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New-onset postoperative atrial fibrillation after heart surgery

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Abstract

Background: New onset post-operative atrial fibrillation (poAF) complicates approximately 20–60% of all cardiac surgical procedures and is associated with an increased periprocedural mortality and morbitity, prolonged hospital stay, increased costs and worse long-term survival. Unfortunately multiple advances in surgery and perioperative care over the last two decades have not led to a reduction in the incidence of poAF or associated complications in the daily clinical practice.

Methods: A narrative review of the available literature was performed.

Results: An extensive review of the pathophysiology of poAF following cardiac surgery, clinical and procedural risk-factors is provided, as well as prophylactic measures and treatment.

Conclusion: Multiple strategies to prevent and manage poAF following heart surgery already exist. Our hope is that this review will facilitate more rigorous testing of prevention strategies, implementaion of prophylaxis regimens as well as optimal treatment of this common and serious complication.

Key Words: Postoperative atrial fibrillation, open heart surgery, risk factors, etiology, outcome, survival, review

Editorial Comment:

This systematic narrative review concerns atrial fibrillation in the specific setting of new onset in post-operative heart surgery patients. While the review does present some pathophysiology in review, it is focused on clinical risk factors, treatments, and clinical course.

Introduction

New onset atrial fibrillation (AF) following surgery, also called postoperative atrial fibrillation (poAF), is the most common complication following open heart surgery.[1,2] The true incidence of poAF following cardiac surgery remains somewhat unclear due to variability in methods of detection and definitions of poAF.[3]

PoAF is most commonly detected on the second to fourth postoperative days and is most often self-limiting and short-lived.[4] In some patients, notably in elderly patients and those with pre-existing congestive heart failure (CHF), even short episodes of poAF is linked to serious early complications, including hemodynamic instability, acute kidney injury (AKI), acute cardiac failure and stroke.[5] Furthermore, patients who experience poAF have a twofold 30-day mortality, significantly increased postoperative morbidity and higher hospital costs, mainly due to an increased length of hospital stay.[6]

This review seeks to provide an evidence-based review of the incidence and epidemiology of poAF, pathophysiology and risk factors, with a special focus on management and prophylactic therapy. The terms ”postoperative atrial fibrillation”, “cardiac surgery”, “coronary artery surgery”, “valve surgery, “incidence”, “risk factors”, "genetics", “gene expression”, “GWAS”, “pathophysiology”, "prophylaxis", "treatment", "outcome", “review” and “guidelines” were used for searches in papers published on PubMED and SCOPUS for the last 10 years. In addition, the reference lists of key articles were searched for additional content. As the review builds on available literature only no ethics approval was obtained .

Definitions and epidemiology

According to the definition of the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database, poAF is a new onset of atrial fibrillation (AF) or atrial flutter requiring treatment.[7] A more specific definition is new onset AF/flutter detected on a rhythm monitor/telemetry and/or electrocardiogram (ECG), with duration of ≥ 5 minutes and initiation of treatment for AF/flutter.[8] Of note, the rather stringent definition of poAF as an event requiring treatment likely leads to a significant underestimation of the true incidence and wider definitions have been suggested.[9]

There is a great variation in poAF incidence depending on factors such as the surgical procedures (e.g. coronary vs. valvular surgery) and the underlying patient characteristics and co-morbidities.[10] Importantly, as the incidence of poAF increases with age it is expected to present an increasing healthcare burden due to the growing population of elderly patients undergoing cardiac surgery.[11]

The majority of studies report poAF rates between 20–40% following coronary artery bypass grafting (CABG), 40–50% after valvular surgery, up to 60% following combined valvular and CABG surgery, and as high as 80% following multiple valve surgery.[3,12-15] In comparison the incidence of poAF is only 10–20% following pulmonary resections[16] and 0.14–26% for non-cardiothoracic surgery.[17]

Despite advances in cardiac surgical techniques and recommendations for the prevention of poAF, e.g. by perioperative use of oral beta-blockers[18,19] the incidence of poAF has remained unchanged over the years.[12,20] The arrhythmia usually occurs within the first five postoperative days with a peak incidence on day two (**Figure 1**).[20-23] Nearly 80% of patients convert to sinus rhythm (SR) within 24 hours, and six weeks after initial diagnosis, 98% of patients have converted to SR, most often related to spontaneous or pharmacologic conversion.[24]

Although initially regarded as a benign and self-limiting condition mounting evidence suggests that poAF may not be as harmless as previously considered. Several studies, including large meta-analyses, have found that poAF is associated with high risk of adverse outcomes in the immediate postoperative period, including; longer hospital and ICU stays, a two- to threefold risk for cerebrovascular insults and higher in-hospital mortality when compared to patients that do not develop poAF.[3,21,25-28] In addition, poAF is associated with higher hospital expenses estimated at $6,743 per patient in a study from the United States

(US).[29] Similarly, poAF is linked to long-term adverse outcomes and several reports have shown that patients with poAF have significantly increased risk for mid- and long-term mortality[26-28,30-32] and stroke.[32-34] Furthermore, it has also been demonstrated that poAF is associated with an eightfold increase in the hazard for later development of AF after CABG when compared with CABG patients who postoperatively remain in SR.[30,34]

Pathophysiology

Like many other clinical conditions, poAF is the final phenotype resulting from an interaction between an environmental trigger and a primed substrate. It is likely that although the environmental trigger initiating poAF differs from the ones initiating ambulatory non-surgery related AF, the properties of the atria that render it susceptible to the arrhythmia are at least partially shared. This is supported by the fact that the ambulatory and postoperative AF share risk factors, such as advanced age, chronic obstructive lung disease (COPD) and atrial enlargement. Additionally, the strongest genetic risk factors associated with AF are also associated with poAF.[35,36]

Several electrophysiological abnormalities that render the atria more sensitive to formation of AF also contribute to poAF. These include early depolarization during repolarization of atrial cells, caused by abnormal diastolic release of calcium from sarcoplasmic reticulum stores.[37] Furthermore, electric remodeling via differential expression of various Na^+, K^+ and Ca^{2+} ion channels can alter the electrophysical properties of the atria, thereby altering the duration and properties of the refractory period that can initiate ectopic electric firing of atrial cells or facilitate re-entry arrythmias.[37] This is supported by an association between variants in the *KCCN3* gene, that codes for a K^+ channel, and both ambulatory AF and poAF.[38] Additionally, a recent analysis of gene expression of the left atria of patients undergoing mitral valve surgery identified several K^+ channel genes with differential expression between patients who developed poAF and those who did not.[39]

Structural remodeling of the atria is important in the pathogenesis of ambulatory AF,[37,40] and this is likely additionally important for poAF. Fibroblasts introduced into the human atria during atrial fibrosis have different electrical properties than cardiomyocytes, and this generates the potential for abnormal conduction and reentry arrythmias.[41] Enhanced atrial

fibrosis is the predominant structural response to elevated left atrial pressure, most commonly found in advanced diastolic dysfunction.[40] Given that elevated left atrial pressure is present in the majority of patients undergoing cardiac surgery secondary to diastolic dysfunction, mitral regurgitation or both, there is likely increased atrial fibrosis in these patients that can predispose to poAF. This is supported by identification of the association of both microRNA and genes associated with cardiac fibrosis and poAF in surgical cohorts.[42,43]

Finally, alterations of the autonomic tone can contribute to the risk of AF and poAF. Interestingly, both increased sympathetic stimulation, via increased calcium influx generating action potential changes, as well as increased parasympathetic stimulus, via shortening of the action potential duration and refractory period, have been associated with poAF.[44] This has led to experiments where botulinum toxin is injected into epicardial fat pads during cardiac surgery to attempt to decrease the likelihood of poAF via modulation of the autonomic tone.[45] This point is also supported by the fact that the perioperative usage of beta-agonists, and acute withdrawal of beta-antagonists are both associated with poAF,[23] indicating that acute changes in baroreceptor tone can serve as environmental triggers.

Clinical risk factors

Multiple perioperative factors have been reported as possible risk factors of poAF both patient specific (e.g. age and underlying morbidity) or surgery related (e.g. inflammation and adrenergic stimulation directly related to the surgical trauma).[46]

Patient related risk factors

Age has shown a consistent relationship with increased risk of poAF. This is believed to stem from both structural and electrophysiological abnormalities (e.g. loss of myocardial fibers, increased atrial fibrosis and decreased conduction velocity) of cardiovascular tissue due to degenerative changes.[20,47] This risk increases non-linearly with age and a large retrospective study of nearly 15,000 patients that underwent cardiac surgery showed that the incidence of poAF increases at higher rates over the age of 55 years.[48]

Amongst other patient-related risk factors are a previous history of AF, as well as other cardiac disease (e.g. coronary artery disease (CAD), CHF, valvular heart disease and cardiomyopathy), COPD, hypertension, a preoperative left atrial diameter of > 4.5 cm, the Caucasian race, male gender and decreased preoperative kidney function (Table I).[4,6,20,49,50] Lastly, obesity, or more specifically, the metabolic syndrome (central obesity, abnormal cholesterol, hypertension and insulin resistance) has been shown to be an independent risk factor for poAF[51]. However, studies have shown an inconsistent relationship between diabetes and the risk of poAF.[52]

Operative risk factors

Perioperatively, factors such as acute volume overload of the atria, hypoxemia, oxidative stress, electrolyte disturbances (mainly hypokalemia and hypo-/hypermagnesemia) and increased perioperative ischemia have been found to predispose to poAF.[53,54] Furthermore, procedural factors such as the duration of the aortic cross-clamp time, location of the venous cannulation and duration of cardiopulmonary bypass (CPB) have in some studies been shown to affect the rates of poAF.[4,55] Prolonged ventilator times, return to intensive care unit (ICU) and the need for reoperation due to bleeding have also been associated with poAF.[56]

Albeit a causal relationship has yet to be shown, inflammation has been suggested as a triggering mechanism of poAF, supported by the contemporaneous time-course of maximal rates of poAF and inflammation.[57,58] Moreover, pleural effusion, cardiac tamponade and postoperative infections, all associated with an increased inflammatory response, may predispose patients to poAF.[10]

Risk models

Given the increased morbidity and mortality associated with poAF, several studies have sought to identify predictors of poAF following cardiac surgery, optimally to allow for preoperative identification of patients at risk and thereby allow for personalized prophylactic treatment.[59,60]

ECG recordings have been suggested as an easily attainable and affordable method, focusing on long P-wave dispersion (i.e. the difference between longest and shortest duration of the P-wave), signs of left atrial enlargement and left ventricular hypertrophy.[59,61] Additionally, echocardiograms have been proposed as a means of preoperative stratification of patients as atrial enlargement, left ventricular (LV) wall hypertrophy and decreased LV output has been shown to be connected to poAF.[62,63] Lastly, bedside risk models have also been proposed to allow for estimation of risk of poAF, using known patients risk factors, e.g. age, race, CHF, a high EuroSCORE rating, COPD, emergency operation, decreased preoperative left ventricular ejection fraction (LVEF) and decreased estimated glomerular filtration rate (eGFR).[10,20,60,64]

Currently, no validated, evidence-based threshold exists to stratify patients according to risk of developing poAF, and published studies to delineate risk factors for poAF differ significantly with regards to factors such as patient cohorts, documentation of preoperative risk factors and surgery types. Nonetheless, many previous guidelines have provided managment recommendations based on patient risk for poAF, without clearly defining the means for risk stratification. In the very recent review by a poAF taskforce formed by members of the Society of Cardiovascular Anesthesiologists and European Association of Cardiothoracic Anaesthestists (2019) the following risk factors were identified; advanced age, a previous history of COPD, AF, heart or renal failure and mitral valve surgery/disease as risk factors that significantly increased the risk for poAF. However, this taskforce literature review did not provide a cutoff to define when patients are considered at elevated risk.[65]

Perioperative poAF Prophylaxis

Specific treatment of established poAF has variable efficacy and can itself adversely affect hemodynamic stability. Therefore, substantial emphasis is placed on identification of patients at high risk of poAF that might most benefit from prophylactic treatment. Numerous medications have been tested in order to prevent the development of poAF after cardiac surgery, but relatively few have found their way into clinical practice (Table II).

Beta-blockers (Vaughan-Williams class II) (e.g. carvedilol, labetalol, propranolol)

In a recent meta-analysis, beta-blockers in general were found to significantly reduce the risk of poAF after cardiac surgery from 32.8% in controls to 20.0%, with an adjusted risk ratio (RR) of 0.50 (95% CI 0.36 – 0.69).[66] Indeed, beta-blockers are the most widely used prophylactic medication for patients undergoing cardiac surgery, and current guidelines from Europe and the US, suggest beta-blocker administration for at least 24 hours prior to surgery as a Class I recommendation for patients undergoing CABG, especially those who have an ejection fraction greater than 30%.[67,68] Importantly, preoperatively instituted beta-blocker treatment is more effective than *de novo* beta-blocker treatment early after the operation, and patients that cease beta-blocker use prior to surgery have a more than a twofold increase in risk of poAF compared to those who remain on treatment (OR of 1.91 (95% CI 1.52 – 2.40).[23,69] This may be due to the synergistic effect of the rebound phenomenon of increased cardiac excitability and automaticity and the generally higher postoperative sympathetic tone.[66,70] However, caution is warranted, as beta -blockers carry a risk of bradycardia, hypotension, bronchospasm and heart failure exacerbation.[17,71] Perioperative withdrawal of β-blocker or angiotensin converting enzyme (ACE) inhibitor therapy has been associated with increased risk of poAF, with an OR of 1.91 (95% CI 1.52 – 2.40) and 1.69, (95% CI 1.38 – 2.08), respectively[23]. Therefore, current guidelines include a Class I recommendation of β-blocker continuation when clinically possible, and prophylactic administration preoperatively or immediately postoperatively in beta-blocker naïve patients.[65]Lastly, some studies indicate that carvedilol is superior to metoprolol in preventing poAF in patients undergoing cardiac surgery.[66,72]

Potassium channel blockers (Vaughan-Williams class III) (e.g. dofetilide, ibutilide, sotalol, amiodarone).

These drugs primarily block the K^+ channels, thereby prolonging the refractory period of the cardiac action potential (phase 2). Notably, class III drugs can be pro-arrhythmic due to lengthening of the QT interval possibly leading to ventricular arrhythmias, namely *torsade de pointes.*[73] Importantly, two of the older drugs (sotalol and amiodarone) have additional properties and are currently considered the most potent class III drugs. Sotalol is a non-selective competitive β-adrenergic receptor blocker and significantly reduces poAF

compared to controls according to a Cochrane meta-analysis (18.1% vs. 40.0%, OR 0.34; 95% CI 0.26 – 0.43).[74] Although sotalol has been found to be superior to regular beta-blocker in reducing poAF rates,[75] it is a less optimal prophylactic drug as it also induces more side effects, such as arrhythmias.[76] Amiodarone exhibits both α- and β-adrenergic blocking properties that attenuate sympathetic overstimulation.[77] It is a potent prophylactic drug for poAF in patients undergoing heart surgery with a reduction of poAF incidence by almost half according to both meta-analysis and a randomized trial (OR 0.48, 95% CI 0.40 – 0.57).[78,79] Furthermore, amiodarone has been found to decrease the length of hospital stay for patients receiving it prophylactically, as fewer patients develop poAF following cardiac surgery (-0.60 days (95% CI -0.92 to -0.29).[79] In a large randomized controlled trial performed in Denmark the results were significantly in favor of using amiodarone as a prophylactic agent with an initial bolus of 300 mg intravenously at postoperative day 1, followed by an oral dose of 1200 mg a day for 5 days. Furthermore, amiodarone was shown to be safe, practical, feasible, and effective regimen for CABG patients.[78] Similar results were reported in another double-blind study on 601 patients where only one oral prophylactic dose was administered.[80] Amiodarone is extensively metabolized in the liver via CYP3A4, CYP2C8 and CYP1A1 iso-enzymes[81] and awareness of drug interactions is essential.[82] Furthermore, the metabolism of amiodarone may be inhibited by dietary products, such as grapefruit juice[83] and green tea.[84] As stated, studies indicate it is a safe prophylactic agent when used for a short period of time, but prolonged usage confers a risk of developing potentially irreversible thyroid disease,[85] irreversible lung fibrosis[86] and several other, mainly reversible, side effects like tiredness, tremor, nausea and constipation.[87]

Sodium channel blockers (Vaughan-Williams class I) (e.g. quinidine, lidocaine, flecainide)

These drugs block the Na^+ channels, thereby reducing automaticity. However, they may initiate arrhythmia by exaggerating electrophysiological abnormalities evoked by ectopic beats and their prophylactic use in surgical patients has not been thoroughly investigated.[88]

Calcium channel blockers (Vaughan-Williams class IV) (e.g. verapamil and diltiazem)

Medications from this class reduce cardiac contraction (negative inotropic effect) and by acting on the conduction tissue they slow down the conduction of electrical activity within the heart (negative chronotropic effect) by calcium channel blockade.[89] These drugs have a minor effect in minimizing the risk of poAF after cardiothoracic surgery but increase the risk of bradycardia and hypotension.[90,91] Of note, studies even indicate that these drugs might increase the risk of poAF, as they reduce the conduction at the sinoatrial node and atrioventricular node.[92]

Digoxin, magnesium and other cardiac drugs

Digoxin enhances the intracellular calcium concentration, prolonging phase 0 and phase 4 of the cardiac action potential and thereby reducing the heart rate.[93] Digoxin also enhances vagal activity, and so prolongs the depolarization of pacemaker cells in the AV node causing a reduction in heart rate.[94] By reducing the heart rate the left ventricle has an increased filling time that can increase cardiac output, but available evidence does not support the use of digoxin, thiazolidinediones or triiodothyronine in the prevention of poAF.[95] Although there are some studies that suggest that perioperative administration of magnesium can prevent poAF,[96,97] this remains controversial since studies are small and the design varies among the different studies. As mentioned earlier, potassium supplementation has not been shown to influence the incidence of poAF.[96]

Magnesium may inhibit substrate formation and the development of re-entrant circuits within the atria and reported adverse effects are few.[74] In a recent Cochrane meta-analysis the administration of magnesium was found to reduce the risk of poAF after cardiac surgery from 26.2% to 16.5% (OR 0.55; 95% CI 0.41 – 0.73).[74] However, a more recent meta-analysis, that was restricted to well-conducted trials, found no evidence of prophylactic effect in regards to poAF in patients undergoing CABG.[98]

Renin-angiotensin inhibition (ACE-inhibitors, Angiotensin II receptor blockers & aldosterone) (e.g. enalapril, ramipril, perindopril).

Aldosterone, a mineralocorticoid, is a steroid hormone produced by the zona glomerulosa of the adrenal cortex in the adrenal gland. It is a part of the renin–angiotensin–aldosterone system (RAAS) that modulates the release of angiotensin.[99] The direct effects of angiotensin

blockade on the structural and electrical properties of the atria, as well as the indirect influence of improved control of heart failure and hypertension, are considered to mediate a potential risk reduction for the development of poAF.[100] Randomized, controlled trials have shown that angiotensin II-receptor blockers (ARBs) reduces poAF (RR = 0.78; 95% CI: 0.66 – 0.92), with similar but non-significant results for ACE- inhibitors (RR = 0.79, 95% CI: 0.62 – 1:00). and aldosterone antagonists (RR = 0.77, 95%CI: 0.55 – 1.08),.[23,100] Finally, a risk score developed in multiple centers for cardiac surgery patients indicates that withdrawal of ACE/ARB had a significant association with increased risk for poAF.[23]

Anti-oxidative stress drugs (e.g. N-acetylcysteine, ascorbate, nitric oxide gas)

Several drugs, including N-acetylcysteine,[101] ascorbate[102] and nitric oxide gas[103] have been suggested to reduce the risk of poAF, although larger studies are required to make recommendations. In smaller studies N-acetylcysteine has shown promising abilities to reduce the risk of poAF and all-cause mortality after cardiac surgery, while in-hospital length of stay was unaffected.[101,104]

Anti-inflammatory drugs (corticosteroid, n-3 polyunsaturated fatty acids, colchicine, statins)

The causative association between inflammation and poAF has been studied in a canine pericarditis model. The studies showed that steroids, n-3 polyunsaturated fatty acids, and HMG-CoA reductase inhibitors (statins) suppressed the inflammatory response as indicated by lower serum CRP levels and reduced AF rates.[105-107] Pre-operative statin therapy is known to decrease inflammation markers and to attenuate myocardial reperfusion injury after cardiac surgery.[108] In recent years, several meta-analysis have indicated that statins significantly reduce the risk of poAF after CABG;[109,110] while statins have not investigated properly for other types of heart surgery. Atorvastatin has been found to be superior to pravastatin to prevent poAF in CABG patients.[111-114] Colchicine has been investigated in the COPPS study with a significant effect in reducing poAF when administrated from the third postoperative day for 1 month. NSAIDS, however, have also been investigated without clear evidence of effect on poAF.[115] Furthermore, the Food and Drug Administration (FDA) in the US has recently published a warning against the use of NSAIDS following CABG.[116] On the other hand a best evidence article published in 2014 concluded that a single prophylactic moderate dose of corticosteroid (50 – 210 mg of dexamethasone equivalent or 200 – 1000

mg/day hydrocortisone) significantly reduces the risk of poAF (from 48% to 30%) with no significant increase in morbidity or mortality.[117] Meta-analyses also suggest that using corticosteroids might reduce the in-hospital length of stay.[118,119]

PoAF prophylaxis with n-3 polyunsaturated fatty acids (fish oil) has been reported to be effective in some smaller studies.[120,121] However, placebo controlled, double-blinded, randomized trials have failed to reproduce this protective effect.[122,123] Overall the effect is debatable and fish oil has not been shown to reduce hospital length of stay, morbidity or mortality.[124,125] Nonetheless, further studies are warranted especially since the latest meta-analysis suggested that fish oil administration to diabetic patients could have a prophylactic effect on the risk of poAF.[126]

Non-pharmacological poAF prophylaxis

Pacing

Atrial pacing is thought to favorably influence intra-atrial conduction and atrial refractoriness and the effect of prophylactic pacing has been investigated in a number of trials.[127] Meta-analyses of these trials have consistently shown that single- or dual-site atrial pacing significantly reduces the risk of poAF (OR 0.60, 95% CI 0.47 – 0.77), despite wide variations in techniques.[74,79,128] At the same time pacing significantly reduced length of stay with an average of -1.3 days (95% CI -2.55 to -0.08).[129] However, few patients have been enrolled in these studies and the pacing sites and protocols vary widely. Furthermore, a major adverse effect of prophylactic atrial pacing is the potential pro-arrhythmic effect, which might be precipitated by inappropriate sensing or loss of pacing through temporary wires.[130]

Posterior pericardiotomy

There is a clear relationship between pericardial effusion and poAF.[131,132] Optimal drainage from the pericardium to the left pleural cavity can be obtained by a four cm longitudinal incision performed parallel and posterior to the left phrenic nerve, extending from the left inferior pulmonary vein to the diaphragm.[133,134] Although smaller studies have shown a four- to fivefold reduction of the risk of AF in patients that undergo posterior

pericardiotomy[131,132,134] such an incision is not widely used in practice and large-scale studies are lacking.

Treatment of poAF

As previously mentioned, poAF may resolve spontaneously within minutes or hours but persistent episodes of AF, especially those provoking hemodynamic instability, require clinical intervention.[56,135,136] Importantly, treatment includes general measures such as optimization of electrolyte abnormalities or fluid balance, treatment of infections and drainage of pleural and pericardial cavities. Cardioversion in itself can be performed by pharmacological and/or electrical means. However, if conversion proves unsuccessful evidence suggests that the majority of the patients should be prescribed oral anticoagulation.[56,135,136]

Medical cardioversion

Amiodarone often proves to be the most potent drug to obtain medical cardioversion[114]. A bolus of 300 mg intravenously over 20 minutes followed by a daily 1200 mg oral dose (q12 or q8 hours) for five days (a total dose of approximately 6.5 grams) have shown favorable results.[78] Amiodarone reduces ventricular rate, and is safe in patients with heart failure, though the risk of *torsades de pointes* pro-arrhythmia, bradycardia or hypotension warrants continuous ECG monitoring regarding QT interval and TU waves, especially when administered intravenously (discussed further in the chapter on oral anticoagulation below).[114]

Electrical cardioversion

This is often an effective way of establishing cardioversion but is most commonly used in symptomatic patients with hemodynamic instability, acute heart failure, myocardial ischemia or poAF refractory to medical cardioversion as it most often necessitates procedural sedation.[137] Electrical cardioversion without anticoagulation is assumed to be safe when performed within 48 hours after development of poAF[138]. Therefore it can be used in symptomatic or even asymptomatic patients within this timeframe as an alternative to medical conversion, though the risk of a new event of poAF remains high if medical

therapy is not instigated. When poAF has been of a longer duration transesophageal echocardiography (TEE) is recommended to exclude the presence of a left atrial appendage thrombus prior to electrical cardioversion.[138]

Medical rate control

Rate control (< 100 beats/min) with either beta-blockers (metoprolol, atenolol, carvedilol, esmolol), calcium channel blockers (nondihydropyridine (diltiazem, verapamil) ordigoxin has previously been shown to be a safe alternative to rhythm control in patients with poAF, though this requires concomitant anticoagulation therapy.[139]

Indication for oral anticoagulant therapy

AF increases the risk of stroke[140] and this risk is mitigated by anticoagulation using oral anticoagulant therapy with vitamin K antagonists (VKA) or with the newer direct oral anticoagulants (DOAC), such as dabigatran, rivaroxaban, apixaban, and edoxaban.[141-145] It is unclear if poAF carries a similar risk and if the benefits of anticoagulation therapy also apply for surgical patients. Current guidelines recommend anticoagulation therapy in patients with poAF for more than 48 hours and with a CHA2DS2-VASc score of two and above, to reduce the risk of thromboembolic events.[56,135,136] The choice of an anticoagulant is not clar in poAF but guidelines recommend initiation of DOAC over VKA in patients with non-surgical AF who are eligible for both treatments.[71,146] However, patients capable of self-management of warfarin therapy using a portable coagulometer to assess the International Normalized Ratio (INR) and adjusting their warfarin accordingly may potentially have a better treatment quality than patients on DOAC.[147]

Outcome and long-term prognosis

Patients who develop poAF often experience other postoperative complications. The most common associated complications associated are ventricular arrhythmias, perioperative MI, congestive heart failure, need for permanent pacemaker implantation, AKI, infection, pneumonia, prolonged mechanical ventilation, increased need for tracheostomy, need for

intra-aortic balloon pump (IABP), increased postoperative bleeding and cardiac tamponade.[5,6] Most importantly the incidence of stroke in association with poAF is threefold higher and 30-day mortality is twofold compared to patients not sustaining poAF.[5] Furthermore, hospital costs are significantly higher, mostly due to the fact that poAF patients' hospital stay is increased by two to four days.[5,6]

While the short-term complications associated with poAF are clear, the direct effect of poAF on long-term adverse events remains a matter of debate. As mentioned in the Introduction section, a significant number of studies have addressed this issue and demonstrated an increased risk for late mortality[26-28,30,31], stroke[32,33] and future AF recurrence.[13,30,34] These studies however have not been able to present convincing evidence on whether poAF is an independent risk factor for these complications or merely a surrogate marker for sicker patients' inferior prognosis. Furthermore, evidence for clinical measures to prevent and treat poAF that improves late outcomes is lacking. For example, there are no prospective studies or randomized, controlled clinical trials that have evaluated the role of oral anticoagulation in preventing ischemic events and reducing mortality in patients with poAF, although there are limited registry-based data suggesting that oral anticoagulation improves survival in patients with poAF.[31, 148] In addition, a recent large registry-based Danish study by Butt et al. reported a similar late thromboembolic risk in CABG patients with and without poAF.[148] Moreover, this study showed that, in terms of late thromboembolism and mortality, poAF is not comparable to non-postoperative AF as poAF was associated with a markedly lower risk for these two outcomes. Despite this conflicting evidence, the mere possibility that poAF has a direct influence on these serious and potentially fatal conditions urges further investigations to evaluate the role of anticoagulation.

Conclusion

Postoperative atrial fibrillation remains a common and serious complication after cardiac surgery. Although poAF is strongly associated with other early complications and perioperative mortality, the long term direct influence of poAF on morbidity and mortality remains unsettled. The exact mechanism behind poAF and the optimal preventive measures as well as optimal short- and long term treatment options also remain unclear. Further well designed prospective and retrospective studies focusing on pathophysiology, prevention,

and therapy in experimental models and in sufficiently large patient populations are warranted.

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Figure 1: Day of initial occurrence of poAF in 484 out of 1682 patients who had poAF following coronary artery bypass grafting surgery, defined as any AF resulting in a change in treatment (Unpublished data from the CABG Genomics group, Simon Body and Jochen D. Muehlschlegel).

Table I. Risk factors of postoperative atrial fibrillation.

Patient related factors

- Increasing age
- Previous history of AF or cardiac disease (particularly mitral valve disease).
- Increased left atrial size or cardiomegaly.
- Chronic obstructive pulmonary disease (COPD)
- Hypertension
- Increased left atrial size of > 4.5 cm or cardiomegaly
- Caucasian race
- Male gender
- Reduced preoperative kidney function
- Obesity (metabolic syndrome)

Operative factors

- Atrial injury or ischemia from surgical handling or cannulation
- Acute atrial enlargement from volume or pressure overload.
- Extended bypass and aortic cross-clamp times.
- Hyperadrenergic state (eg, use of postoperative inotropic medications).
- Inflammation (including pericarditis, postoperative infections, and reoperation for bleeding/cardiac tamponade)
- Electrolyte disturbances (especially hypokalemia and hypomagnesemia)
- Prolonged time on ventilator.

Table II. Commonly used perioperative prophylactic pharmacological therapy of postoperative atrial fibrillation, ordered by the most to the least common treatment modality

- Beta-blockers (e.g. propranolol, carvedilol, labetalol, propranolol)
- Potassium channel blockers (e.g. amiodarone, sotalol, dofetilide, ibutilide)
- Digoxin
- Magnesium
- Sodium channel blockers (e.g. quinidine, lidocaine, flecanide)
- Angiotensin inhibitors, Angiotensin II receptor blockers & aldosterone (enalapril, ramipril, perindopril)
- Anti-oxidative stress drugs (e.g. N-acetylcyteine, ascorbate, nitric oxide gas)
- Antiinflammatory drugs (e.g. corticosteriods, n-3 polyunsaturated fatty acids, colchicine, statins)