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REVIEW ARTICLE

Postoperative atrial fibrillation: mechanism, prevention, and future perspective

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Abstract Postoperative atrial fibrillation (POAF) is the most common complication after cardiac surgery, despite improvements in anesthesia, surgical techniques, and medical therapies. Although beta-blockers have been proven to be effective, the incidence of POAF is around 20 % even with these agents. The mechanism of POAF is not fully elucidated and no optimal strategy has been established for POAF. There are two important elements of "structural" and "electrical" remodelling of the atrium in the mechanism of POAF. A patient's age and preoperative left atrial fibrosis can predict POAF associated with structural remodelling. Although inflammation and oxidative stress during cardiac surgery may be the underlying mechanisms for electrical remodelling causing POAF, there are no reliable clinical parameters for their detection. Nonetheless, postoperative P-wave dispersion and electromechanical delay, which reflects excitation–contraction coupling abnormalities, could be new parameters for POAF. In conclusion, despite the importance of prevention of POAF, there are only a few parameters for predicting POAF. It is therefore necessary to consider both disease-mediated structural remodeling before surgery and electrical remodeling caused by cardiac surgery.

Keywords Cardiac surgery · Postoperative atrial fibrillation

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Introduction

Despite improvements in anesthesia, surgical techniques, and medical therapies, postoperative atrial fibrillation (POAF) is the most common complication after cardiac surgery, with an incidence that ranges between 27 and 40 % [1–3]. POAF is associated with mortality as well as the incidence of stroke and the length of hospital stay, and places substantial financial and clinical burdens on clinicians and patients. POAF has been reported to affect even the late mortality after cardiac surgery [4].

A number of studies have investigated effective prophylactic agents for POAF. There is evidence that beta-blockers (Vaughan-Williams Class II agent) provide for prophylaxis for POAF [5]. Table 1 summarizes several randomized clinical trials using beta-blockers for prevention of POAF [6–11]. The largest meta-analysis of randomized control studies by Crystal et al. reported that the incidence of POAF is 33 % in the controls but patients receiving beta-blockers had a 19 % incidence of POAF. These data suggest that one out of five patients still develop POAF even with beta-blockers [12]. Furthermore, a report by Canadian cardiac surgeons showed only 58 % of practitioners routinely use beta-blockers for prophylaxis of POAF [13]. Sotalol (Vaughan-Williams Class III agent) may be also considered for POAF prophylaxis but it is associated with increased toxicity [5]. Amiodarone can be an alternative for POAF prophylaxis in patients in whom beta-blocker therapy is not possible, but the incidence of POAF is still over 20 % with amiodarone therapy [14]. Therefore, there are no agents that can safely and effectively reduce the incidence of POAF.

One fundamental reason for the lack of an optimal strategy for POAF is that the mechanism of POAF has not been elucidated, even though a number of studies have

Table 1 Randomized clinical trials using beta-blockers for the prevention of POAF

	Patients analyzed	Drugs	Incidence of POAF (vs. control) (%)	*p*
Lúcio Ede et al. [6]	200	Metoprolol	11 vs. 24	0.02
Ali et al. [7]	210	Metoprolol	17 vs. 38	<0.02
Lamb et al. [8]	60	Atenolol	3 vs. 37	0.001
Daudon et al. [9]	100	Acebutolol	0 vs. 40	<0.001
Silverman et al. [10]	100	Propranolol	6 vs. 28	<0.01
Stephenson et al. [11]	223	Propranolol	8 vs. 18	<0.05

POAF postoperative atrial fibrillation

been conducted. Furthermore, there are few reliable clinical parameters for predicting POAF. Reliable parameters would allow the investigators to identify the most significant contributing factors and help develop a novel strategy for the prophylaxis of POAF. Several issues have been identified by previous studies in this area. First, most observational clinical studies of POAF have focused only on the patients' preoperative characteristics, such as their age, left atrial size, etc. [15], but not on the postoperative parameters, which are important in terms of the effect of cardiac surgery. Second, although the pathogenesis of chronic atrial fibrillation (AF) in the general population has been documented [16], this cannot be applied to postoperative settings. This review will discuss the existing parameters for predicting POAF and how the mechanism of POAF should be investigated in the future.

Possible mechanisms of POAF

"Structural" and "electrical" remodeling is associated with the possible mechanism of POAF. Preoperative atrial injuries associated with cardiac diseases (atrial dilatation and fibrosis) are significant elements underlying "structural remodelling" which leads to changes in the conduction properties of the heart, and therefore in the configuration of new re-entry foci [17]. A number of factors play pivotal roles in genesis and perpetuation of postoperative POAF, including ischemic myocardial damage during the procedure due to inadequate cardioprotection, traumatic pericarditis and myocarditis, the chemical and metabolic milieu, increase of adrenergic tone, hypoglycemia, and hypothyroidism. All these factors contribute to "electrical remodelling" based on electrophysiological changes such as shortening of the refractory period and calcium overload [17, 18].

Parameters associated with "structural remodeling"

A number of studies have documented various factors associated with structural remodelling for POAF. Increasing patients' age is independently associated with POAF. Mathew et al. [15] reported an increase of 24 % in the odds of developing POAF for every 5-year increase in age. The most common explanation for the relationship between patients' age and POAF is age-associated structural change in the atrium. Atrial size is related to the risk for AF in the general population, particularly for those with mitral valvular disease or left ventricular dysfunction [19, 20]. Nonetheless, several reports of coronary artery bypass grafting (CABG) revealed no significant difference in atrial size between the POAF and non-POAF groups [21–23]. Goette et al. [24] and Wang et al. [25] have reported that collagen volume fractions, i.e. fibrosis in the atrium independently predicted POAF. The fibrosis is correlated with the patients' age. The latter group also documented a close relationship between atrial collagen volume and integrated backscatter accessed by preoperative echocardiography and they suggested the usefulness of this parameter.

Parameters associated with "electrical remodeling"

Changes in autonomic nervous and hormonal systems

Several studies suggest that the autonomic nervous system plays an important role in both the initiation and/or the maintenance of AF in humans. Vagal nerve stimulation induces shortening of the action potential duration, which in turn facilitates reentrant atrial arrhythmias in the general population [26]. Dimmer et al. used 96-h Holter ECG and analyzed sympathetic tone after CABG using the standard deviation of all RR intervals. They reported a shift in the autonomic balance to a moderate increase in sympathetic tone before the onset of POAF [27]. A possible mechanism of sympathetic activation and AF is calcium overload causing triggered activity (after-depolarization) [26]. However, heart rate variability measurements detect only changes in the relative degree of autonomic nervous system, not the absolute level of sympathetic or parasympathetic discharges. Therefore, it is necessary to perform direct recording of sympathetic and vagal nerve activity to prove this hypothesis [28].

Wazni et al. analyzed 187 patients after cardiac surgery and reported that preoperative brain natriuretic peptide (BNP) level is a strong and independent predictor of POAF. The preoperative BNP was higher in POAF patients (615 vs. 444 pg/ml, $p = 0.005$) [29]. On the other hand, Tavakol et al. [30] conducted a larger cohort study including 398 patients, and found that BNP was not

preoperatively elevated in POAF patients (361 vs. 302 pg/ml, $p = 0.3$). Therefore, the use of the preoperative BNP value as a predicting parameter of POAF is controversial.

Although subclinical hypothyroidism has been reported to have adverse effects in heart failure patients [31], little is known about the effect on patients after cardiac surgery. Park et al. [32] reported that patients with subclinical hypothyroidism have a higher incidence of POAF in comparison to those with normal thyroid function (46 vs. 29 %, $p = 0.026$). Further study is necessary to determine the importance of hypothyroidism in POAF.

Atrial stretch

The P-wave duration is directly related to left atrial pressure in fluid overload conditions such as congestive heart failure [33]. In addition, acute diuresis has been shown to decrease P-wave duration and dispersion in patients with decompensated heart failure [34]. Preoperative P-wave duration on scalar or processed ECG was reported as a predicting parameter of POAF (cut-off values over 140 ms [35] or 155 ms [36]). Chandy et al. [37] reported a greater increase of P-wave dispersion after surgery independently predicted POAF and they speculated that the possible mechanism is inhomogeneous effect of pressure-related atrial stretch that resulted in dispersion of atrial refractoriness. Perioperative volume overload causing atrial stretch might be an important factor in atrial electrical remodeling after surgery.

Inflammation

Anselmi et al. [38] discussed the concept of inflammation as a pathophysiological determinant of POAF. Inflammatory markers, including interleukin-2 (IL-2), IL-6, IL-8, CRP, tumor necrosis factor-α, and indices of neutrophil and platelet activation, are significantly increased in the systemic bloodstream after cardiopulmonary bypass. Neutrophil-dependent inflammation increases both the inhomogeneity of conduction and the refractory period in atrial cardiomyocytes, which may set the stage for multiple reentrant wavelets [39]. Gaudino et al. reported a significant effect of IL-6 polymorphism and postoperative IL-6 levels on the incidence of POAF. Their findings suggest an inflammatory component of POAF and a genetic predisposition to this complication [40].

The concept of inflammation in POAF is supported by several clinical studies designed to suppress inflammatory responses, including the "no-pump" approach. A meta-analysis of recent randomized controlled trials evaluating the incidence of AF after on-pump versus off-pump coronary surgery indicated a significant advantage in terms of new-onset of AF if the pump is avoided (odds ratio 0.427, total 841 patients studied) [38]. Another approach is using anti-inflammatory medications. Randomized studies [41, 42] found that a single dose of dexamethasone (0.6 mg/kg or 1 g) at the induction of anesthesia achieves a statistically significant lower rate of new-onset of AF. Lower dexamethasone doses did not show a benefit in this report. Although no significant major side effects have been reported in most studies, minor postoperative morbidity may increase and this issue should be carefully examined before larger application of dexamethasone. Ruffin et al. reported in the Atrial Fibrillation Suppression Trials (AFIST) that non-steroidal anti-inflammatory drug (NSAID) use is associated with reductions in the adjusted odds ratio of POAF (0.54, 95 % CI [0.32–0.90]) [43]. The limitation of this study is that it was not a randomized trial and the risk of postoperative stroke (odds, 1.1) and myocardial infarction (odds, 1.7) could have been underestimated. More safety data are needed before NSAID can be routinely recommended.

Oxidative stress

A case–control study of CABG by Ramlawi et al. [44] reported that patients who exhibit POAF have significantly increased acute oxidative stress in the myocardium after surgery, indicated by the presence of oxidized proteins. Furthermore, they found that most redox genes uniquely upregulated in the POAF group are genes that support reactions promoting oxidation reactions, contributing to the perpetuation of oxidative stress. This was the first report that documented direct evidence of a relationship between cardiac oxidative stress and POAF in a clinical setting. Oxidation of polyunsaturated fatty acids of membrane phospholipids can cause membrane disintegration, mitochondrial dysfunction, and abnormalities in calcium-handling proteins, which can be a mechanism of electrical remodelling in POAF.

Several clinical trials have examined the efficacy of antioxidant agents for POAF. Oral vitamin C in association with beta-blockers is more effective in preventing POAF than beta-blockers alone [45]. The incidence of POAF was 4 % in the vitamin C group and 26 % in the control group in this study. Baker et al. [46] reported a meta-analysis on the use of *N*-acetylcysteine (NAC) for reduction of post-cardiothoracic surgery complications. The use of NAC significantly lowered the odds of developing POAF by 36 % (95 % CI [2–58 %]). Chen et al. conducted a meta-analysis of eight randomized trials using "statins" for prophylaxis of POAF. Statins were associated with a reduced risk of POAF (odds, 0.57, 95 % CI [0.45–0.72]) and shorter hospital stay [47]. All these preliminary clinical results support the antioxidant strategy to prevent POAF

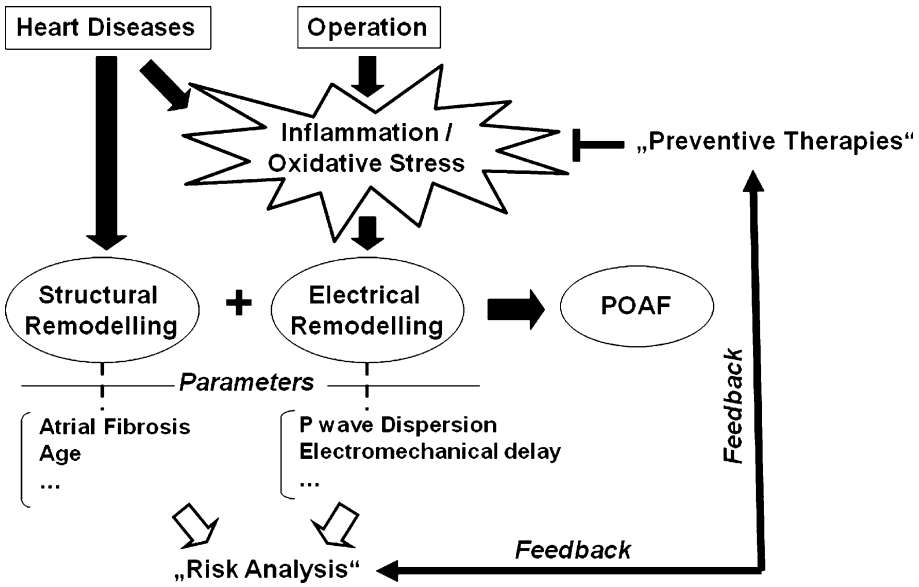

Fig. 1 A schematic illustration of the mechanism and prevention for postoperative atrial fibrillation. *POAF* postoperative atrial fibrillation

and may be focused on in the future because they have fewer side effects in comparison to antiarrhythmic agents.

Electromechanical delay (EMD) as a new parameter for POAF

Experimental studies demonstrated that the dual effects of oxidative stress on cardiac metabolism and calcium-handling have profound implications for excitation–contraction coupling [48]. A recent study [49] hypothesized that electromechanical (excitation–contraction coupling) delay (EMD) measured by echocardiography can monitor POAF and it could be a new parameter for predicting the POAF. “EMD” is the time delay from the electrical activation to the actual systolic motion that is mainly used in clinics for the analysis of left ventricular dyssynchrony, which can be easily quantified by transthoracic tissue Doppler echocardiography. This method detected longer left ventricular EMD in the patients with POAF. Although the preoperative EMD in the POAF and non-POAF groups were not different in this study, the postoperative EMD was significantly longer in patients with POAF. Therefore, this EMD difference can be attributed to surgical effects itself. Roshanali et al. [50] identified the preoperative atrial EMD as a predictor for AF after CABG. However, they did not examine the postoperative changes of this value, and thus the relationship between postoperative EMD and AF remains unclear. Further study is necessary to identify the direct relationship between EMD caused by abnormality in calcium-handling proteins and oxidative stress in patients with POAF.

Future perspectives

Figure 1 shows a schematic drawing which demonstrates the mechanism and prevention for POAF. Aside from the conventional parameters of structural remodelling for POAF, those of electrical remodelling would be new targets for the investigation of POAF. Although it is not possible to modify the structural remodelling before surgery, the perioperative adverse electrical remodelling could be minimized. EMD could be used to access the direct effect of prophylactic agents on excitation–contraction coupling. The identification of the threshold of this parameter for POAF will provide a cut-off value to determine the need for prophylactic medications after surgery. In addition, there should be a comparison of the effect of prophylactic agents that influence excitation–contraction coupling, including anti-oxidant and anti-inflammatory medications.

Conclusion

Despite the significant incidence of POAF, there is still no optimal strategy for its prevention. There are a few reliable predicting parameters for POAF that will contribute to the further investigation of POAF. It is necessary to consider not only disease-mediated structural remodelling before surgery but also electrical remodelling caused by cardiac surgery itself.

Conflict of interest The authors declare no conflict of interest.

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