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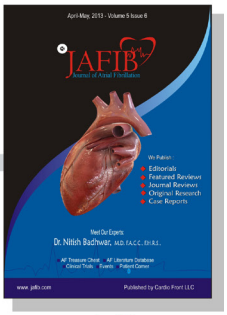

Post-operative Atrial Fibrillation – Pathophysiology, Treatment and Prevention

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Abstract

Atrial fibrillation occurring after cardiac surgery has been the subject of intensive research over the past decades. However, the incidence remains high, despite numerous preventive and treatment strategies. In addition, several reports show that the impact of post-operative atrial fibrillation (POAF) is high. It is an independent risk factor for mortality after several years. These findings make clear that the pathophysiology of POAF is not fully understood and POAF-associated risks to some extent might be underestimated. On the one hand, excessive triggers during the acute post operative phase after cardiac surgery might initiate AF even in atria with low vulnerability. On the other hand, many patients undergoing surgery have an atrial substrate at the time of operation promoting AF not only in the post-operative phase but also in the days and weeks thereafter. Progress in our understanding of the AF mechanisms in general has provided valuable insights into processes involved in atrial structural remodeling due to advanced age, hypertension, obesity, and congestive heart failure. These patient characteristics strongly contribute to cardiac disease, predict POAF and likely have an impact on the risk of thrombus formation in the weeks and months after cardiac surgery. For a better understanding of the mechanisms involved, it is important to not only recognize the occurrence of POAF by continuous monitoring after surgery, but also to identity the extent of atrial vulnerability to AF in these patients.

Introduction

Post-operative atrial fibrillation (POAF) is an important complication after cardiac surgery, which increases short-term hospitalization costs[1] and more importantly, decreases long-term survival.[2,3] 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).[4] 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.[5] 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,[6,7] to sometimes only qualification as AF if it requires therapy.[1] In general, AF is defined as an episode with irregular RR-intervals without a traceable p-wave, during at least 10 seconds.[8,9] It is important to acknowledge even the short episodes of AF,[6] because of the progressive nature of the arrhyth-

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mia,[10,11] but also because even a low AF burden significantly increases the stroke rate.[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.[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.[2,3,14] Of note, some of the AF episodes may remain unnoticed as they can be asymptomatic both during hospitalization and after discharge.[15-17]

Indeed, several studies in patients undergoing cardiac surgery have shown recurrence of AF after discharge.[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.[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.[21] Interestingly, multivariate analysis showed reduced left ventricular ejection fraction, which can cause atrial structural remodeling, to predict recurrences of POAF independently.[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.[17] The value of continuous monitoring seems essential in detecting the true POAF burden,[13] as the importance of asymptomatic "silent AF" in patients with a comparable risk profile as the POAF population has recently been emphasized.[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.[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, [9] depending on the severity of the underlying substrate.[23] Although inducibility of AF by pacing in normal atrial structure is dependent on the protocol of pacing,[24] it has a predictive value for the occurrence of POAF. [25,26] This suggests higher susceptibility for AF at least in some of the patients who subsequently develop POAF.[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.[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.[29] The canine sterile pericarditis model, in which application of sterile talc and subsequent pericarditis enhanced AF susceptibility, supports this hypothesis.[30] Administration of prednisone in this model reduced inflammation and as expected prevented AF.[31] Similarly colchicine was able to reduce the incidence of POAF, as a result of a reduction of the post-cardiotomy syndrome in humans.[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. [33] Indeed, the use of cardio pulmonary bypass is correlated with POAF incidence in most studies.[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.[35]

Furthermore, cardiopulmonary bypass might lead to insufficient cooling of the atria during the cardioplegic arrest.[36] This may induce a temporary substrate to initiate AF as a consequence of ischemia reperfusion injury.[36,37] Indeed, oxidative stress has been shown to cause a transient pro-arrhythmic effect in the post-operative setting.[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.[39] 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.[40] Similarly, the antioxidant N-acetylcysteine reduced the incidence of POAF in the early post-operative phase.[41] 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.[32] Acute atrial stretch decreases conduction velocity, increases conduction block and thereby the vulnerability of the atrial tissue to reentry. [42-44] In addition, premature atrial beats initiate post-operative AF,[45] partly aggravated by high sympathetic activation.[6] Possibly, they are also due to increased L-type calcium currents (Ica^{2+}) in patients developing POAF.[46]Indeed, milrinone, a phosphodiesterase inhibitor inotropic agent, increased the incidence of POAF significantly, presumably through a protein kinase-A activation leading to triggered activity.[47]

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 confine to solely acute phase POAF.

First, POAF is a disease of advanced age.[1,48] The atrial wall becomes fibrotic with age[49] and this has been identified as one of the most important structural substrates for AF perpetuation in the non-operative setting.[10,23] Prolonged signal averaged p-wave duration may reflect atrial fibrosis resulting in conduction delays and has been reported to be a predictor of POAF.[50-52] However, pre-operative AF was not excluded in all these studies.[50,51] 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,[48,53] hypertension,[1] obesity and systolic dysfunction.[1,53] The role of these co-morbidities in the perpetuation of AF has long been established.[8,54] Obesity has been associated with ERP shortening in left atria, diastolic dysfunction and left atrial dilation, all of which predispose to AF.[5]

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.[27] Accordingly, prolongation of conduction time with a higher percentage of double potentials and longer iso-electric intervals is linked to severely disturbed substrates. [10,23] 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.[55] 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 Ica^{2+}-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]

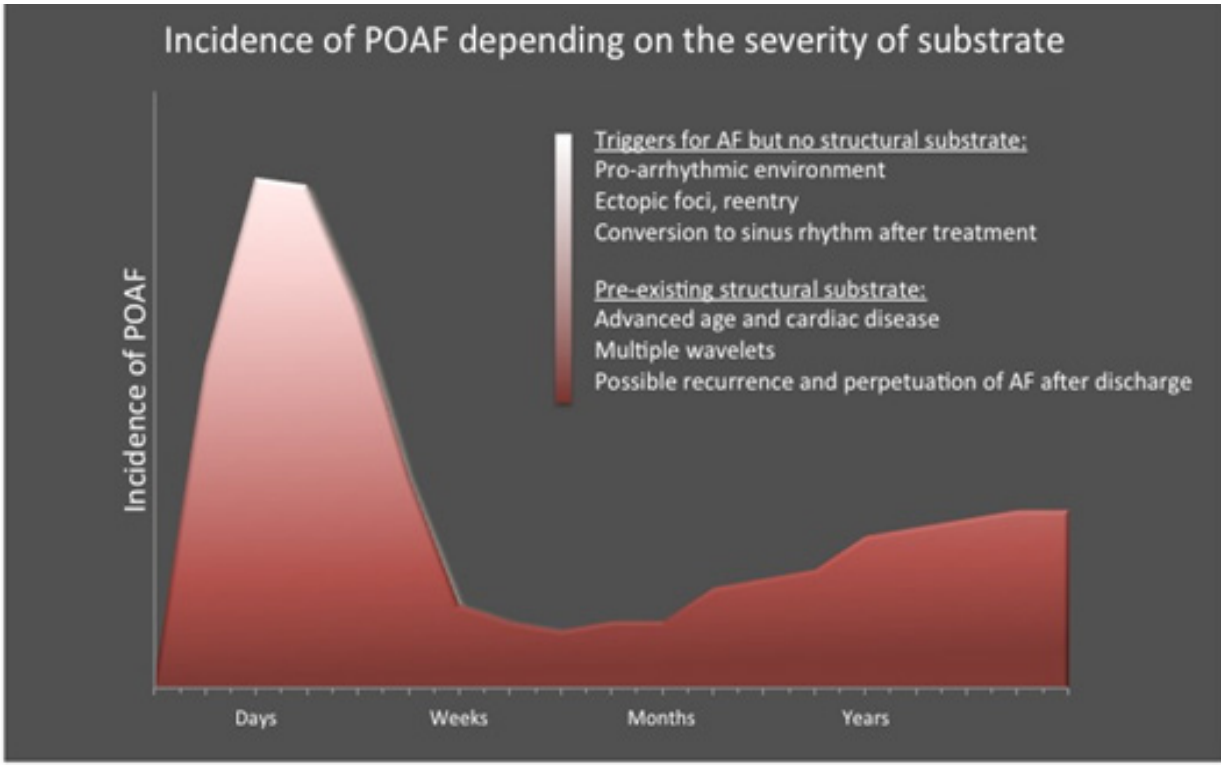
Sotalol

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 extra-cardiac 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



for the development of POAF, according to the international guidelines,[8,54] and should certainly be considered in patients with a contraindication for the use of β-blockers.[69,70]

Biatrial Pacing

Bi-atrial pacing significantly reduces the incidence of POAF,[67,73] 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.[52,77-79] However, when sensing and capture thresholds of the pacemaker leads are followed accurately, particularly simultaneous bi-atrial pacing effectively prevents POAF.[7,80-84] 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 refractoriness and reduces the p-wave duration and dispersion.[52,85] Also, overdrive pacing might prevent ectopic activity.[82] At the ventricular level, overdrive pacing after an ischemic episode has been shown to reduce infarct size, based on prevention of ischemic reperfusion injury.[86] 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 concerting enzyme inhibitors (ACEI's) may be as effective in preventing POAF as they are in preventing permanent AF in the general population.[87] Although administration of ACEI's have been associated with reduced POAF incidence, [48,88] 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,[89,90] or at least no reduction of new onset AF after cardiac surgery.[91] 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. [8] Benefits from other prophylactic measures, such as the administration of corticosteroids, colchicin, or vitamin C, are postulated in some reports,[92] but lack sufficient evidence for standard practice. The use of statins as a prophylactic measure has shown conflicting results[8] although a meta-analysis showed significant POAF reduction in statin treated arm. [93] Intravenous administration of magnesium might reduce the incidence of POAF, although conflicting results on this issue are reported.[67] In patients without renal dysfunction the probability of adverse effects is very low. In these patients some[69] 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.[94]

Oral Anticoagulation

In case of haemodynamically instable patients, cardioversion to sinus rhythm by direct current (ECV) or pharmacologically with ibutilide or amiodarone, should be pursued.[95] Also if patients are highly symptomatic or when rate control is difficult to achieve, electrical direct current shock is recommended[8,54]

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).[10] 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.[2,14,98,99]

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.

References

1. Aranki SF, Shaw DP, Adams DH, Rizzo RJ, Couper GS, VanderVliet M, et al. Predictors of Atrial Fibrillation After Coronary Artery Surgery. Circulation 1996; 94: 390-397
2. El-Chami MF, Kilgo P, Thourani V, Lattouf OM, Delurgio DB, Guyton RA, et al. New-Onset Atrial Fibrillation Predicts Long-Term Mortality After Coronary Artery Bypass Graft. JAC Elsevier Inc 2010 Mar 30; 55(13): 1370–6.
3. Villareal RP, Hariharan R, Liu BC, Kar B, Lee V-V, Elayda M, et al. Postoperative atrial fibrillation and mortality after coronary artery bypass surgery. J Am Coll Cardiol 2004 Mar; 43(5): 742–8.
4. Echahidi N, Pibarot P, O'Hara G, Mathieu P. Mechanisms, Prevention, and Treatment of Atrial Fibrillation After Cardiac Surgery. J Am Coll Cardiol 2008 Feb; 51(8): 793–801.
5. Murphy GJ, Ascione R, Caputo M, Angelini GD. Operative factors that contribute to post-operative atrial fibrillation: insights from a prospective randomized trial. Card Electrophysiol Rev. 2003 Jun; 7(2): 136–9.
6. Kalman JM, Munawar M, Howes LG, Louis WJ, Buxton BF, Gutteridge G, et al. Atrial fibrillation after coronary artery bypass grafting is associated with sympathetic activation. Ann Thorac Surg 1995 Dec; 60(6): 1709–15.
7. Debrunner M, Naegeli B, Genoni M, Turina M, Bertel O. Prevention of atrial fibrillation after cardiac valvular surgery by epicardial, biatrial synchronous pacing. Eur J Cardio-Thorac Surg 2004 Jan; 25(1): 16–20.
8. Camm AJ, Kirchhof P, Lip GYH, Schotten U, Savelieva I, Ernst

S, et al. Guidelines for the management of atrial fibrillation. The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC), Europace 2010; 12: 1360–1420
9. Konings KT, Kirchhof CJ, Smeets JR, Wellens HJ, Penn OC, Allessie MA. High-density mapping of electrically induced atrial fibrillation in humans. Circulation 1994; 89(4): 1665–80.
10. Schotten U, Verheule S, Kirchhof P, Goette A. Pathophysiological Mechanisms of Atrial Fibrillation: A Translational Appraisal. Physiol Rev. 2011 Jan; 91(1): 265–325.
11. Wijffels MCEF, Kirchhof CJHJ, Dorland R, Allessie MA. Atrial Fibrillation Begets Atrial Fibrillation. Circulation. 1995; 92: 1954-1968.
12. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, et al. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med. 2012 Jan 12; 366(2): 120–9.
13. Charitos EI, Stierle U, Ziegler PD, Baldewig M, Robinson DR, Sievers H-H, et al. A comprehensive evaluation of rhythm monitoring strategies for the detection of atrial fibrillation recurrence: insights from 647 continuously monitored patients and implications for monitoring after therapeutic interventions. Circulation. 2012 Aug 14;126(7):806–14.
14. Saxena A, Dinh DT, Smith JA, Shardey GC, Reid CM, Newcomb AE. Usefulness of Postoperative Atrial Fibrillation as an Independent Predictor for Worse Early and Late Outcomes After Isolated Coronary Artery Bypass Grafting (Multicenter Australian Study of 19,497 Patients). AJC Elsevier Inc 2012 Jan; 109(2): 219–25.
15. Landymore RWR, Howell FF. Recurrent atrial arrhythmias following treatment for postoperative atrial fibrillation after coronary bypass operations. Eur J Cardio-Thorac Surg 1990 Dec 31; 5(8): 436–9
16. Camm AJ, Corbucci G, Padeletti L. Usefulness of Continuous Electrocardiographic Monitoring for Atrial Fibrillation. AJC. Elsevier Inc 2012 Jul; 110(2): 270–6.
17. Funk M, Richards SB, Desjardins J, Bebon C, Wilcox H. Incidence, Timing, Symptoms, and Risk Factors for Atrial Fibrillation After Cardiac Surgery. Am J Crit Care 2003; 12: 424-433.
18. Cioffi G, Cemin C, Russo TE, Pellegrini A. Post-discharge recurrences of new-onset atrial fibrillation. Ital Heart J 2000 Oct; 1(10): 691-7.
19. D'Agostino RS, Jacobson J, Clarkson M. Readmission after cardiac operations: Prevalence, patterns, and predisposing factors. J Thorac Cardiovasc Surg 1999; 118: 823-32.
20. Daoud EG, Strickberger SA, Man KC, Goyal R, Deeb GM, Bolling SF, et al. Preoperative amiodarone as prophylaxis against atrial fibrillation after heart surgery. N Engl J Med. 1997 Dec 18; 337(25): 1785–91.
21. Antonelli D, Peres D, Freedberg NA, Feldman A, Rosenfeld T. Incidence of Postdischarge Symptomatic Paroxysmal Atrial Fibrillation in Patients Who Underwent Coronary Artery Bypass Graft. PACE 2004; 27(3): 365–7.
22. Papageorgiou P, Monahan K, Boyle NG, Seifert MJ, Beswick P, Zebede J, et al. Site-dependent intra-atrial conduction delay. Relationship to initiation of atrial fibrillation. Circulation. 1996 Aug; 94(3): 384–9.
23. Allessie MA, de Groot NMS, Houben RPM, Schotten U, Boersma E, Smeets JL, et al. Electropathological Substrate of Long-Standing Persistent Atrial Fibrillation in Patients With Structural Heart DiseaseClinical Perspective. Circ Arrhythm Electrophysiol 2010; 3: 606-615.
24. Kumar S, Kalman JM, Sutherland F, Spence SJ, Finch S, Sparks PB. Atrial fibrillation inducibility in the absence of structural heart disease or clinical atrial fibrillation: critical dependence on induction protocol, inducibility definition, and number of inductions. Circ Arrhythm Electrophysiol 2012 Jun; 5(3): 531–6.
25. Hakala T, Berg E, Hartikainen JEK, Hippelainen MJ. Intraoperative high-rate atrial pacing test as a predictor of atrial fibrillation after coronary artery bypass surgery. Ann Thorac Surg 2002 Dec; 74(6): 2072–5.
26. Kanagaratnam P, Kojodjojo P, Peters NS. Electrophysiological abnormalities occur prior to the development of clinical episodes of atrial fibrillation: observations from human epicardial mapping. PACE 2008 Apr; 31(4): 443–53.
27. Sanders P. Electrical Remodeling of the Atria in Congestive Heart Failure: Electrophysiological and Electroanatomic Mapping in Humans. Circulation 2003 Sep; 108(12): 1461–8.
28. Maesen B, Nijs J, Maessen J, Allessie M, Schotten U. Post-operative atrial fibrillation: a maze of mechanisms. Europace 2012 Jan; 14(2): 159–74.
29. Ishii Y. Inflammation of Atrium After Cardiac Surgery Is Associated With Inhomogeneity of Atrial Conduction and Atrial Fibrillation. Circulation 2005 Jun; 111(22): 2881–8.
30. Pagé PL, Plumb VJ, Okumura K, WALDO AL. A new animal model of atrial flutter. J Am Coll Cardiol 1986 Oct; 8(4): 872–9.
31. GOLDSTEIN RN, RYU K, KHRESTIAN C, van WAGONER DR, WALDO AL. Prednisone Prevents Inducible Atrial Flutter in the Canine Sterile Pericarditis Model. J Cardiovasc Electrophysiol. 2007 Sep; 0(0)
32. Imazio M, Brucato A, Ferrazzi P, Rovere ME, Gandino A, Cemin R, et al. Colchicine Reduces Postoperative Atrial Fibrillation: Results of the Colchicine for the Prevention of the Postpericardiotomy Syndrome (COPPS) Atrial Fibrillation Substudy. Circulation 2011 Nov; 124(21): 2290–5..
33. Bruins P, Velthuis te H, Yazdanbakhsh AP, Jansen PG, van Hardevelt FW, de Beaumont EM, et al. Activation of the complement system during and after cardiopulmonary bypass surgery: postsurgery activation involves C-reactive protein and is associated with postoperative arrhythmia. Circulation 1997 Nov 18; 96(10): 3542–8.
34. Ascione R, Caputo M, Calori G, Lloyd CT, Underwood MJ, Angelini GD. Predictors of atrial fibrillation after conventional and beating heart coronary surgery: A prospective, randomized study. Circulation 2000 Sep; 102(13): 1530–5.
35. Ho KM, Tan JA. Benefits and Risks of Corticosteroid Prophylaxis in Adult Cardiac Surgery. Circulation 2009; 119: 1853-1866.
36. Tchervenkov CI, Wynands JE, Symes JF, Malcolm ID, Dobell ARC, Morin JE. Persistent Atrial Activity during Cardioplegic Arrest: A Possible Factor in the Etiology of Postoperative Supraventricular Tachyarrhythmias. The Society of Thoracic Surgeons; 1983 Oct 1;36(4):437–43.
37. Cox JL. A perspective of postoperative atrial fibrillation in cardiac operations. Ann Thorac Surg 1993 Sep 1;56(3):405–9.
38. Reilly SN, Jayaram R, Nahar K, Antoniades C, Verheule S, Channon KM, et al. Atrial Sources of Reactive Oxygen Species

Vary With the Duration and Substrate of Atrial Fibrillation: Implications for the Antiarrhythmic Effect of Statins. Circulation 2011 Sep 6;124(10):1107–17.
39. Patti G, Chello M, Candura D, Pasceri V, D'Ambrosio A, Covino E, et al. Randomized trial of atorvastatin for reduction of postoperative atrial fibrillation in patients undergoing cardiac surgery: results of the ARMYDA-3 (Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery) study. Circulation 2006 Oct 3;114(14):1455–61.
40. Carnes CA, Chung MK, Nakayama T, Nakayama H, Baliga RS, Piao S, et al. Ascorbate Attenuates Atrial Pacing-Induced Peroxynitrite Formation and Electrical Remodeling and Decreases the Incidence of Postoperative Atrial Fibrillation. Circulation Research 2001 Sep 14;89(6):e32–8.
41. Ozaydin M, Peker O, Erdogan D, Kapan S, Turker Y, Varol E et al., N-acetylcysteine for the prevention of postoperative atrial fibrillation: a prospective, randomized, placebo-controlled pilot study. European Heart Journal. 2008 Mar 1;29(5):625–31.
42. Ravelli F, Masè M, del Greco M, Marini M, Disertori M. Acute atrial dilatation slows conduction and increases AF vulnerability in the human atrium. J Cardiovasc Electrophysiol. 2011 Apr;22(4):394–401.
43. Allessie M. Stretch and Speed: A Complicated Couple. J Cardiovasc Electrophysiol. 2010 Dec 6;22(4):402–4.
44. Elvan A, Adiyaman A, Beukema RJ, Sie HT, Allessie MA. Electrophysiological effects of acute atrial stretch on persistent atrial fibrillation in patients undergoing open heart surgery. HRTHM. Elsevier; 2012 Nov 22;:1–9.
45. Frost L, Christiansen EH, Mølgaard H, Jacobsen CJ, Allermand H, Thomsen PE. Premature atrial beat eliciting atrial fibrillation after coronary artery bypass grafting. J Electrocardiol. 1995 Oct;28(4):297–305.
46. van Wagoner DR, Pond AL, Lamorgese M, Rossie SS, McCarthy PM, Nerbonne JM. Atrial L-Type $Ca2^{+}$ Currents and Human Atrial Fibrillation. Circ Res 1999;85:428-436.
47. Fleming GA, Murray KT, Yu C, Byrne JG, Greelish JP, Petracek MR, et al. Milrinone Use Is Associated With Postoperative Atrial Fibrillation After Cardiac Surgery. Circulation 2008 Oct 14;118(16):1619–25.
48. Mathew JP. A Multicenter Risk Index for Atrial Fibrillation After Cardiac Surgery. JAMA 2004 Apr 14;291(14):1720–9.
49. Goette A, Juenemann G, Peters B, Klein HU, Roessner A, Huth C et al., Determinants and consequences of atrial fibrosis in patients undergoing open heart surgery. Cardiovasc Res. 2002 Apr 30;54(2):390–6.
50. Zaman AGA, Archbold RAR, Helft GG, Paul EAE, Curzen NPN, Mills PGP. Atrial fibrillation after coronary artery bypass surgery: a model for preoperative risk stratification. Circulation. 2000 Mar 27;101(12):1403–8.
51. Amar D, Shi W, Hogue CW, Zhang H. American College of Cardiology Foundation | Journal of the American College of Cardiology | Clinical prediction rule for atrial fibrillation after coronary artery bypass grafting. J Am Coll Cardiol 2004;44:1248–53.
52. Goette A, MITTAG J, FRIEDL A, BUSK H, JEPSEN MS, HARTUNG WM, et al. Pacing of Bachmann's Bundle After Coronary Artery Bypass Grafting. PACE 2002 Jul;25(7):1072–8.
53. Zacharias A, Schwann TA, Riordan CJ, Durham SJ, Shah AS, Habib RH. Obesity and risk of new-onset atrial fibrillation after cardiac surgery. Circulation 2005 Nov 22;112(21):3247–55.
54. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation 2006. pages e257–354.
55. Melduni RM, Suri RM, Seward JB, Bailey KR, Ammash NM, Oh JK, et al. Diastolic dysfunction in patients undergoing cardiac surgery: a pathophysiological mechanism underlying the initiation of new-onset post-operative atrial fibrillation. J Am Coll Cardiol 2011 Aug 23;58(9):953–61.
56. Savelieva I, Camm AJ. Atrial fibrillation and heart failure: natural history and pharmacological treatment. Europace (2004) 5; S5-S19.
57. Asher CR, Miller DP, Grimm RA, Cosgrove DM III, Chung MK. Analysis of risk factors for development of atrial fibrillation early after cardiac valvular surgery. Am J Cardiol 1998 Oct;82(7):892–5.
58. Soylu M, Demir AD, Ozdemir O, Soylu O, Topaloğlu S, Kunt A, et al. Increased dispersion of refractoriness in patients with atrial fibrillation in the early postoperative period after coronary artery bypass grafting. J Cardiovasc Electrophysiol. 2003 Jan;14(1):28–31.
59. De Jong AM, Maass AH, Oberdorf-Maass SU, Van Veldhuisen DJ, Van Gilst WH, Van Gelder IC. Mechanisms of atrial structural changes caused by stretch occurring before and during early atrial fibrillation. Cardiovasc Res. 2011 Feb 15;89(4):754–65
60. Ad NN, Snir EE, Vidne BAB, Golomb EE. Histologic atrial myolysis is associated with atrial fibrillation after cardiac operation. Ann Thorac Surg. 2001 Aug 31;72(3):6–6.
61. Ak K, Akgun S, Tecimer T, Isbir CS, Civelek A, Tekeli A, et al. Determination of Histopathologic Risk Factors for Postoperative Atrial Fibrillation in Cardiac Surgery. The Ann Thorac Surg 2005 Jun;79(6):1970–5.
62. Dupont E, Ko Y, Rothery S, Coppen SR, Baghai M, Haw M, et al., The gap-junctional protein connexin40 is elevated in patients susceptible to postoperative atrial fibrillation. Circulation. 2001 Feb 12;103(6):842–9.
63. RYU K, Li L, Khrestian CM, Matsumoto N, Sahadevan J, Ruehr ML, et al. Effects of sterile pericarditis on connexins 40 and 43 in the atria: correlation with abnormal conduction and atrial arrhythmias. Am J Physiol Heart Circ Physiol 2007 293: H1231–H1241.
64. Allessie MA, Boyden PA, Camm AJ, Kleber AG, Lab MJ, Legato MJ, et al. Pathophysiology and Prevention of Atrial Fibrillation. Circulation 2001 Feb 6;103(5):769–77.
65. Omorphos S, Hanif M, Dunning J. Are prophylactic beta-blockers of benefit in reducing the incidence of AF following coronary bypass surgery? Interactive CardioVascular and Thoracic Surgery. 2004 Dec;3(4):641–6.
66. T Bruce Ferguson J, Coombs LP, Peterson ED, Database FTS-OTSNACS. Preoperative β-Blocker Use and Mortality and Morbidity Following CABG Surgery in North America. JAMA 2002 May 1;287(17):2221–7.

67. Crystal E. Interventions on Prevention of Postoperative Atrial Fibrillation in Patients Undergoing Heart Surgery: A Meta-Analysis. Circulation 2002 Jun 10;106(1):75–80.
68. Wann LS, Curtis AB, January CT, Ellenbogen KA, Lowe JE, Estes NAM III, et al. 2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Updating the 2006 Guideline). J Am Coll Cardiol 2011 Jan;57(2):223–42.
69. Dunning J, Treasure T, Versteegh M, Nashef SAM. Guidelines on the prevention and management of de novo atrial fibrillation after cardiac and thoracic surgery. Eur J Cardio-Thorac Surg 2006 Dec;30(6):852–72.
70. Mitchell LB, Committeeb CAFG. Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: Prevention and Treatment of Atrial Fibrillation Following Cardiac Surgery. CJCA. Elsevier Inc; 2011 Feb 8;27(1):91–7
71. Giri SS, White CMC, Dunn ABA, Felton KK, Freeman-Bosco LL, Reddy PP, et al. Oral amiodarone for prevention of atrial fibrillation after open heart surgery, the Atrial Fibrillation Suppression Trial (AFIST): a randomised placebo-controlled trial. Lancet 2001 Mar 16;357(9259):7–7
72. Bagshaw SM, Galbraith PD, Mitchell LB, Sauve R, Exner DV, Ghali WA. Prophylactic amiodarone for prevention of atrial fibrillation after cardiac surgery: a meta-analysis. Ann Thorac Surg 2006 Nov;82(5):1927–37.
73. Burgess DC, Kilborn MJ, Keech AC. Interventions for prevention of post-operative atrial fibrillation and its complications after cardiac surgery: a meta-analysis. Eur Heart J. 2006 Nov 13;27(23):2846–57.
74. Patel AA, White CM, Gillespie EL, Kluger J, Coleman CI. Safety of amiodarone in the prevention of postoperative atrial fibrillation: a meta-analysis. Am J Health Syst Pharm. 2006 May 1;63(9):829–37.
75. Butler J, Harriss DR, Sinclair M, Westaby S. Amiodarone prophylaxis for tachycardias after coronary artery surgery: a randomised, double blind, placebo controlled trial. Heart. 1993 Jul 1;70(1):56–60.
76. Hohnloser SH, Meinertz T, Dammbacher T, Steiert K, Jähnchen E, Zehender M, et al. Electrocardiographic and antiarrhythmic effects of intravenous amiodarone: Results of a prospective, placebo-controlled study. Am Heart J 1991 Jan;121(1):89–95.
77. KURZ DJ, Naegeli B, KUNZ M, Genoni M, NIEDERHAUSER U, Bertel O. Epicardial, Biatrial Synchronous Pacing for Prevention of Atrial Fibrillation after Cardiac Surgery. PACE 1999 May;22(5):721–6.
78. Gerstenfeld EP, Hill MRS, French SN, Mehra R, Rofino K, Vander Salm TJ, et al. Evaluation of right atrial and biatrial temporary pacing for the prevention of atrial fibrillation after coronary artery bypass surgery. JAC. Am Coll Cardio Found; 1999;33(7):1981–8.
79. Chung MK, Augostini RS, Asher CR, Pool DP, Grady TA, Zikri M, et al. Ineffectiveness and potential proarrhythmia of atrial pacing for atrial fibrillation prevention after coronary artery bypass grafting. Ann Thor Surg 2000 Apr;69(4):1057–63.
80. Gerstenfeld EP, Khoo M, Martin RC, Cook JR, Lancey R, Rofino K, et al. Effectiveness of bi-atrial pacing for reducing atrial fibrillation after coronary artery bypass graft surgery. J Interv Card Electrophysiol. 2001 Sep;5(3):275–83.
81. Levy T, Fotopoulos G, Walker S, Rex S, Octave M, Paul V, et al. Randomized Controlled Study Investigating the Effect of Biatrial Pacing in Prevention of Atrial Fibrillation After Coronary Artery Bypass Grafting. Circulation 2000 Sep 19;102(12):1382–7.
82. Daoud EG, Dabir R, Archambeau M, Morady F, Strickberger SA. Randomized, Double-Blind Trial of Simultaneous Right and Left Atrial Epicardial Pacing for Prevention of Post-Open Heart Surgery Atrial Fibrillation. Circulation. 2000 Aug 15;102(7):761–5.
83. Blommaert DD, Gonzalez MM, Mucumbitsi JJ, Gurné OO, Evrard PP, Buche MM, et al. Effective prevention of atrial fibrillation by continuous atrial overdrive pacing after coronary artery bypass surgery. JAC 2000 Apr 30;35(6):1411–5.
84. Neto VAV, Costa RR, Da Silva KRK, Martins ALMA, Escobar LFL, Moreira LFPL, et al. Temporary atrial pacing in the prevention of postoperative atrial fibrillation. PACE 2006 Dec 31;30 Suppl 1:S79–S83.
85. Fan K, Lee KL, Chiu CS, Lee JW, He GW, Cheung D, et al. Effects of biatrial pacing in prevention of postoperative atrial fibrillation after coronary artery bypass surgery. Circulation 2000 Aug 14;102(7):755–60.
86. Vanagt WY, Cornelussen RN, Baynham TC, Van Hunnik A, Poulina QP, Babiker F, et al. Pacing-induced dyssynchrony during early reperfusion reduces infarct size. J Am Coll Cardiol 2007 May 1;49(17):1813–9.
87. Mayson SE, Greenspon AJ, Adams S, Decaro MV, Sheth M, Weitz HH, et al., The changing face of postoperative atrial fibrillation prevention: a review of current medical therapy. Cardiol Rev. 2007 Sep;15(5):231–41.
88. Ozaydin M, Dede O, Varol E, Kapan S, Turker Y, Peker O, et al., Effect of renin-angiotensin aldosteron system blockers on postoperative atrial fibrillation. Int. J. Cardiol. 2008 Jul 21;127(3):362–7.
89. Miceli A, Capoun R, Fino C, Narayan P, Bryan AJ, Angelini GD, et al., Effects of angiotensin-converting enzyme inhibitor therapy on clinical outcome in patients undergoing coronary artery bypass grafting. JACC 2009 Nov 3;54(19):1778–84.
90. Rouleau JL, Warnica WJ, Baillot R, Block PJ, Chocron S, Johnstone D, et al., Effects of Angiotensin-Converting Enzyme Inhibition in Low-Risk Patients Early After Coronary Artery Bypass Surgery. Circulation. 2008;117:24-31
91. Rader F, van WAGONER DR, Gillinov AM, Blackstone EH. Preoperative angiotensin-blocking drug therapy is not associated with atrial fibrillation after cardiac surgery. Am Heart J. 2010 Aug;160(2):329–336.e1.
92. Masoud Eslami, Oral Ascorbic Acid in Combination with Beta-Blockers Is More Effective than Beta-Blockers Alone in the Prevention of Atrial Fibrillation after Coronary Artery Bypass Grafting. Texas Heart Institute Journal 2007;34(3):268.
93. Liakopoulos OJ, Choi Y-H, Kuhn EW, Wittwer T, Borys M, et al., Statins for prevention of atrial fibrillation after cardiac surgery: a systematic literature review. J Thorac Cardiovasc Surg. 2009 Sep;138(3):678–686.e1.
94. DUNNING J. What is the optimal medical treatment for stable cardiac surgical patients who go into atrial fibrillation after their operation? Interactive CardioVascular and Thoracic Surgery. 2004 Mar;3(1):46–51.
95. Fernando HC, Jaklitsch MT, Walsh GL, Tisdale JE, Bridges CD, Mitchell JD, et al. The Society of Thoracic Surgeons Practice

Guideline on the Prophylaxis and Management of Atrial Fibrillation Associated With General Thoracic Surgery: Executive Summary. ATS. Elsevier Inc; 2011 Sep 1;92(3):1144–52.
96. Daoud EG. Management of atrial fibrillation in the post-cardiac surgery setting. Cardiol Clin. 2004 Feb;22(1):159–66.
97. Epstein AE, Alexander JC, Gutterman DD, Maisel W, Wharton JM. AnticoagulationAmerican College of Chest Physicians Guidelines for the Prevention and Management of Postoperative Atrial Fibrillation After Cardiac Surgery. Chest 2005 Aug 1;128(2_suppl):24S–27S.
98. Filardo G, Hamilton C, Hamman B, Hebeler RF, Adams J, Grayburn P. New-Onset Postoperative Atrial Fibrillation and Long-Term Survival After Aortic Valve Replacement Surgery. ATS. Elsevier Inc; 2010 Aug 1;90(2):474–9.
99. Bramer S, van Straten AHM, Soliman Hamad MA, Berreklouw E, Martens EJ, Maessen JG. The impact of preoperative atrial fibrillation on early and late mortality after coronary artery bypass grafting. Eur J Cardio Thorac Surg 2010 Sep;38(3):373–9.