

Atrial Fibrillation After Cardiac Operation: Risks, Mechanisms, and Treatment

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Atrial fibrillation (AF) is a common complication of cardiac operations that leads to increased risk for thromboembolism and excessive health care resource utilization. Advanced age, previous AF, and valvular heart operations are the most consistently identified risk factors for this arrhythmia. Dispersion of repolarization leading to reentry is believed to be the mechanism of postoperative AF, but many questions regarding the pathophysiology of AF remain unanswered. Treatment is aimed at controlling heart rate, preventing thromboembolic events, and conversion to sinus rhythm. Multiple investigations have examined methods of preventing postoperative AF, but the only firm conclusions that can be drawn is to avoid β -blocker withdrawal after operation and to consider β -blocker therapy for other patients

who may tolerate these drugs. Preliminary investigations showing sotalol and amiodarone to be effective in preventing postoperative AF are encouraging, but early data have been limited to selective patient populations and have not adequately evaluated safety. Newer class III antiarrhythmic drugs under development may have a role in the treatment of postoperative AF, but the risk of drug-induced polymorphic ventricular tachycardia must be considered. Nonpharmacologic interventions under consideration for the treatment of AF in the nonsurgical setting, such as automatic atrial cardioversion devices and multisite atrial pacing, may eventually have a role for selected cardiac surgical patients.

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Atrial fibrillation (and/or flutter; AF) is a common complication of cardiac operations and an important source of patient morbidity and increased resource utilization [1-9]. The incidence of this arrhythmia is dependent on definitions (eg, duration, presence of symptoms), patient characteristics, type of operation, and method of arrhythmia monitoring [1-9]. In a series of 3,983 patients undergoing cardiac operations at our institution, Creswell and colleagues [1] found the incidence of AF detected by continuous electrocardiographic telemetry monitoring to be 32% after coronary artery bypass grafting (CABG), 42% after mitral valve replacement, 49% after aortic valve replacement, and 62% after combined CABG and valve procedures. Other researchers have reported atrial arrhythmias in 27% to 33% of patients after CABG [2, 3]. Of more concern is the finding that the frequency of AF may be increasing. In their series where surgeons and methods of arrhythmia monitoring were constant, Creswell and associates [1] found that the incidence of AF after CABG increased from 26% in 1986 to 36% in 1991. The latter finding was attributable to an increase in the mean age of the surgical patients.

Postoperative AF is usually well tolerated but tachycardia and loss of organized atrial contraction may result in hypotension and congestive heart failure in some patients. Even when hemodynamically tolerated, postoperative AF has consequences. The risk for perioperative stroke has been shown to be nearly threefold higher for

patients with postoperative AF especially for those with low cardiac output [1, 2, 10]. Patients developing postoperative AF are hospitalized 3 to 4 days longer than patients remaining in sinus rhythm leading to increased hospital cost [1-3]. Recent analysis involving 2,417 patients having CABG at 24 U.S. medical centers estimated that postoperative AF increased the cost of operation by \$1,616 per patient [2]. In a single center study, postoperative AF was associated with \$10,055 to \$11,500 of additional hospital charges for CABG [3]. Thus, the health economic implications of postoperative AF are substantial.

Risk Factors

Patient age has consistently been demonstrated to be the most important risk factor for postoperative AF with incidence rates of more than 50% for patients older than 80 years undergoing CABG compared with 5% for patients less than 50 years [1-3]. This association has been explained to be attributable to age-related structural changes in the atrium such as dilation, muscle atrophy, decreased conduction tissue, and fibrosis [11, 12]. Other investigators have shown prolonged atrial conduction detected by routine and signal-averaged electrocardiograms and lowered arrhythmia threshold at the time of operation to be associated with risk for postoperative AF [6, 8, 9]. Recently, we have reported that patients developing AF after CABG have reduced complexity of heart rate variability compared with patients remaining in sinus rhythm and that this finding along with tachycardia identified risk for AF with high predictive accuracy [13].

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Whether these methods or other electrophysiologic measurements can be feasibly applied to routine clinical settings for identifying AF risk remains to be established.

Many other risk factors for postoperative AF have been identified but the results have been inconsistent between studies [1-3, 14, 15]. The latter risks include history of rheumatic heart disease, left ventricular hypertrophy, hypertension, preoperative digoxin use, obstructive lung disease, peripheral vascular disease, and increasing aortic cross-clamp duration [1-3, 14, 15]. The atria are inadequately cooled during hypothermic cardioplegic arrest [16, 17]. Early return of atrial electrical activity during aortic cross-clamping is related to atrial conduction abnormalities and AF risk after operation in experimental and clinical investigations [16, 17]. Type of cardioplegia, however, does not seem to alter the risk for postoperative AF [18, 19].

Mechanisms

The electrophysiologic mechanism of postoperative AF is believed to be reentry that results from dispersion of atrial refractoriness [5, 20, 21]. When adjacent atrial areas have dissimilar or nonuniform refractoriness, a depolarizing wavefront becomes fragmented as it encounters both refractory and excitable myocardium [5, 20, 21]. This allows the wavefront to return and stimulate previously refractory but now repolarized myocardium leading to incessant propagation of the wavefront or reentry [5, 20, 21]. Currently, there is not an adequate explanation for why some patients develop postoperative AF whereas others having the same surgical interventions remain in sinus rhythm. Individuals vulnerable to AF are speculated to have the electrophysiologic substrate (nonuniform dispersion of atrial refractoriness) before operation that is then aggravated by surgical perturbations [5].

It is widely believed that enhanced sympathetic nervous system activity increases susceptibility to postoperative AF [4, 7, 22-25]. Sympathetic activation, however, is highest the first 24 hours after operation, whereas the onset of AF usually occurs between the second and third postoperative days [1-3, 26]. Furthermore, the atrial electrophysiologic effects of autonomic nervous system stimulation are complex. In contrast to the ventricle where sympathetic activation decreases and vagal stimulation increases the threshold for tachycardia and fibrillation, both sympathetic and parasympathetic activation alter atrial refractoriness, possibly contributing to the arrhythmia substrate [27, 28]. Heightened vagal tone has been demonstrated before AF in nonsurgical patients [29]. Recently, we evaluated cardiac sympathovagal balance before the onset of AF in patients recovering from CABG [13]. Either higher or lower measures of heart rate variability were observed before AF, a finding consistent with divergent autonomic conditions before arrhythmia onset [13]. The latter findings support the possibility that in some patients heightened sympathetic tone is present before AF but in others, either higher vagal tone or dysfunctional autonomic heart rate control is present before arrhythmia onset [13]. Thus, measures aimed at

only reducing cardiac sympathetic tone will be ineffective for preventing postoperative AF in all patients.

The reason for the delay in the onset of AF more than 2 to 3 days after operation is not clear. One possibility is that the onset of AF is related to an exaggerated inflammatory response especially involving the pericardium [30, 31]. Mechanical stretching of the atrium can alter cellular electrophysiologic properties suggesting that increased intravascular volume due to postoperative mobilization of interstitial fluid could contribute to the development of AF [32]. Tachycardia or brief episodes of AF lead to shortening of the atrial effective refractory period (electrophysiologic remodeling) promoting the maintenance of AF [33-36]. Alterations in calcium-handling proteins have been suggested to be an important mechanism for this electrophysiologic remodeling [34-37]. Downregulation of mRNA for L-type calcium channels and for sarcoplasmic reticular calcium-ATPase have been demonstrated in atrial tissue obtained before cardiac operations in patients with preexisting AF and perhaps these mechanisms contribute to susceptibility to postoperative AF [38]. The hypothesis that postoperative AF is related to altered gene expression is an attractive explanation for varying individual susceptibility and for the time lag between operation and the onset of the arrhythmia.

Treatment

Ventricular rate control, anticoagulation, and conversion to sinus rhythm are the primary goals of the treatment of AF. Rate control can be achieved with β -adrenergic receptor or calcium channel blocking drugs. Diltiazem and verapamil are effective for heart rate control, but the former is usually better tolerated especially for patients with impaired left ventricular function, whereas use of the latter drug can result in hypotension [39, 40]. Digoxin may be a useful drug for slowing heart rate for situations where β -blockers and calcium channel blocking drugs are contraindicated. Digoxin slows atrioventricular conduction to a large degree by enhancement of vagal tone. In the setting of high sympathetic nervous system drive as occurs perioperatively, its efficacy may be limited [26].

Mural thrombus formation is the most serious complication of AF. In an autopsy series involving nonsurgical patients, 21% of 642 patients with a history of AF had atrial thrombi compared with 2% of control patients [41]. Atrial thrombi were found in 30% of patients with valvular heart disease-related AF compared with 14% of patients with nonvalvular-related AF. In this series, thrombi were twice as likely to occur in the left compared with the right atrium. Left atrial thrombus is reported in 13% to 29% of patients undergoing transesophageal echocardiography and the potential for thrombus formation occurs early after the onset of AF [42-45]. Multiple clinical trials have shown that anticoagulation reduces the risk of thromboembolic stroke in nonsurgical patients with chronic AF, but the use of anticoagulation for these purposes in cardiac surgical patients has not been evaluated with clinical trials [46-48]. The use of anticoagulation therapy in the surgical patient is balanced against

Table 1. Summary of Trials Evaluating β -Adrenergic Receptor Blocking Drugs, Calcium Channel Blocking Drugs, and Type I Anti-Arrhythmic Drugs for the Prevention of Postoperative Atrial Fibrillation/Flutter (AF)

Study	Study Design	Drugs	No. of Subjects	Frequency AF Treatment Group	Frequency AF Control Group
Andrews et al [22]	Meta-analysis	Digoxin vs placebo	507	14% ^a	18%
		Verapamil vs placebo	432	18% ^a	18%
		β -Blockers vs placebo	1,549	9% ^b	34%
Kowey et al [23]	Meta-analysis	Digoxin vs placebo	875	15% ^a	19%
		β -Blockers vs placebo	1,418	10% ^b	20%
		β -Blockers & Digoxin vs placebo	292	2% ^b	29%
Laub et al [63]	R,DB	Procainamide vs placebo	46	4% ^b	11%
Gold et al [64]	R,DB	Procainamide vs placebo	100	26% ^a	38%
Hannes [59]	R	Diltiazem vs nitroglycerin	91	4% ^b	19%
Seitelberger et al [60]	R	Diltiazem vs nitroglycerin	120	5% ^b	18%
Merrick et al [62]	R,DB	Propafenone vs atenolol	207	12% ^a	11%

^a $p = \text{NS}$ vs control group. ^b $p \leq 0.05$ vs control group.

DB = double-blind; R = prospectively randomized.

the individual risk of pericardial hemorrhage. Anticoagulation has been recommended for patients with AF after cardiac procedures when the arrhythmia is persistent or when there is associated valvular heart disease or impaired left ventricular function [14, 15].

Electrical cardioversion is indicated whenever AF is associated with hemodynamic deterioration. Some forms of atrial flutter (atrial flutter rate, $\approx < 340/\text{min}$) can be converted to sinus rhythm with overdrive atrial pacing. There is no consensus regarding when antiarrhythmic drug therapy should be started for postoperative AF. Procainamide, amiodarone, and propafenone are effective for these purposes, but only the former two drugs are available in parental formulations in the United States [49-54]. There are little data that have compared the safety and efficacy of each of these antiarrhythmic drugs in cardiac surgical patients. In a small prospectively randomized trial, amiodarone and propafenone were equally effective in converting AF developing after CABG to sinus rhythm [54]. Conversion was more delayed with amiodarone (19% at 1 hour versus 83% at 24 hours), but control of ventricular rate was observed within 10 minutes. The use of sotalol for treatment of postoperative AF has also been reported, but a parental form of this drug is not available in the U.S. and its use was associated with a high frequency of hypotension [55]. Ibutilide is a pure class III antiarrhythmic agent (prolongation of repolarization) that received Food and Drug Administration approval in 1996. The efficacy of ibutilide for converting AF has been demonstrated, but these data were derived from clinical trials that did not include cardiac surgical patients [56]. Although intravenous ibutilide has a rapid onset of action and is hemodynamically well tolerated, a concern with its use was the high rate of polymorphic ventricular tachycardia (8% of patients receiving ibutilide).

Arrhythmia Prophylaxis

β -Blockers have been the most widely studied drugs for the prevention of postoperative AF [4, 22-25]. Separate meta-analyses have shown that the frequency of AF after cardiac operations in patients receiving β -blockers was collectively 9% to 10% compared with incidence rates of

20% to 34% for placebo-treated patients ($p < 0.01$) (Table 1) [22, 23]. These studies have limitations: the data is 10 to 15 years old, the patients were mostly men, had normal or mildly impaired left ventricular function, and few patients had diabetes [22, 23]. There are also limitations inherent with meta-analysis such as publication bias where small negative studies are less likely to be published than similar sized positive studies (ie, the studies used for this type of retrospective analysis) [57]. Interpretation of these investigations must also consider the inconsistent methods of arrhythmia monitoring and the inconsistent management of patients whom were receiving β -blockers before operation in these trials. That is, some patients receiving placebo postoperatively were subjected to β -blocker withdrawal [22, 23]. Failure to restart β -blockers after CABG has been shown to be associated with a greater than twofold higher rate of postoperative AF [58].

Other pharmacologic approaches evaluated for the prevention of postoperative AF are listed in Table 1. Digoxin and verapamil are no more effective than placebo (Table 1) [22]. A nonblinded, single center study showed that diltiazem when given for 24 hours after operation reduced the frequency of AF [59, 60]. In light of experimental data suggesting that calcium channel blockers promote the development of AF, further investigations of the efficacy of diltiazem seem warranted [61]. Small trials have produced inconsistent results on the efficacy of procainamide in preventing postoperative AF and propafenone was found to be no more effective than atenolol for AF prophylaxis [62-64].

Sotalol and amiodarone possess both membrane-stabilizing properties (class III effects) and β -blocking properties that make them appealing for AF prophylaxis. Sotalol has been shown to be effective for this use (Table 2) [9, 25, 65-67]. Many of these trials, however, had open-labeled, nonblinded study design and the methods of monitoring the electrocardiogram were inconsistent. Furthermore, the management after operation for patients receiving preoperative β -blocker therapy was not always clearly defined [9, 25, 65-67]. Finally, in some of

Table 2. Clinical Investigations of Sotalol for the Prevention of Atrial Fibrillation After Cardiac Surgery

Trial	n	Drug/Dose	ECG Monitoring	Incidence of Atrial Fibrillation
Jansen et al [65]	131	Metoprolol: 0.1 mg/kg IV then 50 mg TID, PO Sotalol: 0.3 mg/kg IV; 80 mg TID, PO Controls: routine care	Telemetry ECG for 48 h then 12 lead ECG TID.	Metoprolol: 15.3% ^a Sotalol: 2.4% ^{a,b} Controls: 36%
Suttorp et al [25]	429	Sotalol: 40 mg TID, PO Sotalol: 80 mg TID, PO Propranolol: 10 mg QID, PO Propranolol: 20 mg QID, PO	Telemetry ECG for 60 h then 12 lead ECG with symptoms	Sotalol 40 mg: 13.9% Sotalol 80 mg: 10.9% Propranolol 10 mg: 18.8% Propranolol 20 mg: 13.7%
Nystrom et al [66]	101	Sotalol: 160 mg BID, PO Controls: half-dose of preoperative β -blocker	Telemetry for 48 h; daily 12 lead ECG's	Sotalol: 10% ^a Controls: 29%
Suttorp et al [67]	300	Sotalol: 40 mg QID, PO Controls: Placebo	Telemetry for 60 h; 12 lead ECG with symptoms	Sotalol: 16% ^a Controls: 33%
Weber et al [9]	114	Sotalol: 80 mg BID, PO Controls: Placebo	Telemetry 24 h; 12 lead ECG with symptoms	Sotalol: 26% ^a Controls: 44%

^a $p < 0.05$ vs controls. ^b $p < 0.05$ vs β -adrenergic blocking drug.
 BID = 2 times a day; PO = orally; QID = 4 times a day; TID = 3 times a day.

the trials the frequency of postoperative AF was no different between patients receiving sotalol versus a β -blocker, questioning whether any prophylactic effect of sotalol was as a result of the membrane-stabilizing effects or β -blocking properties of the drug [25].

Early data on the efficacy of amiodarone for the prevention of postoperative AF have been inconsistent (Table 3) [68, 69]. Daoud and colleagues [70], however, found that amiodarone therapy beginning 1 week before cardiac operation and continued until hospital discharge reduced the incidence of AF compared with placebo (25% versus 53%, $p = 0.003$). The management of postoperative β -blockers for the 30% of placebo patients receiving these drugs preoperatively is not clear. In the placebo group, postoperative AF was more frequent for patients receiving preoperative β -blockers compared with patients not receiving these drugs before operation (61% versus 33%, $p = 0.09$). In the amiodarone group, the frequency of postoperative AF for patients receiving preoperative β -blockers was 27%.

Potential Antiarrhythmic Toxicity

The risk/benefit ratio for administering drugs for AF prophylaxis is different than for arrhythmia treatment

because most patients either do not develop the arrhythmia or it is transient and of little consequence. β -Blockers are usually well tolerated but clinically important side effects requiring discontinuation of sotalol were reported in 13% of patients after cardiac operation [9, 25]. Toxicity (pulmonary fibrosis, worsening of heart failure, hypothyroidism, and hepatic toxicity) occurs in 5% to 10% of patients receiving chronic amiodarone therapy, but the lower doses and shorter duration of treatment for perioperative arrhythmia control is better tolerated [71-74]. In a small series, preoperative low-dose amiodarone (mean dose, 205 ± 70 mg/day) treatment did not increase the risk of pulmonary toxicity but it was associated with a higher need for inotropic support after cardiac operation [73]. Proarrhythmic side effects of antiarrhythmic drugs is a bigger concern. In nonsurgical patients, there is a threefold increased risk for life-threatening ventricular arrhythmias with class I antiarrhythmics [75]. The proarrhythmic risk associated with sotalol and amiodarone is believed to be less but these life-threatening side effects have been reported in 4.3% to 5.9% of patients receiving sotalol after myocardial infarction and from less than 1% to 2% for patients receiving amiodarone [76, 77]. Data regarding the safety of sotalol and amiodarone for the prevention of postoperative AF from adequately

Table 3. Clinical Investigations of Amiodarone for the Prevention of Atrial Fibrillation After Cardiac Surgery

Trial	n	Dose	ECG Monitoring	Incidence of Atrial Fibrillation
Hohnloser et al [68]	77	300 mg over 2 h after surgery; 1.2 gm/24 h \times 2 days; 900 mg/24 h \times 2 days	Holter for 48 h then 12 lead ECG with symptoms	Amiodarone: 5% ^a Control: 21%
Butler et al [69]	12	15 mg/kg after cross-clamp is removed; 200 mg TID \times 5 days, PO	Holter \times 6 days	Amiodarone: 10% ^b Controls: 20%
Daoud et al [70]	12	200 mg TID, PO for 7 days before surgery; 200 mg PO daily after surgery until discharge	Telemetry \times 7 days	Amiodarone: 23% & 25% ^a Controls: 42% & 53%

^a $p < 0.05$ vs control. ^b $p =$ no significance vs control. ^c Frequency of atrial fibrillation during hospitalization and combined for hospitalization and after discharge, respectively.
 PO = orally; TID = 3 times a day.

powered studies are not available, especially for patients at high risk for proarrhythmia (eg, impaired ventricular function or myocardial ischemia) [76, 77].

Atrial Fibrillation Prophylaxis and Patient Outcomes

Patients most susceptible to postoperative AF often have other characteristics associated with surgical complications and longer hospitalization (ie, the elderly, patients with chronic lung disease, peripheral vascular disease, prolonged aortic cross-clamp time). A possibility exist that in some situations AF is merely a marker and not necessarily the cause for other morbidity and higher hospital cost. Few investigators have examined whether drug prophylaxis for AF improves outcomes. Kowey and colleagues [4] found that acebutolol and digitalis led to a lower frequency of AF compared with digitalis alone, but this treatment did not lead to shorter duration of hospitalization or reduced cost of cardiac operation. The data of Daoud and associates [70] reiterates that patients with AF have longer hospitalization and higher hospital cost, but whether prophylactic amiodarone therapy positively improved patient outcomes was not clearly demonstrated.

Other and Developing Treatments

Total and ionized serum magnesium concentrations are reduced by cardiopulmonary bypass [78]. Although hypomagnesemia may be related to supraventricular arrhythmias after cardiac operation, it is not clear whether magnesium replacement reduces this risk [71-81]. Cardiopulmonary bypass also results in an euthyroid sick state [82]. Preliminary trials in patients with reduced left ventricular function undergoing CABG and receiving thyroid hormone to improve cardiac performance found a lower incidence of AF in patients receiving triiodothyronine compared with controls [83].

Pharmacologic prolongation of atrial repolarization (class III effect) is an effective antifibrillatory strategy. Several new class III antiarrhythmic agents lacking autonomic blocking properties and other toxicity of sotalol and amiodarone are under development and these compounds may have eventual usefulness for patients undergoing cardiac operations. As a class, these drugs prolong repolarization, refractoriness, increase ventricular fibrillation threshold, and slow the rate of ventricular tachycardia [84]. For the most part, pure class III compounds do not have negative inotropic effects but they do have proarrhythmic potential [84]. These agents have actions on different membrane currents such as specific blockade of the delayed rectifier potassium current (eg, dofetilide, sotalolol, *d*-sotalolol), augmentation of the inactivated sodium channel (eg, ibutilide), or semiselective blockade of the slow component of the delayed rectifier potassium current (eg, azimilide) [84-86]. Clinical trials in nonsurgical patients using ibutilide and dofetilide have reported conversion rates of more than 30% for atrial fibrillation and more than 50% for atrial flutter of relatively recent onset [56, 87].

Concerns about drug proarrhythmic side effects have sparked interest in developing nonpharmacologic treat-

ments for AF. Overdrive atrial pacing can reduce the frequency of AF in patients with sick sinus syndrome but its efficacy after CABG has not been confirmed [88]. Pacing the right and left atrium simultaneously (dual site pacing) reduces the recurrence of AF in nonsurgical patients with intraatrial conduction abnormalities possibly by reducing dispersion of refractoriness [89]. A randomized study in patients undergoing CABG found a trend for a lower frequency of AF in patient having biatrial pacing, especially for patients receiving β -blockers [90].

Implantable automatic atrial defibrillator systems similar to those used to terminate ventricular arrhythmias are under investigation for nonsurgical patients with recurring AF but energy levels needed for successful atrial cardioversion (≈ 1 to 5 J) are associated with discomfort [91]. Innovations in electrode configurations and energy delivery characteristics result in lowered atrial defibrillation thresholds to levels that are tolerable [92, 93]. The feasibility of low-energy cardioversion of AF with temporary epicardial wire electrodes after cardiac operations has been demonstrated [94]. This latter report and other data from earlier trials in nonsurgical patients with AF suggest that, with further advances, temporary automatic atrial defibrillator/pacing systems using temporary epicardial leads could conceivably be developed for the treatment of postoperative AF. This approach could lead to early termination of postoperative AF, lowering the risk of thromboembolism, as well as allowing for early pharmacologic therapy.

Conclusions

Postoperative AF is a frequent complication of cardiac operations that increases health care resource utilization and is associated with other serious adverse events. Treatment AF is aimed at ventricular rate control, anticoagulation, and restoration of sinus rhythm. At present there is a lack of consensus regarding routine prophylaxis for this arrhythmia other than resuming β -blocker therapy early after operation and, possibly starting β -blockers in other patients who may tolerate these drugs [14, 15]. Perhaps, in the future, nonpharmacologic methods of either AF prevention or early, automatic cardioversion will contribute to improved treatment or prevention of this arrhythmia.

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