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EDITORIAL COMMENTARY

Atrial fibrillation post-cardiac surgery: changing perspectives

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ABSTRACT

Perioperative atrial fibrillation (AF) is one of the most frequent complications of cardiac surgery. Its development is associated with an increased morbidity and mortality, for example from perioperative stroke, as well as ventricular arrhythmias, postoperative myocardial infarction, congestive cardiac failure, renal failure, increased use of inotropic medications and the need for intra-aortic balloon pump. Furthermore, AF after cardiac surgery results in prolonged hospitalization after the procedure, as well as an excess utilization of hospital resources and increased hospital costs. Given the importance of AF for patient outcome, a wide variety of prophylactic pharmacologic strategies have been evaluated. The risk of post-operative AF should be reduced by the administration of amiodarone, a beta-blocker, sotalol or rate-limiting calcium antagonists. In addition, in patients undergoing cardiac surgery on pre-existing beta-blocker therapy, this treatment should be continued unless contraindications develop (such as post-operative bradycardia or hypotension). Unless contraindicated, a rhythm control strategy is recommended as the initial option for the treatment of post-operative AF following cardiothoracic surgery. More recently, some data regarding magnesium, statins and n-3 polyunsaturated fatty acids in reducing post-op AF are available. Clearly, perspectives are changing in our management of this common arrhythmia.

Introduction

Perioperative atrial fibrillation (AF) is one of the most frequent complications of cardiac surgery, and occurs in 10–65% of patients post-operatively[1]. Its prevalence is lower for coronary artery bypass graft surgery (CABG; 11–40% of patients)[2] than for valvular heart surgery (up to 60% of patients)[3]. This difference in prevalence depends on many variables, in particular, the type of procedure and patient characteristics (such as the presence of co-existing risk factors for developing AF).

The advent of percutaneous coronary intervention has reduced the 'routine' operative workload of cardiothoracic surgeons somewhat, but this has transformed the operative list to include many older and higher-risk patients. In fact, an older age appears to be one of the strongest predictors of postoperative AF[4–6]. In one study, the rate of AF was 18% for patients aged < 60 years of age, compared to 52% for those aged > 80 following their cardiac procedure[4]. Indeed, there is a 24% rise in the frequency of postoperative AF for every additional 5-years of age[6]. We should not forget other factors which may predispose the patient to AF, including operative trauma from surgical dissection and manipulation, inflammation (with or without pericarditis), increased atrial pressure from postoperative ventricular stunning, chemical stimulation from catecholamines and other inotropic agents and reflex sympathetic activation from volume loss, anaemia or pain[7,8].

Historically, postoperative AF was considered a relatively benign, transient and generally self-limiting complication of cardiac surgery. However, accumulating evidence now suggests otherwise. AF usually occurs in the early postoperative period, with 70% of events developing within 4 days, although AF may sometimes occur later, even after hospital discharge[6]. Indeed, postoperative AF may be persistent or recurrent in nature and AF is the commonest reason

for readmission after cardiac surgery, accounting for approximately 23% of readmissions[9].

Of particular concern is the recognition that post-operative AF is associated with an increased morbidity and mortality[10]. This includes a nearly threefold higher risk of perioperative stroke[11] as well as limitation of the patient's physical rehabilitation potential. The occurrence of AF also correlates with a higher rate of other serious complications such as ventricular arrhythmias, postoperative myocardial infarction, congestive cardiac failure, renal failure, increased use of inotropic medications and the need for an intra-aortic balloon pump[3,6]. Furthermore, treatment of AF after cardiac surgery results in prolonged hospitalization after cardiac surgery[3], as well as an excess utilization of hospital resources and increased hospital costs[12].

Given the importance of AF for patient outcome, a wide variety of prophylactic pharmacologic strategies have been evaluated. The most widely studied drugs for prophylaxis are the beta-adrenergic receptor blockers. Indeed, prophylactic therapy with beta-blockers is effective in reducing the frequency of postoperative AF. A meta-analysis of 28 trials demonstrated a significant increase in the percentage of postoperative AF from 31% in the control group to 18% in the beta-blocker group[13]. However, significant variability in results was found between trials, the reasons for which have not yet fully been explained, and appears to be more complex than being simply due to the specific beta-blockers used or the proportion of patients taking the drug[14]. It is also possible that this effect may in part be attributable to beta-blocker withdrawal in some of those patients randomized to the placebo arms. Certainly, the withdrawal of beta-blockers can lead to an increased incidence of postoperative AF[15]. Of note, even treatment with beta-blockers does not markedly reduce hospital stay after surgery[14].

The current ESC/ACC/AHA guidelines suggest beta-blockers as a first-line medication for prevention of AF after CABG in patients without contraindications[16]. Importantly, these drugs should be recommenced postoperatively, without delay, to minimize arrhythmia development. The recently issued UK National Institute for Health and Clinical Excellence (NICE) Guidelines on AF management[17] begin in a more pragmatic manner, by emphasizing that in the prophylaxis and management of post-operative AF, the appropriate use of antithrombotic therapy and correction of identifiable precipitants (such as electrolyte imbalance or hypoxia) is initially recommended. The guideline then recommends that in patients undergoing cardiothoracic surgery, the risk of post-operative AF should be reduced by the administration of one of the following: amiodarone, a beta-blocker, sotalol or rate-limiting calcium antagonists. In addition, in patients undergoing cardiac surgery on pre-existing beta-blocker therapy, this treatment should be continued unless contraindications develop (such as post-operative bradycardia or hypotension). Unless contraindicated, a rhythm control strategy (e.g. cardioversion) was recommended as the initial option for the treatment of post-operative AF following cardiothoracic surgery.

Pharmacotherapy for the management of post-operative AF

Sotalol

Sotalol is a unique beta-blocker, with potassium channel blocking properties (Class II and III antiarrhythmic effects), and has been used for the prevention of AF after cardiac surgery. A meta-analysis of eight randomized trials with a total of 1279 patients has shown convincingly that sotalol reduces the percentage of patients with postoperative AF (37% in controls, vs. 17% in the sotalol treatment group)[14]. The frequency of side effects for sotalol was comparable to that for beta-blocker usage. Nonetheless, while sotalol appears to be relatively safe in clinical trials, it is important to note that patients included in the studies were carefully selected to minimize the risk of ventricular proarrhythmia and excessive QT-interval prolongation. The potential for promotion of ventricular proarrhythmias with sotalol aside, should this drug be recommended in place of other beta-blockers which have only class II properties? Some studies specifically addressed this question. In comparative studies, the prophylactic use of sotalol was associated with a lower frequency of postoperative AF (Table 1) as well as less postoperative supraventricular tachycardia (SVT)[18–21]. In one study, sotalol appeared to be more effective than propranolol in preventing SVT, but the difference did not reach statistical significance[22]. No life-threatening proarrhythmia was reported in the sotalol group in this study.

What about combinations of antiarrhythmic drugs that include sotalol? In general, these should be used by specialists, as the risk of proarrhythmia and other adverse effects is greater. Interestingly, combination therapy with amiodarone plus metoprolol or sotalol had a significantly lower frequency of AF compared with those receiving placebo, but that reduction in frequency of AF with metoprolol alone was not significant[23].

Given the evidence apparently in favour of sotalol, should those stabilized on other beta-blockers be switched? It should be noted that sotalol has an appreciable Class III action only at doses > 240 mg/day, and at the low doses commonly prescribed in the

UK, the main antiarrhythmic effect is its Class II (i.e. beta-blocker) action. Given that sotalol has some beta-blocker activity, it could be assumed that the risk of AF switching drugs should be relatively low; however, there are currently no direct data available to justify the change. Thus, additional studies are needed before firm conclusions can be drawn. Of course, if this drug is prescribed, the dose should be titrated carefully with regular QT interval monitoring in order minimize side effects, while the drug should only be used cautiously in subjects of small stature as well as in the presence of renal insufficiency.

Amiodarone

In a recent meta-analysis, amiodarone – a class III anti-arrhythmic drug – may be an effective and safe choice for postoperative AF prophylaxis[14]. Importantly, a loading period of 7 days or longer is required to achieve a significant reduction in the incidence of postoperative AF[24]. Whether amiodarone is superior to beta-blockers in the prophylaxis of postoperative AF is unclear. However, the combination of amiodarone and metoprolol after cardiac surgery has been demonstrated to be more effective than metoprolol alone in the prevention of AF[23]. In one study, amiodarone even tended to be superior over propranolol for AF prevention[25]. However, this effect may in part be attributable to the fact that 42% of the patients in the amiodarone group continued to use beta-blockers. No direct comparison of amiodarone treatment with sotalol treatment has been performed and, thus, amiodarone is a good alternative in those with contraindications to beta-blockers.

Magnesium

A series of studies have shown that serum hypomagnesaemia is a common occurrence following CABG and other types of cardiac surgery[26]. In a recent meta-analysis of 20 randomized trials enrolling a total of 2490 patients, magnesium supplementation reduced the frequency of AF from 28% in the control group to 18% in the treatment group, but with significant heterogeneity between trials[27]. In addition, a positive effect for intravenous magnesium administration was demonstrated in another systematic review and meta-analysis[28]. Moreover, combination therapy with magnesium and sotalol markedly reduced the occurrence of AF after cardiac surgery, when compared to either sotalol or magnesium alone[29]. However, these results were not confirmed in a smaller but similar trial[30].

While isolated magnesium administration is not a first-line choice for prophylaxis of AF after cardiac surgery, it may be helpful in combination with other drugs. The randomized clinical trial presented by Behmanesh *et al.*[31] in this issue demonstrates that a combination of the cardio-selective beta-blocker bisoprolol with magnesium is safe and effective for the prevention of postoperative AF. Importantly, this effect was shown in the presence of a control group who remained on their preoperative treatment with beta-blockers. It is also noteworthy that the suggested regimen was particularly efficacious in elderly patients, with an associated reduction in post-operative hospital stay.

Other drugs and changing perspectives

An increasing body of evidence suggests a link between AF and inflammation. Studies have suggested that inflammation may contribute to both the initiation and persistence of this arrhythmia[32].

Why is this relevant to cardiac surgery? Inflammation associated with cardio-surgical procedures, together with catecholamine release, was suggested as having a pivotal role in postoperative AF[33]. Amar *et al.*[34] reported that patients who developed AF after major thoracic surgery had a nearly twofold increase in postoperative C-reactive protein (CRP) levels in comparison to control subjects. The HMG-coenzyme A reductase inhibitors (statins) also have a long-recognized property to reduce inflammation[35]. The protective effects of statins against AF were demonstrated in patients with stable chronic coronary artery disease[36]. Furthermore, statins may reduce the frequency of AF recurrence after successful cardioversion[37] as well as the risk of

Table 1. *Sotalol versus other beta-blockers for the prevention of postoperative atrial arrhythmias*

Study	Beta-blockers in control group	Efficacy of sotalol vs. beta-blockers	Beta-blockers	Sotalol
Sanjuan *et al.*[18]	Atenolol	↑	22	10
Nystrom *et al.*[19]	Not specified	↑	29	10
Parikka *et al.*[20]	Metoprolol	↑	32	16
Janssen *et al.*[22]	Metoprolol	↑	15.3	2.4
Suttorp *et al.*[21]	Propranolol	NS	13.7–18.8	10.9–13.9

NS = not significant

recurrent ventricular tachyarrhythmias in patients with an implantable cardioverter-defibrillator[38].

Given these data, statins may have a positive effect on the risk of postoperative AF. Three studies have evaluated the impact of statin treatment on the risk of AF after thoracic surgery, and all of them have consistently reported a beneficial effect[39–41]. Interestingly, the effects of statins on postoperative AF was independent of CRP levels, and one may speculate that other antioxidant or cell membrane fatty acid-modulating activities may be responsible for this, possibly by altering transmembrane ion channel properties[42]. The place of statins in the prophylaxis of postoperative AF needs to be estimated in larger prospective trials. Indeed, the effect that concomitant statin treatment might have on AF (despite beta-blocker prophylaxis), shown the study by Behmanesh *et al.*[31], merits consideration.

In a similar manner to the statins, the n-3 poly-unsaturated fatty acids (PUFAs) may have anti-arrhythmic properties related to putative anti-inflammatory effects. In one randomized trial, 2 g/day PUFA administration during hospitalization in patients undergoing CABG substantially reduced the incidence of postoperative AF (by 54.4%) and was associated with a shorter in-hospital stay[43].

Conclusion

In conclusion, the importance of AF as a cardiac arrhythmia should not be underestimated, particularly during the perioperative period. The substantial morbidity, mortality and health-care burden imparted by this arrhythmia continues to rise. Current rhythm management strategies remain sub-optimal and the quest for the optimal drug prophylaxis against post-operative AF remains far from over. Perhaps we need to look beyond antiarrhythmic drugs, as combination management with drugs that influence the inflammatory state associated with AF, such as statins, PUFAs and/or magnesium, may optimize our approach to this common condition. Clearly, perspectives are changing in our management of this arrhythmia.

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