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Impact of Epicardial Anterior Fat Pad Retention on Postcardiothoracic Surgery Atrial Fibrillation Incidence

The AFIST-III Study

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Objectives We conducted a randomized, blinded, controlled study evaluating the impact of anterior fat pad (AFP) maintenance on postoperative atrial fibrillation (POAF) incidence.

Background Drugs with antiadrenergic effects reduce POAF. Because the epicardial AFP is parasympathetically innervated, its routine excision during coronary artery bypass grafting (CABG) might precipitate autonomic imbalance and induce POAF.

Methods Patients (n = 180, mean age = 66 ± 10 years, 80% men, 5% with previous atrial fibrillation) undergoing CABG surgery were randomized to either AFP maintenance or AFP removal. Routine prophylaxis against POAF with beta-blockers (85%) and amiodarone (28%) was allowed on the basis of caregivers' discretion. The development of POAF, total hospital costs, and heart rate variability was compared between groups.

Results Anterior fat pad maintenance did not reduce POAF incidence (34.8% vs. 35.2%, p = 0.950) or total hospital costs (data as medians with 25%, 75% percentiles: $22,940 [$17,629, $29,274] vs. $23,866 [$18,602, $30,370], p = 0.647) but was associated with higher heart rate variability (SD of normal-to-normal RR intervals [SDNN]: 31.7 ± 24.6 vs. 22.7 ± 8.3, p = 0.05 and SD of all 5-min mean RR intervals [SDANN 5]: 17.1 ± 11.9 vs. 10.1 ± 5.5, p = 0.003) than AFP removal.

Conclusions Maintaining the AFP prevents attenuation of parasympathetic tone after CABG but does not reduce POAF or total hospital costs in any appreciable way. (J Am Coll Cardiol 2007;49:298–303) © 2007 by the American College of Cardiology Foundation

The heart has 3 epicardial fat pads (FPs) containing parasympathetic ganglia (1–4). In 1997, an anterior fat pad (AFP) was discovered and located on the anterior surface of the atria between the aorta and right pulmonary artery (1). In canines, the AFP is the conduit of most efferent parasympathetic nerve fibers en-route to the "superior vena caval-right atrial (SVC-RA) FP" and "inferior vena caval-left atrial (IVC-LA) FP" (1). Nerve stimulation of the AFP in canines increases atrial cycle length, slows the atrioventricular conduction time, and shortens the atrial effective refractory period (AERP) (1,2). Shortening AERP decreases the wavelength of atrial excitation wave fronts and increases the chances of developing atrial fibrillation. Catheter ablation of the AFP in 2 canine studies has been shown to prevent or attenuate AERP shortening with nerve stimulation (1,2). In these studies, ablation of the AFP was also shown to prevent inducibility for atrial fibrillation. In patients, nerve stimulation of the SVC-RA FP increases the atrial cycle length, whereas stimulation of the IVC-LA FP slows atrioventricular conduction times (3,4).

The AFP is frequently removed in cardiothoracic surgery patients to fully expose the aortic root (5–7). Extrapolation of canine data suggests that AFP excision during cardiothoracic surgery would reduce the risk of developing postoperative atrial fibrillation (POAF) (3,4). In 1 small cardiothoracic surgery patient study (n = 55), nerve stimulation of the AFP reduced the heart rate, whereas no change occurred with repeat nerve stimulation to the area of the removed tissue (5). Paradoxically, as a secondary end point, the rate of POAF with AFP removal was 37% as compared with 7%

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in patients whose tissue was left intact ($p < 0.01$) (5). In a randomized pilot study (n = 131), the incidence of POAF in patients who had the AFP removed was 21% versus 7% of patients with AFP retention (p = 0.051) (6,7). In a nonrandomized (i.e., convenience sample on the basis of clinical judgment at surgery) extension of this study, 189 more patients were included (n = 320 total) (7). With logistic regression analysis, there was no benefit associated with AFP retention versus removal (odds ratio [OR] 1.0, 95% confidence interval [CI] 0.4 to 2.4).

Given conflicting preliminary data (1,2,5–7), we conducted the AFIST-III (Atrial Fibrillation Suppression Trial-III), a randomized, blinded, and controlled trial designed to evaluate the impact of maintaining the AFP on POAF. In addition, we evaluated the impact of AFP maintenance on heart rate variability, an established marker of parasympathetic tone, in order to explore the underlying mechanism (8,9).

Methods

Study design. Patients (n = 180) undergoing coronary artery bypass graft surgery (CABG) were randomized to either removal or maintenance of the AFP and were followed for 30 days after their surgery. Although the cardiothoracic surgeons were not blinded, study subjects and data collectors did not know treatment group allocation.

The primary aims were to determine the impact of AFP maintenance on the incidence of POAF and the cost of CABG surgery. Secondary aims of this study were to evaluate hospital length of stay, determine the impact of AFP removal on parasympathetic activity via heart rate variability (HRV) measurement, and determine the impact of AFP retention on several safety parameters (another arrhythmia, myocardial infarction, hypotension, bradycardia, mortality, and stroke). Current standard of care measures, including surgical techniques (on- vs. off-pump surgery) and medications (prophylactic beta-blockers and amiodarone), were completely under the discretion of the patients' caregivers. The Institutional Review Board at Hartford Hospital approved the study with written informed consent obtained before surgery.

Study subjects. From August 2004 through October 2005, patients over 50 years of age scheduled to undergo their first CABG surgery (the AFP would already be removed for re-do CABG and would be a confounder) at Hartford Hospital, a 600-bed teaching hospital, were screened. Patients were excluded if: 1) they were experiencing an atrial arrhythmia (atrial fibrillation or flutter) at the time of enrollment, 2) they were scheduled to undergo concomitant procedures along with their CABG surgery such as valve replacement, or 3) they were enrolled in any other clinical trial.

Overall, 356 of 536 patients screened were excluded from participating for the following reasons: age <50 (n = 19), atrial arrhythmia at the time of enrollment (n = 15), already enrolled in a competing study (n = 21), concomitant valve replacement or MAZE procedure (n = 193), physician refusal (n = 1), or refusal to participate (n = 108) (Fig. 1).

Abbreviations and Acronyms

AFP = anterior fat pad
CABG = coronary artery bypass graft (surgery)
CI = confidence interval
HRV = heart rate variability
OR = odds ratio
POAF = postoperative atrial fibrillation

Surgical methodology. Sternotomy and endoscopic vein harvesting along with standard surgical techniques, including both on- and off-cardiopulmonary bypass (CPB) surgeries, were conducted by 1 of 3 surgeons. For removal of the AFP, excision was made with cautery and scissors, and the epicardial adipose tissue located between the aorta and the pulmonary artery often extending onto much of the anterior surface was dissected. The AFP excision was made for the purpose of exposing the aorta but was not necessary to conduct the operation. In patients randomized to AFP maintenance, the surgeon would avoid excision into the area of the AFP, thereby preserving the nerve fibers if possible.

Patient management. As part of the institution's cardiothoracic surgery critical pathway, the preprinted admission order sheet includes beta-blockers. After direct transfer from the operating room, patients were initially cared for within the surgical intensive care unit before being transferred to a monitored bed. The hospital telemetry instruments (Marquette, Milwaukee, Wisconsin) save all rhythms for 24 h and all abnormal rhythms until disconnected. A blinded certified technician continuously monitors and prints alarm-triggered abnormal strips. Blinded hospital

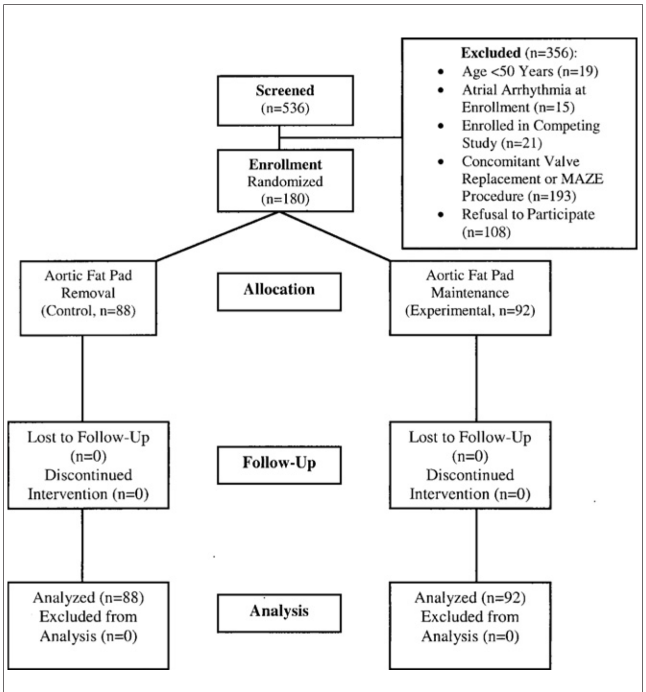

Figure 1 Schematic Diagram of Study

clinicians provided patient care of all arrhythmias, including the prophylaxis and treatment of POAF. A blinded study investigator monitored the time of occurrence, duration, and treatment of all arrhythmias and collected study data. Patients were followed daily until hospital discharge and then followed up periodically for 30 days after surgery.

Definitions. The following definitions were used: "POAF": POAF of more than 5 min in duration; "symptomatic POAF": POAF associated with hemodynamic compromise (hypotension, heart failure), requiring treatment (intravenous administration of an intravenous rate-controlling or antiarrhythmic agent), or feelings of subjective discomfort (palpitations, chest pain, shortness of breath, syncope); "recurrent POAF": POAF after being in sinus rhythm for more than 24 h after the initial episode; "cerebrovascular accident": development of a stroke (documentation by an attending neurologist of a focal deficit lasting more than 24 h, with confirmation or cerebral infarction by brain computed tomography or magnetic resonance imaging) or transient ischemic attack (documentation of a focal neurological deficit lasting for <24 h); and "ventricular tachycardia": ventricular tachycardia lasting at least 30 s or requiring treatment for termination.

Total hospital costs. Our cost analysis was conducted from a hospital perspective. Total hospital costs for each patient enrolled in the trial was determined, including all costs accrued starting from the day of admission for surgery through hospital discharge. Hospital charges as well as a breakdown of charges/cost center were obtained from our institution's medical claims database. Hospital-derived, departmental cost/charge ratios were used to convert hospital charges to hospital costs. Owing to the short-term nature of the study, discounting was not performed. All costs were adjusted to and reported in 2005 U.S. dollars (as median with 25% and 75% ranges) with the Consumer Price Index for Medical Care.

HRV. Holter monitors were placed on patients for at least 30 min on postoperative day 2. Holter monitors were attached by a trained study investigator or certified technician to patients in a supine position at a similar time each day, at least 1 h after the afternoon meal. The HRV was not determined in subjects experiencing POAF at the scheduled Holter monitoring time.

Digital Holter images were scanned and analyzed with Philips Zymed Holter 2120 Plus (Philips Medical Systems Andover, Massachusetts) by a certified technician. Analysis of HRV included measurement of the SD of normal-to-normal time duration between 2 consecutive R waves (RR intervals) (SDNN) and the SD of all 5-min mean RR intervals (SDANN 5). Patients having any atrial fibrillation or 5 or more supraventricular beats within the analysis period were excluded before between-group statistical comparison in order to reduce the influence of sinus alternans on our results. Average heart rates from Holter data were also determined and analyzed.

Statistical analysis. All demographic, clinical, safety, and length of stay data are presented as means ± SD. Cost data is expressed as medians with 25% and 75% percentiles. Values of $p \le 0.05$ are considered statistically significant. Dichotomous variables were compared with chi-square analysis, whereas continuous variables were compared with unpaired *t* tests. All statistical tests were run with SPSS version 11.0 (SPSS Inc., Chicago, Illinois).

Logistic regression. Univariate analysis was conducted to examine the association between the occurrence of POAF (dependant variable) and preoperative, intraoperative, and postoperative variables (independent variables). All variables with a p value of ≤0.2 in the univariate analysis were entered into a multivariate logistic regression model. In addition, variables that were not identified as univariate predictors of POAF but that have been previously identified as predictors were also included into the multivariate model. In the multivariate model, variables were selected by stepwise, backward elimination, and a p value < 0.05 was considered significant. Odds ratios and 95% CIs were calculated for all independent predictors of POAF. Statistical analysis was conducted with SPSS version 11.0 (SPSS Inc.).

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the report as written.

Results

Patients were well matched at baseline except that patients in the AFP removed group had a lower incidence of smoking than those receiving AFP maintenance (60.2% vs. 72.8%, $p = 0.043$) and showed a trend toward fewer vein grafts (2.0 ± 1.3 vs. 2.4 ± 1.3, $p = 0.059$) (Table 1). Prophylactic beta-blockers and amiodarone were used in approximately 85% and 28% of subjects, respectively.

No difference in the incidence of POAF (OR 0.981; 95% CI 0.531 to 1.810), symptomatic POAF, or recurrent POAF occurred between groups (Table 2). Similarly, no difference in any safety or length-of-hospital-stay parameter or total hospital costs occurred between groups (Table 2).

Subjects with AFP removal had lower HRV than those with AFP maintenance as determined by the SDNN (22.7 ± 8.3 vs. 31.7 ± 24.6, $p = 0.05$) and SDANN 5 (10.1 ± 5.5 vs. 17.1 ± 11.9, $p = 0.003$). The average heart rate during Holter monitoring was similar between the AFP removed and maintained groups (84.7 ± 12.4 vs. 84.9 ± 10.5, $p = 0.924$). Subjects who subsequently developed atrial fibrillation had average heart rates during Holter monitoring similar to those without atrial fibrillation (83.3 ± 10.5 beats/min vs. 85.2 ± 11.7 beats/min, $p = 0.529$).

With stepwise logistic regression analysis for predictors of POAF, AFP maintenance was not an independent predictor (OR 1.18, 95% CI 0.56 to 2.49), but 4 predictors were found with 3 trends (Table 3).

Table 1 Study Demographics

	Removed (n = 88)	Maintained (n = 92)	p Value
Age (yrs)	66.0 ± 10.1	65.1 ± 8.7	0.519
Age >70 yrs (%)	42.0	31.5	0.175
Gender (% male)	77.3	80.4	0.736
History of atrial fibrillation (%)	4.5	4.3	1.000
History of other arrhythmia (%)	10.2	5.4	0.238
History of heart failure (%)	9.1	9.8	0.837
History of neurologic disease (%)	9.1	6.5	0.548
History of myocardial infarction (%)	50.0	45.7	0.656
Pre-CABG beta-blockers (%)	81.8	77.2	0.623
Pre-CABG calcium blockers (%)	12.5	6.5	0.186
Pre-CABG digoxin (%)	1.1	0.0	0.494
History of diabetes (%)	36.4	32.6	0.711
History of smoking (%)	60.2	72.8	0.043
History of chronic obstructive pulmonary disease (%)	19.3	14.1	0.385
Family history of coronary disease (%)	38.6	44.6	0.458
History of hypertension (%)	76.1	79.3	0.418
History of angina symptoms (%)	64.8	64.1	0.996
Left ventricular ejection fraction (%)	52.6 ± 12.3	52.4 ± 12.5	0.905
Vessels >50% stenosed (n)	2.8 ± 0.6	2.9 ± 0.4	0.239
Mitral regurgitation (%)	19.3	10.9	0.135
Left ventricular aneurysm (%)	0.0	1.1	0.999
Surgical characteristics			
CABG + valve surgery (%)	2.2	2.2	0.999
On-pump surgery (%)	46.6	54.3	0.232
Duration of surgery (min)	288.1 ± 65.0	295.4 ± 103.5	0.581
Defibrillation attempts (n)	0.3 ± 1.0	0.2 ± 0.3	0.188
Vein grafts (n)	2.0 ± 1.3	2.4 ± 1.3	0.059
Artery grafts (n)	1.9 ± 1.2	1.8 ± 1.2	0.580
Total fluid in during surgery (ml)	3,279.0 ± 1,041.7	3,436.7 ± 1,816.0	0.485
Net fluid balance (ml)	1,638.1 ± 1,370.1	1,711.9 ± 1,644.9	0.750
Heart rate >100 beats/min >10 min (%)	8.0	9.8	0.617
Systolic blood pressure >180 mm Hg (%)	14.8	9.8	0.347
Systolic blood pressure <90 mm Hg (%)	38.6	28.3	0.184
ST-segment change (%)	5.7	5.4	0.999
Need for atrial pacing (%)	9.1	3.3	0.130
Need for ventricular pacing (%)	12.5	5.4	0.105
Inotropic agents needed (%)	77.3	80.4	0.393
Left atrial appendage stapling (%)	26.1	28.3	0.681
Medication characteristics			
Beta-blockers after surgery (%)	83.0	85.9	0.460
Calcium channel blocker after surgery (%)	9.1	12.0	0.515
Digoxin after surgery (%)	10.2	9.8	0.940
Corticosteroids after surgery (%)	25.0	23.9	0.897
High-dose nonsteroidal anti-inflammatory drug (%)	29.5	28.3	0.884
Amiodarone prophylaxis (%)	28.4	27.2	0.853
Cumulative amiodarone oral dose equivalents (mg)	3,709.9 ± 2,155.5	3,648.2 ± 2,577.5	0.928

CABG = coronary artery bypass graft surgery; Maintained = anterior fat pad maintained; Removed = anterior fat pad removed.

Discussion

Anterior fat pad maintenance did not positively or negatively impact clinical end points, particularly POAF, in the AFIST-III study. We would have needed over 9,720 subjects to show that this difference in POAF between the AFP maintenance and AFP removed groups was significant. Because we were not able to impact POAF, our length of stay and total hospital costs were similar between groups.

Our POAF data is consistent with the results of the extension study by Davis et al. (7). In contrast to their randomized pilot study of 131 patients in which the incidence of POAF was reduced 66.3% with AFP maintenance (p = 0.051), the extension study (n = 320, which included the 131 subjects from the pilot) showed no benefit (OR 1.0; 95% CI 0.4 to 2.4, p = 1.0) (6,7). Because the extension study was not randomized like the pilot study, it was

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Table 2 Study End Points

	Removed (n = 88)	Maintained (n = 92)	p Value
Any POAF (%)	35.2	34.8	0.950
Highest ventricular rate (beats/min)	140.2 ± 20.1	131.4 ± 32.2	0.208
Duration of POAF (h)	23.6 ± 47.4	15.7 ± 24.4	0.426
Post-CABG day of initiation (#)	2.2 ± 0.8	2.5 ± 1.8	0.349
Symptomatic POAF (%)	33.0	29.3	0.835
Recurrent POAF (%)	13.6	12.0	0.905
Safety end points			
Another arrhythmia identified (%)	17.0	17.4	0.892
Myocardial infarction (%)	1.1	0.0	0.494
Significant hypotension (%)	83.0	83.7	0.947
Significant bradycardia (%)	13.6	8.7	0.414
In-hospital mortality (%)	0.0	3.3	0.246
Stroke (%)	0.0	1.1	0.999
Length of stay			
Time from CABG to D/C (days)	7.7 ± 5.1	8.1 ± 8.0	0.694
Total time in hospital (h)	9.7 ± 6.6	9.9 ± 8.7	0.885
Cost—end points			
Total hospital costs ($)	23,866 [18,602, 30,370]	22,940 [17,629, 29,274]	0.647

Cost data is expressed as medians [25%, 75% percentiles].
D/C = discharge from hospital; POAF = postoperative atrial fibrillation; other abbreviations as in Table 1.

hard to discern whether the results of the extension study reflected biases associated with a convenience sample (reserving surgery for those who were at higher risk). The study by Cummings et al. (5) was a randomized trial primarily designed to assess parasympathetic activity in the AFP, not to assess the impact of AFP maintenance on POAF. However, this 55-patient study showed an 81% reduction in POAF in the AFP maintenance group ($p < 0.01$). It could not be discerned whether this represented a real phenomenon or the impact of small sample size and chance. As an example, if 1 additional patient in the AFP maintenance group from the Cummings trial had developed POAF and the results in the AFP removed group was the same, the results would have lost significance ($p = 0.060$), and if 2 subjects had developed POAF in the AFP maintenance group, there would not have been a statistical trend ($p = 0.130$).

The AFIST-III study is also at odds with canine data showing that parasympathetic nerve activity flowing through the AFP increases the inducibility for atrial fibrillation and that elimination of the AFP via ablation attenuated atrial fibrillation inducibility (1,2). In canines, AERP shortening secondary to parasympathetic nerve effects on the atria is presumed to be the causative factor in atrial arrhythmogenesis and is corrected after AFP ablation (1,2). As such, it could have been predicted that AFP dissection would reduce POAF in clinical studies.

Table 3 Stepwise Logistic Regression Analysis for Predictors of Post-CABG AF

Independent Variables	Odds Ratio (95% CI)	p Value
Amiodarone prophylaxis	0.31 (0.13–0.74)	0.008
Age >70 yrs	2.01 (0.98–4.12)	0.058
History of AF	7.15 (1.24–41.23)	0.028
Mitral regurgitation	2.59 (1.00–6.68)	0.050
High-dose nonsteroidal anti-inflammatory drug use	0.42 (0.17–1.01)	0.052
Beta-blocker intolerance	3.46 (1.18–10.14)	0.024

AF = atrial fibrillation; CABG = coronary artery bypass graft surgery; CI = confidence interval.

Evaluation of HRV might provide insight on POAF initiation and the role of the autonomic nervous system. In a previous trial of 96 patients undergoing thoracic surgery, the postoperative average RR interval 5 min before the onset of atrial fibrillation was lower (i.e., faster heart rate) than at a corresponding time from surgical control subjects (657 ± 112 vs. 717 ± 134, $p = 0.05$), suggesting elevated sympathetic tone (10). However, both time-domain and frequency domain indices of HRV were also elevated during this time, suggesting increased parasympathetic tone interjecting in this adrenergic-dominated environment. This would be consistent with canine data showing that the use of isoproterenol with acetylcholine can induce atrial fibrillation more readily than either agent alone (11).

Holter monitoring on postoperative day 2, the most common day for POAF occurrence (12), did not find a difference in resting heart rate between experimental groups, and the heart rates were in the low- to mid-80 beats/min range in the AFIST-III study, suggesting that sympathetic dominance had not occurred. The HRV was higher in the AFP maintenance group than the control group in the AFIST-III study, suggesting that parasympathetic tone was enhanced. It is possible that the use of prophylactic beta blockade and amiodarone in the AFIST-III study attenuated postoperative sympathetic dominance, so the elevated parasympathetic activity with AFP maintenance in POAF was muted (13,14).

Our study has 4 main limitations. First, the cardiothoracic surgeons were not blinded to study group allocation.

We minimized the impact of this by randomizing subjects and having blinded data collectors, clinicians who treated the patients, and the patients themselves. As such, unless the surgeons had treated subjects differently in the operating room (aside from retaining the AFP in 1 group), there would not be an impact on study results. Second, we did not have control over the use of other prophylactic strategies to reduce POAF. We had a high and similar use of beta blockade in both groups, so the benefits of AFP retention might have been attenuated by the sympathetic blockade. Although this might reduce the internal validity somewhat, it enhances the external validity, because beta-blockers are standard-of-care prophylactic drugs in CABG surgery (13,14). It was important to discern the benefits in addition to standard of care. The previous Davis trials did not disclose the use of prophylactic beta-blockers, but the Cummings trial had a very high use (over 94%) of beta-blockers (5–7). As such, the differential use of beta-blockers might not explain the different results between our trials, but dosing intensity might. However, data on beta-blocker dosing intensity are not provided in these previous trials (5–7). The previous trials also did not disclose the prophylactic use of amiodarone. The antiadrenergic effects of amiodarone might have accentuated the sympathetic control, and the antiarrhythmic properties might have suppressed POAF in some individuals (13,14). Third, we were unable to perform frequency domain HRV analyses. It would have been particularly useful to determine the high-frequency component of HRV, which is more specific to vagal tone, and the low-frequency/high-frequency ratio for HRV, because this is a more specific marker of sympathetic/parasympathetic balance (10,11). However, a previous study has determined that time-domain HRV indices, like in our present study, and frequency domain HRV indices show the same direction of effect in thoracic surgery patients (10). Last, we cannot be sure that preservation or excision of the AFPs were complete in all patients, because we did not use nerve stimulation to probe the area and check for acute changes in sinus cycle length (1,2,5). If dissection and preservation were not complete, residual parasympathetic activity in both groups would have attenuated differential results that might have occurred from AFP maintenance.

Conclusions. Maintaining the AFP does not alter the incidence of POAF after CABG or total hospital costs in any appreciable way, even though it preserves parasympathetic tone.

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