



## Age as a Risk factor for Atrial Fibrillation and Flutter after Coronary Artery Bypass Grafting

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### Introduction

Atrial fibrillation affects approximately 3 million people in the United States and creates a huge burden on the health care system, both in terms of morbidity, mortality, and cost.<sup>1</sup> The prevalence of atrial fibrillation rises sharply with increases in age. It is estimated that 8% of people above 70 years of age have atrial fibrillation.<sup>2-4</sup> Atrial fibrillation has long been recognized as a powerful risk factor for stroke,<sup>5</sup> heart failure,<sup>6</sup> and mortality.<sup>7</sup> Advancing age amplifies the risk of all of these sequelae of atrial fibrillation.<sup>8</sup>

As a subset, post-operative atrial fibrillation (POAF) after cardiac surgery is a common entity that is associated with significant morbidity and increased long-term mortality.<sup>9-11</sup> POAF in the setting of coronary artery bypass graft surgery CABG has been associated with increases in health care costs estimated around \$10000 per patient affected.<sup>12</sup> Procedural risk factors of post-operative AF include valve surgery, pulmonary vein venting, bicaval venous cannulation, and longer cross-clamp times.<sup>10</sup> Patient risk factors for POAF include male gender, renal dysfunction, congestive heart failure, and left atrial enlargement,<sup>10</sup> the most powerful predictor, however, remains age.<sup>13</sup> <sup>14</sup> As the number of elderly patients undergoing surgery increases, there has been more interest in

investigating the predictors and sequelae of post-operative atrial fibrillation. The search for cost-effective, efficacious, and safe preventive therapies in high-risk patients is increasingly important.

### *Pathophysiology*

Post-operative atrial fibrillation typically occurs<sup>48-72</sup> post-operatively and is, in large part, driven by the systemic pro-inflammatory state that follows surgery.<sup>15</sup> 70% of POAF occurs by post-operative day 4, and 95% occurs by post-operative day 6.<sup>12</sup> Direct atrial irritation from surgical manipulation pericardiotomy, atriotomy of the heart during cardiac surgery makes POAF far more common in the cardiac surgery population than in the non-cardiac surgery population. Large volume shifts that occur in the peri-operative period create atrial stretch and changes in autonomic tone, which can also increase the propensity for atrial fibrillation. Other elements of the post-operative state, including pain, further contribute to a catecholamine surge that alters atrial electrophysiologic properties i.e. shortened refractory period and promotes the development of atrial fibrillation. Continuous ambulatory monitoring with serial blood testing performed in patients after CABG showed increases in sinus rate, ectopic atrial beats, and right atrial plasma norepinephrine levels in patients developing POAF.<sup>16</sup> Age has consistently been shown to be a risk fac-

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tor for the development of POAF in patients undergoing cardiac surgery, as well as non-cardiac surgery.<sup>17, 18</sup> The biologic basis for why age is a risk factor for post-operative atrial fibrillation is multi-factorial. First, the elderly patient is much more likely to have accumulated more of the traditional risk factors for developing atrial fibrillation. Given that these risk factors interact, and therefore compound risk in a synergistic manner, adjusting for these various co-morbidities individually does not entirely account for the age effect. It was previously believed that atrial fibrosis increased with age and played a major role in the development of AF, including POAF. Recent data, however, contradict this finding.<sup>19</sup> There remain a number of other mechanisms by which aging predisposes to atrial fibrillation. As the left ventricle becomes less compliant with age, the left atrium dilates, creating a more favorable substrate for atrial fibrillation.<sup>20, 21</sup> The less compliant atria of elderly patients will also tend to generate higher filling pressures in response to volume load; these elevated filling pressures, in turn, contribute to atrial stretch, which increases the propensity for atrial fibrillation.<sup>22-24</sup> Corroborating this pathophysiology is a recent study that showed a strong correlation between diastolic dysfunction and the incidence of POAF following CABG.<sup>25</sup> Finally, sinus node dysfunction, which is much more common with advanced age, can promote pauses which allow for greater dispersion of atrial tissue and facilitate the development of atrial fibrillation.

### Epidemiology

Atrial fibrillation is a very common dysrhythmia in the setting of cardiac surgery. Valve surgery has been shown to proffer higher risk than bypass surgery.<sup>18</sup> The overall incidence of atrial fibrillation is approximately 30% after isolated CABG, 40% after valve surgery, and 50% after combined valve and bypass procedures.<sup>26, 27</sup> Published rates of POAF following cardiac surgery vary widely, due to major methodological differences in how the dysrhythmia is detected. Important recognized risk factors for POAF after cardiac surgery include previous history of atrial fibrillation, Caucasian race, male gender, heart failure, renal insufficiency, and diabetes.<sup>10, 12, 18, 28, 29</sup> The most consistent and powerful risk factor is, however, age.<sup>10, 13, 14, 30, 31</sup> Shah et al studied a cohort of elderly patients 75 and older undergoing valve and/or bypass surgeries and found that a very high percentage of

47% developed POAF.<sup>32</sup> Atrial flutter (AFL) is far less common than AF following cardiac surgery, with an incidence of about 5%; patients developing AFL are younger and less likely to have had valve surgery. Further, patients with atrial flutter are less likely to have dysrhythmias recur after restoration of sinus rhythm.<sup>33</sup>

In quantifying the effect of age on POAF risk post-CABG, Aranki et al showed an Odds Ratio of 2.0 for age 70-80 and Odds Ratio of 3.0 for age greater than 80 when compared to the overall cohort.<sup>12</sup> Mathew et al demonstrated an Odds Ratio of 1.7 for every 10-year increase in age.<sup>18</sup> An analysis of a cohort comprised entirely of patients 65 and older found that advancing age along with renal insufficiency remained one of the key risk factors for AF following CABG.<sup>34</sup>

### Consequences

Mounting evidence shows that atrial fibrillation portends a worse prognosis, even in those who are otherwise healthy.<sup>7</sup> POAF following cardiac surgery has been associated with a broad spectrum of worse outcomes including a higher risk of mortality. Elderly patients developing POAF tend to have more prolonged and clinically significant dysrhythmia than their younger counterparts.<sup>35</sup> Villareal et al showed that POAF after CABG was associated with an Odds Ratio of 1.7 for in-hospital mortality and a 13% increase in 5-year mortality in their case-matched analysis.<sup>36</sup> Additionally, POAF after CABG has been shown to be associated with neurocognitive decline.<sup>9, 18</sup> Though the association between POAF and stroke is less well established, Hogue et al demonstrated an association between POAF and significantly increased stroke risk when it is accompanied by a low cardiac output state.<sup>37</sup> In another cohort of elderly patients undergoing cardiac surgery, there was a trend toward more stroke in the patients who developed POAF.<sup>32</sup> In quantifying the effect of POAF on the usage of health care resources, Aranki et al showed that POAF was associated with a 4.9 day lengthening of hospital stay and a \$10000 increase in hospitalization costs.<sup>12</sup> Older studies with short-term follow-up had made the argument that POAF, at least in the paroxysmal form, is a self-limited disease, with 98% of affected individuals achieving restoration of normal sinus rhythm at 6 weeks post-op.<sup>38</sup> However, among a cohort of 571 patients

with a median follow-up of 6 years with no prior history of atrial fibrillation, the development of POAF portended an 8-fold increase in the risk of developing long-term atrial fibrillation in addition to a doubled long-term cardiovascular mortality.<sup>39</sup> This data reinforces the notion that patients, particularly the elderly, who develop POAF following cardiac surgery need close long-term monitoring. Atrial flutter tends to occur in younger patients and patients not undergoing valve surgery. The recurrence rate after conversion to sinus rhythm is quite low and less than one-third of patients require long-term anti-arrhythmic drugs.<sup>33</sup>

### Prevention

A cornerstone of POAF prevention is optimization of medical therapy in the preoperative setting. This includes ensuring that patients undergoing elective surgery have their volume status optimized and are on appropriate medical therapy for their coronary artery disease and heart failure. A number of strategies and pharmacologic agents have been studied specifically for the purpose of preventing POAF in patients undergoing cardiac surgery. There is equipoise surrounding the efficacy of overdrive atrial pacing in preventing POAF. Blommaert et al showed increased efficacy of atrial pacing in elderly patients, though other studies call into question those findings and even suggest a pro-arrhythmic effect of atrial pacing.<sup>40-42</sup> Agents that have beta-blocker properties Vaughan-Williams class II anti-arrhythmics have consistently been shown to be efficacious in preventing POAF. The guidelines suggest the use of beta-blocker medications in cardiac surgery patients in whom POAF prophylaxis is indicated class IA recommendation.<sup>43</sup> Importantly, peri-operative withdrawal of beta-blocker in patients on chronic therapy has been shown to be deleterious.<sup>44</sup> Of note, beta-blockers have been shown to be less effective in POAF prophylaxis in elderly patients<sup>13</sup> underscoring the need for other preventative therapies/strategies in that population. The routine use of amiodarone in high-risk patients has garnered a great deal of interest as the result of several randomized trials that demonstrated clinical benefit and cost-effectiveness.<sup>45, 46</sup> The PAPABEAR trial demonstrated efficacy of amiodarone across many subgroups, including those patients also taking conventional beta-blockers; in patients aged 65 and older, amiodarone reduced the incidence of POAF from 41% to 22%.<sup>47</sup> The AFIST trial demonstrated efficacy of

an oral pre-operative amiodarone load in reducing POAF and lowering stroke risk.<sup>48</sup> Statin medications have also shown promise as anti-arrhythmic agents in the peri-operative period; one randomized controlled trial has shown a significant decrease in POAF in cardiac surgery with the administration of high dose statin.<sup>49</sup> Other agents with more significant short term toxicities, specifically NSAIDs and steroids have shown benefit with regard to post-operative arrhythmia<sup>50, 51</sup>; however, their tendency to promote post-operative bleeding and retard wound healing make them unattractive agents for use in the peri-operative period. These toxicities are likely to be more common and more consequential in the elderly patient, though this has not been clearly elucidated. Interestingly, in a recent clinical trial, colchicine showed promise as a prophylactic agent, though those findings require corroboration.<sup>52</sup> To synthesize this data with regard to the care of elderly patients, any patient over the age of 65 should be considered at high risk for POAF, whether or not they carry a pre-existing diagnosis of atrial fibrillation. There is evidence that beta-blockers are less effective for POAF prevention in the elderly population. As such, it may be reasonable to treat all patients in this age category without contraindications with amiodarone and beta-blockers. Other adjunct preventative therapies, such as the administration of peri-operative statin medications, can be considered. Peri-operative use of calcium-channel blockers and digoxin is not recommended for POAF prevention.<sup>43</sup>

### Treatment

The cornerstones for the therapy of POAF in the elderly patient are philosophically the same as for any patient. Atrial fibrillation that causes congestive heart failure, coronary ischemia, or hemodynamic compromise requires immediate cardioversion. Stable POAF requires control of the ventricular rate using AV nodal blocking agents.<sup>53</sup> Thromboembolism prophylaxis is indicated for patients who develop POAF lasting for more than 24-48 hours.<sup>54, 55</sup> In the setting of recent cardiac surgery, however, the benefit in preventing stroke must be carefully weighed against the risk of significant bleeding. After cardio-pulmonary bypass, hemostatic mechanisms are altered and the propensity to bleed is higher. The elderly patient, on average, is at higher risk for

bleeding and is less likely to tolerate bleeding. In any patients who develop atrial fibrillation, age is a key predictor of stroke risk,<sup>5,56</sup> and there is a significant treatment-age interaction. With both warfarin and dabigatran, anti-coagulation comes with a higher risk of bleeding in the elderly patient.<sup>57,58</sup> With dabigatran, as compared with warfarin, extra-cranial bleeding is increased in patients older than 75, though the risk for intracranial bleeding is attenuated. While warfarin has been used extensively after cardiac surgery valve surgery in particular, the use of dabigatran in the post-operative setting is unproven and the lack of a reversal agent should signal caution. Newer oral factor Xa inhibitors, which have the potential for more immediate reversibility,<sup>59</sup> may be more appropriate to be studied for safety and efficacy in this clinical scenario. Patients who are considered to be at prohibitively high risk for anti-coagulation should receive full-dose aspirin.

With regard to rate and rhythm control, anti-arrhythmic drugs and AV nodal blocking agents may be less well tolerated in elderly patients. Given the higher incidence of sinus node dysfunction in elderly patients, administration of these classes of medications may manifest as a tachycardia-bradycardia syndrome. The general rule that the toxicities of medications are amplified in elderly should be minded.

In higher risk patients, including the elderly, it may be reasonable to take more aggressive surgical approaches to the prevention of POAF and hence long-term AF, such as concomitant surgical pulmonary vein isolation or ventral cardiac denervation at the time of bypass or valve surgery.<sup>60,61</sup> Such combined procedures for rhythm control need to be evaluated more thoroughly in clinical trials before they can be recommended for routine use. In those patients developing new onset POAF after CABG, restoring sinus rhythm prior to discharge and using anti-arrhythmic drugs for 1 week seems to provide excellent clinical results.<sup>62</sup> Guidelines support the use of therapeutic anti-coagulation for 1 month after the reversion to sinus rhythm.<sup>55</sup>

## Conclusions

POAF is a common and impactful rhythm disturbance after cardiac surgery. With increasing

age, the incidence of POAF after cardiac surgery increases sharply. The consequences of POAF include increased morbidity, mortality, and health care expenditure; these sequelae are magnified in elderly patients. Strategies to prevent POAF are needed, and available means for prophylaxis should be utilized, particularly in the elderly, who represent a high-risk population. Preventative pharmacologic interventions, such as peri-operative beta-blockers and amiodarone, and careful management of volume status, should be considered. Sinus rhythm should be restored prior to discharge and close short-term follow-up to titrate anti-arrhythmic drug and the period of anti-coagulation and long-term follow-up to monitor for late recurrence of atrial fibrillation should be instated. Newer surgical techniques, including minimally invasive bypass approaches and combined pulmonary vein isolation procedures, and alternative anti-coagulant regimens need to be prospectively evaluated for safety and efficacy in elderly patients.

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