Introduction

Post-operative atrial fibrillation (POAF) is an important complication after cardiac surgery, which increases short-term hospitalization costs and more importantly, decreases long-term survival. This makes POAF an important target for prevention and treatment. Great discrepancy remains between reported incidences of POAF in different studies. Reported incidences vary from 10-60% depending on the type of surgery, with higher incidences in valve surgery compared to coronary artery bypass surgery (CABG). This is certainly affected by the more invasive structural changes arising from valvular diseases such as atrial dilatation and fibrosis, but also by the more prolonged and invasive nature of the surgical interventions in valve surgery. The incidence of POAF is however also influenced by the definition of AF. The minimal duration of AF needed to qualify as POAF varies in reports between minutes of AF, to sometimes only qualification as AF if it requires therapy. In general, AF is defined as an episode with irregular RR-intervals without a traceable p-wave, during at least 10 seconds. It is important to acknowledge even the short episodes of AF because of the progressive nature of the arrhythm-
mial,\textsuperscript{10,11} but also because even a low AF burden significantly increases the stroke rate.\textsuperscript{12} The unpredictability of AF onset and duration poses a great challenge to the intermittent rhythm detectors such as ECG or Holter monitoring after discharge.\textsuperscript{13} Reports on long-term follow up after cardiac surgery suggest that POAF is an independent predictor of mortality, which might well be related to the fact that it is a recurrent arrhythmia.\textsuperscript{2,3,14} Of note, some of the AF episodes may remain unnoticed as they can be asymptomatic both during hospitalization and after discharge.\textsuperscript{15-17}

Indeed, several studies in patients undergoing cardiac surgery have shown recurrence of AF after discharge.\textsuperscript{18,19} In a randomized trial of 124 patients on the effects of Amiodarone after cardiac surgery, 12\% of the patients in the placebo group were in AF at a mean of 12 days after discharge.\textsuperscript{20} In a retrospective study of 305 patients undergoing cardiac surgery, the annual incidence of symptomatic AF during a 4 year follow up was 5.1\% in patients who had developed POAF.\textsuperscript{21} Interestingly, multivariate analysis showed reduced left ventricular ejection fraction, which can cause atrial structural remodeling, to predict recurrences of POAF independently.\textsuperscript{21} In line with this, other predictors of POAF after discharge that have been reported are valve surgery, history of myocardial infarction and pulmonary hypertension.\textsuperscript{17} The value of continuous monitoring seems essential in detecting the true POAF burden,\textsuperscript{13} as the importance of asymptomatic “silent AF” in patients with a comparable risk profile as the POAF population has recently been emphasized.\textsuperscript{12} Therefore, to be able to treat or at least to restrain the consequences of POAF, a better understanding of the pathophysiology of POAF is mandatory.

Pathophysiology

Even in normal atria in sinus rhythm inter-atrial and site-specific conduction heterogeneities are present, which may lead to spatial non-uniformity of conduction anisotropy.\textsuperscript{22} In the presence of triggers with sufficient incidence, AF can be induced both in normal and in abnormal atria. The wave pattern and type of AF may vary in complexity,\textsuperscript{9} depending on the severity of the underlying substrate.\textsuperscript{23} Although inducibility of AF by pacing in normal atrial structure is dependent on the protocol of pacing,\textsuperscript{24} it has a predictive value for the occurrence of POAF.\textsuperscript{25,26} This suggests higher susceptibility for AF at least in some of the patients who subsequently develop POAF.\textsuperscript{27} Furthermore, AF occurring as a consequence of cardiac surgery in patients without a history of AF postulates a significant pathophysiological role for the surgical intervention itself.

Early Pro-Arrhythmic Environment

In a recent review, we discussed the acute and chronic factors contributing to initiation of POAF, and emphasized that different mechanisms are responsible for AF in a post operative setting.\textsuperscript{28} Inflammation in the acute post-operative phase has been subject of extensive research as it has been linked to several local and systemic pro-arrhythmic effects.

First of all, direct atrial trauma, e.g. the venous cannulation through the right atrium, has been shown to induce an inflammatory reaction leading to inhomogeneity in conduction in a canine model.\textsuperscript{29} The canine sterile pericarditis model, in which application of sterile talc and subsequent pericarditis enhanced AF susceptibility, supports this hypothesis.\textsuperscript{30} Administration of prednisone in this model reduced inflammation and as expected prevented AF.\textsuperscript{31} Similarly colchicine was able to reduce the incidence of POAF, as a result of a reduction of the post-cardiotomy syndrome in humans.\textsuperscript{32} Secondly, systemic inflammatory effects expressed as increased C-reactive protein levels, and therefore complement activation during cardio pulmonary bypass and during the acute post operative phase, were demonstrated to coincide with the peak POAF incidence, advocating a direct immune reaction mediated by the complement system.\textsuperscript{33} Indeed, the use of cardio pulmonary bypass is correlated with POAF incidence in most studies.\textsuperscript{5,34} Thus as expected, oral corticosteroids reduce not only the post-operative inflammatory markers, but also the incidence of POAF as demonstrated by an extensive meta-analysis.\textsuperscript{35}

Furthermore, cardiopulmonary bypass might lead to insufficient cooling of the atria during the cardioplegic arrest.\textsuperscript{36} This may induce a temporary substrate to initiate AF as a consequence of ischemia reperfusion injury.\textsuperscript{36,37} Indeed, oxidative stress has been shown to cause a transient pro-arrhythmic effect in the post-operative setting.\textsuperscript{38} This
can explain the anti-arrhythmic effects of statins in POAF prevention. Despite the anti-inflammatory effects of the HMG-CoA enzyme inhibitors, statins had no effect in predetermined substrates for AF, such as enlarged left atria. In line with the effect of oxidative stress in the direct post-operative occurrence of AF, administration of ascorbate acid preserved the length of the effective refractory period (ERP) during rapid pacing in a canine model, and reduced POAF especially in the very early post-operative phase in humans. Similarly, the antioxidant N-acetylcysteine reduced the incidence of POAF in the early post-operative phase. These findings suggest that independent of a pre-existing vulnerability to AF, surgery itself can have several pro-arrhythmic consequences on the atrial tissue based on ischemic and inflammatory effects.

Post-operatively, as a counterbalance to anesthesia induced hypotension and cardiac stunning after aortic crossclamping, fluid administration is required to keep up the cardiac output. Especially in hypertrophic ventricles, e.g. in aortic valve stenosis, significant volume therapy is applied for hemodynamic stabilization in the acute post-operative phase. In this setting, atrial enlargement seems to be an important factor in predicting POAF. Acute atrial stretch decreases conduction velocity, increases conduction block and thereby the vulnerability of the atrial tissue to reentry. In addition, premature atrial beats initiate post-operative AF, partly aggravated by high sympathetic activation. Possibly, they are also due to increased L-type calcium currents (I\(_{\text{Ca}}\)) in patients developing POAF. Indeed, milrinone, a phosphodiesterase inhibitor inotropic agent, increased the incidence of POAF significantly, presumably through a protein kinase-A activation leading to triggered activity.

It can be concluded that transient local and systemic changes in the acute post-operative phase after cardiac surgery are linked to POAF. They cause conduction disturbances and may enhance triggers for AF which both together will enhance the susceptibility to AF.

**Histopathological Substrate**

In addition to post-operative acute phase triggers, several long-term mechanisms have been identified to also predict POAF. These mechanisms are known to produce a more sustained substrate for AF, which favors AF maintenance rather than initiating it. The complexity of AF in these patients is therefore higher and recurrences are more likely after discharge, compared to AF in the less pronounced substrates, which are confined to solely acute phase POAF.

First, POAF is a disease of advanced age. The atrial wall becomes fibrotic with age and this has been identified as one of the most important structural substrates for AF perpetuation in the non-operative setting. Prolonged signal averaged p-wave duration may reflect atrial fibrosis resulting in conduction delays and has been reported to be a predictor of POAF. However, pre-operative AF was not excluded in all these studies. Nevertheless this finding suggests an increased AF vulnerability in patients with intra-atrial conduction delays particularly in a pro-arrhythmic environment.

Several co-morbidities have also been shown to increase the chances of POAF development, such as chronic obstructive pulmonary disease, hypertension, obesity and systolic dysfunction. The role of these co-morbidities in the perpetuation of AF has long been established. Obesity has been associated with ERP shortening in left atria, diastolic dysfunction and left atrial dilation, all of which predispose to AF.

In congestive heart failure, Sanders et al. demonstrated increased vulnerability to AF due to prolonged p-wave duration, prolonged ERP duration at the right atrial wall and significantly longer sinus node recovery time. Accordingly, prolongation of conduction time with a higher percentage of double potentials and longer iso-electric intervals is linked to severely disturbed substrates. These pro-arrhythmic changes seem to occur due to chronic dilated atria, as a consequence of congestive heart failure or longstanding valve pathology for example. In line with these findings, left ventricular diastolic dysfunction was determined as an additional predictor of POAF. On the biochemical level, stretch activated channels (SAC’s) increase intracellular Na* concentrations. As a consequence, the Na*/Ca\(^{2+}\) exchanger extrudes less Ca\(^{2+}\) to the extracellular space, thereby enhancing Ca\(^{2+}\) binding to the actin-myosin response. In this setting intracellular calcium overload causes a down
regulation of Ica²⁺-gene expression, subsequently shortening the ERP.⁵⁶ Also chronic stretch has been associated with altered matrix metalloproteinase expression and angiotensin II mediated fibrosis.¹⁰ Thus as expected, preoperative atrial enlargement has been shown to increase risk for POAF.⁵⁷ Furthermore, preoperative dispersion of refractoriness and a prolonged PR interval predicted POAF after CABG.⁵⁸ Atrial structural changes have been attributed to the uncontrolled ventricular rate and congestive heart failure leading to atrial stretch, apoptosis and myolysis.⁵⁹ Although apoptosis has not consistently been found in the atrial tissue of patients developing POAF, myolysis has been advocated as a preexisting structural substrate in these patients.⁶⁰,⁶¹

Another important structural abnormality, which is closely linked to the propagating abilities of the atrial wall, is the gap-junctional connexin (Cx) distribution. Higher and more heterogeneously distributed levels of Cx 40 have been demonstrated in POAF patients.⁶² Also local inflammation caused a reduction in Cx 40 and 43 expressions in the epicardial level, compared to normal distribution in non-inflammatory circumstances.⁶³ The exact role of connexin expression changes in POAF still needs to be defined.

From these findings it can be concluded that at least in some of the patients developing POAF after cardiac surgery, severely altered atrial architecture already is present before the operation. These structural alterations make the atria prone to not only POAF but also to AF in general. This is important because POAF might be an expression of the atrial vulnerability that is detected due to continuous monitoring in a period with excessive triggers, a “poor man’s exercise” effect. This strongly implies close monitoring of these patients later on. Figure 1 gives a possible course of POAF development and perpetuation after cardiac surgery and after discharge.

Treatment strategies also provide additional information for the possible mechanism that is responsible for POAF. The positive effects of class III anti-arrhythmic drugs for example, suggest a role for a reentry mechanism, in which shortening of the excitable gap might be the key element in their effectiveness, while beta-adrenergic blockers advocate a more prominent role for the sympathetic activation and triggers for AF.⁵,⁶⁴

Prevention

Beta-Blockers

It has become clear from multiple meta-analyses, reviews, and large cohort studies, that the peri-operative use of β-blocking agents reduces the incidence of atrial fibrillation after cardiac surgery.⁶⁵-⁶⁷ Furthermore, it is evident that the peri-operative use of β-blockers reduces mortality.⁶₆ This knowledge has led to unambiguous recommendations of the use of β -blockers as standard of care in the prophylaxis of POAF in patients without contra-indications.⁸,⁶₈-⁷₀

Sotalol

Sotalol has a greater efficacy in preventing POAF than standard β-blockers,⁶⁷ but has possibly more unfavorable adverse event profile. The extent of side effects of sotalol, such as prolongation of the QT-interval, compared to standard β-blockers is debated. Because sotalol exposes patients to the risk for torsade des pointes, its use requires close monitoring, and under these conditions may be considered for the prevention of POAF.⁸,⁵⁴,⁶⁹,⁷₀

Amiodarone

Amiodarone with its class III anti-arrhythmic effects is a strong preventive drug in the acute post-operative setting.²⁰,⁷¹ Prophylactic amiodarone, with or without concomitant use of β-blockers also has a positive effect on duration of hospital stay, postoperative stroke, and post-operative ventricular tachyarrhythmia.²⁰,⁶⁷,⁷¹,⁷₂,⁷₃ However, in one trial the effects of amiodarone were not superior to placebo in patients with enlarged atria and in patients undergoing valve surgery. These are important characteristics of patients with a strong structural substrate,⁴₃,⁷¹ suggesting its effectiveness relies on the prevention of triggers in the early pro-arrhythmic environment. Common adverse effects of amiodarone are bradycardia and hypotension,⁷₄,⁷₅ which lead – together with extracardiac side-effects – to cessation of the treatment with amiodarone in up to 20% of all patients.⁷₆ The pre-operative administration of amiodarone should be considered in patients with high risk
Figure 1: A schematic sketch of incidence of POAF in the early post-operative phase (i.e. the first post-operative week) and during the late post-operative phase (i.e. weeks to years following cardiac surgery) after discharge. In severely aggravated atrial substrates, POAF might continue to exist and reoccur. Red area under the curve represents patients with a preexistent structural substrate, e.g. atrial enlargement or heart failure, which is not easily reversible. White area under the curve represents patients with less severe structural substrate but who are exposed to the pro-arrhythmic environment of the acute-postoperative phase.

Biatrial Pacing

Bi-atrial pacing significantly reduces the incidence of POAF, although it has been reported to be difficult to apply. Some studies demonstrated even pro-arrhythmic side effects and also unintentional diaphragmatic or left ventricular pacing are common. However, when sensing and capture thresholds of the pacemaker leads are followed accurately, particularly simultaneous bi-atrial pacing effectively prevents POAF. The main effects of post-operative atrial pacing on the atria are still unclear. It has been proposed that simultaneous biatrial pacing reduces dispersion of refactoriness and reduces the p-wave duration and dispersion. Also, overdrive pacing might prevent ectopic activity. At the ventricular level, overdrive pacing after an ischemic episode has been shown to reduce infarct size, based on prevention of ischemic reperfusion injury. More research is required to define the exact mechanisms of AF prevention by pacing at the atrial level, and to determine the population in which pacing is effective.

ACE-Inhibitors

Angiotensin converting enzyme inhibitors (ACEI’s) may be as effective in preventing POAF as they are in preventing permanent AF in the general population. Although administration of ACEI’s have been associated with reduced POAF incidence, recent reports show conflicting results. Most importantly increased adverse effects are reported in some studies, including hypotension, renal failure, higher mortality and a paradoxical increased risk of POAF incidence, or at least no reduction of new onset AF after cardiac surgery. More research is therefore required to find true effects of
ACEI’s in the acute and late post-operative setting for the prevention of POAF. Benefits from other prophylactic measures, such as the administration of corticosteroids, colchicine, or vitamin C, are postulated in some reports, but lack sufficient evidence for standard practice. The use of statins as a prophylactic measure has shown conflicting results although a meta-analysis showed significant POAF reduction in statin treated arm. Intravenous administration of magnesium might reduce the incidence of POAF, although conflicting results on this issue are reported. In patients without renal dysfunction the probability of adverse effects is very low. In these patients some but not all guidelines recommend the perioperative use of magnesium. Further research on the usefulness, and applicability of these, and other preventive strategies is warranted.

Treatment

In the majority of patients, POAF will spontaneously convert to sinus rhythm within 24 hours after surgery. In hemodynamically stable patients, correction of predisposing factors such as hypoxia, anemia, and electrolyte imbalance, should be the first step in the management of POAF. The superiority of a certain drug regarding rate control remains to be proven. Therefore the decision of the drug to be administered should be based on the side effect profile, contraindications, and local familiarity with the drug. 

Oral Anticoagulation

In case of hemodynamically unstable patients, cardioversion to sinus rhythm by direct current (ECV) or pharmacologically with ibutilide or amiodarone, should be pursued. Also if patients are highly symptomatic or when rate control is difficult to achieve, electrical direct current shock is recommended.

Conclusions

The pathophysiology of POAF is not completely understood. In general, AF initiation and perpetuation has been attributed to (or a combination of) ectopic focal discharges and reentry (primarily represented by multiple wavelets). In the post-operative setting, it is conceivable that in different patients, different mechanisms perpetuate AF. This is reflected by the fact that the preventive and therapeutic strategies are only helpful in some patients in the early phase after cardiac surgery. In patients with highly diseased atrial tissue e.g. due to chronic atrial stretch or advanced age, AF might not only occur in the early post-operative phase, but also during the days and weeks thereafter. Indeed, data on late POAF is accumulating and shows a potential role for prolonged monitoring in high-risk patients.

Future research needs to address the incidence of ‘late POAF’ in the weeks and months after discharge. It is also of interest how this incidence depends on the heart disease and other clinical factors. Finally, the therapeutic implications of ‘late POAF’ need to be defined. As a first step towards these objectives, more studies systematically studying ‘late POAF’ in different indication groups are urgently needed.

Disclosures

No disclosures relevant to this article were made by the authors.

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