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Review

Amiodarone for Atrial Fibrillation Following Cardiac Surgery: Development of Clinical Practice Guidelines at a University Hospital

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Summary

Atrial fibrillation (AF) usually develops within the first 72 h following cardiac surgery, and is often self-limiting. Within 48 h of acute onset of symptoms, approximately 50% of patients spontaneously convert to normal sinus rhythm. Thus, the relative risks and benefits of therapy must be carefully considered. The etiology of AF following cardiac surgery is similar to that in non-surgical patients except that pericardial inflammation and increased adrenergic tone play an increasingly important role. Further, AF after surgery may be associated with transient risk factors that resolve as the patient moves out from surgery, and the condition is less likely to recur compared with AF arising in other circumstances. Immediate heart rate control is important in preventing ischemia, tachycardia-induced cardiomyopathy, and left ventricular dilatation.

At our institution, amiodarone is frequently used as a first-line drug for treating AF after cardiac surgery. Inconsistent prescribing practices, variable dosage regimens, and a lack of consensus regarding the appropriate use of amiodarone prompted the need for developing practice guidelines. Multidisciplinary collaboration between the departments of cardiac surgery, pharmacy, and anesthesiology led to the development of a protocol for postoperative AF. We review the clinical evidence from published trials and discuss our guidelines, defining amiodarone use for AF in the cardiac surgery setting.

Key words: amiodarone, atrial fibrillation, rhythm, rate, cardiac surgery

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Introduction

Atrial fibrillation (AF), the most common arrhythmia following cardiac surgery, occurs in 15–40% of patients during the early postoperative period after coronary artery bypass graft (CABG) surgery, 37–50% after valve surgery, and up to 60% after a CABG plus valve procedure.[1,2] Postoperative AF increases the risk for stroke and other complications that can prolong hospitalization and increase health care costs.[2–4]

Historically, strategies to restore and maintain normal sinus rhythm have been presumed to provide better cardiovascular outcomes than regimens to control only the ventricular heart rate. Antiarrythmic drugs including quinidine, procainamide, propafenone, flecainide, ibutilide, dofetilide, sotalol, and amiodarone have comprised the mainstay of therapy. The primary concern with antiarrythmic drugs is the possibility of proarrythmic complications including ventricular arrhythmia, QT-interval prolongation, and life-threatening torsades de pointes.

Amiodarone

Amiodarone slows AV nodal conduction and prolongs AV nodal refractoriness through its calcium-channel

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blocking and beta-blocking properties. In recent years, amiodarone has been the drug most frequently used for atrial stabilization because it rarely causes pro-arrhythmic complications. In a meta-analysis of double-blind, placebo-controlled trials that included patients with underlying heart failure or myocardial infarction, there were no cases of torsade de pointes in 738 patients receiving amiodarone therapy for at least 1 year.[5] However, amiodarone is associated with noncardiac toxicity including pulmonary, hepatic, thyroid, and neurologic side-effects.[5] Intravenous (IV) administration can cause hypotension, bradycardia, and thrombophlebitis.

Prevention of AF in patients scheduled to undergo cardiac surgery is a reasonable goal, and trials have evaluated the effectiveness of prophylactic amiodarone therapy.[6,7] The largest trial in cardiac surgery patients is the Prophylactic Oral Amiodarone for the Prevention of Arrythmias that Begin Early After Revascularization, (PAPABEAR) Valve Replacement, or Repair study.[7] In this randomized, double-blind, placebo-controlled trial, 601 patients undergoing CABG surgery, valve replacement/repair, or both, were randomized to receive oral amiodarone or placebo, starting 6 days prior to surgery and continuing for 6 days postoperatively. More than half the patients in each treatment group also received preoperative beta-blockers. Amiodarone therapy was associated with a 52% relative risk reduction in AF compared with placebo (16.1% versus 29.5%; $p<0.001$), and sustained postoperative ventricular tachyarrythmias occurred less frequently with amiodarone than placebo (0.3% versus 2.6%; $p = 0.04$). While prophylactic amiodarone has been shown to be effective, its advantage over prophylactic beta-blocker therapy has not been demonstrated. A meta-analysis of 52 randomized trials of beta-blockers, sotalol, or amiodarone, showed that the three drug treatments each prevented AF with the following odds ratios (OR): beta-blockers, 0.39 (95% CI, 0.28 to 0.52); sotalol, 0.35 (95% CI, 0.26 to 0.49); and amiodarone, 0.48 (95% CI, 0.37 to 0.61).[8] Thus, the three drugs appear to have similar efficacy for preventing AF in patients undergoing cardiac surgery.

Large-scale placebo controlled trials have not specifically focused on postoperative medical cardioversion, and well-designed trials evaluating amiodarone for treating postsurgical AF are lacking. Two randomized trials assessed the efficacy of amiodarone compared with propafenone in reversing AF after cardiac surgery.[9,10] In the first study, 84 patients with sustained AF were randomized to receive IV amiodarone or IV propafenone. Within 24 h, 38 of 46 patients (82.6%) given amiodarone and 26 of 38 patients (68.4%) given propafenone converted to sinus rhythm, the difference was not significant. Side effects were more common with propafenone treatment, although the difference did not achieve statistical significance. Mean blood pressure was not significantly influenced by either drug. In the second study,[10] forty patients undergoing cardiac surgery either received propafenone IV or amiodarone IV for treatment of post-surgical AF. Sinus rhythm was restored in 12 of 18 (67%) propafenone patients and in 17 of 22 (77%) amiodarone patients, the difference was not statistically significant.

Beta-blockers and Calcium-channel Blockers

Rate control strategies target the ventricular response without attempting to convert AF to normal sinus rhythm. Drugs for rate control have included digoxin, beta-blockers, and calcium-channel blockers. Clinical trials with digoxin are limited by lack of randomization, small sample size and postoperative withdrawal of beta-blocker therapy. The onset of action of digoxin can take from 4 to 6 h, and the drug is relatively ineffective in high catecholamine states that exist after cardiac surgery.

Beta-blockers are generally accepted as the mainstay of therapy for ventricular rate control in patients with AF. Beta-blockers prolong AV nodal conduction time, antagonize the cardiac effects of catecholamine through their sympatholytic properties, and offer additional benefits in the setting of ischemia or infarction. The drugs promote atrial stabilization, and reportedly decrease post-operative mortality.[11,12] The 2005 American College of Chest Physicians guidelines for the Prevention and Management of Postoperative Atrial Fibrillation after Cardiac Surgery recommends beta-blockers as first-line therapy for patients with AF who do not require urgent cardioversion.[13]

Many patients with coronary artery disease receive beta-blockers preoperatively, and their withdrawal has been shown to increase the risk of postoperative AF,[12,13] emphasizing the need to continue beta-blocker therapy postoperatively. One randomized, controlled trial compared the efficacy of esmolol with that of diltiazem in the management of 30 patients with postoperative AF following cardiac surgery.[14] Esmolol was as effective as diltiazem for ventricular rate control at 24 h in patients who did not convert to sinus rhythm. Limitations of the study include the small sample size and differences in ancillary medications between the groups. The largest trial evaluating the effectiveness of beta-blocker therapy in postoperative AF is the Beta-Blocker Length of Stay (BLOS) study.[15] In this double-blind, placebo-controlled randomized trial of 1,000 patients undergoing cardiac surgery, metoprolol was associated with a 20% relative risk reduction in AF (31% versus 39%; $p = 0.01$).

Among calcium-channel blockers, both verapamil and diltiazem are effective for heart rate control in patients with AF. The drugs prolong AV nodal refractory period and slow AV nodal conduction through blockade of the L-type calcium channel. Concerns with verapamil relate to the drug's negative inotropic effect, especially in patients with left ventricular dysfunction. In addition, verapamil is a potent peripheral vasodilator that may produce severe hypotension when given IV. In comparison,

diltiazem has little peripheral vasodilating effects, less negative inotropic effects, and causes less hypotension than verapamil. In a large study evaluating the efficacy and safety of IV diltiazem for AF, the overall response rate was 94% with a maximal decrease in heart rate observed at 4.3 min from the start of infusion.[16] There were no cases of symptomatic hypotension, and the mean decrease in systolic blood pressure was 8 mmHg.

Beta-blocker versus Calcium-channel Blockers

Well-designed randomized trials comparing calcium-channel blockers with beta-blocker therapy for postsurgical AF are lacking. Findings from available studies are difficult to interpret because of different study designs and exclusion of patients with congestive heart failure, decreased left ventricular function and conduction abnormalities.

One randomized placebo-controlled trial comparing diltiazem and propranolol showed that diltiazem was not effective while propranolol was associated with a significant reduction in AF following CABG surgery.[17] Mooss et al.[14] conducted a prospective, open-label, randomized study of IV esmolol versus IV diltiazem in patients with postoperative AF. The findings showed a higher rate of conversion of AF at 6 h with esmolol, but there was no difference in conversion rates at 24 h. This study is marked by limitations, notably 50% of patients in the diltiazem group had their beta-blocker therapy discontinued.

Rate versus Rhythm Control in Light of New Evidence

There is limited data supporting a strategy for rhythm control versus rate control in the postcardiac surgery patient. Large randomized trials have primarily included patients with persistent AF in the nonsurgical setting.

In the Pharmacological Intervention in Atrial Fibrillation (PIAF) trial, 252 patients with persistent symptomatic AF of 7–360 days' duration were randomized to rate control using oral diltiazem or rhythm control with oral amiodarone.[18] Both groups showed symptomatic improvement over time and the quality of life scores were similar. Rhythm control patients however, required more hospitalizations related to drug side effects (69% versus 24%; $p = 0.001$).

The largest randomized trial that tested rate versus rhythm control in patients with AF is the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial.[19] The study included 4,060 patients with persistent AF who were at least 65 years of age, or who had at least one risk factor for stroke or death. The mean follow-up time was 3.5 years with a maximum of 6 years. Patients were randomized to rate control using oral digoxin, beta-blocker, and/or calcium-channel blockers, anticoagulation with warfarin; or to rhythm control therapy. The most frequently used antiarrythmic drugs were amiodarone and sotalol; warfarin use was left to the discretion of the investigator. Rate control was achieved in 80% of patients receiving rate control while in the rhythm control arm 60% of patients achieved sinus rhythm; neither strategy was found superior in the primary outcome of total mortality or in the secondary composite end point of total mortality, stroke, major bleeding, or cardiac arrest. After adjustment for variables such as age and ejection fraction, the risk of adverse drug effects and death was significantly lower in the rate control group. The incidence of ischemic strokes was similar between the groups and strongly related to the lack of or subtherapeutic anticoagulation, highlighting the need for continued and adequate anticoagulation regardless of the strategy used. Quality of life scores were also similar in both groups. Thus, the presumed benefits of rhythm control over rate control strategies were not confirmed in the study.

Thus, randomized trials comparing rate with rhythm control strategies have shown no distinct advantage to either strategy in various primary endpoints, which ranged from cardiovascular events and quality of life to total mortality. Complications related to arrythmia, discontinuation of therapy, or hospitalization secondary to drug toxicity occurred more often with rhythm control. A recently published meta-analysis of AF trials shows significant risk reduction for the combined endpoint of all cause death and thromboembolic stroke with rate-control versus rhythm-control ($p = 0.02$).[20]

It is important to note that randomized trials showing lack of advantage of rhythm versus rate control were conducted outside the setting of recent heart surgery, and primarily included patients with persistent AF in whom long-term treatment was warranted. The AF that develops after cardiac surgery is often self-limiting, associated with transient risk factors that resolve as the patient moves out from surgery, and less likely to recur compared with AF arising in other circumstances. Given the high spontaneous conversion rate, patients may revert to sinus rhythm simply with heart rate control and observation. Thus, the decision of rate versus rhythm control needs to be determined for each patient based on individual characteristics.

University of Michigan Clinical Practice Guidelines

Figure 1 summarizes our proposed guidelines for managing AF following cardiac surgery. The protocol has two pathways based on the presenting heart rate. We recommended rate control with beta-blockers as first-line therapy. Recently published guidelines by the American College of Chest Physicians for the Prevention and

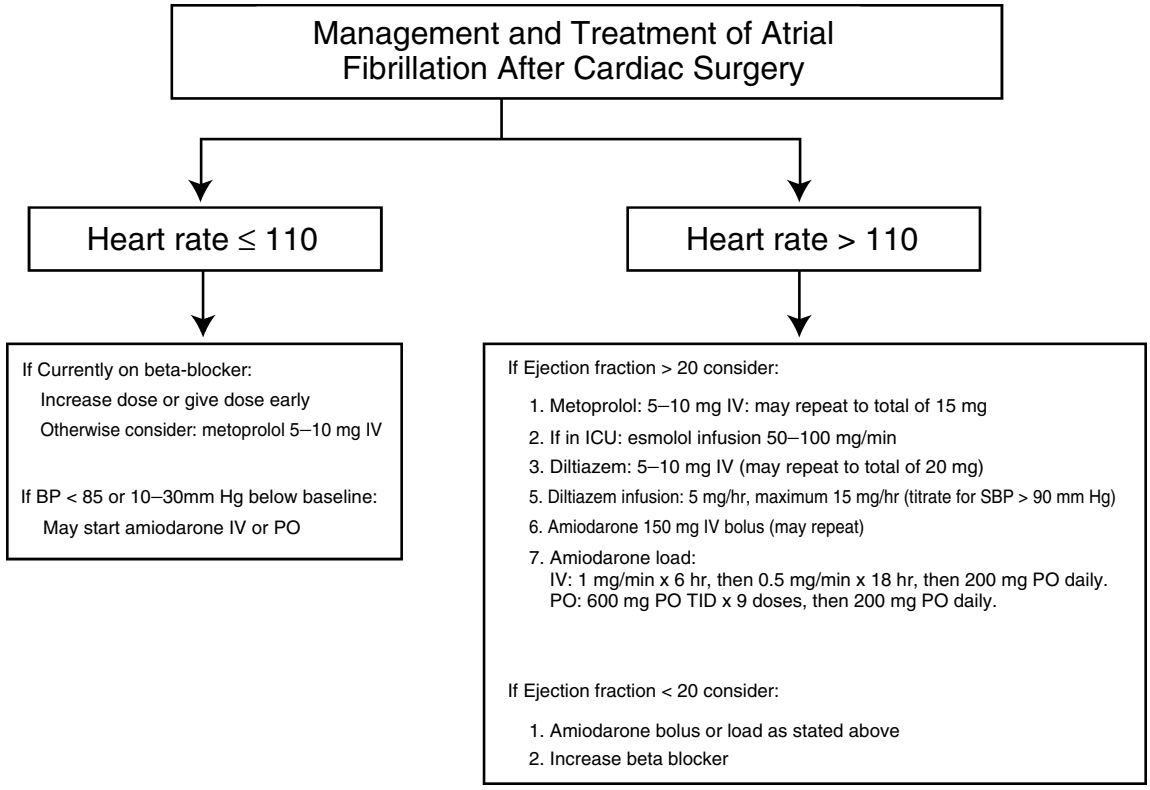

FIG. 1 Management and treatment of atrial fibrillation after cardiac surgery. BP = blood pressure; IV = intravenous; PO = oral; TID = 3times daily; SBP = systolic blood pressure; ICU = intensive care unit.

Management of Postoperative AF after cardiac surgery, supports this decision.[13,21,22] Beta-blockers remain a good initial choice because of their ability to counteract the hyperadrenergic state after surgery. We recommended calcium-channel blockers as second-line agents, reserving amiodarone for unstable or recalcitrant AF. For immediate rate control in hemodynamically stable patients, we recommended IV metoprolol, converting to the oral route as soon as possible. In the intensive care unit, an esmolol infusion could be started and titrated closely. Patients previously maintained on beta-blockers were to continue with the therapy after surgery. Among calcium-channel blockers, we selected diltiazem as the preferred drug because of its more favorable hemodynamic properties. After an IV bolus of diltiazem, reduction in ventricular response occurs rapidly. If necessary, a continuous infusion of diltiazem could be started, dosages are shown in Figure 1. Patients refractory to monotherapy with metoprolol or diltiazem could receive both drugs concomitantly.

For patients with recalcitrant AF, we recommended treatment with amiodarone. Amiodarone could be initiated IV for patients unable to take oral therapy, and transitioned to the oral route when tolerated. For patients able to tolerate oral therapy, oral loading of amiodarone may restore sinus rhythm and continued therapy is effective for maintaining sinus rhythm. Amiodarone was also the preferred therapy for patients with AF who were hemodynamically stable but had low blood pressure, based on evidence showing its safety in this situation.[9,23] The IV beta-blockers or calcium-channel blockers in such patients can cause further hypotension. For patients with depressed left ventricular function and those with ejection fraction < 20%, amiodarone was recommended as first-line therapy based on its lack of negative inotropic effects and low proarrythmia potential.[24] Although some clinicians recommend against the use of beta-blockers in patients with low ejection fractions it must be noted, however, that the drugs have provided survival benefit in nonsurgical patients with heart failure.[13]

Conclusions

The proarrythmic potential of antiarrythmic drugs is critical in the setting of open heart surgery, highlighting the need for individualization of therapy. Multidisciplinary collaboration between the departments of cardiac surgery, pharmacy, and anesthesiology led to the development of practice guidelines for managing AF after cardiac surgery. The guidelines emphasized rate control first with beta-blockers, then calcium-channel blockers, reserving amiodarone for unstable or recalcitrant AF. In patients with relatively low blood pressure, depressed left ventricular function, or ejection fraction less than

20%, we recommended the use amiodarone as the first-line therapy. As new information, new drugs, and results from new studies become available, we plan to update our current guidelines.

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