.4)           | 3 (27.3)        | 0.721|
| Above the aortic arch          | 81 (61.8)           | 6 (54.5)        | 0.812|
| Below the aortic arch          | 22 (16.8)           | 2 (18.2)        | 0.921|
| Right thorax approach          | 12 (9.2)            | 1 (9.1)         | 0.994|
| Intraoperative hypotension     | 9 (6.9)             | 1 (9.1)         | 0.798|
| Postoperative fever            | 29 (22.1)           | 3 (27.3)        | 0.76 |
| Postoperative hypoxia          | 11 (8.4)            | 4 (36.4)        | 0.018|
| Thoracic–gastric dilatation    | 16 (12.2)           | 5 (45.5)        | 0.021|
| NT-proBNP, pg/mL               |                     |                 |      |
| Before surgery                 | 121.3 ± 18.3        | 396.1 ± 42.6    | 0.016|
| After surgery                  | 160.3 ± 17.3        | 589.5 ± 51.2    | 0.009|

**Table 2 Multivariable analysis for assessing predictors of postoperative atrial fibrillation**

| Variables                     | Odds ratio | P     | 95% CI          |
|-------------------------------|------------|-------|-----------------|
| NT-proBNP                     | 4.711      | 0.008 | 1.212-7.644     |
| Postoperative hypoxia         | 3.111      | 0.027 | 0.098-4.891     |
| Thoracic–gastric dilatation   | 2.857      | 0.017 | 1.105-5.325     |
| Age                           | 2.151      | 0.048 | 0.981-4.239     |
| History of cardiac disease    | 1.576      | 0.069 | 0.658-3.985     |
| History of hypertension       | 1.397      | 0.263 | 0.603-2.276     |
| Site of anastomosis           | 1.218      | 0.192 | 0.792-2.947     |
| Right thorax approach         | 1.185      | 0.531 | 0.538-1.584     |
| Intraoperative hypotension     | 1.107      | 0.361 | 0.506-2.176     |
| Postoperative fever           | 1.049      | 0.583 | 0.473-2.428     |
| History of diabetes mellitus  | 0.938      | 0.624 | 0.378-1.297     |

**COMMENTS**

**Background**

Atrial fibrillation (AF) is a frequent arrhythmia after esophageal procedures and is associated with an increased morbidity and mortality. Although some risk factors for AF can be predicted after surgery for esophageal carcinoma, no accurate assessment tool or biomarker has been identified that can predict the occurrence of AF early after esophageal procedures. Therefore, a sensitive blood biomarker that can predict the occurrence of AF in patients after surgery for esophageal carcinoma with a high specificity is desirable.

**Research frontiers**

Previous studies have identified some risk factors as predictors of AF after surgery for esophageal carcinoma, such as postoperative hypoxia, history of obstructive pulmonary disease (COPD), thoracic-gastric dilatation, age over 65 years, male gender, and history of cardiac disease. However, the ability to accurately identify patients at a high risk for AF is still limited.

**Innovations and breakthroughs**

This study evaluated the role of NT-proBNP in predicting postoperative AF in patients undergoing surgery for esophageal carcinoma. The results showed that an elevated level of plasma NT-proBNP obtained before or soon after surgery for esophageal carcinoma was a strong and independent predictor of the occurrence of postoperative AF. These results may allow us to stratify patients according to their risk of postoperative AF and have important clinical implications.

**Applications**

An elevated level of perioperative NT-proBNP is a strong and independent predictor of AF occurrence in patients undergoing surgery for esophageal carcinoma. This finding may allow us to stratify patients with perioperative risk for AF and to plan preventive strategies for selected high-risk patients.

**Terminology**

N-terminal pro-brain natriuretic peptide (NT-proBNP) is a neurohormone which is stored mainly in myocytes of the cardiac ventricles and released as a result of volume and pressure overload or myocardial damage. NT-proBNP has been proved useful for diagnostic and prognostic purposes in patients with congestive heart failure and other cardiac conditions.

**Peer review**

In this study, the authors examined whether NT-proBNP level is associated with AF after surgery for esophageal carcinoma, showing that an elevated perioperative plasma NT-proBNP level is an independent predictor of postoperative AF in patients undergoing surgery for esophageal carcinoma. This study has certainly provided important implications for identifying higher risk patients.
REFERENCES

1. Amar D, Roistacher N, Burt M, Reinsel RA, Ginsberg RJ, Wilson RS. Clinical and echocardiographic correlates of symptomatic tachydyssrhythmias after noncardiac thoracic surgery. Chest 1995; 108: 349-354
2. Aranki SF, Shaw DP, Adams DH, Rizzo RJ, Couper GS, VanderVliet M, Collins JJ Jr, Cohn LH, Burstin HR. Predictors of atrial fibrillation after coronary artery surgery. Current trends and impact on hospital resources. Circulation 1996; 94: 390-397
3. Mathew JP, Parks R, Savino JS, Friedman AS, Koch C, Mangano DT, Browner WS. Atrial fibrillation following coronary artery bypass graft surgery: predictors, outcomes, and resource utilization. MultiCenter Study of Perioperative Ischemia Research Group. JAMA 1996; 276: 300-306
4. Borzak S, Tisdale JE, Amin NB, Goldberg AD, Frank D, Padhi ID, Higgins RS. Atrial fibrillation after bypass surgery: does the arrhythmia or the characteristics of the patients prolong hospital stay? Chest 1996; 113: 1489-1491
5. Kim MH, Deeb GM, Morady F, Bruckman D, Hallock LR, Smith KA, Karave DJ, Bolling SF, Pagani FD, Wahr JA, Sonnad SS, Kazanjian PE, Watts C, Williams M, Eagle KA. Effect of postoperative atrial fibrillation on length of stay after cardiac surgery (The Postoperative Atrial Fibrillation in Cardiac Surgery study (PACS)). Am J Cardiol 2001; 87: 881-885
6. Ma JY, Wang Y, Zhao YF, Wu Z, Liu LX, Kou YL, Yang JJ. Atrial fibrillation after surgery for esophageal carcinoma: clinical and prognostic significance. World J Gastroenterol 2006; 12: 449-452
7. de Lemos JA, McGuire DK, Drazner MH. B-type natriuretic peptide in cardiovascular disease. Lancet 2003; 362: 316-322
8. Sudoh T, Kangawa K, Minamino N, Matsuo H. A new natriuretic peptide in porcine brain. Nature 1988; 332: 78-81
9. Yasue H, Yoshimura M, Sumida H, Kikuta K, Kugiyama K, Jougasaki M, Ogawa H, Okumura K, Mukoyama M, Nakao K. Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. Circulation 1994; 90: 195-203
10. Nishikimi T, Yoshihara F, Morimoto A, Ishikawa K, Ishimitsu T, Saito Y, Kangawa K, Matsuo H, Omae T, Matsuoka H. Relationship between left ventricular geometry and natriuretic peptide levels in essential hypertension. Hypertension 1996; 28: 22-30
11. Richards AM, Nicholls MG, Yandle TG, Frampton C, Espiner EA, Turner JG, Buttimore RC, Lainchbury JG, Elliott JM, Ikram H, Coozier IG, Smyth DW. Plasma N-terminal pro-brain natriuretic peptide and adenomodulin: new neurohormonal predictors of left ventricular function and prognosis after myocardial infarction. Circulation 1998; 97: 1921-1929
12. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. Lancet 2000; 355: 1126-1130
13. Mabuchi N, Tsutamoto T, Maeda K, Kinoshita M. Plasma cardiac natriuretic peptides as biochemical markers of recurrence of atrial fibrillation in patients with mild congestive heart failure. Jpn Circ J 2000; 64: 765-771
14. Mabuchi N, Tsutamoto T, Maeda K, Masahiko K. Plasma cardiac natriuretic peptide as a biological marker of recurrence of atrial fibrillation in elderly people. Nippon Ronen Igakkai Zasshi 2000; 37: 535-540
15. Maisel A. B-type natriuretic peptide levels: diagnostic and prognostic in congestive heart failure: what's next? Circulation 2002; 105: 2328-2331
16. Morita E, Yasue H, Yoshimura M, Ogawa H, Jougasaki M, Matsumura T, Mukoyama M, Nakao K. Increased plasma levels of brain natriuretic peptide in patients with acute myocardial infarction. Circulation 1993; 88: 82-91
17. Talwar S, Squire JB, Downie PF, Davies JE, Ng LL. Plasma N terminal pro-brain natriuretic peptide and cardiophrin 1 are raised in unstable angina. Heart 2000; 84: 421-424
18. Mukoyama M, Nakao K, Saito Y, Ogawa H, Hosoda K, Suga S, Shiraaki G, Jougasaki M, Imura H. Increased human brain natriuretic peptide in congestive heart failure. N Engl J Med 1990; 323: 757-758
19. 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. B-type natriuretic peptide levels predict postoperative atrial fibrillation in patients undergoing cardiac surgery. Circulation 2004; 110: 124-127
20. Ellinor PT, Low AF, Patton KK, Shea MA, Macrae CA. Discordant atrial natriuretic peptide and brain natriuretic peptide levels in lone atrial fibrillation. J Am Coll Cardiol 2005; 45: 82-86
21. Morrison LK, Harrison A, Krishnaswamy P, Kanagreza R, Clapton P, Maisel A. Utility of a rapid B-natriuretic peptide assay in differentiating congestive heart failure from lung disease in patients presenting with dyspnea. J Am Coll Cardiol 2002; 39: 202-209
22. Asamura H, Naruke T, Tsuchiya R, Goya T, Kondo H, Suemasu K. What are the risk factors for arrhythmias after thoracic operations? A retrospective multivariate analysis of 267 consecutive thoracic operations. J Thorac Cardiovasc Surg 1993; 106: 1104-1110
23. Cardinale D, Martinoni A, Cipolla CM, Cevelli M, Lamantia G, Fiorentini C, Mazzetti M. Atrial fibrillation after operation for lung cancer: clinical and prognostic significance. Ann Thorac Surg 1999; 68: 1827-1831
24. Vapoorciyan AA, Correa AM, Rice DC, Roth JA, Smythe WR, Swisher SG, Walsh GL, Putnam JB Jr. Risk factors associated with atrial fibrillation after noncardiac thoracic surgery: analysis of 2588 patients. J Thorac Cardiovasc Surg 2004; 127: 779-786
25. Passman RS, Gingold DS, Amar D, Lloyd-Jones D, Bennett CL, Zhang H, Rusch WV. Prediction rule for atrial fibrillation after major noncardiac thoracic surgery. Ann Thorac Surg 2005; 79: 1698-1703
26. Amar D, Zhang H, Leung DH, Roistacher N, Kadish AH. Older age is the strongest predictor of postoperative atrial fibrillation. Anesthesiology 2002; 96: 352-356
27. Murthy SC, Law S, Whooley BP, Alexandrou A, Chu KM, Wong J. Atrial fibrillation after esophagectomy is a marker for postoperative morbidity and mortality. J Thorac Cardiovasc Surg 2003; 126: 1162-1167
28. Lahtinen J, Biancari F, Salmea E, Mosorin M, Satta J, Rainio P, Rimpilainen J, Lepojarvi M, Juvonen T. Postoperative atrial fibrillation is a major cause of stroke after on-pump coronary artery bypass surgery. Ann Thorac Surg 2004; 77: 1241-1244
29. Passman RS, Gingold DS, Amar D, Lloyd-Jones D, Bennett CL, Zhang H, Rusch WV. Prediction rule for atrial fibrillation after major noncardiac thoracic surgery. Ann Thorac Surg 2005; 79: 1698-1703
30. Cheung BM, Kumana CR. Natriuretic peptides—relevance in cardiovascular disease. JAMA 1998; 280: 1983-1984