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

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Objectives: We previously reported that patients with preoperative B-type natriuretic peptide levels of 30 pg/mL or more have increased risk of postoperative atrial fibrillation after pulmonary resection. This study evaluated the effects of human atrial natriuretic peptide on postoperative atrial fibrillation in patients undergoing pulmonary resection for lung cancer.

Methods: A prospective, randomized study was conducted with 40 patients who had preoperative elevated B-type natriuretic peptide (≥30 pg/mL) and underwent a scheduled pulmonary resection for lung cancer. Results were compared between patients who received low-dose human atrial natriuretic peptide and those who received a placebo. The primary end point was the incidence of postoperative atrial fibrillation during the first 4 days after surgery.

Results: The incidence of postoperative atrial fibrillation was significantly lower in the human atrial natriuretic peptide group than in the placebo group (10% vs 60%; $P < .001$). Patients in the human atrial natriuretic peptide group also showed significantly lower white blood cell counts and C-reactive protein levels after surgery.

Conclusions: Continuous infusion of low-dose human atrial natriuretic peptide during lung cancer surgery had a prophylactic effect against postoperative atrial fibrillation after pulmonary resection in patients with preoperative elevation of B-type natriuretic peptide levels. A larger sample size is needed to establish the safety and efficacy of this intervention. (J Thorac Cardiovasc Surg 2012;143:488-94)

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia encountered during the early postoperative period after a pulmonary resection procedure.[1,2] Although transient in most cases, AF sometimes results in a serious outcome, including thromboembolic events and hemodynamic deterioration, which finally leads to increased mortality.[3,4]

Human atrial natriuretic peptide (hANP) consists of 28 amino acids and has shown a variety of biologic effects when used as treatment for heart failure in Japan. It is now known that hANP exhibits a wide range of cardioprotective effects, including antifibrosis, antihypertrophy, anti-inflammation, and inhibition of sympathetic nerve activity, the renin–angiotensin–aldosterone system, and endothelin synthesis.[5,6] Beneficial effects of hANP on postoperative left ventricular remodeling have been reported in patients undergoing cardiac surgery.[7,8] AF is often caused by hemodynamic, structural, and electrophysiologic changes in the atria.[9] Because hANP exerts beneficial effects on hemodynamics[10] and atrial electrical remodeling,[11] it is plausible to expect some protective effects of hANP against postoperative AF, and our retrospective analysis showed that the treatment with hANP was associated with the reduction of postoperative AF (unpublished data).

We previously reported that patients with lung cancer who have a preoperative plasma B-type natriuretic peptide (BNP) level of 30 pg/mL or more have increased risk of development of postoperative AF.[12] The purpose of this study was to examine prospectively the effects of hANP on postoperative AF in such high-risk patients undergoing pulmonary resection for lung cancer.

MATERIALS AND METHODS

Patients

This study was conducted at National Toneyama Hospital in Japan. All patients who underwent an elective pulmonary resection procedure for non–small cell lung cancer were evaluated for potential enrollment. Inclusion criterion was a preoperative BNP level of 30 pg/mL or more. The cutoff value of BNP (30 pg/mL) was selected on the basis of our previous results,[12] which showed that this cutoff value of preoperative BNP can predict the incidence of postoperative AF with high sensitivity and specificity among patients undergoing pulmonary resection for lung cancer. Exclusion criteria for this analysis were previous AF, antiarrhythmic drug use, dysthyroidism, renal failure requiring hemodialysis, repeated pulmonary resection, benign tumor, and recent (<1 month) angina pectoris or myocardial infarction. Patients were not excluded if they were taking β-blockers for reasons other than cardiac arrhythmia.

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Abbreviations and Acronyms
AF = atrial fibrillation
BNP = B-type natriuretic peptide
CRP = C-reactive protein
hANP = human atrial natriuretic peptide
WBC = white blood cell

Study Protocol

This was a prospective, double-blind, randomized, placebo-controlled, parallel-groups study. A description of patients screened, consenting, randomly assigned, and enrolled in the study is shown in Figure 1. Patients were randomly allocated to receive hANP or placebo. The specific randomization sequence was computer generated. In the hANP group, the subjects received hANP (0.025 μg/kg/min without a bolus dose; Daiichisankyo Pharmaceutical Inc, Tokyo, Japan), whereas those in the placebo group received a 5% glucose physiologic solution for 3 days. Each treatment was started after the pulmonary artery and vein had been divided. All patients received preoperative epidural anesthesia for pain management, which usually remained in place for 2 to 4 days or until the chest drainage tubes were removed, after which patients were switched to oral analgesia. Other postoperative management methods included early ambulation and low-flow nasal oxygen supplementation, as necessary. The study protocol was approved by the institutional review board of National Toneyama Hospital, and all patients provided written informed consent before participation (trial registration number JPRN-UMIN 000001524).

Measurements

The levels of BNP were determined before surgery. The levels of atrial natriuretic peptide and C-reactive protein (CRP), as well as white blood cell (WBC) counts, were determined before surgery and on postsurgical days 1, 3, and 7, and again 1 month after surgery. The plasma concentrations of atrial natriuretic peptide and BNP were determined with an immunoradiometric assay (Shionoria ANP; Shionogi Pharmaceutical, Osaka, Japan) and a chemiluminescence enzyme immunoassay (MI02 Shionogi BNP; Shionogi Pharmaceutical), respectively. Intravenous fluid was administered at a constant rate (80 mL/h) through a peripheral venous catheter or a central venous catheter before oral intake was resumed. Hemodynamic parameters such as systolic blood pressure, diastolic blood pressure, heart rate, and urinary volume were recorded before surgery and for the first 4 days after surgery. Transthoracic echocardiography was performed before surgery, as previously described elsewhere.[13]

Postoperative AF

The primary end point of the study was the incidence of postoperative AF during the first 4 days after surgery. The peak incidence of AF has been reported to occur on the second postoperative day, with most events seen during the first 4 postoperative days.[14] Any episode of AF that was registered by the continuous monitoring system within the first 4 days on a rhythm strip or the 12-lead electrocardiogram that lasted for longer than 5 minutes, with or without symptoms, was defined as postoperative AF.[14]

Adverse Events

In this study, adverse events other than AF were monitored for 30 days after surgery. These were defined as death, congestive heart failure, myocardial infarction, angina pectoris, pneumonia, acute respiratory failure, pulmonary embolism, and hypotension.

Sample Size

Sample size calculations for the primary end point were conducted on the basis of a retrospective analysis of our institutional database, which revealed an incidence of postoperative AF of 68% among patients with a preoperative BNP level of 30 pg/mL or more, whereas the incidence of postoperative AF was only 17% among patients with a preoperative BNP level of 30 pg/mL or more who were treated with hANP. We calculated the sample size with a statistical power of 80% ($\beta = .8$) and a significance level of 5% ($\alpha = .05$),

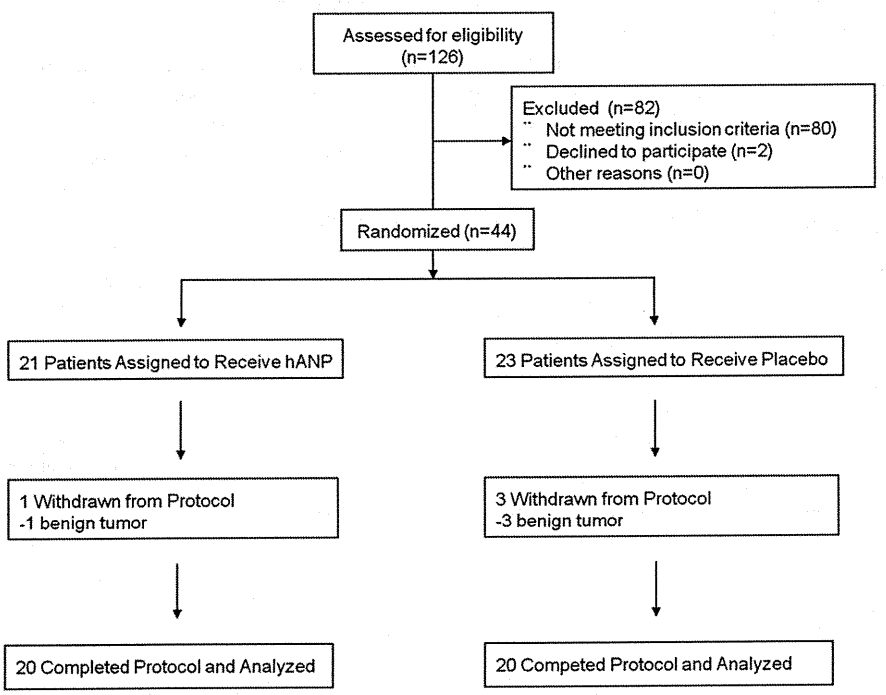

FIGURE 1. Summary of patients screened, giving consent, randomly allocated, and included in the study. *hANP,* Human atrial natriuretic peptide.

which indicated that 16 patients were to be enrolled in each group. After considering a dropout rate of 20%, we enrolled 20 patients for each arm.

Statistical Analysis

Data are expressed as the mean ± SD or as the median with interquartile range. Comparisons among all repeated parameters were analyzed by repeated-measures analysis of variance. Comparisons between the 2 groups were assessed by Student t test for normally distributed variables, by the Mann-Whitney U test for nonnormally distributed variables, and by χ^2 test for categoric variables. All data were analyzed with the SPSS statistical software package (version 11.0; IBM Corporation, Armonk, NY).

RESULTS

Study Population

Between April 2008 and April 2009, a total of 44 patients were enrolled in the study (Figure 1). Ultimately, 20 patients were randomly assigned to each arm and analyzed. There were no significant differences between the 2 groups with regard to baseline characteristics, surgical data, preoperative cardiopulmonary function, and serum levels of atrial natriuretic peptide and BNP (Table 1). None of the subjects

TABLE 1. Patient characteristics and preoperative cardiopulmonary function variables

Variables	hANP group (n = 20)	Placebo group (n = 20)	*P* value
Age (y, mean ± SD)	73 ± 7	70 ± 8	.39
Male (no.)	10 (50%)	13 (65%)	.17
Body mass index (kg/m^2, mean ± SD)	22.4 ± 2.5	22.2 ± 3.0	.43
Hypertension (no.)	9 (45%)	11 (55%)	.54
Hypercholesterolemia (no.)	8 (40%)	5 (25%)	.32
Diabetes mellitus (no.)	2 (10%)	2 (10%)	.99
Ischemic heart disease (no.)	2 (10%)	2 (10%)	.99
Medication (no.)			
β–Blockers	1 (5%)	1 (5%)	.99
Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers	2 (10%)	3 (15%)	.64
Statins	3 (15%)	2 (10%)	.64
Estimated glomerular filtration rate (mL/[min · 1.73 m^2], mean ± SD)	68.2 ± 15	69.9 ± 19	.78
Procedure (no.)			
Wide wedge resection	1 (5%)	2 (10%)	.56
Segmentectomy	1 (5%)	1 (5%)	.99
Lobectomy	17 (85%)	17 (85%)	.99
Pneumonectomy	1 (5%)	0 (0%)	.32
Complete video-assisted thoracoscopic surgical procedure (no.)	12 (60%)	11 (55%)	.49
Operating time (min, mean ± SD)	234 ± 75	242 ± 80	.38
Blood loss (mL, mean ± SD)	157 ± 58	139 ± 99	.41
Mediastinal lymph node dissection (no.)	17 (85%)	15 (75%)	.19
Use of catecholamines (no.)	1 (5%)	3 (15%)	.30
Lung cancer staging (no.)			
IA, IB	16 (80%)	14 (70%)	.48
IIA, IIB	3 (15%)	3 (15%)	.99
IIIA, IIIB	1 (5%)	3 (15%)	.30
Vital capacity(% predicted, mean ± SD)	98.0% ± 21%	103% ± 19%	.28
FEV_1 (% predicted, mean ± SD)	85.2% ± 13%	87.9% ± 21%	.36
FEV_1/FVC (%, mean ± SD)	74.9% ± 6.8%	75.2% ± 9.4%	.47
Diffusing capacity of the lung for carbon monoxide(% predicted, mean ± SD)	94.7% ± 19%	90.6% ± 22%	.28
Pao_2 (mm Hg, mean ± SD)	85.1 ± 13	90.4 ± 14	.66
$Paco_2$ (mm Hg, mean ± SD)	41.9 ± 2.6	39.6 ± 3.5	.38
LV end-diastolic diameter (mm, mean ± SD)	41.8 ± 3.9	41.9 ± 5.0	.56
LV end-systolic diameter (mm, mean ± SD)	26.8 ± 2.4	27.1 ± 3.9	.21
LV ejection fraction (%)	66.3 ± 3.8	65.5 ± 4.3	.24
LV mass index (g/m^2, mean ± SD)	122 ± 30	107 ± 61	.35
Left atrial diameter (mm, mean ± SD)	35.3 ± 3.9	36.1 ± 7.4	.36
Systolic pulmonary arterial pressure (mm Hg, mean ± SD)	34.4 ± 4.8	34.1 ± 2.8	.87
e′ (cm/s, mean ± SD)	7.41 ± 2.4	7.28 ± 1.1	.52
E/e′ (mean ± SD)	9.82 ± 3.1	9.50 ± 2.5	.16
Atrial natriuretic peptide (pg/mL, mean ± SD)	25.7 ± 11	28.2 ± 18	.41
B-type natriuretic peptide(pg/mL, median and interquartile range)	48.5 (32–62)	41.8 (34–82)	.65

hANP, Human atrial natriuretic peptide; *FEV_1*, Forced expiratory ventilation in 1 second; *FVC*, forced vital capacity; *LV*, left ventricular; *e′*, tissue Doppler mitral annular early diastolic velocity; *E/e′*, early transmitral velocity/tissue Doppler mitral annular early diastolic velocity.

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had significant valvular disease. The mean left ventricular ejection fraction in both groups was similar and greater than 60%. Both groups had relatively high preoperative BNP levels, and lobectomies were performed in most cases.

Incidence of Postoperative AF

Postoperative AF was identified in 12 subjects in the placebo group and 2 in the hANP group during the first 4 days after surgery. The incidence of postoperative AF was significantly lower in the hANP group (10% vs 60%; $P < .001$). The total group peak incidence of AF was on the first 2 postoperative days (86%), with all events occurring on the first postoperative day in the hANP group (Figure 2). Most of the patients in whom AF developed received β-blockers or the combination of digoxin and verapamil on the onset day. All the patients with postoperative AF had restoration of sinus rhythm within 2 weeks.

Adverse Events

There were no postoperative deaths, thromboembolic events, or incidents of congestive heart failure associated with AF in either group. There were no subjects with an adverse event in the hANP group and only 1 subject with an adverse event in the placebo group. That patient had acute respiratory distress syndrome develop but recovered after a few days.

Hemodynamics

There were no statistical differences between the groups with regard to systolic blood pressure, diastolic blood pressure, heart rate, and urinary volume (Figure 3, *A*). None of the subjects received a blood transfusion. There were also no statistical differences in the dosage of catecholamines between the groups. None of the subjects had the hANP infusion discontinued as a result of hypotension. In our analysis of urinary volume, a second peak was recognized on day 2 after surgery in the placebo group, the so-called "refilling phenomenon," whereas such a peak was not observed in the hANP group.

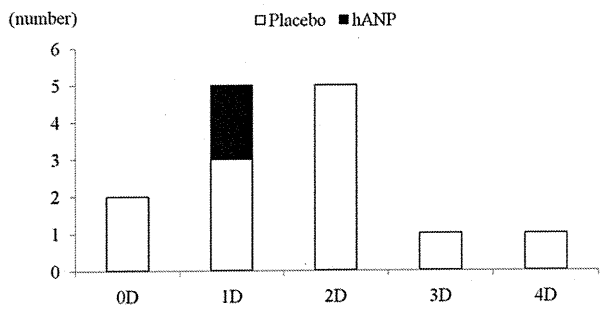

FIGURE 2. Daily distribution of postoperative atrial fibrillation in the placebo and human atrial natriuretic peptide *(hANP)* groups. *D*, Postoperative day.

Postoperative Levels of Atrial Natriuretic Peptide

The hANP group showed significantly higher levels of atrial natriuretic peptide than did the placebo group on days 1 and 3 after surgery. These levels decreased after the discontinuation of treatment (Figure 3, *B*).

Postoperative WBC Counts and CRP Levels

The hANP group showed significantly lower WBC counts and CRP levels than did the placebo group on postsurgical days 3 and 7 and 1 month after surgery (Figure 3, *C*).

DISCUSSION

These results are the first to show that continuous infusion of low-dose hANP has a prophylactic effect against postoperative AF in patients at risk for development of AF who undergo pulmonary resection for lung cancer. The infusion of low-dose hANP did not significantly change postoperative hemodynamics; however, it did decrease the postoperative WBC counts and CRP levels. These findings suggest attenuation of inflammatory changes associated with the prevention of postoperative AF. We also found that continuous infusion of low-dose hANP was well tolerated, with no clinically significant adverse effects, including hypotension, being observed. Our findings indicate that low-dose hANP is a viable treatment option to prevent postoperative AF in high-risk patients undergoing noncardiac thoracic surgery.

Cardinale and colleagues[14] and our group[12] have reported that elevated preoperative levels of N-terminal proBNP fragment or BNP serve as remarkably accurate predictors of incidence of AF among patients undergoing noncardiac thoracic surgery. On the basis of our previous study,[12] we used 30 pg/mL of plasma BNP as a cutoff value for the inclusion criteria of high-risk patients. This figure is probably justified, as indicated by the finding that the subjects in the placebo group had AF develop at a high frequency (60%) after surgery.

Administration of hANP is considered to have various effects on postoperative AF in patients undergoing pulmonary resection. First, it produces vasodilatory and natriuretic effects, leading to the reduction of cardiac overload. Several studies have shown that infusion of hANP increases stroke volume index and decreases pulmonary capillary wedge pressure, while at the same time also improving hemodynamics and clinical status in patients with congestive heart failure.[10,15] Sezai and coworkers,[7] however, recently reported that low-dose hANP infusion (0.02 μg/kg/min) did not significantly change hemodynamics, although it did reduce the postoperative peak level of creatine kinase isoenzyme MB and improve postoperative left ventricular function after coronary artery bypass grafting. Consistent with those results, we found no statistical differences between the hANP and placebo groups with regard to

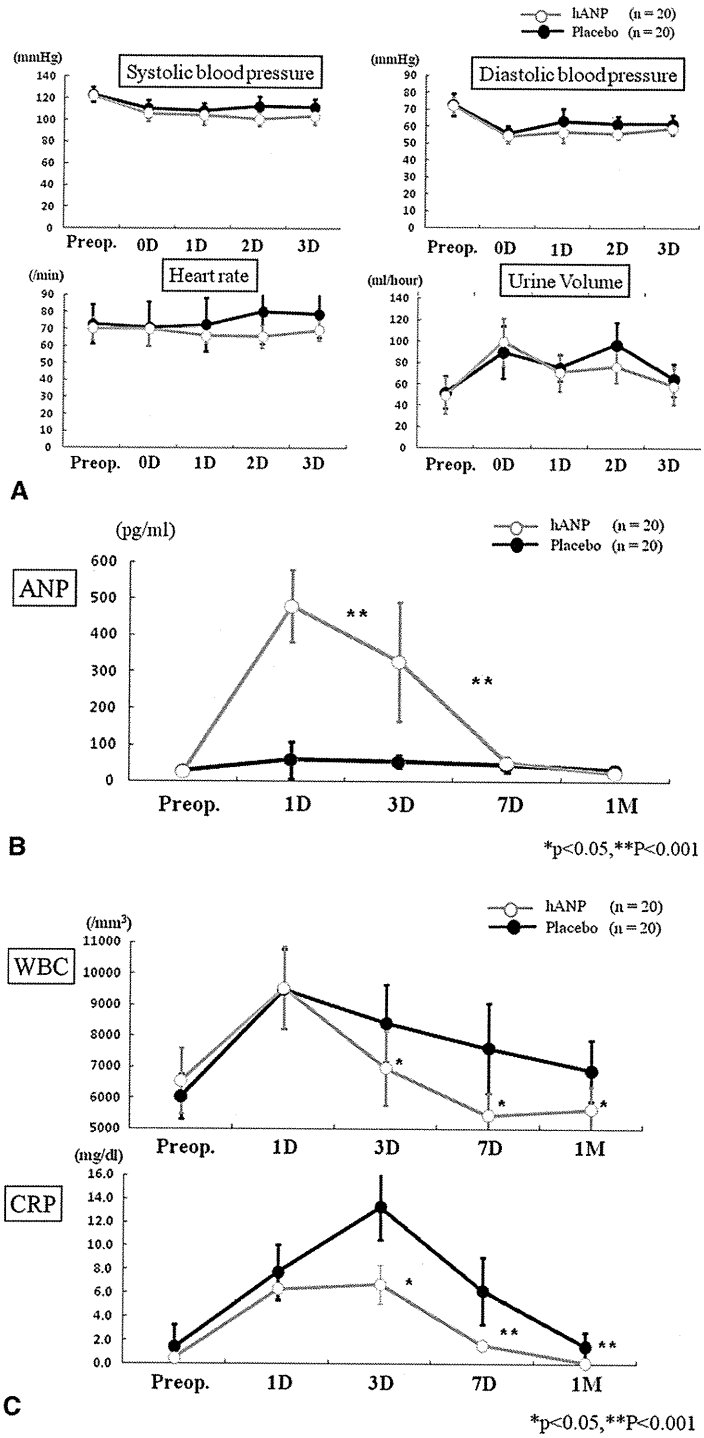

FIGURE 3. Changes from preoperative baseline *(Preop.)* in perioperative parameters by postoperative day *(D)* and at 1 postoperative month *(M)*. Each *point* with *bars* shows the mean ± SD. A, Changes in perioperative systolic blood pressure, diastolic blood pressure, heart rate, and urinary volume. There were no statistical differences between the placebo and human atrial natriuretic peptide *(hANP)* groups. B, Changes in plasma concentrations of atrial natriuretic peptide *(ANP)* in patients undergoing elective pulmonary resection for lung cancer who received an infusion of human atrial natriuretic peptide *(hANP)* or a placebo for 3 days. *Double asterisk* indicates $P < .001$. C, Changes in white blood cell counts *(WBC)* and C-reactive protein levels (CRP) in patients undergoing elective pulmonary resection for lung cancer who received an infusion of human atrial natriuretic peptide *(hANP)* or a placebo for 3 days. *Asterisk* indicates $P < .05$; *double asterisk* indicates $P < .001$.

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postoperative hemodynamics. In the placebo group, a second peak of urinary volume was observed on day 2 after surgery, whereas this refilling phenomenon was not observed in the hANP group. These results suggest that infusion of low-dose hANP does not significantly change hemodynamics, although it does prevent the refilling phenomenon, which could lead to a reduction in acute volume overload, resulting in prevention of postoperative AF.

Administration of hANP also inhibits inflammatory reactions. AF is often caused by structural and electrophysiologic changes in the atria that are induced by inflammation.[16] Epidemiologic and clinical studies have shown an association between CRP and AF.[17] Chen and colleagues[18] also reported that inflammatory cell infiltration was increased in the atrial myocardium of patients with AF, whereas Ishii and associates[19] found increased neutrophil cell infiltration in the atrial wall in a canine pericardiotomy and lateral right atriotomy model. In addition, the degree of atrial inflammation in the latter study was associated with proportional increases in the inhomogeneity of atrial conduction after cardiac surgery, as well as increases in the incidence and duration of AF. Moreover, anti-inflammatory therapy with methylprednisolone significantly decreased the inhomogeneity of atrial conduction after the atriotomy and shortened the duration of AF. Yoshida and coworkers[11] reported that exogenous atrial natriuretic peptide prevented atrial electrical remodeling in a canine rapid atrial stimulation model and speculated that this effect might have been the result of direct action on the atrial myocardium. In this study, patients in the hANP group showed significantly lower WBC counts and CRP levels after surgery than did those in the placebo group. Previous studies have also reported that hANP inhibited sympathetic nerve activity and oxidative stress.[15] The administration of hANP might prevent atrial electrical remodeling through the attenuation of inflammatory changes, oxidative stress, and sympathetic nerve activation, resulting in prevention of postoperative AF.

Finally, it is important to note that the hANP group had significantly lower WBC counts and CRP levels than did the placebo group at 1 month after surgery, even though the period of hANP infusion lasted only 3 days. We believe that it is important to observe and report long-term prognoses in a larger population in future studies.

Study Limitations

This was a single-site clinical study, and thus the number and characteristics of the patients enrolled were restricted. A multicenter study with a larger sample size is necessary to validate and generalize the findings reported here and the safety of this intervention. Furthermore, echocardiographic and cardiac catheter examinations were not performed after surgery in this study, and there are no data regarding possible beneficial effects on left ventricular function or invasive hemodynamic parameters during the early period after surgery. In addition, the use of catecholamines is not common among patients undergoing pulmonary resection with preserved left ventricular function; however 3 patients in the placebo group and 1 patient in the hANP group did receive catecholamines, which may have caused the incidents of AF.

CONCLUSIONS

This study is the first to show that continuous infusion of low-dose hANP during lung cancer surgery can exert a prophylactic effect against postoperative AF after pulmonary resection without major adverse events in patients with preoperative elevation of BNP levels. Additional studies with larger sample sizes are warranted to determine whether these effects can be observed in other patients and translated into improved clinical outcomes.

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Clinical implication of pulmonary excision for undiagnosed peripheral lung cancer

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Institutional report - Thoracic oncologic

Clinical implication of pulmonary excision for undiagnosed peripheral lung cancer

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Institutional Report

Abstract

Surgical excision is an option to diagnose small-sized lung cancer, although this procedure has potential to disseminate tumor cells from the surgical margin. This retrospective study enrolled 252 patients with clinical stage IA non-small cell lung carcinoma who had undergone lobectomy during the period 1998–2004. Except for 25 patients with ground-glass attenuation (GGA) lesions on computed tomography, all underwent preoperative biopsy using flexible fiberoptic bronchoscopy (FFB). A total of 148 patients were diagnosed by FFB, and 86 were diagnosed by surgical excision. In the surgical excision cases, 67 tumors were negative for malignancy at the surgical margins and 19 were positive. Diagnosis by surgical excision was associated significantly more often with smaller tumor size ($P<0.0001$), a greater number of GGA lesions ($P=0.0006$) and a lower pathological stage ($P=0.001$) than those diagnosed by FFB. Furthermore, these patients showed better survival ($P=0.03$) and fewer local recurrences than patients diagnosed by FFB. In the groups that underwent excision, there was no significant difference in survival between those with positive and negative cytological margins. The survival of patients diagnosed by surgical excision was significantly better than that of those diagnosed by FFB in clinical stage IA disease. Surgical excision is an optimal method to diagnose small lung cancer because the malignant status of the margin does not appear to influence the outcome.

Keywords: Flexible fiberoptic bronchoscopy; Margin cytology; Non-small cell lung carcinoma; Surgical excision; Survival; Tumor recurrence

1. Introduction

Lung cancer is the leading cause of death in most industrial countries [1], and therefore we should identify an appropriate method of treatment. Recently, the size of lung cancers has decreased, and the chance of needing to surgically excise such small pulmonary nodules is increasing [2]. This is because techniques, such as biopsy using flexible fiberoptic bronchoscopy (FFB) and computed tomography (CT)-guided fine-needle biopsy have limited ability in diagnosing such small pulmonary nodules [2–4].

Although surgical excision is an accepted method for diagnosing small lung cancer, surgical manipulation may spread isolated tumor cells at the margins [5, 6] and may lead to a relapse of the malignancy. We therefore we conducted a study to evaluate whether surgical excision is an optimal diagnostic technique in terms of tumor recurrence and prognosis, and to clarify the effect on the cytology at the surgical margins.

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2. Methods

2.1. Patient selection

This retrospective analysis was based on records collected in a database of patients with primary lung cancer who had been histologically diagnosed and had undergone thoracotomy at the National Hospital Organization Toneyama Hospital in Japan.

Between 1998 and 2004, 590 consecutive patients underwent thoracotomy for primary lung cancer. Among them, 252 patients had had a lobectomy for clinical stage IA non-small cell lung carcinoma (NSCLC) with a diameter ≤3.0 cm. A total of 148 patients were diagnosed by FFB before surgery (group B), and 86 patients were diagnosed by surgical excision (group E). Thirteen patients diagnosed by needle biopsy (six under CT guidance and seven under open thoracotomy) and five patients diagnosed after lobectomy were excluded. Of these 234 patients, 25 patients had ground-glass attenuation (GGA) lesions (>50%) on CT-scan. Except for the 25 patients with GGA lesions, FFB was preoperatively attempted on all patients.

2.2. Procedure

During FFB, the lesions were diagnosed using a curette cytology technique followed by a lavage cytology technique

without autofluorescence and a navigation system. During surgical excision, we designed these methods to, in principle, have a macroscopically greater safe margin than the tumor diameter [7]. Specimens taken by wedge resection using staplers were diagnosed using frozen sections. Surgical excision under open thoracotomy was performed in 24 patients, and surgical excision under video-assisted thoracic surgery (VATS) in 62.

Immediately after surgical excision but before cross-sectioning of the specimen, cytological examination of the stump was performed with the Papanicolaou method, as previously described [5]. Papanicolaou classes IV and V were regarded as positive cytological findings. A total of 67 patients had negative findings at the surgical stump (group EN), and 19 had positive findings (group EP). When the tumor was diagnosed as NSCLC, a further pulmonary resection was undertaken. Before closure, the pleural cavity was washed with >3000 ml of physiological saline solution. Pleural recurrence was defined as pleural dissemination or malignant effusion or both in the hemithorax of the operated side at first relapse.

All patients underwent staging according to the 2009 TNM classification criteria [8]. An institutional review board approved this retrospective study, and written informed consent for the surgical intervention was obtained from each patient.

2.3. Statistical analysis

The χ^2 method was used to compare differences between the two groups, and the Student's *t*-test was used to analyze continuous variables. Survival was defined as the time between the date of operation and death. The survival rates were calculated using the Kaplan–Meier method and compared by log-rank test. A *P*-value <0.05 was considered significant. All statistical manipulations were performed using StatView 5.0 (Abacus Concepts Inc, Berkeley, CA, USA).

3. Results

3.1. Patient characteristics

The clinical characteristics of the patients enrolled in the study are presented in Table 1. There was no significant difference in gender, age, smoking status and the chance of detecting lung cancer. However, patients diagnosed by surgical excision had a lower performance status than those diagnosed by FFB (P=0.05).

The tumor characteristics of the patients are presented in Table 2. There was no significant difference in the primary lesion and the histological type. The mean tumor size for group E was significantly less than that for group B (1.5±0.5 cm vs. 2.2±0.6 cm; P<0.0001). In group E, there were significantly more GGA lesions than in group B (20% vs. 5%, P=0.0006). The distributions of pathological N status and pathological stage were significantly different: patients in group E had a lower pathological N status (P=0.002) and lower pathological stage (P=0.003) than those in group B.

The clinical characteristics of the patients in group E according to the cytology at the surgical margin are presented in Table 3. There was no statistical difference between groups EN and EP.

Table 1. Patient characteristics

	Group B (n=148)	Group E (n=86)	*P*-value
Gender			0.08
Male	83	38	
Female	65	48	
Age			0.40
Mean±S.D. (years)	63.3±9.7	62.3±10.1	
Performance status			0.05
0	127	81	
1	21	5	
Smoking status (packs/year)			0.06
≤20	83	59	
>20	65	27	
Chance of detecting lung cancer			0.46
Symptoms	19	12	
Lung cancer screening	91	46	
Post-resection screening for other diseases	38	28	

Group B, patients diagnosed by flexible fiberoptic bronchoscopy before surgery; group E, patients diagnosed by surgical excision.

Table 2. Tumor characteristics

	Group B (n=148)	Group E (n=86)	*P*-value
Primary lesion			0.07
Right upper lobe	54	27	
Right middle lobe	7	10	
Right lower lobe	29	20	
Left upper lobe	37	12	
Left lower lobe	21	17	
Histology			0.19
Adenocarcinoma	119	79	
Squamous cell carcinoma	22	2	
Others	7	5	
Tumor size			<0.0001
Mean±S.D. (cm)	2.2±0.6	1.5±0.5	
GGA >50%	8	17	0.0006
Pathological T status			0.01
1a, 1b	130	84	
2a, 2b	16	1	
3	2	1	
4	0	0	
Pathological N status			0.002
0	122	83	
1	7	0	
2	19	3	
Pathological stage			0.003
I	118	81	
II	9	1	
III	20	3	
IV	1	1	

Group B, patients diagnosed by flexible fiberoptic bronchoscopy before surgery; group E, patients diagnosed by surgical excision. GGA, ground-glass attenuation.

3.2. Tumor recurrence

In group B, 42 patients (28.4%) had a recurrence. At first relapse, seven had recurrences in the pleural cavity and two had pleural and distant recurrences (6.1%). In group

Table 3. Characteristics of patients diagnosed by pulmonary wedge resection

	Group EN (*n*=67)	Group EP (*n*=19)	*P*-value
Gender			
Male	31	7	0.47
Female	36	12	
Age			
Mean±S.D. (years)	61.5±10.2	65.3±9.5	0.16
Performance status			
0	64	17	0.32
1	3	2	
Smoking status (packs/year)			
≤20	44	15	0.08
>20	23	4	
Histology			
Adenocarcinoma	63	16	0.16
Squamous cell carcinoma	2	0	
Others	2	3	
Tumor size			
Mean±S.D. (cm)	1.5±0.5	1.6±0.5	0.25
GGA >50%	15	2	0.25
Pathological stage			
I	66	16	0.09
II	0	0	
III	0	3	
IV	1	0	

Group EN, patients had negative findings at the surgical stump; group EP, patients had positive findings. GGA, ground-glass attenuation.

E, seven patients (8.9%) had recurrences; among these, all seven patients had distant metastases, while there was no recurrence in the pleural cavity (Table 4).

3.3. Survival rate of patients according to diagnostic techniques

The 30-day mortality was 0% (0/148) in group B and 1.2% (1/86) in group E. The mean follow-up period was 98.7 months. There was a significant difference in overall survival between groups B and E (*P*=0.003; Fig. 1). The five-year survival rate was 80.5% for group B and 91.7% for group E. To avoid any differences arising from tumor staging, we analyzed the survival rate of patients with pathological stage IA disease excluding GGA lesions. The same trend was apparent, although the difference was not significant (*P*=0.17; Fig. 2). The five-year survival rate was 80.5% for group B and 90.2% for group E.

Finally, we analyzed the survival rate of patients diagnosed by surgical excision according to the cytological status of the excision margin. There were no significant differences in overall survival between groups EN and EP, with a five-year survival of 90.8% and 94.7%, respectively (*P*=0.94; Fig. 3a). Among patients with pathological stage IA disease excluding GGA lesions, there was also no significant difference in survival between the two groups (*P*=0.73; Fig. 3b).

Table 4. Tumor recurrence

	Group B (*n*=148)	Group E (*n*=86)
Without recurrence	106	79
With recurrence	42	7
Distant	33	7
Pleural cavity	7	0
Pleural cavity+distant	2	0

Group B, patients diagnosed by flexible fiberoptic bronchoscopy before surgery; group E, patients diagnosed by surgical excision.

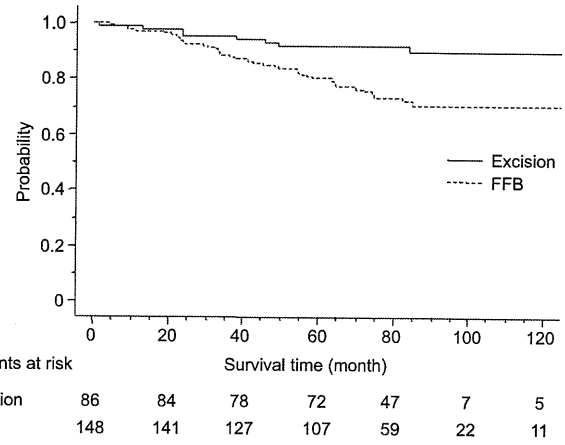

Fig. 1. Overall survival rate of patients according to diagnostic techniques. Group B, patients diagnosed by flexible fiberoptic bronchoscopy before surgery; group E, patients diagnosed by surgical excision. The five-year survival rate was 80.5% for group B and 91.7% for group E (*P*=0.003). FFB, flexible fiberoptic bronchoscopy.

4. Discussion

Although there has been a recent increase in the number of relatively smaller sized or early-stage lung cancers, there has also been more opportunity to diagnose them intraoperatively. More than half of the indeterminate small pulmonary nodules that cannot be diagnosed using FFB are malignant, as previously reported [9]. VATS exploration methods have been documented to be both minimally-invasive and very useful [10–12]. Thus, surgical excision (especially with VATS) is considered to be useful to detect and cure early-stage lung cancer. However, whether surgical

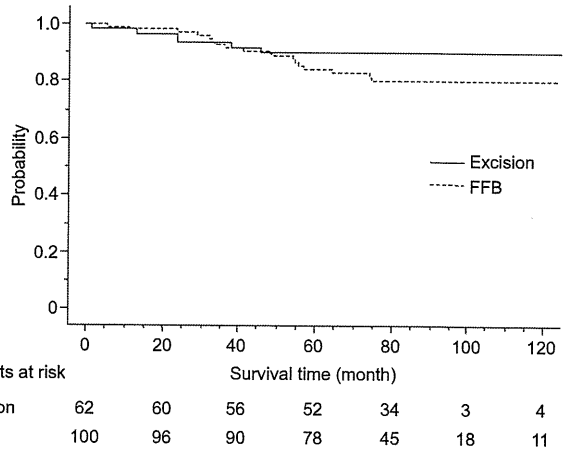

Fig. 2. Survival rate of patients with pathological stage IA excluding ground-glass attenuation lesions according to diagnostic techniques. Group B, patients diagnosed by flexible fiberoptic bronchoscopy before surgery; group E, patients diagnosed by surgical excision. The five-year survival rate was 80.5% for group B and 90.2% for group E (*P*=0.17). FFB, flexible fiberoptic bronchoscopy.

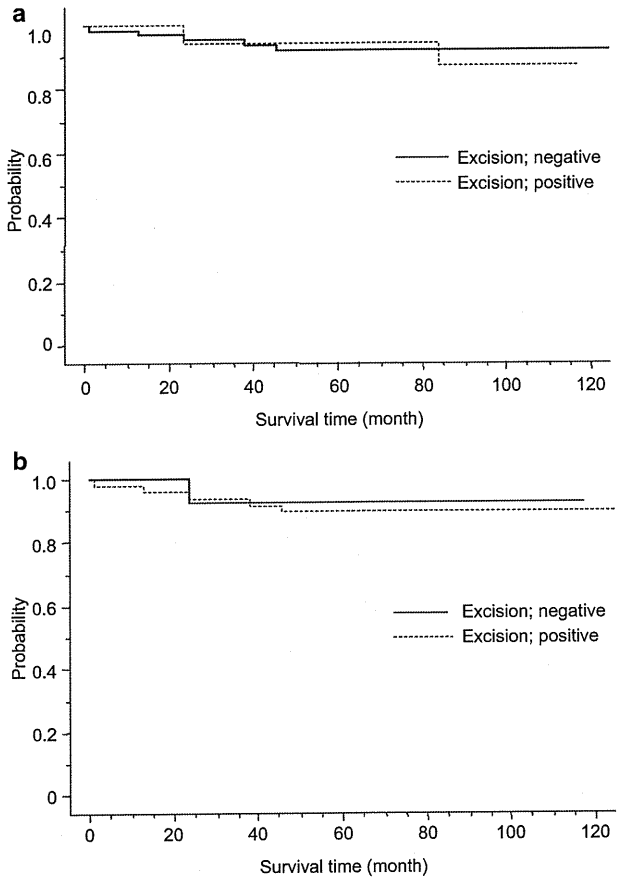

Fig. 3. Survival rate of patients diagnosed by surgical excision according to the cytology at the surgical margin. Group EN, patients had negative findings of the surgical stump; group EP, patients had positive findings. (a) There were no significant differences in overall survival between groups EN and EP, with a five-year survival of 90.8% vs. 94.7% (P=0.94). (b) Among patients with pathological stage IA disease excluding ground-glass attenuation lesions, there were also no significant differences in survival between the two groups (P=0.73).

excision as a diagnostic tool may increase the risk of local recurrence by tumor spillage remains unknown.

In this study, the tumor size of patients diagnosed by surgical excision was significantly smaller than of those diagnosed by FFB. Furthermore, in patients diagnosed by surgical excision, the distributions of GGA lesions and pathological stage I lesions were significantly greater than those diagnosed by FFB. A lower pathological stage was mainly attributed to a lower pathological N status. These results suggest that surgical excision is a useful method to diagnose early-stage lung cancer after unsuccessful FFB. Especially for GGA lesions, surgical excision with VATS may be very useful because this category is much more difficult to diagnose by FFB.

One of the unfavorable recurrent patterns after limited resection for NSCLC is local failure, especially at the surgical margin in the pulmonary parenchyma. Cytological examination of the surgical margins of wedge-resected malignant tumors was found to be useful to detect malignant cell contamination, as previously reported [5]. In cases of limited resection, a cytologically positive margin has the potential for surgical margin recurrence [5, 6, 13, 14]. Thus, intraoperative margin cytology is clinically useful in checking for complete resection in these cases [5, 7].

With regard to the pattern of recurrence, we found that, among 79 patients diagnosed by surgical excision, there was no recurrence in the pleural cavity, even in the group with cytologically positive margins, although there were seven recurrences with distant metastasis. Surgical manipulation did not affect shedding of tumor cells into the pleural cavity in this study. With regard to prognosis, the survival rate of patients diagnosed by surgical excision was significantly better than that of patients diagnosed by FFB. The same tendency was found among patients with pathological stage IA disease excluding GGA lesions. Furthermore, survival was not significantly different between patients with cytologically positive and negative margins.

To prevent the spread of malignant cells into the pleural cavity, surgical excision with a safe margin is desirable [6, 7]. Accordingly, we designed the method of surgical excision to include a macroscopically greater margin than the tumor size. However, there is a possibility of margin cytology becoming positive. Even if the resected margin of surgical excision was cytologically positive, this did not affect the pattern of recurrence and the prognosis in cases that underwent further residual lobectomy in this series. Contaminated malignant cells may have a low potential for growth in the pleural cavity because further resection was performed following surgical excision with washing of the pleural cavity using a large volume of physiological saline solution.

Surgical excision is the most accurate technique for the diagnosis of small pulmonary nodules. Both VATS and thoracotomy have specific advantages, as a residual lobectomy can be carried out if the results of frozen-section histology lead to a diagnosis of malignancy during surgery. It is possible to treat this by surgical excision immediately after obtaining the diagnosis. Residual lobectomy was undertaken in all 86 patients of ours who were diagnosed by surgical excision. Furthermore, in our series, most cases were diagnosed during pathological stage N0 disease by surgical excision. This can therefore be recommended for a small pulmonary nodule after unsuccessful FFB.

A limitation of this study that should be noted, however, is that this analysis was retrospective and the sample of patients diagnosed by surgical excision was small. Furthermore, there is a bias in this study as the size and location of the tumors were different between the two groups: most patients in group E had small peripheral adenocarcinomas (T1aN0). Thus, a greater number of peripheral T1aN0 patients should be compared in future studies.

5. Conclusions

In conclusion, pulmonary wedge resection was a useful method to detect and cure early-stage lung cancer discovered as undiagnosed pulmonary nodules. The survival of patients diagnosed by surgical excision was significantly better than that of those diagnosed preoperatively by FFB in clinical stage IA disease. Surgical excision was beneficial as a diagnostic technique because this method did not

affect relapse and prognosis, even if the surgical margin was cytologically positive.

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ORIGINAL ARTICLE

Efficacy of low-dose landiolol, an ultrashort-acting β-blocker, on postoperative atrial fibrillation in patients undergoing pulmonary resection for lung cancer

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Abstract
Purpose. Postoperative atrial fibrillation is the most common complication encountered during the early postoperative period following a pulmonary resection procedure. Landiolol is a newly developed, ultrashort-acting, β-adrenoceptor antagonist. The objective of the present study was to evaluate the efficacy and safety of low-dose landiolol for postoperative atrial fibrillation in patients undergoing pulmonary resection for lung cancer.
Methods. Of 553 patients who underwent an elective pulmonary resection procedure for lung cancer at National Toneyama Hospital from January 2005 to December 2009, this analysis involved 30 consecutive patients who developed atrial fibrillation after surgery and needed treatment. These patients were divided into two groups: the landiolol group ($n = 15$) and the historical control group (treated with a combination of verapamil and digoxin, $n = 15$). Hemodynamic changes before and 30 min, 2 h, and 12 h after medication, the time required to restore sinus rhythm, and adverse events were evaluated.
Results. There were no significant differences between the two groups regarding blood pressure before and after medication. Heart rate was reduced immediately in both groups after medication and was significantly lower in the landiolol group than in the control group. The time to restore sinus rhythm was significantly shorter in the landiolol group than in the control group (8.1 ± 11.0 h vs. 23.0 ± 26.0 h, $P < 0.05$). In none of the subjects with the landiolol infusion was it discontinued because of side effects.
Conclusion. Low-dose landiolol can be effective quickly and used safely in patients who develop atrial fibrillation after pulmonary resection for lung cancer.

Key words Arrhythmia · Lung cancer surgery · Perioperative care

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Introduction

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia encountered during the early postoperative period following a pulmonary resection procedure.[1, 2] Although AF is transient in most cases, a serious outcome, including thromboembolic events and hemodynamic deterioration, may occur, leading to increased

mortality.[3,4] Patients with hemodynamically unstable postoperative AF cannot start early rehabilitation easily, and other complications such as pneumonia can occur.[2,5] Therefore, it is important to control the heart rate immediately in the presence of postoperative AF.

The common therapy for postoperative AF includes various drugs, including digoxin,[6] calcium channel blockers,[7,8] β-blockers,[9] amiodarone,[9] quinidine, sotalol, and procainamide, to control heart rate and restore sinus rhythm. Although β-blockers have been reported to be successful for preventing postoperative AF after cardiac surgery,[10] their use for heart rate control has been avoided in lung resection surgery because currently available β-blockers have a relatively longer half-life and lower cardioselectivity and might cause adverse respiratory effects. Digitalis and verapamil were widely used to control the heart rate for AF until recently in Japan.[11]

Landiolol hydrochloride (Onoact, Ono Pharmaceutical, Osaka, Japan), a newly developed, commercially available agent in Japan, is an ultrashort-acting β-adrenoceptor antagonist. Recently, beneficial effects of low-dose landiolol have been reported in patients undergoing cardiac surgery who develop postoperative AF.[12] The objective of the present study was to evaluate the safety and efficacy of low-dose landiolol for postoperative AF in patients undergoing pulmonary resection for lung cancer.

Materials and methods

Study design and population

A total of 553 patients underwent an elective pulmonary resection procedure for lung cancer at National Toneyama Hospital from January 2005 to December 2009. Among them, 59 (11%) consecutive patients who developed AF after surgery were included in this study. The exclusion criteria for the present analysis were a history of AF, antiarrhythmic drug use including β-blockers, thyroid dysfunction, renal failure requiring hemodialysis, repeated pulmonary resection, and recent (<1 month) angina pectoris or myocardial infarction. As a result, 14 patients were excluded. Of the remaining 45 patients, the types of treatments between 2005 and 2007 (n = 30) were: digoxin in 25, verapamil in 16, disopyramide in 2, and diltiazem in 1, including combinations of these treatments. Because treatment with digoxin plus verapamil (n = 15) was the most common, patients who received this treatment were chosen as the historical control group. After January 2008, low-dose landiolol was given to all patients (n = 15). National Health Insurance has approved the use of landiolol for emergency treatment of intraoperative and postoperative arrhythmias in Japan. The recommended maintenance dosage is 10–40 μg/kg/min.

The results of the landiolol group (n = 15) and the historical control group (digoxin plus verapamil, n = 15) were compared. In the control group, the subjects received 0.25 mg digoxin and 5 mg verapamil intravenous loading every 12 h for 1 day and then 0.125–0.25 mg digoxin and 120 mg verapamil orally daily for 1 month. In the landiolol group, the subjects received continuous infusion of low-dose landiolol (5 μg/kg/min without a bolus) after AF development that was continued for the next day, followed by 2.5–5.0 mg carvedilol orally daily for 1 month. If heart rate control was insufficient, the dose of landiolol was increased to 10 μg/kg/min while monitoring the heart rate and blood pressure. When severe bradycardia or hypotension was observed in the landiolol group, landiolol administration was discontinued.

All patients received preoperative epidural anesthesia for pain management, which usually remained in place for 2–4 days or until the chest drainage tubes were removed, after which they were switched to oral analgesia. Other postoperative management methods included early ambulation and low-flow nasal oxygen supplementation, as necessary. Complete preoperative and follow-up data were obtained for all patients. The institutional review board of National Toneyama Hospital approved the study, and all patients gave their written informed consent (trial registration number UMIN 000001941).

Postoperative AF

The incidence of AF has been reported to peak on the second postoperative day (POD 2), with most events seen during PODs 1–4.[13] Any episode of AF that was registered by the continuous monitoring system within the first 4 days on a rhythm strip or the 12-lead electrocardiogram (ECG) that lasted for more than 30 min and needed treatment was defined as postoperative AF in this study. Also, continuous monitoring was in place until sinus conversion in patients with AF development.

Measurements

Preoperative evaluations included a detailed history and physical examination, blood gas analysis, 12-lead ECG, spirometry, and determination of serum B-type natriuretic peptide (BNP) levels. None of the patients had symptomatic coronary artery disease or congestive heart failure. Hemodynamic parameters, including systolic blood pressure, diastolic blood pressure, heart rate, and oxygen saturation were recorded before and 30 min, 2 h,

and 12 h after the start of the medication. The time to restore sinus rhythm was also recorded.

Adverse events

In this study, adverse events were monitored for 30 days after treatment and defined as bradycardia, hypotension, congestive heart failure, myocardial infarction, angina pectoris, pneumonia, acute respiratory failure, respiratory insufficiency requiring tracheostomy, respiratory failure requiring mechanical ventilation, atelectasis with bronchoscopic therapy, home oxygen treatment, thromboembolic events, and death. Because prolonged air leak and bronchopleural fistulas are considered surgical factors, they were excluded.

Statistical analysis

Data are expressed as the mean ± SD or as proportions. Comparisons among all parameters were analyzed by one-way analysis of variance (ANOVA). Comparisons between the two groups were made using the Mann-Whitney test, with the χ^2 test for categorical variables. All data were analyzed using SPSS version 11.0 (SPSS, Chicago, IL, USA). $P < 0.05$ was considered significant.

Results

Subjects

Of the 30 patients, 19 (63%) were men, and the mean age was 70.6 ± 6.3 years. In all, 22 (73%) patients had a smoking history. There were no significant differences between the two groups in terms of baseline characteristics, surgical data, use of catecholamines during operation and postoperatively, preoperative pulmonary function, or serum BNP levels (Table 1). None of the subjects received a blood transfusion. Both groups had relatively higher preoperative BNP levels than the normal range and underwent lobectomy in most cases.

Landiolol administration

In the landiolol group, 10 patients received 5 μg/kg/min and 5 received 10 μg/kg/min as the maximum dosage of landiolol. In none of the subjects was the landiolol infusion discontinued because of side effects.

Hemodynamics

There were no significant differences between the groups in terms of systolic blood pressure, diastolic blood pressure, or oxygen saturation before and after medication (Fig. 1). The heart rate was reduced in both groups immediately after receiving the medication; and at 30 min, 2 h, and 12 h after medication the heart rate was significantly lower in the landiolol group than in the control group. Restoration of sinus rhythm was noted in all patients within 10 days after surgery. None of the patients received anticoagulation therapy. The time to restore sinus rhythm was significantly shorter in the landiolol group than in the control group (8.1 ± 11.0 h vs. 23.0 ± 26.0 h, $P < 0.05$). Most of the landiolol group had restored sinus rhythm within 12 h after treatment, so additional analysis was performed. The heart rate of AF was compared if AF was not converted to sinus rhythm (Fig. 2). The heart rate 30 min and 2 h after medication was significantly lower in the landiolol group, but no significant difference was observed at 12 h after starting the medication (Fig. 2).

Adverse events

There were no postoperative deaths, thromboembolic events, or congestive heart failure associated with AF in either group. There was one (7%) case of pneumonia in the landiolol group; among the control group there were four (27%) cases of pneumonia, two (13%) cases of hypotension, and one (7%) case of acute respiratory distress syndrome. All patients recovered with treatment.

Discussion

The results presented here are the first to demonstrate that continuous infusion of low-dose landiolol, an ultra-short-acting β-blocker, has a novel effect on postoperative AF in patients following pulmonary resection for lung cancer. The infusion of low-dose landiolol did not significantly change the systolic or diastolic blood pressure; it did reduce the heart rate immediately, with no clinically significant adverse effects. Our findings indicate that low-dose landiolol is a viable treatment option for postoperative AF in patients undergoing thoracic surgery.

Postoperative AF after pulmonary resection is associated with various surgical stresses, such as excitation of sympathetic nerve activity, right ventricular overload, and systemic inflammatory responses.[14] β-Blockers have been reported to prevent postoperative AF after general thoracic surgery.[15,16] For cardiac surgery, β-blockers have been recommended for the prevention and treatment of AF after coronary artery bypass graft surgery by the American Heart Association, the American College of Cardiology, the American College of Chest

Table 1 Patients' characteristics and preoperative pulmonary function variables*

Variables	Landiolol group ($n = 15$)	Control group ($n = 15$)	P
Age (years)	72.2 ± 5.7	69.5 ± 7.3	0.18
Male sex	10 (67%)	9 (60%)	0.72
Hypertension	9 (60%)	7 (47%)	0.48
Hypercholesterolemia	5 (33%)	4 (27%)	0.70
Diabetes mellitus	4 (27%)	3 (20%)	0.68
Ischemic heart disease	3 (20%)	3 (20%)	0.99
Smoking history	12 (80%)	10 (67%)	0.43
Medication			
Calcium channel blockers	5 (33%)	4 (27%)	0.70
ACE inhibitors or ARBs	3 (20%)	4 (27%)	0.68
Statins	3 (20%)	2 (13%)	0.64
Estimated GFR	58.6 ± 10.0	60.2 ± 12.0	0.82
Procedure			
Wide wedge resection or segmentectomy	1 (7%)	1 (7%)	0.99
Lobectomy	14 (93%)	14 (93%)	0.99
VATS procedure	10 (67%)	8 (53%)	0.24
Operating time (min)	249 ± 70	276 ± 95	0.45
Blood loss (ml)	150 ± 224	168 ± 156	0.79
Mediastinal lymph node dissection	14 (93%)	14 (93%)	0.99
Lung cancer staging			
IA, IB	10 (67%)	13 (87%)	0.21
IIA, IIB	2 (13%)	1 (7%)	0.56
IIIA, IIIB	3 (20%)	1 (7%)	0.30
Use of catecholamines	3 (20%)	3 (20%)	0.99
VC (% predicted)	103.3 ± 19.0	105.0 ± 17.0	0.81
FEV_1 (% predicted)	85.8 ± 18.0	89.3 ± 13.0	0.57
FEV_1/FVC (%)	72.6 ± 9.9	75.9 ± 9.5	0.38
DLco (% predicted)	86.4 ± 19.0	88.4 ± 14.0	0.74
PaO_2 (mmHg)	85.1 ± 11.0	83.8 ± 10.0	0.41
$PaCO_2$ (mmHg)	40.2 ± 3.0	40.2 ± 4.1	0.96
BNP (pg/ml)	60.3 ± 59.0	47.5 ± 23.0	0.26

Values are shown as numbers or means ± SD unless otherwise indicated
ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; BNP, B-type natriuretic peptide; DLco, diffusion capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GFR, glomerular filtration rate; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; VATS, video-assisted thoracoscopic surgery; VC, vital capacity

Physicians, and the European Society of Cardiology.[17] However, their use is more limited by side effects than other drugs and thus less broadly applicable in general thoracic surgery. Many patients undergoing lung cancer surgery have a smoking history and some respiratory diseases, such as emphysema and chronic obstructive pulmonary disease. Therefore, when we use β-blockers in patients after pulmonary resection surgery, respiratory tract disorders (e.g., bronchospasm, atelectasis), in addition to bradycardia and hypotension, are of concern.

In Japan, three β-blockers are available for intravenous injection: landiolol, esmolol, and propranolol. Landiolol has a shorter plasma half-life (4 min) than the other two (esmolol 9 min, propranolol 2 h) and higher β_1 selectivity (β_1/β_2: landiolol 277; esmolol 20; propranolol 0.6).[18,19] These properties suggest that adverse respiratory effects will rarely develop with landiolol, which makes it more suitable for postoperative AF after pulmonary resection. The clinical efficacy and safety of low-dose landiolol for postoperative tachycardia have been recognized.[12,20] Wariishi et al.[20] reported, in a single-arm study, that low-dose landiolol (maximum dosage 7.5 ± 7.6 μg/kg/min) significantly reduced the heart rate and elevated the systolic blood pressure in patients with postoperative supraventricular arrhythmia. In this study, low-dose landiolol (mean maximum dosage 6.6 ± 2.4 μg/kg/min) demonstrated sufficient efficacy for the treatment of postoperative AF following pulmonary resection without side effects.

In this study, the heart rate 12 h after treatment was significantly lower in the landiolol group because the time to restore sinus rhythm was significantly shorter. In the analysis of limited to continued AF, there was no significant difference in the heart rate 12 h after treatment in the two groups. Therefore, the final heart rate control effects for postoperative AF were considered to

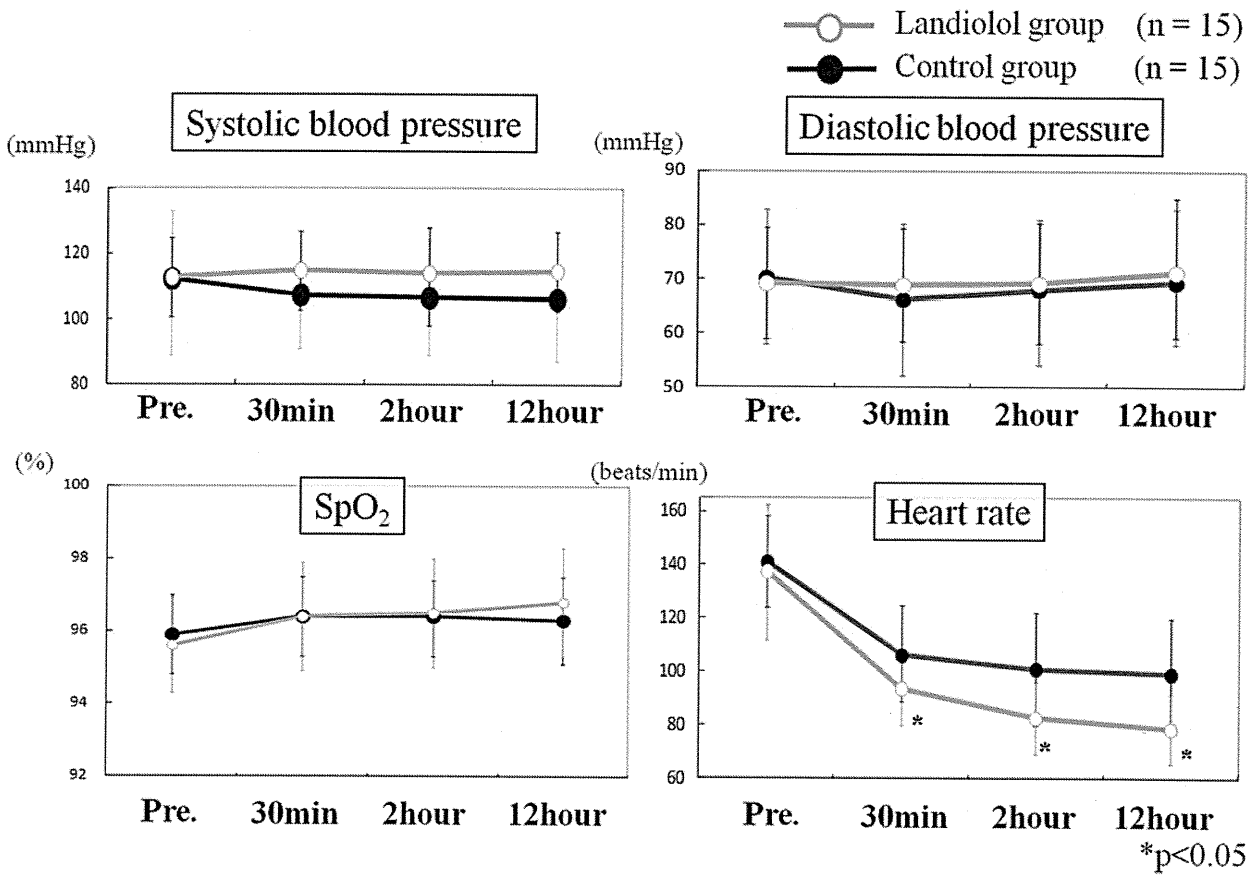
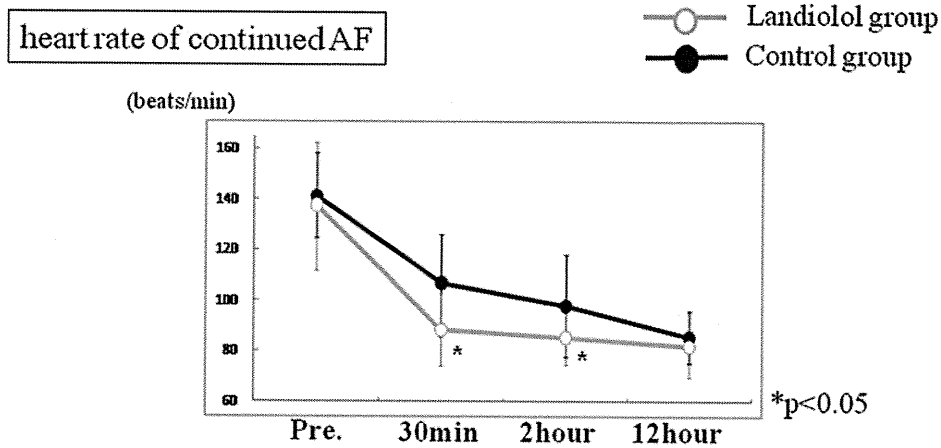


Fig. 1 Changes in systolic blood pressure, diastolic blood pressure, heart rate, and oxygen saturation (SpO_2) before and after medication. Each *point with bars* shows the mean ± SD. $*P < 0.05$

Fig. 2 Change in the heart rate of patients with continued atrial fibrillation (*AF*) before and after medication. Each *circle with bars* shows the mean ± SD. $*P < 0.05$



Numbers of patients				
Control group	15	15	12	7
Landiolol group	15	10	7	4

be equal in the two groups, but the quick response was an advantage with landiolol. Postoperative AF has been associated with respiratory complications such as pneumonia and acute respiratory failure in patients undergoing pulmonary resection,[2,5] therefore, controlling the heart rate immediately is important and may improve perioperative outcomes for patients with postoperative AF. In this study, the incidence of pneumonia was relatively lower in the landiolol group than in the control group, but the difference was not significant. Also, it has been reported that patients with persistent AF (>48 h) have an increased risk of thromboembolism.[21] Thus, landiolol treatment might help avoid the need for anticoagulation therapy during the perioperative period. More recently, landiolol was reported to have protective effects on not only cardiac but also pulmonary diseases.[22] Uraoka et al. reported that administration of landiolol prevented the development of pulmonary edema after cardiopulmonary resuscitation with epinephrine in a rat model.[22] In the future, new clinical findings may be obtained using landiolol in more patients with pulmonary diseases.

One limitation of this study was that it was a single-institution clinical study, which restricts our ability to generalize the results. In addition, patients were not assigned to the groups randomly, and a historical difference existed between the two groups. The number of patients in the study cohort was small as well. Additional investigations with a larger number of patients from multiple institutions are necessary to determine the benefit of this agent before it can be considered for routine use.

Conclusion

The present study is the first to demonstrate the efficacy of low-dose landiolol for postoperative AF without major adverse events in patients undergoing pulmonary resection for lung cancer. Additional studies are warranted to determine whether these effects can be observed in other patients and translated into improved clinical outcomes.

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