GENERAL THORACIC SURGERY

EFFECTS OF DILTIAZEM PROPHYLAXIS ON THE INCIDENCE AND CLINICAL OUTCOME OF ATRIAL ARRHYTHMIAS AFTER THORACIC SURGERY

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Objectives: We sought to determine whether early prophylaxis with an L-type calcium channel blocker reduces the incidence and morbidity associated with atrial fibrillation/flutter and supraventricular tachyarrhythmia after major thoracic operations.

Methods: In this randomized, double-blind, placebo-controlled study, 330 patients were given either intravenous diltiazem ($n = 167$) or placebo ($n = 163$) immediately after lobectomy (≥ 60 years) or pneumonectomy (≥ 18 years) and orally thereafter for 14 days. The primary end point with respect to efficacy was a sustained (≥ 15 minutes) or clinically significant atrial arrhythmia during treatment.

Results: Postoperative atrial arrhythmias (atrial fibrillation/flutter = 60; supraventricular tachyarrhythmias = 5) occurred in 25 (15%) of the 167 patients in the diltiazem group and 40 (25%) of the 163 patients in the placebo group ($P = .03$). When compared with placebo, diltiazem nearly halved the incidence of clinically significant arrhythmias (17/167 [10%] vs 31/163 [19%], $P = .02$). The 2 groups did not differ in the incidence of other major postoperative complications or overall duration or costs of hospitalization. No serious adverse effects caused by diltiazem were seen.

Conclusions: After major thoracic operations, prophylactic diltiazem reduced the incidence of clinically significant atrial arrhythmias in patients considered at high risk for this complication. (*J Thorac Cardiovasc Surg* 2000;120:790-8)

Of the 600,000 Americans who undergo major cardiothoracic operations annually, more than 150,000 will have postoperative atrial arrhythmias, of which atrial flutter/fibrillation (AF) is the most common.¹⁻³ Patients with postoperative AF have an extended hospi-

tal stay with accompanying increased costs, as well as greater need for hospital readmission after discharge. The risk of stroke is greater in patients with postoperative AF.^{1,2,4} The etiologic mechanisms of this complication are poorly understood. As in AF unrelated to operations, age of 60 years or older is consistently the only independent preoperative risk factor most strongly associated with postoperative AF.¹⁻⁵ Biochemical studies done in our laboratory have shown a persistent downregulation and desensitization of the lymphocyte β -adrenergic receptor/adenyl cyclase system that corresponded to global reductions in measures of heart rate variability throughout the first postoperative week.⁶ These and other data^{7,8} support the presence of increased sympathetic activity, parasympathetic withdrawal, or both during this critical period. We hypothesized that postoperative AF may be mediated, in part, by calcium channel mechanisms in response to adrenergic hyperactivity. Recent investigations in animals⁹ and human subjects¹⁰⁻¹² showed that L-type calcium channel

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blockers possess antiarrhythmic capability against AF. Favorable pilot data from our institution established that diltiazem is well tolerated after thoracotomy.¹³ Thus, this study was designed to determine whether early L-type calcium channel blockade with diltiazem reduces the incidence and morbidity of postoperative atrial arrhythmia.

Methods

Patient population. This study was approved by the Institutional Review Board of Memorial Sloan-Kettering Cancer Center, and written informed consent was obtained from each patient before the operation. To be eligible, patients had to be in sinus rhythm and at increased risk for postoperative arrhythmias either because they were scheduled to undergo a pneumonectomy or were over 60 years of age and scheduled to have a lobectomy. Patients were excluded if they had a history of chronic atrial arrhythmia or second-degree atrioventricular block or were taking class I or class III antiarrhythmic drugs or calcium-channel blockers for ischemic heart disease. Patients who had new signs of myocardial ischemia or infarction or required inotropic support on arrival to the postanesthesia care unit were also excluded. Preoperative medications were continued until the time of the operation. Patients taking L-type calcium-channel blockers for hypertension ($n = 8$) received other antihypertensive medications postoperatively, as clinically indicated. β -Blockers were continued postoperatively to avoid withdrawal.

A total of 503 patients with pulmonary or pleural malignant tumors were enrolled from February 1997 to August 1999. Patients who were found to have unresectable disease at the time of operation because of extensive spread of tumor ($n = 32$) or those who underwent a lesser operation ($n = 135$) were excluded from the study. Four patients were excluded from the study after randomization but before the study medication was given: two patients had acute myocardial ischemia or infarction during or immediately after the operations; one patient had persistent hypotension (systolic blood pressure < 80 mm Hg) requiring vasopressor therapy for greater than 12 hours; and one patient had a persistent sinus bradycardia (heart rate < 50 beats/min). In addition, two patients were wrongly enrolled into the study: one patient was being treated with a class III antiarrhythmic drug for paroxysmal AF, and the other had poorly controlled hyperthyroidism and paroxysmal AF. These 6 patients were not included in the intention-to-treat analysis. The 330 consecutive patients who underwent lobectomy ($n = 232$), pneumonectomy ($n = 63$), or extrapleural pneumonectomy ($n = 35$) were randomly allocated in a double-blind fashion in the immediate postoperative period to receive diltiazem or placebo (see below).

Study end points. The primary end point of the study was the new onset of sustained (≥ 15 minutes) or clinically significant (requiring intervention) AF or supraventricular tachyarrhythmia (SVT) during the first 14 days after the operation. AF was defined by an irregular cardiac rhythm,

other than sinus rhythm, confirmed by either ambulatory electrocardiography (ECG) or 12-lead ECG. SVT was defined as the new onset of paroxysmal supraventricular tachycardia or multifocal atrial tachycardia necessitating treatment. Once the primary end point was reached, the assignment code was unblinded, and the primary physician was allowed to cross over to diltiazem from placebo or administer additional diltiazem or other medications as clinically indicated. Patients in whom the heartbeat failed to convert to sinus rhythm within 24 to 48 hours of AF onset were given heparin followed by warfarin. The incidence of late (> 14 days) AF was recorded during hospitalization or if documented as outpatients within 30 days of operation. Need for intensive care unit (ICU) admission for any reason during the 14-day treatment period was also recorded. Data on total hospitalization costs for the study population were provided through the use of a commercially available decision-support information software system (Financial Management System; Shared Medical Systems, Malvern, Pa) used by the patient account office at our institution. Professional service fees were not included in these charges. The 3M APR-DRG (All Patient Refined-Diagnostic Related Groups; 3M Health Information Systems, Salt Lake City, Utah) severity adjustment model was used in adjusting for age, sex, comorbidity, operation, and the interactions thereof. These adjustments were based on the 1996 northeast normative data file. A relative resource weight was established for each patient. These weights were summed for each group and divided by the total patients in the group, yielding a group case mix index. The average cost per group was then divided by the case mix index to develop a neutral cost per case. This neutralized cost was then multiplied by the case mix index for all patients analyzed (2.78) to yield an adjusted average cost.

Anesthesia, operation, and postoperative care. All patients were premedicated with midazolam and glycopyrrolate (INN: glycopyrronium bromide) and received standard anesthetic management that consisted of isoflurane and nitrous oxide supplemented by intravenous fentanyl and morphine as needed. Intentional crystalloid restriction (< 25 mL/kg) during the operation was attempted in all patients. The operations were performed by experienced thoracic surgeons using standard thoracotomy approaches. Entry into the pericardial space or resection of the pericardium was recorded. Resection was carried out in a manner designed to completely remove all neoplastic disease along with an ipsilateral mediastinal lymph node dissection. Intraoperative estimated blood loss was recorded. Postoperative pain relief was provided to all patients by continuous administration of either epidural opioid (usually fentanyl) administration ($n = 195$) or intravenous opioid (usually morphine) patient-controlled analgesia ($n = 135$). After an overnight stay in the postanesthesia care unit, patients were transferred to the thoracic surgical floor on the first postoperative day. Postoperative complications were recorded throughout the hospital stay. A research nurse monitored patients for complications as outpatients for 30 days and queried patients

about intercurrent hospitalizations or emergency department visits. An investigator reviewed these medical records.

Ambulatory ECG. Continuous dual-lead ECG recordings (leads CM2 and CM1 or CM5) were made on Marquette 8500 Holter recorders for 72 to 96 hours after the operation. QRS complex recognition and arrhythmia detection were done automatically by template matching. The decisions made automatically by the computer were reviewed and corrected by an experienced technician and then by a cardiologist.

Antiarrhythmic prophylaxis. Patients were randomly assigned to receive either diltiazem or placebo with stratification on the basis of the type of operation (ie, lobectomy, pneumonectomy, or extrapleural pneumonectomy). Randomization of patients in permuted blocks was done between the epidemiology and biostatistics departments and the hospital pharmacy with sealed, opaque, treatment-code envelopes. All clinical and study personnel were blinded to the study group assignments throughout the trial. On admission to the postanesthesia care unit, treated patients ($n = 167$) received an intravenous loading dose of diltiazem (0.25 mg/kg [50 mL]) given over 30 minutes, followed by $0.1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ (constituted as 1 mg/mL) intravenously for 18 to 24 hours. Diltiazem was temporarily discontinued for systolic hypotension ($<80 \text{ mm Hg}$) or marked bradycardia ($<50 \text{ beats/min}$). Similarly, control patients ($n = 163$) received intravenous placebo loading doses of 50 mL given over 30 minutes, followed by a placebo infusion at $0.1 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ given over the first 18 to 24 hours. Starting in the morning of postoperative day 1, patients received either diltiazem SR 120 mg or placebo orally twice daily for a total of 14 days. Patients who could not take oral medication during the treatment period were temporarily switched to the intravenous route. Adjustments in the oral dose were made for patients weighing less than 50 kg , those who had a systolic blood pressure of less than 90 mm Hg , or those showing other adverse effects to diltiazem. Venous blood was drawn to determine plasma diltiazem and magnesium levels on the morning of postoperative day 3 before receiving the morning dose. Plasma diltiazem concentration was determined by high-performance liquid chromatography with ultraviolet detection by Bioassay Laboratory (Houston, Tex).

Statistical analysis. We estimated that the overall incidence of postoperative AF in this group would be 15% .³ To detect an absolute reduction of 10% in the incidence of early AF with a 2-tailed test at an α level of 5% with 80% power, a sample size of 330 patients (165 per arm) would be required. The sample size was adjusted for one interim analysis with monitoring boundaries in the spirit of the O'Brien-Fleming rule but with early rejection of either the null or the alternative hypothesis.¹⁴ An interim analysis was performed after 189 patients were enrolled. Atrial arrhythmias occurred in 21 (22%) of 95 control subjects and 15 (16%) of 94 treated patients ($P = \text{not significant}$). The overall incidence of AF with or without SVT was tested among all 3 subgroups (lobectomy, pneumonectomy, and extrapleural pneumonectomy) with the Mantel-Haenszel test for differences in proportions. All analyses were performed on an intention-to-treat

basis, and all P values are 2-tailed. Statistical analysis was performed with the software SAS version 6.12 (SAS Institute, Inc, Cary, NC). To determine the difference of patient and operative characteristics between the 2 treatment groups, we examined all variables by univariate analysis (Student t test and Fisher exact test). Data are presented as mean value $\pm$ SD unless otherwise indicated.

Results

Study population and surgical data. The 2 groups were well matched in age, sex distribution, severity of tumor stage, comorbidity, and surgical data (Table I). Plasma magnesium concentrations taken on postoperative day 3 were nearly identical in diltiazem-treated patients ($1.57 \pm 0.17 \text{ mEq/L}$) versus control subjects ($1.56 \pm 0.16 \text{ mEq/L}$, $P = \text{not significant}$; normal range, $1.4\text{--}2.2 \text{ mEq/L}$). Heart rate was identical in the diltiazem and placebo groups at baseline before the operation ($77 \pm 13 \text{ beats/min}$). However, during the first 72 hours after the operation, mean heart rate was greater by 6 to 7 beats/min in the placebo group when compared with that found in the diltiazem-treated patients ($P < .01$). The 2 groups did not differ in the incidence of nonsustained ventricular or supraventricular ectopy, as determined by Holter monitoring.

Postoperative atrial arrhythmias. A total of 65 patients had sustained atrial arrhythmias detected, as determined by Holter criteria, clinical criteria, or both, within the first 14 days of operation: AF ($n = 60$), paroxysmal supraventricular tachycardia ($n = 3$), and multifocal atrial tachycardia ($n = 2$). Diltiazem significantly reduced the overall (with or without symptoms) incidence of postoperative atrial arrhythmias when compared with placebo ($25/167$ [15%] vs $40/163$ [25%], $P = .03$) and nearly halved the incidence of clinically significant atrial arrhythmias ($17/167$ [10%] vs $31/163$ [19%], $P = .023$; Table II). Five of 46 patients with clinically significant AF were initially noted to have asymptomatic episodes of sustained AF, as determined by Holter monitoring. AF occurred a mean of 2.7 ± 1.7 days (median, 2 days) after the operation in patients assigned to diltiazem and 3.3 ± 2.5 days (median, 3 days) in patients assigned to placebo ($P = .32$). In 41 of 60 AF episodes, the average heart rate in the hour preceding AF could be determined and was found to be similar between the diltiazem and placebo groups (91 ± 15 vs $92 \pm 10 \text{ beats/min}$, $P = .87$). The maximal ventricular rate during AF was significantly lower in the diltiazem group than in the placebo group (145 ± 34 vs $163 \pm 26 \text{ beats/min}$, $P = .02$). There was no significant difference between the groups in the duration of AF (diltiazem: 21.8 ± 38.1 hours vs placebo: 16.2 ± 21.9

Table I. Patient characteristics

Characteristic	Diltiazem (n = 167)	Placebo (n = 163)	P value
Age (y)	66 ± 10	67 ± 10	.7
Male sex, n (%)	91 (54)	86 (53)	.83
Weight (kg)	74 ± 15	74 ± 16	.94
Smoking, n (%)	132 (79)	132 (81)	.68
Diabetes mellitus, n (%)	15 (9)	12 (7)	.69
Coronary artery disease, n (%)	8 (5)	13 (8)	.27
Hypertension, n (%)	49 (29)	52 (32)	.63
Preoperative medications			
β-Blockers, n (%)	17 (10)	17 (10)	.99
Calcium-channel blockers, n (%)	7 (4)	1 (1)	.07
Digoxin, n (%)	2 (1)	3 (2)	.89
β-Agonist inhalers, n (%)	16 (10)	16 (10)	.99
Preoperative chemotherapy, n (%)	41 (25)	34 (21)	.43
Operation type			.99
Lobectomy, n (%)	117 (70)	115 (71)	
Pneumonectomy, n (%)	32 (19)	31 (19)	
Extrapleural pneumonectomy, n (%)	18 (11)	17 (10)	
Right thoracotomy, n (%)	94 (56)	80 (49)	
Intraoperative data			
Estimated blood loss (L)	0.5 ± 0.7	0.4 ± 0.5	.31
Pericardiotomy, n (%)	30 (18)	33 (20)	.68
Tumor stage			.99
I + II, n (%)	95 (57)	97 (60)	
III + IV, n (%)	52 (31)	53 (33)	
Not staged, n (%)	20 (12)	13 (8)	

hours, $P = .52$; Table III). Late AF (>14 days) occurred in 2 diltiazem-treated patients on postoperative days 17 and 20 and in 1 patient from the placebo group on postoperative day 18. One of these episodes was associated with acute pulmonary embolism and 1 with pneumonia.

AF or SVT episodes that did not respond to diltiazem therapy were initially managed by a class III antiarrhythmic drug in 2 patients assigned to placebo and 1 patient assigned to diltiazem. β-Blockers were given to 4 patients assigned to placebo and 2 patients in the diltiazem group. Five patients in each group were given digoxin. No patient required electrical cardioversion. Once the ventricular response was controlled, no patient had evidence of myocardial ischemia or infarction. Nine (15%) of 60 patients with AF required anticoagulation on discharge from the hospital, of whom 4 were originally assigned to the diltiazem group. Two of these 9 patients who were originally assigned to placebo remained in AF 2 months after their operations.

Length of hospital stay and total costs. Length of hospital stay did not differ between patients assigned to diltiazem in comparison with control subjects (8.9 ± 7.9 vs 8.7 ± 7.8 days, $P = .82$). The median length of hospital stay was 7 days for both groups. The mean total hospitalization costs for the diltiazem group were $\$23,773 \pm \$19,443$ compared with $\$23,515 \pm \$18,152$

for the placebo group ($P = .90$). Patients with a clinically significant arrhythmia ($n = 48$) had a longer length of hospital stay (14.4 ± 13.0 vs 7.9 ± 6.1 days, $P = .001$) when compared with patients who did not have an arrhythmia ($n = 282$) and were more frequently 60 years or older ($47/290$ vs $1/40$, $P = .02$). Mean hospitalization costs for patients who had a clinically significant arrhythmia were $\$26,013 \pm \$21,636$ versus $\$23,070 \pm \$16,730$ in those patients who did not ($P = .28$). There was a trend for patients who had clinically significant arrhythmias and received diltiazem ($n = 17$) to have lower hospitalization costs than similar control subjects ($n = 31$; $\$22,498 \pm \$15,378$ vs $\$28,508 \pm \$26,144$, $P = .16$). Nonbillable services associated with every symptomatic arrhythmia included more intense nursing coverage, additional monitoring, and more frequent house staff visits.

Subgroup analyses. Diltiazem therapy reduced the incidence of early postoperative AF in patients undergoing lobectomy when compared with placebo ($16/117$ vs $29/115$, $P = .03$), as well as in patients 60 years or older (all 3 subgroups; $P = .05$; Table II). In the diltiazem group the incidence of AF was 24% (4/17 patients) among the patients receiving β-blockers and 13% (20/150 patients) among those not receiving β-blockers. In the placebo group the incidence of AF was

Table II. Incidence of atrial arrhythmias

	Diltiazem		Placebo		P value
	No.	%	No.	%	
All atrial arrhythmias	25/167	14	40/163	26	.03
AF	24/167	14	36/163	22	.07
Lobectomy	16/117	14	29/115	25	.03
Pneumonectomy	7/32	22	3/31	10	.32
Extrapleural pneumonectomy	1/18	6	4/17	24	.18
Patients $\geq$ 60 y					
All atrial arrhythmias	24/149	16	38/141	27	.03
Clinically significant arrhythmias	17/149	11	30/141	21	.03
AF	23/149	15	35/141	25	.05
Clinically significant AF	16/149	11	28/141	20	.03

Table III. Duration of AF*

Duration	Diltiazem (n = 24)	Placebo (n = 36)
<8 h	11	18
8-24 h	9	11
>24 h	4	7

Values are in numbers of patients.

*There was no significant difference in the duration of AF between the 2 groups ($P = .88$, Fisher exact test).

also 24% (4/17 patients) among the patients receiving β -blockers and 22% (32/146 patients) among those not receiving β -blockers. The use of β -blockers did not influence the incidence of AF in either study group ($P = .40$, Fisher exact test).

When all patients were combined, those in whom AF developed were found to be older than those in whom AF did not develop (71 ± 7 vs 66 ± 10 years, $P < .01$). Patients with AF had a longer length of hospital stay (12.9 ± 12.1 vs 7.9 ± 6.2 days, $P = .002$). More patients with AF had ICU admission (9/60) compared with patients without AF (6/270, $P < .01$). The use of β -blockers did not differentiate patients who did or did not have AF (8/60 [13%] vs 26/270 [10%], $P = .36$). Side of operation and presence of pericardiotomy did not differentiate patients in whom AF did or did not develop (data not shown).

Morbidity and mortality in the hospital. There was no significant difference in the incidence of postoperative complications between the two groups (Table IV). Among patients who had a clinically significant arrhythmia, other major postoperative complications occurred in 4 (24%) of 17 patients assigned to diltiazem and in 8 (26%) of 31 assigned to placebo ($P = .99$). One patient who was treated with diltiazem had a cerebrovascular accident attributed to new-onset AF within 24 hours of its

onset. In this patient the first 12 hours of AF were asymptomatic. The length of stay in the ICU did not differ between patients assigned to diltiazem (8.0 ± 4.7 days, $n = 7$) compared with patients assigned to placebo (8.4 ± 4.8 days, $n = 8$; $P = .88$). The reasons for ICU admission were pneumonia ($n = 8$), acute respiratory distress syndrome ($n = 3$), AF ($n = 2$), and pulmonary embolism ($n = 2$). Death within 30 days of the operation occurred in 3 patients assigned to placebo and in 1 patient assigned to diltiazem ($P = .37$, Table IV).

Compliance with treatment and adverse effects.

Six patients receiving diltiazem and 1 receiving placebo required a transient interruption in therapy because of mild hypotension in the postoperative anesthesia care unit ($P = .12$). Two diltiazem-treated patients had an interruption of intravenous drug therapy for more than 12 hours because of a borderline systolic blood pressure but continued with their oral therapy. In no patient was there a precipitous drop in blood pressure seen with any dose of diltiazem. The oral dose of diltiazem was decreased in 2 patients whose sitting systolic blood pressure was 90 to 100 mm Hg before discharge from the hospital. Seven patients refused to continue on the study within the first 48 hours, and 2 patients elected to drop out after 7 days of treatment. Side effects potentially related to diltiazem included dyspepsia (1 patient) and rash (1 patient). The mean plasma diltiazem level determined on the morning of postoperative day 3 was 310 ± 164 ng/mL (range, 26-742 ng/mL; median, 283 ng/mL) and was within the reported therapeutic range (79-294 ng/mL).¹⁵ In a subset of 17 of 24 patients in whom AF developed during diltiazem treatment, the plasma diltiazem levels did not differ from levels found in those without AF ($n = 121$; 294 ± 150 vs 312 ± 167 ng/mL, $P = .67$).

Discussion

Main findings. The use of prophylactic diltiazem starting immediately after thoracic operations and continuing for 2 weeks was well tolerated and reduced the incidence of clinically significant atrial arrhythmias by approximately 45%. When compared with placebo, diltiazem reduced the average heart rate early after the operation, as well as the ventricular response rates during acute AF or SVT. Diltiazem reduced the rate of AF occurrence significantly in the lobectomy subgroup but not in the pneumonectomy groups. In our experience,^{3,13} the observed incidence of AF was lower than expected in patients undergoing pneumonectomy who were assigned to placebo. This is likely a result of the sample size and relatively younger age of patients undergoing pneumonectomy compared with that of the lobectomy subgroup.

Diltiazem therapy did not alter the overall length of hospital stay despite reducing the number of clinically significant episodes of AF and SVT. This may be due to the relatively early onset of AF when compared with the median length of hospital stay of 1 week in both groups and our practice of discharging patients after early anticoagulation. AF has recently been shown to be the single most important cause for hospital readmission after fast-track cardiac operations.¹⁶ Unlike patients undergoing cardiac operations who are fast-tracked, it is possible that our patients' postoperative comorbidities, such as pneumonia or a prolonged air leak, masked the effect of diltiazem on the overall length of hospital stay. The significantly higher length of hospital stay in our patients with an arrhythmia is consistent with findings in other studies.¹⁻⁴ The burden of AF after cardiac operations on hospital costs is well documented.^{1,2,4} In our study the mean hospitalization cost attributed to a clinically significant arrhythmia was close to \$3000. Our results demonstrated that a 14-day course of intravenous and oral diltiazem (\$120 hospital cost, $n = 167$) was responsible for a 45% (14 patients) risk reduction of clinically significant atrial arrhythmias. Assuming that these 14 patients were to have an arrhythmia and that their total costs would exceed that of patients without an arrhythmia by \$3000, this would translate into cost savings after the cost of diltiazem is deducted. Because extended monitoring, intensity of nursing care, and house staff interventions were not billed for at our institution, our cost savings with diltiazem are probably underestimated. Strategies that can further maximize the cost effectiveness of diltiazem could include beginning oral therapy before the operation, shortening the course of intravenous diltiazem therapy after the operation, and

Table IV. Postoperative major morbidity and mortality

Variable	Diltiazem (n = 167)	Placebo (n = 163)
Major morbidity		
Pneumonia	7	8
Prolonged air leak	9	7
Paralytic ileus	3	1
Pulmonary embolism	3	1
Acute respiratory failure	1	2
Acute renal failure	0	2
Wound infection	0	2
Cerebrovascular accident	1	0
Total*	24 (14%)	23 (14%)
Hospital readmission within 30 d of operation		
Pneumonia	2	2
AF	1	1
Fever	1	1
Other	2	0
Total*	6 (3.6%)	4 (2.5%)
Mortality within 30 d of operation		
Acute respiratory distress syndrome	1	2
Sudden death	0	1
Total*	1 (0.6%)	3 (2%)

* $P =$ not significant, diltiazem versus placebo.

reducing the duration of postoperative therapy to 10 days because the majority of arrhythmias occurred before this time in our study.

Previous studies. Our early experience with the prophylactic use of diltiazem after pneumonectomy showed an overall reduction of AF or SVT by 50% when compared with that of patients treated with digoxin or with a comparison control group.¹³ The sample size of that study was relatively small, and this difference only approached significance. The use of verapamil by other investigators immediately after thoracic operations for 72 hours was associated with similar reductions in the AF rate but with greater side effects related to a large loading dose.¹⁷ In another study of patients undergoing coronary artery bypass grafting (CABG), short-term diltiazem therapy that was started during cardiopulmonary bypass and continued for 24 hours was shown to significantly reduce the AF incidence from 18% to 5%.¹⁸ The limitations of that study, however, were the lack of arrhythmia definition and monitoring reported for only 24 hours. β -Blockers have also been used for many years to prevent AF after cardiothoracic operations, but their efficacy for this purpose has been marginal.^{1,2,19-21}

In contrast to rate-control drugs, more recent reports have investigated the use of the class III antiarrhyth-

mics amiodarone and ibutilide in patients undergoing cardiac operations.²²⁻²⁴ The first report involved a relatively small group of patients given amiodarone for 1 week before CABG, valvular operation, or both and showed a significant effect of therapy on the incidence of AF (25% vs 53%), on hospital stay, and on cost when compared with placebo.²² In a larger trial limited to patients undergoing CABG, amiodarone prophylaxis reduced the AF incidence from 47% to 35% but had no effect on hospital stay or cost.²³ Despite these reported reductions in AF rates with amiodarone,^{22,23} the overall incidence of AF remained high, and when coupled with its significant cost and the potential for side effects, its routine use for prophylaxis against postoperative AF has been discouraged.²⁵ The concern of lung injury associated with amiodarone therapy in a small study of patients undergoing thoracic operations requires further confirmation.²⁶ Ibutilide has been shown to be effective in the conversion of acute AF after cardiac operations but was associated with a 1.8% risk of polymorphic ventricular tachycardia.²⁴ As in AF unrelated to an operation, it is not clear whether antiarrhythmics are superior to rate-control drugs in the management of postoperative AF.²⁵ In fact, a recent preliminary study of postoperative AF reported that the strategy of rhythm control is not superior to that of rate control for attainment of any clinical end point.²⁷

Limitations of the study. First, on the basis of our prior work,^{3,13} we expected that younger age would not affect the incidence of AF after pneumonectomy. By study design, patients undergoing pneumonectomy were younger than patients undergoing lobectomy. We believe that this, combined with the smaller sample size in the pneumonectomy groups and the lower than expected AF occurrence, limited our ability to find a meaningful comparison between diltiazem-treated and control patients. Second, Holter recordings were made during the first 72 to 96 hours after the operation, a period when most arrhythmias are known to occur. Our conclusions beyond this monitoring period are limited to clinically evident episodes of AF. Third, our practice setting precluded doing a more exact cost analysis to assess the true burden of AF.

Potential mechanisms. Postoperative atrial arrhythmias and AF specifically may be seen in 2% to 4% of elderly patients undergoing noncardiothoracic operations.^{28,29} The clinical presentation is identical whether a patient has had cardiac, thoracic, or other types of operations. What differs is the greater incidence of AF after cardiothoracic operations.²⁸ Although the etiologic mechanisms of postoperative AF are poorly understood, it has been shown that AF is generally initiated

by an ectopic beat.³⁰ Whether the ectopic beat triggers AF depends on the vulnerability of the atrium. Atrial vulnerability is determined by a complex interaction of factors: dispersion of refractoriness, electrical remodeling, wavelength of the re-entrant impulse (product of the refractory period by the conduction velocity), and autonomic balance.³¹ To date the only consistent clinical predictor of postoperative AF is older age.¹⁻⁵ It is widely known that aging causes degenerative changes in atrial anatomy^{32,33} that are accompanied by shorter atrial effective refractoriness, longer sinoatrial and atrioventricular nodal conduction times, atrial stiffening, and splitting of the atrial excitation waveform caused by the pectinated trabeculae.³⁴ Experimental studies have shown that sympathetic stimulation by itself will not produce AF, whereas regional sympathetic denervation indirectly changed the vagal effects on atrial refractoriness to facilitate sustained AF.^{34,35} We speculate that cardiac and thoracic operations provide a model of regionally denervated atria as a result of varying degrees of unavoidable trauma to sympathovagal fibers originating from the deep and superficial cardiac plexi to the atria.¹³ Whether there is a yet undefined atrial denervation supersensitivity phenomenon to circulating plasma catecholamines in response to cardiothoracic operations is unknown, but this has been contemplated to explain atrial arrhythmias in a totally denervated transplanted heart.³⁶

The higher incidence of AF and other re-entry type atrial arrhythmias in the control group confirms the data from laboratory⁹ and clinical studies¹⁰⁻¹² suggesting that intracellular calcium-lowering drugs mitigate some of the atrial electrophysiologic mechanisms that predispose to AF onset. The likely multifactorial composition of the substrate for postoperative AF partially explains why more than 60% of patients do not have this complication after cardiothoracic operations.²⁸ It also explains why clinical studies examining one mechanism, such as prolonged intra-atrial conduction (prolonged signal-averaged P-wave duration) as a predictor of postoperative AF, have provided conflicting results.³⁷⁻³⁹

Conclusions

Postoperative AF is a frequent and serious complication in elderly patients undergoing thoracic operations. It is commonly associated with hemodynamic compromise, greater need for ICU stay, increased hospital stay and readmission, and, less frequently, with stroke. Prophylactic diltiazem in this study was safe and nearly halved the incidence of clinically significant AF, SVT, or both, in patients known to be at increased risk for this complication. To the best of our knowledge,

this is the first large, randomized, controlled trial to demonstrate that calcium-channel blockers clearly prevent the occurrence of AF after major thoracic operations. On the basis of these results, we consider it appropriate to use diltiazem prophylaxis as standard care in patients over the age of 60 years undergoing major pulmonary resection.

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