Brain natriuretic peptide and risk of atrial fibrillation after thoracic surgery

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Objectives: Postoperative atrial fibrillation (POAF) complicating general thoracic surgery is a marker of increased morbidity and stroke risk. Our goal was to determine whether increased preoperative brain natriuretic peptide (BNP) levels are able to stratify patients by the risk of POAF.

Methods: Using a prospective database of 415 patients aged 60 years or older, who had undergone lung or esophageal surgery during a 1-year period, the preoperative clinical data, including BNP levels, were compared between patients who developed POAF lasting longer than 5 minutes during hospitalization and those who did not.

Results: POAF occurred in 65 (16%) of the 415 patients and was more frequent among patients who had undergone esophagectomy or anatomic lung resection (22% or 58 of 269) compared with those who did not (5% or 7 of 146; $P < .0001$). After esophagectomy or anatomic lung resection, 46 (34%) of the 135 patients with BNP levels greater than the median (≥ 30 pg/mL) developed POAF compared with only 12 (9%) of 134 patients with BNP levels less than 30 pg/mL ($P < .0001$). The rates of POAF in patients undergoing other thoracic procedures were low and not associated with the BNP levels. Multivariate logistic regression analysis showed that in patients undergoing esophagectomy or anatomic lung resection, older age (5-year increments, odds ratio [OR], 1.28; 95% confidence interval [CI], 1.01-1.61; $P = .04$), male gender (OR, 2.61; 95% CI, 1.12-4.17; $P = .02$), and BNP level 30 pg/mL or greater (OR, 4.52; 95% CI, 2.19-9.32; $P < .0001$) were independent risk factors for POAF. The length of hospital stay was significantly increased in patients who developed POAF compared with those who did not ($P < .0001$).

Conclusions: Among patients undergoing anatomic lung resection or esophagectomy, increased age, male gender, and preoperative BNP level of 30 pg/mL or greater were significant risk factors for the development of POAF. The identification of patients who are more likely to develop POAF will allow the development of trials assessing prevention strategies aimed at reducing this complication. (J Thorac Cardiovasc Surg 2012;144:1249-53)

Postoperative atrial fibrillation (POAF) occurs in 18% of patients after noncardiac thoracic surgery, with patient age, male gender, and the extent of surgical resection known to be independent risk factors.^{1,2} The mechanisms implicated as predisposing after surgery to enhance susceptibility to re-entrant arrhythmias such as POAF include altered sympathovagal balance, operative injury to autonomic fibers, and/or oxidative and inflammatory changes. We, and others, have recently shown that preoperative echocardiographic indexes of atrial dysfunction are associated with the risk of POAF after thoracic surgery.^{3,4} Echocardiography, however, is not performed routinely

before thoracic surgery, and, if performed, the special measurements needed require significant expertise and additional cost. In contrast, blood biomarkers are easy to analyze. An accumulating body of published data has illustrated that increased brain natriuretic peptide (BNP) levels predict postoperative major adverse cardiovascular events, in general,⁵ and for POAF, specifically.⁶⁻¹¹ It is unclear which preoperative natriuretic peptide provides the best prognostication or which BNP level would stratify patients for the risk of developing POAF. Thus, we studied a cohort of patients undergoing thoracic surgery for lung or esophageal cancer with prospectively obtained BNP levels to assess the relative prognostic significance of preoperative BNP in predicting the risk of POAF.

METHODS

With approval of the Memorial Sloan-Kettering Cancer Center institutional review board, we reviewed the charts of 433 consecutive patients, aged 60 years or older, who had undergone lung or esophageal surgery from June 2009 to June 2010. These patients participated in a prospective observational quality improvement project using an abnormal preoperative BNP level as a suggested guide for the individual surgical team to identify patients at greater risk of POAF, who might require longer telemetry

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Disclosures: Authors have nothing to disclose with regard to commercial support. Received for publication Feb 21, 2012; revisions received June 5, 2012; accepted for publication June 18, 2012; available ahead of print July 27, 2012.

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0022-5223/\$36.00

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<http://dx.doi.org/10.1016/j.jtcvs.2012.06.051>

Abbreviations and Acronyms

BNP = brain natriuretic peptide

POAF = postoperative atrial fibrillation

monitoring and rate control drugs such as diltiazem and/or metoprolol to attenuate the incidence of POAF.¹² The choice of drug and the dose and length of administration were not controlled. Additional BNP samples in the postoperative period were not measured, because others have shown that the preoperative BNP level was more predictive of POAF than the postoperative BNP levels.⁹ The primary clinical endpoint of the study was the new onset of POAF lasting greater than 5 minutes during hospitalization and detected by continuous telemetry (48-72 hours) or 12-lead electrocardiography if the patient developed clinically significant POAF after telemetry was discontinued. We excluded those patients ($n = 18$) who were not in sinus rhythm at the evaluation before surgery, those taking antiarrhythmic drugs, and patients whose surgery was postponed. Previous work had demonstrated that the risk of POAF after lung surgery was associated with the extent of resection; therefore, for the purposes of analysis, we stratified the patients into 2 groups: those undergoing anatomic resection and those undergoing exploratory thoracotomy or wedge resection only. Postoperative pain relief was provided to all patients undergoing esophagectomy or anatomic lung resection by continuous administration of epidural opioid (usually hydromorphone and bupivacaine). After an overnight stay in the postanesthesia care unit, the patients were transferred to the thoracic surgical floor on the first postoperative day. Major postoperative cardiac or pulmonary complications were recorded throughout the hospital stay.

To determine the difference in clinical characteristics between patients with and without POAF, univariate analysis was conducted using Student t or the chi-square test. The data are presented as the mean $\pm$ standard deviation, unless otherwise indicated. P values were computed for each variable for all available data. The surgical duration was log transformed before analysis. We examined 2 cutoffs for BNP (≥ 100 pg/mL, because this is considered abnormal in our laboratory, and ≥ 30 pg/mL because this was the median value of the study patients) as the predictors of risk of POAF in those who had undergone anatomic lung or esophageal resection. Multivariate stepwise logistic regression analysis was used to identify the independent risk factors of POAF only in those patients who had undergone anatomic lung or esophageal resection. Variables with $P \leq .15$ on univariate analysis were included in the initial model. The area under the receiver operating characteristic curve was calculated to measure the predictive power of the identified parameters. The correlation between age and BNP was assessed using Spearman's correlation analysis. Statistical analysis was performed with the software SAS, version 9.2 (SAS Institute, Cary, NC).

RESULTS

The clinical characteristics of the entire patient cohort are listed in Table 1. POAF occurred in 65 (16%) of the 415 patients at a median of 2 days (range, 0-6) after surgery. The incidence of POAF was greater among the 269 patients who had undergone esophagectomy or anatomic lung resection ($n = 58$; 22%) than in the 146 patients who did not ($n = 7$; 5%; $P < .0001$). The patient characteristics, surgical data, and POAF incidence for those who had undergone nonanatomic lung resection using a median BNP level of 30 pg/mL as the cutoff are listed in Table 2. The patients whose BNP level was greater than the median were older ($P = .01$), had more coronary artery disease ($P = .05$), and more were taking β -blockers preoperatively ($P = .01$)

than those with a BNP less than the median (Table 2). Among the patients who had undergone nonanatomic lung resection, the mean BNP level did not differ between those with and without POAF (48 ± 59 vs 48 ± 93 pg/mL; $P = .75$) nor by the BNP median cutoff level (Table 2). Therefore, we excluded the patients who had undergone nonanatomic lung resection from the prognostic factor analysis. The patient characteristics and surgical data of those who had undergone esophagectomy or anatomic lung resection are presented in Table 3. On univariate analysis (Table 2), the patients who developed POAF were more likely to be men ($P = .02$). They were, on average, older than those who did not develop POAF ($P = .0002$), had hypertension ($P = .02$), used preoperative β -blockers ($P = .001$), had a higher baseline BNP level ($P < .0001$), and underwent pneumonectomy (global chi-square test, $P = .04$; pneumonectomy vs all other operations, $P = .02$; no significant difference in POAF rate for the other operations, $P = .59$). The incidence of POAF was similar whether video-assisted thoracic surgery or standard open thoracotomy was done for anatomic lung resection. The use of postoperative metoprolol or diltiazem in the immediate postoperative period did not affect the incidence of POAF and was not confounded by the preoperative BNP level. Using the BNP level of 100 pg/mL to stratify patients, 14 (48%) of 29 patients with a BNP level of 100 pg/mL or greater developed POAF and 44 (18%) of 240 with a BNP level less than 100 pg/mL had POAF. However, using the median BNP level of 30 pg/mL to stratify the patients improved the prediction, with POAF developing in 46 (34%) of 135 patients with a BNP level of 30 pg/mL or greater but in only 12 (9%) of 134 with a BNP level of less than 30 pg/mL ($P < .0001$).

Seven variables (age, male gender, hypertension, coronary artery disease, preoperative use of β -blockers, BNP dichotomized at the median level of 30 pg/mL, and pneumonectomy) with $P \leq .15$ on univariate analysis were considered candidates for the multivariate logistic regression analysis. That analysis showed that older age, male gender, and BNP level of 30 pg/mL or greater were independent risk factors associated with POAF (Table 4). The area under the receiver operating curve for this model was 0.75, and the Hosmer-Lemeshow goodness-of-fit statistic was $P = .89$. By Spearman correlation analysis, older age was significantly associated with a greater BNP level ($\rho = 0.35$, $P < .0001$). The length of hospital stay was significantly increased among patients who developed POAF (median, 8 days; range, 1-52 compared with those who did not (median, 5 days; range, 3-84; $P < .0001$).

An exploratory analysis of the clinical characteristics of the 58 patients who developed POAF after esophagectomy or anatomic lung resection was performed to compare those with BNP levels greater than and less than the median (Table 5). Patients with a BNP level of 30 pg/mL or more

TABLE 1. Summary of patient characteristics (n = 415)

Characteristic	Value
Age (y)	70 ± 7
Male gender	223 (54)
Preoperative heart rate >72 beats/min	196 (47)
Diabetes	62 (15)
Coronary artery disease	85 (20)
Hypertension	248 (60)
Smoking	331 (80)
Chemotherapy	117 (28)
Preoperative β-blocker use	138 (33)
Preoperative calcium channel blocker use	31 (8)
Preoperative statin use	155 (37)
BNP (pg/mL)	47 ± 67
Surgical procedure	
Esophagectomy	43 (10)
Lobectomy	191 (46)
Pneumonectomy	11 (3)
Segmentectomy	24 (6)
Nonanatomic resection	146 (35)

Data presented as mean ± SD or n (%). BNP, Brain natriuretic peptide.

were older ($P = .07$) and had a much greater BNP level ($P < .0001$) but did not differ in the other clinical variables or the length of hospital stay.

DISCUSSION

POAF occurred in 22% of patients undergoing anatomic lung or esophageal resection and was associated with

TABLE 2. Nonanatomic lung resection patients and median BNP as cutoff level

Variable	BNP ≥30 pg/mL (n = 71)	BNP <30 pg/mL (n = 75)	P value
Age (y)	71 ± 8	68 ± 6	.01
Male gender	35 (48)	38 (52)	.50
Preoperative heart rate (beats/min)	73 ± 14	76 ± 12	.17
Diabetes	13 (13)	10 (18)	.49
Coronary artery disease	18 (25)	9 (12)	.05
Hypertension	44 (62)	39 (52)	.25
Smoking	55 (78)	50 (67)	.15
Chemotherapy	19 (27)	26 (35)	.30
Preoperative β-blocker use	32 (45)	15 (20)	.01
Preoperative calcium channel blocker use	8 (11)	3 (4)	.10
Preoperative statin use	27 (38)	24 (32)	.45
Surgery duration (min)	116 ± 64	125 ± 68	.37
Surgical procedure			
Wedge resection	45 (63)	51 (68)	.56
Biopsy	26 (37)	24 (32)	
Postoperative metoprolol	51 (72)	46 (61)	.20
Postoperative diltiazem	6 (8.5)	11 (15)	.19
POAF	3 (4)	4 (5)	.89

Data presented as mean ± SD or n (%). BNP, Brain natriuretic peptide; POAF, postoperative atrial fibrillation.

TABLE 3. Characteristics of patients who underwent anatomic resection

Variable	No POAF (n = 211)	POAF (n = 58)	P value
Age (y)	70 ± 7	73 ± 7	.0002
Male gender	110 (52)	40 (69)	.02
Preoperative heart rate >72 beats/min	90 (43)	24 (41)	.86
Diabetes mellitus	29 (14)	10 (17)	.50
Coronary artery disease	41 (19)	17 (29)	.11
Hypertension	122 (58)	43 (74)	.02
Smoking	178 (84)	48 (83)	.77
Chemotherapy	54 (26)	18 (31)	.41
Preoperative β-blocker use	61 (29)	30 (52)	.001
Preoperative calcium channel blocker use	46 (22)	10 (17)	.58
Preoperative statin use	83 (39)	21 (36)	.66
BNP (pg/mL)	39 ± 44	70 ± 58	<.0001
Surgery duration (min)	218 ± 92	256 ± 122	.055
Surgical procedure			
Esophagectomy	32 (15)	11 (19)	.04*
Lobectomy	154 (73)	37 (64)	
Pneumonectomy	5 (2)	6 (10)	
Segmentectomy	20 (10)	39 (7)	
VATS	67 (37)	15 (32)	.48
Postoperative metoprolol use	152 (72)	46 (79)	.27
Postoperative diltiazem use	46 (22)	10 (17)	.45

Data presented as mean ± SD or n (%). VATS, Video-assisted thoracic surgery for lung resection; POAF, postoperative atrial fibrillation; BNP, brain natriuretic peptide. *By global test; pneumonectomy versus all other operations, $P = .02$.

a longer hospital stay. The incidence of POAF was similar whether video-assisted thoracic surgery or standard open thoracotomy was used for anatomic lung resection. The main findings of our study were that in patients undergoing esophagectomy or anatomic lung resection, older age, male gender, and increasing preoperative BNP are important independent risk factors for POAF, with BNP the strongest. A joint model incorporating these 3 risk factors indicated moderate predictive ability supporting the premise that POAF has a multifactorial etiology. Patients with a BNP level of 30 pg/mL or greater had a near fourfold increased risk of POAF compared with those with a BNP level less than the median cutoff. The BNP levels did not stratify patients undergoing nonanatomic resection by the risk of POAF. The patients with POAF with elevated BNP levels did not have clinical signs of congestive heart failure, suggesting “subclinical” signs of left atrial distension or myocardial dysfunction. This is consistent with recent work in

TABLE 4. Multivariate analysis of risk factors for POAF

Variable	OR	95% CI	P value
Age (per 5-y increment)	1.28	1.01-1.61	.04
Male gender	2.16	1.12-4.17	.02
BNP ≥30 pg/mL	4.52	2.19-9.32	<.0001

BNP, Brain natriuretic peptide; CI, confidence interval; OR, odds ratio; POAF, postoperative atrial fibrillation.

TABLE 5. Subgroup analysis of patients with POAF and BNP cutoff

Variable	BNP ≥ 30 pg/mL (n = 46)	BNP < 30 pg/mL (n = 12)	P value
Age (y)	74 $\pm$ 7	70 $\pm$ 6	.07
Male gender	30 (65)	10 (83)	.31
Preoperative heart rate (beats/min)	71 $\pm$ 14	70 $\pm$ 8	.98
Diabetes	7 (15)	3 (25)	.42
Coronary artery disease	15 (33)	2 (17)	.48
Hypertension	33 (72)	10 (83)	.71
Smoking	38 (83)	10 (83)	.99
Chemotherapy	15 (33)	3 (25)	.74
Preoperative β -blocker use	26 (57)	4 (33)	.15
Preoperative calcium channel blocker use	6 (13)	0 (0)	.33
Preoperative statin use	17 (37)	4 (33)	.81
Surgical procedure			.48
Esophagectomy	9 (20)	2 (17)	
Lobectomy	30 (65)	7 (58)	
Pneumonectomy	5 (11)	1 (8)	
Segmentectomy	2 (4)	2 (17)	
Postoperative metoprolol use	37 (80)	9 (75)	.70
Postoperative diltiazem use	6 (13)	4 (33)	.19

Data presented as mean $\pm$ SD or n (%). BNP, Brain natriuretic peptide; POAF, postoperative atrial fibrillation.

which, using echocardiographic methods such as the integrated left atrial volume and left atrial emptying fraction, we showed that patients with POAF have signs of left atrial distension and mechanical dysfunction.⁴ In previous work, we devised a clinical prediction rule and point score for POAF risk using the easily available preoperative clinical characteristics of age older than 55 years, male gender, and preoperative heart rate greater than 72 beats/min, with age as the most important risk factor.² In contrast to that earlier study, in the present cohort of patients, the preoperative heart rate did not discriminate patients likely to develop POAF, possibly because among those with POAF, preoperative hypertension and a greater use of β -blockers were more prevalent. It is likely that the high use of postoperative metoprolol in this cohort was reflective of a trend in many institutions in the period in which these patients underwent surgery to prophylactically administer these medications to reduce overall perioperative cardiovascular morbidity, not limited to POAF.

Our data are consistent with previous work by other investigators. Cardinale and colleagues⁹ evaluated more than 400 patients undergoing thoracic surgery for lung cancer. They showed that in patients who developed POAF, the pre- and postoperative N-terminal pro-BNP values were significantly greater than in those patients who did not develop POAF.⁹ Although N-terminal pro-BNP might have a longer half-life, it is more affected by age, gender, and renal function than BNP.¹³ Interestingly, in a smaller study, Nojiri and colleagues¹⁰ found that a median BNP cutoff

of greater than 30 pg/mL was also a significant predictor of POAF in 80 patients undergoing lung resection. Gibson and colleagues¹¹ reported that a BNP level greater than 30 pg/mL and a N-terminal pro-BNP level greater than 74 pg/mL were similarly predictive of POAF in 275 patients undergoing coronary artery bypass grafting. Traditionally, elevated atrial natriuretic peptides have been demonstrated in patients with heart failure and either ventricular or atrial wall distension. However, BNP can increase with chronic conditions that include aging, atrial fibrosis, and inflammation, factors also known to contribute to POAF occurrence without clinical evidence of cardiac wall stretch or heart failure.¹³

In a pneumonectomy model of young and old dogs, we found neutrophil cell infiltration of the atrial myocardium in the older dogs, which were more prone to develop post-pneumonectomy arrhythmias than were the younger dogs without this finding.¹⁴ We also examined whether systemic inflammation contributed to POAF but could not demonstrate greater levels of plasma C-reactive protein among the patients who developed POAF.¹⁵ In cardiac surgical patients, others have shown local myocardial, but not systemic, evidence of inflammation in experimental animals and in patients with POAF.^{16,17} Together with our results, these studies suggest that the presence of preoperative subclinical left atrial dysfunction before surgery, as measured using echocardiography or elevated BNP levels, contribute to postoperative myocardial systemic inflammation and altered sympathovagal balance necessary to initiate POAF in older patients undergoing major thoracic surgery.¹⁴⁻¹⁷

Study Limitations

The patients selected for the present study were 60 years or older, targeting those at greater risk of POAF. Although our conclusions might not be applicable to younger patients, most patients who undergo surgery for lung or esophageal cancer will be within our study population's age range. Our rationale for including esophagectomy patients was based on similar POAF rates in anatomic lung resection patients.² We also included those who underwent lung resection by video-assisted thoracic surgery, because the incidence of POAF is similar.¹⁸ Nevertheless, the characteristics and clinical outcomes of the patients in the present study population were very similar to others from single-center studies comparable to ours.^{1,2} Although no patient was excluded because they had a history of heart failure or severe valvular heart disease, these are uncommon conditions in the population of patients referred to our institution for thoracic surgery.

CONCLUSIONS AND CLINICAL IMPLICATIONS

We found an association linking POAF in patients aged 60 years or older undergoing major lung or esophageal

cancer resection and an elevated preoperative BNP level, with the median of 30 pg/mL working better as a cutoff. Age, male gender, and increasing BNP are quantifiable risk factors that are easily available before surgery to the anesthesiologist, surgeon, and cardiologist. The use of a BNP cutoff of 30 pg/mL or greater might help in identifying a subset of patients at the greatest risk of developing POAF who would most benefit from stratified prophylactic interventions and careful observation. From these results, we have modified our practice to incorporate preoperative BNP for patients scheduled for major resections and consider diltiazem prophylaxis when the BNP level is 30 pg/mL or greater.¹² Traditional antiarrhythmic drugs, however, have a modest success rate in reducing POAF and could have untoward effects.^{12,19} In a pilot study, Nojiri and colleagues²⁰ used a BNP level of 30 pg/mL or greater to stratify patients before lung resection and almost ironically showed that giving human atrial natriuretic peptide to patients significantly reduced the rate of POAF. Human atrial natriuretic peptide is used for treatment of heart failure in some countries but has not been approved by the U.S. Food and Drug Administration. We propose that this novel approach of using the BNP cutoff of 30 pg/mL to target patients at high risk of POAF be incorporated in future editions of practice prevention guidelines.²¹ Subsequent randomized, controlled trials should test traditional and nontraditional prevention strategies using preoperative BNP.

References

- Roselli EE, Murthy SC, Rice TW, Houghtaling PL, Pierce CD, Karchmer DP, et al. Atrial fibrillation complicating lung cancer resection. *J Thorac Cardiovasc Surg.* 2005;130:438-44.
- Passman RS, Gingold DS, Amar D, Lloyd-Jones D, Bennett CL, Zhang H, et al. Prediction rule for atrial fibrillation after major noncardiac thoracic surgery. *Ann Thorac Surg.* 2005;79:1698-703.
- Nojiri T, Maeda H, Takeuchi Y, Funakoshi Y, Maekura R, Yamamoto K, et al. Predictive value of preoperative tissue Doppler echocardiographic analysis for postoperative atrial fibrillation after pulmonary resection for lung cancer. *J Thorac Cardiovasc Surg.* 2010;140:764-8.
- Raman T, Roistacher N, Liu J, Zhang H, Shi W, Thaler HT, et al. Preoperative left atrial dysfunction and risk of postoperative atrial fibrillation complicating thoracic surgery. *J Thorac Cardiovasc Surg.* 2012;143:482-7.
- Karthikeyan G, Moncur RA, Levine O, Heels-Ansdell D, Chan MTV, Alonso-Coello P, et al. 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.* 2009;17:1599-606.
- Wazni OM, Martin DO, Marrouche NF, Abel Latif A, Ziada K, Shaaraoui M, et al. Plasma B-type natriuretic peptide levels predict postoperative atrial fibrillation in patient undergoing cardiac surgery. *Circulation.* 2004;110:124-7.
- Gurgo AM, Ciccone AM, D'Andrilli A, Ibrahim M, Musumeci B, Quarta G, et al. Plasma NT-pro-BNP levels and the risk of atrial fibrillation after major lung resection. *Minerva Cardioangiol.* 2008;56:581-5.
- Hou J-L, Gao K, Li M, Ma J-Y, Wang Y, Zhao Y-F. Increased N-terminal pro-brain natriuretic peptide level predicts atrial fibrillation after surgery for esophageal carcinoma. *World J Gastroenterol.* 2008;14:2582-5.
- Cardinale D, Colombo A, Sandri MT, Lamantia G, Colombo N, Civelli M, et al. Increased perioperative N-terminal pro-B-type natriuretic peptide levels predict atrial fibrillation after thoracic surgery for lung cancer. *Circulation.* 2007;115:1339-44.
- Nojiri T, Maeda H, Takeuchi Y, Funakoshi Y, Kimura T, Maekura R, et al. Predictive value of B-type natriuretic peptide for postoperative atrial fibrillation following pulmonary resection for lung cancer. *Eur J Cardiothorac Surg.* 2010;37:787-91.
- Gibson PH, Croal BL, Cuthbertson BH, Rae D, McNeilly JD, Gibson G, et al. Use of preoperative natriuretic peptides and echocardiographic parameters in predicting new-onset atrial fibrillation after coronary artery bypass grafting: a prospective comparative study. *Am Heart J.* 2009;158:244-51.
- Amar D, Roistacher N, Rusch VW, Leung DHY, Ginsburg I, Zhang H, et al. Effects of diltiazem prophylaxis on the incidence and clinical outcome of atrial arrhythmias after thoracic surgery. *J Thorac Cardiovasc Surg.* 2000;120:790-8.
- Marsiliani D, Buccelletti F, Carroccia A, Gilardi E, Gentiloni Silveri N, et al. Natriuretic peptides and atrial fibrillation. *Eur Rev Med Pharmacol Sci.* 2010;14:855-60.
- Amar D, Heerdt PM, Korst RJ, Zhang H, Nguyen H. The effects of advanced age on the incidence of supraventricular arrhythmias after pneumonectomy in dogs. *Anesth Analg.* 2002;94:1132-6.
- Amar D, Zhang H, Heerdt PM, Park B, Fleisher M, Thaler HT. Statin use is associated with a reduction in atrial fibrillation after noncardiac thoracic surgery independent of C-reactive protein. *Chest.* 2005;128:3421-7.
- Ishii Y, Schuessler RB, Gaynor SL, Yamada K, Fu AS, Boineau JP, et al. Inflammation of atrium after cardiac surgery is associated with inhomogeneity of atrial conduction and atrial fibrillation. *Circulation.* 2005;111:2881-8.
- Kim YM, Kattach H, Ranatunga C, Pillai R, Channon KM, Casadei B. Association of atrial nicotinamide adenine dinucleotide phosphate oxidase activity with the development of atrial fibrillation after cardiac surgery. *J Am Coll Cardiol.* 2008;51:68-74.
- Park B, Zhang H, Rusch VW, Amar D. Video-assisted thoracic surgery does not reduce the incidence of postoperative atrial fibrillation following pulmonary lobectomy. *J Thorac Cardiovasc Surg.* 2007;133:775-9.
- Tisdale JE, Wroblewski HA, Wall DS, Rieger KM, Hammoud ZT, Young JV, et al. A randomized trial evaluating amiodarone for prevention of atrial fibrillation after pulmonary resection. *Ann Thorac Surg.* 2009;88:886-95.
- Nojiri T, Yamamoto K, Maeda H, Takeuchi Y, Funakoshi Y, Inoue M, et al. Effect of low-dose human atrial natriuretic peptide on postoperative atrial fibrillation in patients undergoing pulmonary resection for lung cancer: a double-blind, placebo-controlled study. *J Thorac Cardiovasc Surg.* 2012;143:488-94.
- Fernando HC, Jaklitsch MT, Walsh GL, Tisdale JE, Bridges CD, Mitchell JD, et al. The Society of Thoracic Surgeons practice guideline on the prophylaxis and management of atrial fibrillation associated with general thoracic surgery: executive summary. *Ann Thorac Surg.* 2011;92:1144-52.