Post-operative atrial fibrillation: a maze of mechanisms

Bart Maesen1,2, Jan Nijs1, Jos Maessen1, Maurits Allessie2, and Ulrich Schotten2*

1Department of Cardiothoracic Surgery, University Hospital of Maastricht, PO Box 5800, 6202 AZ Maastricht, The Netherlands; and 2Department of Physiology, University Maastricht, PO Box 616, 6200 MD Maastricht, The Netherlands

Received 24 March 2011; accepted after revision 7 June 2011; online publish-ahead-of-print 6 August 2011

Post-operative atrial fibrillation (POAF) is one of the most frequent complications of cardiac surgery and an important predictor of patient morbidity as well as of prolonged hospitalization. It significantly increases costs for hospitalization. Insights into the pathophysiological factors causing POAF have been provided by both experimental and clinical investigations and show that POAF is ‘multi-factorial’. Facilitating factors in the mechanism of the arrhythmia can be classified as acute factors caused by the surgical intervention and chronic factors related to structural heart disease and ageing of the heart. Furthermore, some proarrhythmic mechanisms specifically occur in the setting of POAF. For example, inflammation and beta-adrenergic activation have been shown to play a prominent role in POAF, while these mechanisms are less important in non-surgical AF. More recently, it has been shown that atrial fibrosis and the presence of an electrophysiological substrate capable of maintaining AF also promote the arrhythmia, indicating that POAF has some proarrhythmic mechanisms in common with other forms of AF. The clinical setting of POAF offers numerous opportunities to study its mechanisms. During cardiac surgery, biopsies can be taken and detailed electrophysiological measurements can be performed. Furthermore, the specific time course of POAF, with the delayed onset and the transient character of the arrhythmia, also provides important insight into its mechanisms.

This review discusses the mechanistic interaction between predisposing factors and the electrophysiological mechanisms resulting in POAF and their therapeutic implications.

Keywords
Atrial fibrillation • Post-operative atrial fibrillation • Inflammation • Sympathetic activation • Oxidative stress • Atrial remodelling • Fibrosis • Ageing

Introduction

Atrial arrhythmias and atrial fibrillation (AF) in particular are well-known complications after cardiac surgery with a reported incidence between 10 and 60%.1–17 The incidence is higher in patients undergoing valve surgery than in patients undergoing coronary artery bypass surgery (CABG).12,7,8,10,11,17,18 Post-operative atrial arrhythmias also occur after non-cardiac surgery, especially after oesophagectomy,19 lung surgery,20–24 and large abdominal surgery.25–27 The incidence after non-cardiac surgery is, however, lower with incidences ranging from 0.3 to 29%.22,28,29 Postoperative atrial arrhythmias are associated with prolonged hospital stay, haemodynamic instability, an increased risk of stroke, and increased mortality.2–4,6,10,12,24,28,30–33

The exact pathophysiological mechanisms responsible for the onset and perpetuation of post-operative atrial arrhythmias are incompletely understood. Factors facilitating post-operative AF (POAF) can be classified in acute factors directly related to surgery (e.g. adrenergic stimulation) and factors that are reflecting a chronic and progressive process of remodelling or ageing of the heart (e.g. left atrial enlargement).34,35 These predisposing factors can on the one hand provoke triggers able to initiate the arrhythmia and on the other hand enhance the development of a substrate capable of perpetuating AF.

The association of POAF with specific kinds of surgery and the time course of the arrhythmia can help to better understand its mechanisms. First, the association of POAF with cardiac surgery and degree of structural heart disease suggests a direct role for
cardiac surgical trauma and pre-existing cardiac pathology in the occurrence of POAF. Secondly, the arrhythmia follows a specific time course. In most studies, the incidence peaks on the second day after surgery and rapidly declines to around 2% at discharge, suggesting that some of the pro-arrhythmic mechanisms require some time to become operative. Furthermore, the transient nature of the arrhythmia suggests a reversible mechanism, caused by factors which come into play shortly after surgery, but seem to subside on the long run.

This review discusses the mechanistic interaction between predisposing factors, alterations in intracellular signalling, and the electrophysiological mechanisms of POAF.

Epidemiology

The incidence of POAF after cardiac surgery varies considerably between different studies (Table 1). This variation in incidence is due to differences in patient demographics, techniques for rhythm monitoring and criteria for diagnosis. Mathew et al. found diverging POAF incidences according to different regions. The authors reported a similar POAF incidence among patients in the USA (33.7%), Canada (36.6%), Europe (34%), and the Middle East (41.6%), but a lower POAF incidence in South America (17.4%) and Asia (15.7%). Another example that stresses the importance of patient demographics is the identification of Caucasian race as an independent predictor of POAF in several studies. Fluctuation in reported POAF incidence due to differences in rhythm follow-up is illustrated by the comparison of the following three studies. Siebert et al. found an incidence as low as 9.8% after isolated CABG. However, only AF occurrence during stay on the intensive care unit was studied, with a mean period of 2.3 days. In another example, Leitch et al. found an incidence of 17.2% after isolated CABG. Again, only during the first 48 h AF and atrial flutter (AFL) were detected by continuous electrocardiogram (ECG) monitoring. After these 48 h, AF and AFL were solely identified if clinical symptoms occurred. On the other hand, in a large retrospective study Shen et al. found an incidence of 29% after isolated CABG. In this report, all patients over the past years is due to more frequent use of beta-blockers and other anti-arrhythmic drugs. 

Mechanisms based on acute factors

Inflammation

The similarity between the time course of AF occurrence after cardiac surgery and the activation of the complement system with the release of pro-inflammatory cytokines suggests an inflammatory component in the mechanism triggering POAF. Complement activation during cardiac surgery with cardiopulmonary bypass (CPB) occurs in two steps. The first phase occurs during CPB, results from interaction of blood with the surface of
Table 1  Incidence of post-operative atrial fibrillation

| Author          | Year of publication | n (% male) | Age (overall) | Study type | Multicentre (number) | Definition of POAF | CPB (% of patients) | History of AF | Incidence of POAF (%) |
|-----------------|---------------------|------------|---------------|------------|----------------------|-------------------|---------------------|---------------|----------------------|
| Fuller et al    | 1989                | 1666 (88.6) | 62.2 ± 12.3   | Prospective| No                   | AF detected by continuous telemetry or by clinical symptoms and signs | 100                | None         | 28.4                  |
| Leitch et al    | 1990                | 5807 (NS)  | NS            | Prospective| No                   | AF detected by continuous telemetry or by clinical symptoms and signs | 100                | None         | 17.2                  |
| Creswell et al  | 1993                | 3983 (66.7) | 67            | Prospective| No                   | AF detected by continuous telemetry or by clinical symptoms and signs | 100                | None         | 34.6 (1378/3983)      |
| Aranki et al    | 1996                | 570 (69)   | NS            | Prospective| No                   | New onset AF, AFL, PAT | 100                | None         | 29.6 (1143/3885)      |
| Almassi et al   | 2001                | 3853 (98.6) | 66.8 ± 8.3    | Prospective| No                   | AF requiring medication/pacing | 100                | None         | 32.9                  |
| Siebert et al   | 2002                | 10050 (71) | NS            | Prospective| No                   | NS                | 100                | None         | 6.8                  |
| Mahoney et al   | 2004                | 4657 (79.8) | 67            | Retrospective| Yes (70)            | Entry in case report form AF detected by ECG | 100                | None         | 67.9 ± 9.6            |
| Mathew et al    | 2004                | 6777 (73.8) | NS            | Retrospective| Yes(12)             | AF of any duration, any time based on ECG | 100                | None         | 66 ± 7.8              |
| Villareal et al | 2006                | 1200 (66.6) | 66.2 ± 9.5    | Retrospective| No                   | No                | 100                | None         | 69.2 ± 7.6            |
| Barach et al    | 2009                | 9495 (73.2) | NS            | Retrospective| No                   | NS                | 100                | None         | 66 ± 6 (28% arrhythmias) |
| Mariscalco et al| 2009                | 571 (78)   | NS            | Retrospective| AF, AFL > 15 min    | NS                | 100                | None         | 623 ± 12.9           |
| Ahlsson et al   | 2010                | 10390 (65) | NS            | Retrospective| No                   | No                | 100                | None         | 47.5                  |

Table showing incidences for POAF in different studies. 

n, number of patients included; CABG, coronary artery bypass grafting; AVR, aortic valve replacement; MVR, mitral valve repair/replacement; NS, not stated; CPB, cardiopulmonary bypass; AFL, atrial flutter; PAT, paroxysmal atrial tachycardia; OPCAB, off-pump coronary artery bypass.
Table 2 Risk factors for post-operative atrial fibrillation

| Author          | Fuller et al. | Leitch et al. | Creswell et al. | Aranki et al. | Zaman et al. | Hakala et al. | Mathew et al. | Auer et al. | Zacharias et al. | Banach et al. | Shen et al. |
|-----------------|---------------|---------------|-----------------|---------------|--------------|---------------|---------------|-------------|-----------------|---------------|-------------|
| Year of publication | 1989         | 1990         | 1993           | 1996         | 2000         | 2002         | 2004         | 2005       | 2005           | 2006         | 2010        |
| Number of Patients | 1666       | 5807        | 3983           | 570          | 3855         | 326          | 88           | 4657       | 253           | 8051         | 1200       |

**Risk Factors**

| Risk Factor | P | OR | Reference |
|-------------|---|----|-----------|
| **Age**     | 0.0001 | 1.7 | 10 yr decile |
| **History of AF** | 0.001 | 2.11 |  
| **COPD**    | 0.006 | 1.5 |  
| **Hypertension** | ns | 1.6 | 0.03 |
| **Male gender** | 0.02 | 1.7 |  
| **Diabetes** | ns | 1.6 | 0.01 |
| **Prior MI** | ns | 1.7 | 0.01 |
| **CHF**     | ns | 1.2 |  
| **BMI**     | ns | 1.3 |  
| **No pre-operative β-blocker therapy** | ns | 1.2 | 0.011 |
| **Left atrial enlargement** | ns | 1.29 | 0.01 |
| **RCA stenosis** | ns | 1.74 | 0.001 |
| **Postoperative withdrawal of β-blocker** | ns | 1.91 |  
| **Postoperative withdrawal of ACE-I** | ns | 1.69 | 0.001 |
| **(No) post-operative β-blocker therapy** | ns | 1.69 |  
| **Postoperative ACE-I therapy** | ns | 0.62 | 0.001 |

This table shows an overview of risk factors for POAF in different studies. The numbers in the boxes are statistical values (P value, odds ratio, relative risk). ns means not significant after multivariate analysis. If risk factors are not mentioned in the study, the boxes are empty.

COPD, chronic obstructive pulmonary disease; ACE-I, angiotensin-converting enzyme inhibitor; RCA, right coronary artery; MI, myocardial infarction; CHF, chronic heart failure.
the extracorporeal circuit, and is mediated via the ‘alternative pathway’ involving tumour necrosis factor α. The second phase acts via the ‘classical pathway’ which is initiated by protamine usually administered after CPB. Interestingly, fever and POAF do not occur before the first post-operative days and thus coincide with the second phase rather than with the first. Their time course corresponds to changes in activity of markers indicating complement activation and inflammation, such as C-reactive protein (CRP), complement-CRP complexes, interleukin-2, interleukin-6. The similarity in the post-operative time course of POAF incidence and CRP is illustrated in Figure 1. Also, a more pronounced increase in post-operative white blood cell count as a marker of inflammatory response independently predicts the development of post-operative AF in some studies, but not in others. Furthermore, patients developing POAF have up-regulated monocyte activation and higher monocyte and neutrophil levels post-CPB.

Besides the systemic inflammatory reaction caused by use of CPB, also local inflammation caused by surgical incision contributes to the occurrence of POAF. It is known that the degree of atrial inflammation increases with the invasiveness of surgery, but even after pericardiotomy alone the atrium becomes mildly inflamed. This transient sterile pericarditis, which is part of the healing process, might help to explain the temporal occurrence of POAF. Comparison of AF incidence after off-pump and on-pump surgery facilitates to distinguish the importance of systemic inflammation from that of surgical incision and manipulation. As such, off-pump CABG (OPCAB) is believed to elicit less systemic inflammation than on-pump surgery because of reduced cytokine responses and less myocardial injury. However, several studies failed to show statistical association between OPCAB and a lower incidence of POAF. This lack of association suggests that surgical stress as such is a more important determinant than systemic inflammation in triggering POAF. It has to be noted, however, that some of these studies are limited by their retrospective nature and sample size, and that they all showed at least a non-significant trend towards lower AF incidence in off-pump surgery. Other controlled randomized studies do reveal CPB in combination with cardioplegic arrest as the main predictor of POAF, especially in elderly and high-risk individuals. Furthermore, minimal invasive OPCAB resulted in lower AF incidence compared with conventional, more extensive OPCAB in one study, but surprisingly failed to reach significance in another. This might indicate that the trauma and the successive inflammation of the pericardium that easily spreads within the pericardial sac rather than the manipulation of the myocardial tissue itself renders the atria more prone to AF.

Several experimental and clinical studies have been undertaken to explore how inflammation enhances AF susceptibility of atrial tissue. A prominent example of involvement of inflammation in the development of AF is the study by Frustaci et al., showing lymphomononuclear infiltrates compatible with atrial myocarditis in atrial tissue of 66% of patients with lone AF. Also Chen et al. found CD45-positive cells to be independently and significantly higher in right atrial appendages of patients with AF compared with patients with sinus rhythm. An excellent experimental model to study post-operative AF/AFL is the canine sterile pericarditis model of Page et al. In this model, sterile pericarditis is created by epicardial application of sterile talcum. The time course of atrial arrhythmias in patients after open heart surgery is consistent with inducibility of AF/AFL in this model, both peaking between day 2 and 4 after surgery. In response to sterile pericarditis, proliferation, and activation of epicardial fibroblasts takes place in the atria, with loss of epicardial myocytes and altered distribution of connexins 40 and 43. These changes are associated with non-uniform slowing of conduction and promote induction and maintenance of AF/AFL. The causative association between inflammation and post-operative AF/AFL was further studied in the canine pericarditis model by suppression of the inflammatory response with steroids and HMG-CoA reductase inhibitors (statins). Administration of prednisone inhibited tissue inflammation and reduced serum CRP and AF inducibility. Also atorvastatin, an HMG-CoA reductase inhibitor, significantly reduced CRP levels and AF duration, and attenuated perimyocarditis. Finally, the use of n-3 polyunsaturated fatty acids in the sterile pericarditis model was associated with lower levels of inflammatory markers, a reduction in AF inducibility and AF duration, prolongation of the refractory period, and shortening of intra-atrial conduction times.

Atrial inflammation is known to cause conduction disturbances. For example, in a study with mongrel canines, Ishii et al.
measured myeloperoxidase activity and neutrophil cell infiltration in atrial myocardium. The degree of atrial inflammation was associated with a proportional increase in the heterogeneity of atrial conduction after experimental cardiac surgery and increased the incidence and duration of AF. In another canine study, acute inflammation provoked by arachidonic acid produced slowing and enhanced anisotropy of conduction but did not affect atrial refractoriness.

In several clinical trials, drugs with anti-inflammatory effects have shown to be effective in lowering AF incidence after CABG and/or valve surgery. Corticosteroids reduce the incidence of new-onset POAF by inhibition of cytokine release (tumour necrosis factor-α and interleukin-6), thereby reducing complement activation. A recent meta-analysis of 17,643 patients undergoing cardiac surgery suggests that pre-operative use of statins significantly reduces POAF incidence. The exact mechanism by which statins lower POAF incidence is, however, likely pleiotropic. Besides its lipid-lowering effect, pre-operative statin therapy is known to decrease inflammation markers, and also to attenuate myocardial reperfusion injury after cardiac surgery. According to the European guidelines, corticosteroids (class IIb recommendation) may be and statins (class IIa recommendation) should be considered for prevention of POAF after CABG and/or valve surgery. Treatment with n-3 polyunsaturated fatty acids to prevent POAF has been reported with success in some studies; however, placebo-controlled, double-blinded, randomized trials have failed to reproduce this protective effect of fish oil.

Finally, it is known that chronic inflammation in patients can cause atrial structural remodelling. C-reactive protein is associated with an increased incidence of POAF, and predicts patients at risk of developing future non-surgical atrial structural remodelling. C-reactive protein is associated with prevention of POAF after CABG and/or valve surgery. Administration of milrinone, a phosphodiesterase inhibitor that increases cardiac cyclic adenosine monophosphate (cAMP), dobutamine, and dopamine, both binding on the β-adrenoreceptor, is associated with an increased incidence of POAF. Activation of protein kinase A by cAMP can lead to stimulation of multiple cardiac currents, including the L-type calcium current (I calcium), thereby promoting the occurrence of early and delayed afterdepolarizations. Mechanisms by which inotropic drugs can promote POAF consist of abbreviation of atrial refractoriness (presumably due to activation of the slowly activating delayed rectifier current (I current)) and increased ectopic activity.

In theory, blocking the sympathetic activation by β-adrenoreceptor blocking drugs should reduce the incidence of POAF. Indeed, patients receiving β-blockers post-operatively have fewer episodes of AF compared with patients receiving placebo. However, these results must be interpreted with caution as arrhythmia detection varies between studies and some of the patients, assigned to the placebo group, were withdrawn from their pre-operative β-blocker therapy. The withdrawal of pre-operative β-blockade after CABG is associated with a more than two-fold increase in POAF. The peak effect of this rebound phenomenon correlates well with the time course of POAF, suggesting that the continuity of pre-operative β-blocking therapy after surgery has a stronger reductive effect on POAF incidence than β-blocking treatment started de novo after surgery. The increase in POAF incidence after β-blocker withdrawal might be due to the synergistic effect of the rebound phenomenon and the higher sympathetic tone post-operatively.

Workman et al. found pre-operative β-blockade to be associated with significant prolongation of atrial cell action potential duration (APD) and atrial effective refractory period (AERP) in...
isolated cells of patients undergoing open heart surgery. The authors called this adaptive response ‘pharmacological remodeling’, as it appeared to be caused by the previous exposure to but not by the acute presence of β-blocker. Contribution of this prolongation of refractoriness to the anti-arrhythmic effect of β-blockers can act via lengthening the minimum pathlength for reentry. In their study, however, this β-blocker-induced AERP prolongation was identical between patients who did and did not developed POAF. The authors concluded that, as pre-operative b-blockade did reduce POAF incidence in their study without involvement of β-blocker-induced AERP prolongation, attenuation of triggered atrial extrasystoles may also underlie the anti-arrhythmic effect of β-blockers.

In conclusion, it seems that sympathetic activation, by altering atrial refractoriness and promoting ectopic activity, contributes to the onset of POAF. The fact that β-blockade does not abolish all episodes of POAF once more stresses the multifactorial etiology of POAF. However, oral β-blocker therapy started at least 1 week before surgery remains the first choice in preventing POAF after cardiac surgery.

**Oxidative stress**

Oxidative stress occurs from an imbalance between pro-oxidants and antioxidants in favour of pro-oxidants. The use of CPB in cardiac surgery involves controlled ischaemia followed by reperfusion of the heart. During reperfusion, increased production of reactive oxygen species takes place, leading to myocardial stunning, tissue damage, and cell death.

The interaction between oxidative stress and electrical remodeling has been studied in experimental studies. In a canine rapid atrial pacing (RAP) model of AF, pacing-induced reduction of AERP was attenuated by ascorbate, a potent antioxidant. Production of atrial peroxynitrite, a free radical, was enhanced while endogenous atrial ascorbate levels were diminished during RAP. Supplementation of vitamin C prevented atrial tissue ascorbate depletion and the increased peroxynitrite formation. These results suggest a direct effect of oxidative stress on early electrical remodeling (24–48 h after RAP). In another canine RAP study, AF promotion after 7 days of RAP was attenuated by simvastatin but not by antioxidant vitamins C and E. The dosages in both studies were comparable. Therefore, these results might indicate that vitamin C can attenuate AF promotion in very early remodeling, but that it loses its protective effect during later stages of the electrical remodeling process. The fact that simvastatin attenuated AF promotion can be partly due to an anti-inflammatory mechanism. As discussed before, statins possess antioxidant as well as anti-inflammatory properties.

Atrial myocytes of patients with persistent AF show oxidative damage following cardiac production of peroxynitrite, which oxidizes cellular lipids, proteins, and DNA and promotes death of cardiomyocytes via necrosis/apoptosis. This oxidation contributes to the loss of fibrillar protein function and thus to atrial contractile dysfunction. Moreover, atrial nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity is increased in right atrial appendages of patients with non-surgical forms of AF compared with patients without AF. Nicotinamide adenine dinucleotide phosphate oxidase is known to be an important source of reactive oxygen species in human atrial myocytes. Direct measurement of free radicals in atrial tissue of patients during episodes of POAF is impossible. Therefore, evidence for the role of oxidative stress has been obtained by measuring concentrations of antioxidants as lipid peroxidation products and by administering antioxidant substances.

Indications that oxidative stress plays a role in the occurrence of POAF can be summarized as follows. First of all, reperfusion of patients undergoing CABG results in oxidative stress and the amount of oxidative stress depends on the severity of the ischaemic period and left ventricular ejection fraction. Secondly, Ramlawi et al. confirmed that patients with POAF, compared with patients without the arrhythmia, have a larger increase in systemic oxidative stress as well as at the myocardial level. Third, in a follow-up study Kim et al. measured NADPH oxidase activity in right atrial appendage samples from patients undergoing CABG. The authors identified NADPH oxidase activity as the most important independent predictor of POAF. Surprisingly, in their preliminary data there was no difference in NADPH oxidase activity before CPB and after reperfusion. They hypothesized that the peri-operative inflammatory response, rather than ischaemia and reperfusion, stimulates atrial NADPH oxidase activity, thereby increasing oxidative stress. Interestingly, also Clermont et al. argue that oxidative stress related to myocardial ischaemia/reperfusion might be overwhelmed by systemic radical activation, which is due to the activation of neutrophils and high-oxygen tension level during CPB.

The involvement of oxidative stress in the multifactorial mechanism of POAF has been further studied by administering antioxidant drugs to patients undergoing heart surgery. Indeed, antioxidant drugs are reported to lower the incidence of POAF after cardiac surgery involving CPB use. For example, Carnes et al. showed that administration of ascorbate to patients undergoing CABG decreased the incidence of POAF. Moreover, combination of ascorbic acid and β-blockers seems to be more effective than β-blockers alone in reducing post-CABG AF. Another example is the administration of the antioxidant N-acetylcysteine. N-acetylcysteine lowered the incidence of POAF after CABG and/or valve surgery significantly. By scavenging reactive oxygen species with N-acetylcysteine, myocardial oxidative stress is attenuated in patients undergoing CABG with CPB and cardiopulmonary arrest. Furthermore, nitric oxide (NO) gas has been reported to significantly inhibit oxidative stress when administered to patients undergoing CABG. Sodium nitroprusside (SNP), an NO donor, significantly lowered the incidence and duration of post-CABG AF in a recent pilot study. Finally, also statins are known to lower the incidence of POAF, presumably in part through their antioxidative properties.

Another argument supporting a causative relation between oxidative stress and POAF is the higher occurrence of the arrhythmia in the elderly. Ageing hearts are more susceptible for ischaemia/reperfusion injury. It can be hypothesized that cellular damage due to oxidation is more important in older patients undergoing cardiac surgery and that this, in part, explains the higher incidence of POAF in this population.

Finally, the relation between the specific setting of off-pump surgery and oxidative stress has also been studied. Off-pump surgery not only allows avoidance of ischaemia/reperfusion, but
has also been associated with a reduced systemic inflammatory reaction.
Furthermore, inflammation seems to be at least as important as ischaemia/reperfusion in producing oxidative radicals during on-pump surgery. Indeed, some studies indicate that off-pump surgery is associated with less oxidative stress. For example, Fontaine et al. reported that only plasmas isolated after on-pump, but not after OPCAB, induce superoxide generation in the vascular wall of rat aorta, leading to oxidative stress. Moreover, levels of oxidative stress markers (lipid hydroperoxides, protein carbonyls, and nitrotyrosine) in peripheral plasma of patients undergoing CABG were significantly lower in OPCAB compared with on-pump CABG. In another study, Orhan et al. found reduced systemic inflammation in patients undergoing OPCAB compared with on-pump CABG. However, they failed to show a reduction in myocardial oxidative stress in the off-pump group. 142

Mechanisms based on pre-existing factors

Presence of a substrate

Besides AF promotion by acute, surgery-induced factors (Table 3), also the pre-existence of a substrate for AF can predispose to onset of the arrhythmia in the post-operative setting (Table 4). Development of such an AF substrate can involve (A) ion channel alterations resulting in shortening and/or enhanced dispersion of atrial refractoriness and (B) heterogeneities in conduction due to interstitial alterations like, for example, accumulation of collagen fibres, inflammatory infiltration or amyloidosis. Both mechanisms and their relationship with POAF will be separately discussed.

A. Alterations in electrical ion channels as predisposing factor for POAF

The question as to whether propensity to POAF can be explained by pre-existing alterations of ion-channel function in these patients has been addressed by several investigators.

Calcium (Ca$^{2+}$) influx through the L-type Ca$^{2+}$ channels is the main current to produce the plateau phase of the atrial action potential. High atrial rates as they occur during AF or RAP are known to down-regulate I_{CaL} which contributes to shortening of atrial refractoriness as a consequence of AF. Some studies have investigated whether changes of this current can also predispose to AF in the setting of cardiac surgery. In a study by Van Wagoner et al., I_{CaL} in isolated atrial myocytes of non-AF patients was larger in patients developing POAF compared with those without the arrhythmia. Also, a higher sympathetic tone after surgery will further increase calcium influx through L-type Ca$^{2+}$ channels. Enhanced calcium load might elicit triggered activity (e.g. delayed afterdepolarizations) potentially initiating POAF. However, a more recent and very detailed study by Workman et al. could not confirm any differences in I_{CaL} between patients with and without POAF. This recent study and the significant overlap in the Ca$^{2+}$ current density data for most patients in the

Table 3 Overview of studies with important findings regarding the role of acute surgery-induced factors in the mechanism of post-operative atrial fibrillation

| Author, year | Acute factor          | Species       | Main finding                                                                 |
|--------------|-----------------------|---------------|-------------------------------------------------------------------------------|
| White (1984) | Adrenergic Activation | Human         | Prophylactic use of timolol after CABG decreases frequency and severity of supraventricular arrhythmias. |
| Kalman (1995)| Adrenergic Activation | Human         | Significant association between norepinephrine levels and the development of POAF |
| Bruins (1997)| Inflammation          | Human         | The second phase of complement activation during CPB involves CRP and is associated with POAF |
| Frustaci (1997)| Inflammation        | Human         | Lymphomononuclear infiltrates compatible with atrial myocarditis in atrial tissue of 66% of patients with lone AF |
| Carnes (2001)| Oxidative stress      | Canine/human  | Ascorbate attenuates rapid pacing-induced atrial ERP shortening and decreases the incidence of POAF after CABG. |
| Kumagai (2004)| Inflammation/oxidative stress | Canine | Atorvastatin prevents AF by inhibiting inflammation in the sterile pericarditis model |
| Shiroshita-Takeshita (2004)| Oxidative Stress/ inflammation | Canine | AF promotion by atrial tachycardia is attenuated by simvastatin, but not by antioxidant vitamins. |
| Ishii (2005) | Inflammation          | Canine         | Atrial inflammation after cardiac surgery is associated with inhomogeneity of atrial conduction |
| Workman (2006)| Adrenergic activation | Human         | Chronic β-blocker therapy is associated with reduced POAF incidence, unrelated to pre-operative ERP-prolonging |
| Kim (2008) | Oxidative stress      | Human         | NADPH oxidase activity in right atrial appendage is the most important independent predictor of POAF. |
| Fleming (2008)| Adrenergic Activation | Human         | Perioperative milrinone use is associated with an increased incidence of POAF |
| Ozaydin (2008)| Oxidative stress      | Human         | Treatment with N-acetylcysteine, an antioxidant, decreases the incidence of post-operative AF. |
| Ho (2009) | Inflammation          | Human         | Corticosteroid prophylaxis is effective in reducing the risk of atrial fibrillation |
earlier report\textsuperscript{144} suggest that changes in L-type Ca\textsuperscript{2+} channel might have contributed to POAF initiation in some patients, but certainly not in all.

Potassium (K\textsuperscript{+}) channels, which are altered in patients with persistent AF, are apparently not involved in the occurrence of POAF. First, Brandt \textit{et al.}\textsuperscript{145} reported that the ultra-rapid delayed rectifier K\textsuperscript{+} current (I\textsubscript{K1}) is reduced in human persistent AF. In non-AF patients developing AF after cardiac surgery, however, only a non-significant trend towards a decrease in I\textsubscript{Kur} and no difference in the transient outward K\textsuperscript{+} current (I\textsubscript{o}) were detected compared with patients without POAF.\textsuperscript{146,147} Dobrev \textit{et al.}\textsuperscript{145,146} found the larger basal inward rectifying K\textsuperscript{+} current in patients with persistent AF to consist of increased activity of the inward rectifier K\textsuperscript{+} current (I\textsubscript{K1}) and constitutive activity of the acetylcholine-activated K\textsuperscript{+} current (I\textsubscript{K,ACH}). Again, both I\textsubscript{K1} and I\textsubscript{K,ACH} were not altered in non-AF patients developing POAF compared with patients not having AF after surgery. Thirdly, Workman \textit{et al.}\textsuperscript{150} found no differences in I\textsubscript{Kur}, I\textsubscript{KS}, or in the sustained outward K\textsuperscript{+} current (I\textsubscript{SUS}) between patients who did and did not develop POAF. These findings are consistent with unaltered APD or ERP in their study\textsuperscript{50} and with results in other reports.\textsuperscript{146,147} Finally, a recent study of Swartz \textit{et al.}\textsuperscript{148} confirmed the lack of difference in K\textsuperscript{+} channels in atrial biopsies of patients who did and did not develop AF after cardiac surgery.

Altogether, these data suggest that, unlike in persistent AF, preoperative changes in cellular Ca\textsuperscript{2+} and K\textsuperscript{+} channels do not play an important role in the occurrence of POAF.

### B. Alterations of the atrial interstitium and extracellular matrix predisposing to POAF

Ageing is an important risk factor for POAF and slowing of conduction is known to occur as atria structurally remodel with age. Spach and Dolber\textsuperscript{149} were the first to report that progressive electrical uncoupling of the side-to-side connections between parallel-orientated atrial fibres occurs in atrial muscle with advancing age. This uncoupling results in a decrease of transverse conduction and enhances anisotropy of conduction velocity.\textsuperscript{149} Such an alteration in conduction is often associated with the presence of extensive collagenous septa and favours reentry.\textsuperscript{149} The relationship between this age-dependent remodelling and the occurrence of POAF is strengthened by several studies. First, Ad \textit{et al.}\textsuperscript{150} reported that the severity of pre-operative atrial myolysis in right atrial biopsies of non-AF patients undergoing CABG correlated well with the occurrence of POAF. In this study and in a study by Mariscalco \textit{et al.},\textsuperscript{151} no histological differences were noted in atrial specimens before and after CPB. This suggests that any contribution of CPB to POAF must be independent from histological changes. Secondly, Ak \textit{et al.}\textsuperscript{152} found that pre-operative morphologic alterations such as atrial myocardial vacuolization and increased myocardial apoptosis may constitute a pathologic substrate for post-operative AF. Third, a study of Goette \textit{et al.}\textsuperscript{153} further strengthens this role for pre-existent structural alterations. In this report, the incidence of POAF increased with the amount of fibrosis in right atrial appendages of patients undergoing cardiac surgery. Moreover, atrial fibrosis was not only age dependent, but also correlated with P-wave duration suggesting macroscopic slowing of conduction.\textsuperscript{153} Finally, a larger amount of fibrosis was found in left atria of patients developing POAF.\textsuperscript{148} On the other hand, one study reported no differences in right atrial histology between patients who do and do not develop POAF.\textsuperscript{154}

By comparing POAF incidences between different types of cardiac surgery, the important contribution of atrial structural alterations to the mechanisms of POAF is further supported. For

### Table 4 Overview of studies with important findings regarding the pre-existence of a substrate in the mechanism of post-operative atrial fibrillation

| Author, year | Substrate factor | Species | Main finding |
|--------------|------------------|---------|--------------|
| Steinberg (1993) | Structural alteration | Human | Signal-averaged surface P-wave duration is a potent, accurate, and independent predictor of POAF. |
| Von Wagoner (1999) | Alteration in ion channels | Human | Positive correlation between I\textsubscript{Cal} measured at the time of surgery and the occurrence of POAF. |
| Brandt (2000) | Alteration in ion channels | Human | No difference in I\textsubscript{o} and a non-significant trend towards a decrease in I\textsubscript{Kur} between patients with and without POAF. |
| Ad (2001) | Structural alteration | Human | Atrial myolysis and lipofuscin levels identified as an independent histologic finding associated with POAF. |
| Goette (2002) | Structural alteration | Human | Amount of atrial fibrosis in association with prolongation of the surface P-wave or ageing correlates with POAF. |
| Dobrev (2002) | Alteration in ion channels | Human | Atrial myocytes of patients developing POAF have no alterations in I\textsubscript{K1} and I\textsubscript{K,ACH}. |
| Ak (2005) | Structural alteration | Human | Degree of atrial myolysis and increased apoptotic pattern are significant predictors for development POAF. |
| Mariscalco (2006) | Structural alteration | Human | Atrial histology is similar in patients undergoing on- or off-pump surgery and is similar before and after CPB. |
| Workman (2006) | Alteration in ion channels | Human | No differences in I\textsubscript{Cal}, I\textsubscript{Kur}, I\textsubscript{K1}, and I\textsubscript{SUS} in right atrial biopsies of patients who do and do not develop POAF. |
| Kanagaratnam (2008) | Structural alteration | Human | Only patients with sustained induced AF develop POAF and have prolonged unipolar electrograms. |
example, Anné et al. found more profound structural changes in patients with mitral valve disease than in patients undergoing CABG: larger atria, hypertrophied cells, more interstitial fibrosis, and signs of cellular degeneration. Left atrial fibrosis was more pronounced in patients undergoing mitral valve surgery compared with patients undergoing CABG, independently of the underlying heart rhythm. It appears reasonable to assume that the higher AF incidence after mitral valve surgery is due to these structural alterations. Also, Asher et al. found left atrial enlargement to be independently associated with POAF in patients undergoing only valve surgery.

Other studies more directly demonstrate the pre-existence of an arrhythmogenic substrate in patients who do develop POAF. For example, Lowe et al. screened patients at risk for developing POAF by electrical stimulation of the mid-right atrium during surgery. Of a total of 36 patients in whom AF was inducible, 17 patients developed POAF. One patient was not inducible, but did develop POAF. Another example is the study by Kanagaratnam et al., where AF was induced during cardiac surgery by burst pacing in patients without a history of AF. Only patients with sustained induced AF developed any episodes of POAF. Also in the same study, patients with sustained AF had prolonged unipolar electrograms compared with patients not able to sustain AF and this prolongation was more marked in the region of the crista terminals than in the trabeculated right atrium. The authors stated that this prolongation of local electrograms is suggestive of microscopic conduction abnormalities. Finally, connexin 40 expression, one of the three connexins present in atrial myocytes, is significantly higher in patients who develop POAF compared with sinus rhythm patients. Cell-to-cell conduction properties are determined by gap junctions, which are clusters of transmembrane channels built up from connexins. As such, enhanced expression and heterogeneous distribution of connexin 40 could result in local conduction heterogeneities.

Some indirect evidence for the existence of a structural substrate for AF comes from studies investigating surface-ECG parameters in patients with POAF. In a study of Steinberg et al., measurement of P-wave duration on the standard ECG was longer in patients with POAF, but this did not reach significance. In the same study, however, signal-averaged P-wave duration proved to be an independent predictor of AF after cardiac surgery. In another study, increase in P-wave dispersion post-operatively predicted POAF after CABG.

The concept of a pre-existing substrate for AF as an important predictor of POAF is also supported by a study of Ahlsson et al. who recently published the remarkable finding that one-fourth of patients with POAF developed AF of any form during a follow-up of 5 years. A possible explanation is that these patients already had a pre-existing substrate for AF at the time of surgery, that this substrate was unmasked by occurrence of acute factors increasing the activity of pro-arrhythmic factors in the perioperative period and eventually led to a non-surgical form of AF later on. The hypothetical relationship between acute and chronic factors is illustrated in figure 2. In this figure, the time course of two hypothetical patients is depicted. Both patients have no AF history at the time of surgery and undergo on-pump CABG at the same age. In patient 1, acute surgery-related factors enhance the AF susceptibility, but the ‘AF threshold’ is not reached and sinus rhythm is maintained in the post-operative phase. In patient 2, synergistic interaction of acute, surgery-induced factors and the pre-existence of a substrate for AF due to structural heart disease enhances AF susceptibility that much that the ‘AF threshold’ is exceeded. In this sense, the post-operative setting can be regarded as a ‘stress test’ for the propensity to the arrhythmia.

**Risk factors for POAF and the development of an AF substrate**

After having discussed the mechanisms predisposing to POAF, this section describes the relation between these mechanisms and clinical risk factors for AF and POAF.

**Age**

Advancing age correlates strongly with the occurrence of new onset AF and POAF. Moreover, several arguments support that ageing enhances the development of a substrate capable of perpetuating AF. As discussed above, ageing goes along with fibrosis and is associated with slowing of conduction. Surprisingly, in one study endocardial AF inducibility in patients without any AF history did not increase with age and even decreased in elderly patients (>70 years). These older patients had a significant longer AERP compared with younger patients (40 years). However, as wavelength, measured as the product of conduction velocity and ERP, is a more reliable predictive index for induction of atrial arrhythmias than conduction velocity or ERP alone, the pro-arrhythmic effect of slowing of conduction likely outweighs the protective effect of prolongation of atrial refractoriness.

**Structural heart disease**

Left atrial enlargement, mitral valve disease, congestive heart failure, and hypertension are well-known risk factors for non-surgical AF. Atrial structural remodelling consequent to these risk factors can predispose to the onset of POAF. Indeed, in large epidemiological studies, these risk factors are also associated with the incidence of POAF. This suggests that underlying mechanisms enhance the propensity to AF similarly in cardiac surgery patients as in patients not undergoing cardiac surgery. However, it appears that the association of structural heart disease with POAF is weaker than with persistent non-surgical AF. It can be hypothesized that in the case of non-surgical AF, structural alterations enhanced the development of an AF substrate so far that AF occurs ‘spontaneously’. In the setting of POAF, however, superimposition of acute surgery-induced factors is required to exceed the ‘AF threshold’. As such, a weaker association would be expected between these risk factors and POAF incidence compared with non-surgical AF incidence.

**Left atrial enlargement and mitral valve disease**

Chronic structural alterations in the left atrium, rather than changes in ion channels, seem responsible for the higher POAF susceptibility in patients with enlargement of the left atrium. In non-AF patients with mitral regurgitation, prolongation rather than shortening of AERP is seen in the left atrium. Moreover, a line...
of conduction block runs vertically between the pulmonary veins in the posterior left atrium.\textsuperscript{170} In patients with greater left atrial enlargement, this line of block is more extensive compared with ‘unremodelled’ patients. Furthermore, complex-fractionated electrograms, which can be found at a line of block, are relatively stable in this region and thus most likely related to the underlying architecture of the atrial wall.\textsuperscript{169} Finally, also experimental data support this rationale. In a canine study of chronic left atrial dilatation due to mitral regurgitation, persistence of induced AF went hand in hand with the degree of left atrial dilatation.\textsuperscript{171} Histological analysis of these atria revealed areas of chronic inflammation and increased interstitial fibrosis.\textsuperscript{171}

**Congestive heart failure**

Congestive heart failure is known to cause (i) left atrial dilatation due to increased atrial filling pressures secondary to decreased ventricular function, (ii) increased atrial fibrosis, and (iii) regional conduction abnormalities.\textsuperscript{172,173}

**Hypertension**

Elevated blood pressure causes left ventricular hypertrophy, left atrial dilatation, and modifications of atrial mechanical function, all promoting AF.\textsuperscript{174} However, administration of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker has not yet been clearly associated with a decrease in POAF incidence.\textsuperscript{91,175,176}

**History of atrial fibrillation**

High propensity to POAF in patients with previous episodes of AF is not surprising.\textsuperscript{3,6} The fact that spontaneous episodes of AF already occurred shows that the activity of pro-arrhythmic mechanisms in these patients exceeded the ‘AF threshold’.\textsuperscript{161} Superimposition of acute surgery-induced factors will only facilitate new episodes of the arrhythmia. On the other hand, AF itself might have contributed to the development of an AF substrate secondary to electrical and structural remodelling of the atria.

**Risk factors for atrial fibrillation but not for post-operative atrial fibrillation**

Some but not all studies identified diabetes as independent risk factor for AF.\textsuperscript{162,163,177,178} Also in POAF, the predictive value of diabetes for the incidence of the arrhythmia is low.\textsuperscript{1,4,6–8,15,17} In a recent meta-analysis reviewing 100,217 patients, no difference in POAF incidence was found between patients with and without diabetes.\textsuperscript{179} Furthermore, men have a 1.5 times greater likelihood of developing new onset AF compared with women.\textsuperscript{162} The mechanism behind the higher AF susceptibility remains unclear. In POAF, male gender fails to reach significance in many studies,\textsuperscript{1,3,6,7,15,17} and in studies that find male gender to be associated with POAF, the number of women included is often low.\textsuperscript{4,8,47,48} Association between chronic obstructive pulmonary disease (COPD) and new onset AF is still under discussion.\textsuperscript{162,178} COPD has been identified

---

**Figure 2** Time course of substrate development and surgery-related factors in the occurrence of atrial fibrillation. Time course of pro-arrhythmic mechanisms is depicted in two hypothetical patients undergoing cardiac surgery. Both chronic as well as acute factors related to the operation on day 0 are shown. When the intensity of pro-arrhythmic factors reaches a certain threshold,\textsuperscript{161} atrial fibrillation will occur. Patient 1 has no relevant cardiovascular history, only hypertension (green) at the age of 57. Patient 2 already developed hypertension (red) at a younger age, followed by diabetes (red), mitral regurgitation (red), and COPD (red) at an older age, respectively. Both patients have no history of AF and undergo on-pump coronary artery bypass grafting at the same age. However, patient 2 has developed an AF substrate by the time of operation due to above mentioned cardiovascular diseases. Acute, surgery-related factors occur in both patients: cardiopulmonary bypass (CPB, yellow), inflammation (CRP, purple), oxidative stress (yellow), and sympathetic activation (yellow). Patient 2 develops post-operative atrial fibrillation (exceeds the ‘AF threshold’), while patient 1 remains with sinus rhythm. AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease.
as an independent predictor of AF progression.\textsuperscript{180} In the occurrence of POAF, COPD is often identified as a risk factor.\textsuperscript{1–3,9,47} The pathogenesis of AF in patients with COPD is unclear,\textsuperscript{3} but pulmonary hypertension, inflammation, hypoxia, acidosis, and right atrial and ventricular dilatation might contribute to the formation of a substrate for AF in these patients.\textsuperscript{181}

**Conclusions**

From the numerous experimental and epidemiological studies addressing the mechanisms of POAF several conclusions can be drawn.

(i) **Both transient factors related to surgery as well as factors developing slowly and progressively contribute to the occurrence of POAF.** The time course of POAF\textsuperscript{170} unMASKS the importance of temporary surgery-induced factors as inflammation, sympathetic stimulation, and oxidative stress. However, transient factors cannot be the only responsible mechanism for the occurrence of the arrhythmia, as many patients in whom one or even several of these factors are clearly operative do not develop POAF.

(ii) **Among the transient predisposing mechanisms of POAF, sympathetic activation appears to be more relevant than inflammation and oxidative stress.** Withdrawal from and treatment with β-blockers has been shown to largely affect POAF incidence,\textsuperscript{50,117–119} while reducing oxidative stress,\textsuperscript{124,135} or inflammation\textsuperscript{86,87} were less effective. In line with this the 2010 European Society of Cardiology guidelines recommend β-blocker treatment as first-line therapy of POAF.\textsuperscript{91}

(iii) **Occurrence of POAF is strongly determined by the pre-existence of an AF substrate.** Despite the importance of transient surgery-induced factors, the majority of POAF cases occur in atria with a pre-existing AF substrate due to a long-lasting structural remodelling process. Moreover, patients developing POAF have an eightfold increased risk of developing AF in the future.\textsuperscript{12} If transient factors were the only cause of onset of POAF, AF after surgery would not be expected to be associated with occurrence of AF later on. This emphasizes the important role for more chronic factors, not directly related to surgery.

(iv) **AF after cardiac surgery and non-surgical AF have common clinical risk factors.** Patients developing AF after surgery have pre-operatively increased intra-atrial conduction times (longer signal-averaged P-wave duration)\textsuperscript{159} and more profound atrial structural changes like fibrosis\textsuperscript{148,153} compared with patients who maintain sinus rhythm after surgery. This presence of structural ‘remodelling’ of atria before the onset of POAF is very similar to the setting of non-surgical AF. In agreement with this hypothesis, the risk factors for POAF are surprisingly similar to the classical risk factors identified for AF as such.

(v) **Susceptibility to AF after surgery is not due to changes in ionic currents.** In non-surgical AF, alterations in ion channels as a consequence of AF enhance the perpetuation of AF.\textsuperscript{143,145–147} However, the function of these ion channels is not altered in pre-operative atrial biopsies of patients developing AF after cardiac surgery.\textsuperscript{50,145,147,148}

(vi) **Progress in the preventive treatment of POAF has been made during the past decade.** As age is the strongest risk factor for POAF\textsuperscript{1,2,4,6–9,15–18,44–48} and cardiac surgery nowadays is performed in older patients,\textsuperscript{49} one would expect POAF incidence to rise over time. The fact that recent epidemiological studies\textsuperscript{10,17} were not able to confirm this trend suggests significant progress in preventive treatment of POAF.

Reviewing mechanisms predisposing to the occurrence of AF after cardiac surgery clearly reveals that the pathogenesis of POAF is multifactorial. Therefore, subclassification of POAF based on these mechanisms does not appear adequate. Identifying leading mechanisms in individual patients, however, might improve treatment in the future. The clinical setting of POAF offers numerous opportunities to study not only mechanisms of POAF but also of AF in general, as cardiac surgery enables direct access to the heart. This opportunity appears to be underused so far.

**Conflict of interest:** none declared.

**Funding**

This work was supported by the Dutch Research Organization (NOW, VIDI-grant 016.086.379) and the Foundation Leducq (07 CVD 03). Funding to pay the Open Access publication charges for this article was provided by the University of Maastricht.

**References**

1. Creswell LL, Schuessler RB, Rosenbloom M, Cox JL. Hazards of postoperative atrial arrhythmias. Ann Thorac Surg 1993;56:539–49.
2. Almassi GH, Schowalter T, Nicolosi AC, Aggarwal A, Moritz TE, Henderson WG et al. Atrial fibrillation after cardiac surgery: a major morbid event! Ann Surg 1997;226:501–11. discussion 11–3.
3. Mathew JP, Fontes ML, Tudor IC, Ramsay J, Duke P, Mazzer CD et al. A multicenter risk index for atrial fibrillation after cardiac surgery. JAMA 2004;291:1720–9.
4. Aranke SF, Shaw DP, Adams DH, Rizzo RJ, Couper GS, VanderVliet M et al. Predictors of atrial fibrillation after coronary artery surgery. Current trends and impact on hospital resources. Circulation 1996;94:390–7.
5. Frost L, Molgaard H, Christiansen EH, Hjortholm K, Paulsen PK, Thomsen PE. Atrial fibrillation and flutter after coronary artery bypass surgery: epidemiology, risk factors and preventive trials. Int J Cardiol 1993;36:253–61.
6. Banach M, Ryz J, Drozdza JA, Okonski P, Misztal M, Barylak M et al. Risk factors of atrial fibrillation following coronary artery bypass grafting: a preliminary report. Circ J 2006;70:438–41.
7. Auer J, Weber T, Berent R, Ng CK, Lamm G, Eber B. Risk factors of postoperative atrial fibrillation after cardiac surgery. J Cardiothorac Vasc Anesth 2004;18:425–31.
8. Fuller JA, Adams GG, Buxton B. Atrial fibrillation after coronary artery bypass grafting: is it a disorder of the elderly? J Thorac Cardiovasc Surg 1989;97:821–5.
9. Leitch JW, Thomson D, Baird DK, Harris PJ. The importance of age as a predictor of atrial fibrillation and flutter after coronary artery bypass grafting. J Thorac Cardiovasc Surg 1990;100:338–42.
10. Mariscalco G, Engstrom KG. Postoperative atrial fibrillation is associated with late mortality after coronary surgery, but not after valvular surgery. Ann Thorac Surg 2009;88:1871–6.
11. Siebert J, Anisimowicz L, Lango R, Rogowsky J, Pawlaczyk R, Brzezinski M et al. Atrial fibrillation after coronary artery bypass grafting: does the type of procedure influence the early postoperative incidence? Eur J Cardiothorac Surg 2001;19:455–9.
12. Ahlsson A, Fengrud E, Bodin L, Englund A. Postoperative atrial fibrillation in patients undergoing aorto-coronary bypass surgery carries an eightfold risk of future atrial fibrillation and a doubled cardiovascular mortality. Eur J Cardiothorac Surg 2010;37:1353–59.
Post-operative atrial fibrillation

13. Villareal RP, Harharan R, Liu BC, Kar B, Lee VV, Elsayy M et al. Postoperative atrial fibrillation and mortality after coronary artery bypass surgery. J Am Coll Cardiol 2004;43:742–8. 
14. Kalman JM, Munawar M, Howes LG, Louis WJ, Buxton BF, Gutteridge G et al. Atrial fibrillation after coronary artery bypass grafting is associated with symptomatic activation. Ann Thorac Surg 1995;60:1709–15. 
15. Hakala T, Hedman A, Turpeinen A, Ketonen R, Vuolleenaho O, Hippelainen M. Prediction of atrial fibrillation after coronary artery bypass grafting by measuring atrial peptide levels and preoperative atrial dimensions. Eur J Cardiothorac Surg 2002;22:939–43. 
16. Zhangrillo A, Landoni G, Sparicio D, Benussi S, Aletti G, Pappalardo F et al. Predictors of atrial fibrillation after off-pump coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 2004;18:704–8. 
17. Shen J, Lii S, Zheng V, Buckley P, Damianno RJ Jr., Schuessler RB. The persistent problem of postoperative atrial fibrillation: A single-institution experience over two decades. J Thorac Cardiovasc Surg 2011;141:559–70. 
18. Mahoney EM, Thompson TD, Vedeler E, Williams J, Weintraub WS. Cost-effectiveness of targeting patients undergoing cardiac surgery for therapy with intravenous amiodarone to prevent atrial fibrillation. J Am Coll Cardiol 2002;40:737–45. 
19. Ma JF, Wang Y, Zhao YF, Wu Z, Liu LX, Kou YL et al. Atrial fibrillation after surgery for esophageal carcinoma: clinical and prognostic significance. World J Gastroenterol 2006;12:1279–91. 
20. Amar D, Zhang H, Heerdt PM, Park B, Fleisher M, Thaler HT. Statin use is associated with a reduction in atrial fibrillation after noncardiac thoracic surgery. Ann Thorac Surg 2005;79:1698–703. 
21. Curtis JJ, Parker BM, McKenney CA, Wagner-Plaas CC, Walls JT, Denny TL et al. Incidence and predictors of supraventricular dysrhythmias after pulmonary resection. Ann Thorac Surg 1998;66:1766–71. 
22. Lanza LA, Vidal AI, DeValeria AI, Zinmesier AR, Diehl NN, Trastek VF. Low-dose oral amiodarone prophylaxis reduces atrial fibrillation after pulmonary resection. Ann Thorac Surg 2003;75:223–30, discussion 30. 
23. Amar D, Roistacher N, Burt M, Reinsel RA, Ginsberg RJ, Wilson RS. Clinical and echocardiographic correlates of symptomatic tachydysrhythmias after noncardiac thoracic surgery. Chest 1995;108:349–54. 
24. Walsh SR, Oates JE, Anderson JA, Blair SD, Makin CA, Walsh CJ. Postoperative arrhythmias in colorectal surgical patients: incidence and clinical correlates. Colorectal Dis 2006;8:212–6. 
25. Batra GS, Molyneux J, Scott NA. Colorectal patients and cardiac arrhythmias detected on the surgical high dependency unit. J Cardiovasc Surg (Torino) 1993;34:687–9. 
26. Sui CW, Tung HM, Chu KW, Jim MKH, Lau CP, Tse HF. Prevalence and predictors of new-onset atrial fibrillation after elective surgery for colorectal cancer. Pacing Clin Electrophysiol 2005;28:Suppl 1):S23–30. 
27. Christians KK, Wu B, Quebbemann ET, Vuolleenaho O, Hippelainen M. Prediction of atrial fibrillation after noncardiac thoracic surgery. J Am Coll Cardiol 2002;39:1384–90. 
28. Batra GS, Molyneux J, Scott NA. Colorectal patients and cardiac arrhythmias detected on the surgical high dependency unit. J Cardiovasc Surg (Torino) 1993;34:687–9. 
29. Christians KK, Wu B, Quebbemann ET, Vuolleenaho O, Hippelainen M. Prediction of atrial fibrillation after noncardiac thoracic surgery. J Am Coll Cardiol 2002;39:1384–90. 
30. Christians KK, Wu B, Quebbemann ET, Vuolleenaho O, Hippelainen M. Prediction of atrial fibrillation after noncardiac thoracic surgery. J Am Coll Cardiol 2002;39:1384–90.
60. Fontes ML, Mathew JP, Rinder HM, Zelterman D, Smith BR, Rinder CS. Atrial fibrillation after cardiac surgery/cardiopulmonary bypass is associated with monocyte activation. Anesth Analg 2005;101:17–23.

61. Gibson PH, Cuthbertson BH, Croal BL, Rae D, El-Shafei H, Gibson G et al. Usefulness of neutrophil/lymphocyte ratio as predictor of new-onset atrial fibrillation after coronary artery bypass grafting. Am J Cardiol 2010;105:186–91.

62. Wilkin S, Izazat MB, Andrews SW, Van YP, Tan NH, Yim APC. Avoiding cardiopulmonary bypass in multivessel CABG reduces cytokine response and myocardial injury. Ann Thorac Surg 1999;68:52–56.

63. Enc Y, Keterci B, Otsay D, Camur G, Kayacaglita I, Terz S et al. Atrial fibrillation after surgical revascularization: is there any difference between on-pump and off-pump? Eur J Cardio-Thorac Surg 2002;26:1129–33.

64. Siebert J, Lewiski L, Mlodicki M, Rogowski J, Langr A, Anisimowicz L et al. Atrial fibrillation after conventional and off-pump coronary artery bypass grafting: two opposite trends in timing of atrial fibrillation occurrence! Med Sci Monit 2003;9:CR137–41.

65. van Dijk D, Nierich AP, Jansen EWL, Nathoe HM, Suyker WJJ, Diephuis JC et al. Early outcome after off-pump versus on-pump coronary bypass surgery: results from a randomized study. Circulation 2001;104:1761–66.

66. Legare JF, Buth RJ, King S, Wood J, Sullivan JA, Friesen CH et al. Coronary bypass surgery performed off pump does not result in lower in-hospital morbidity than coronary artery bypass grafting performed on pump. Circulation 2004;109:887–92.

67. Zamvar V, Williams D, Hall J, Payne N, Cann C, Young K et al. Assessment of neurocognitive impairment after off-pump and on-pump techniques for coronary artery bypass graft surgery: prospective randomised controlled trial. BMJ 2002;325:1268.

68. Czerny M, Baumr H, Kilo J, Zuckermann A, Grubhofer G, Chevtchik O et al. Complete revascularization in coronary artery bypass grafting with and without cardiopulmonary bypass. Ann Thorac Surg 2001;71:65–69.

69. Ascione R, Caputo M, Calon G, Lloyd CT, Underwood MJ, Angelini GD. Predictors of atrial fibrillation after conventional and beating heart coronary surgery: a prospective, randomized study. Circulation 2000;102:1530–35.

70. 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;7:136–9.

71. Boyd WD, Desai ND, Del Rizzo DF, Nowicki RJ, McKenzie FN, Menkis AH. Off-pump surgery decreases postoperative complications and resource utilization in the elderly. Ann Thorac Surg 1999;68:1490–93.

72. Van Bellegem Y, Caes F, McCreane L, Van Overbeke H, Moerman A, Van Nooten G. Off-pump coronary surgery: surgical strategy for the high-risk patient. Cardiovasc Surg 2003;11:75–79.

73. Panesar SS, Athanasiou T, Nair S, Rao C, Jones C, Nicolau M et al. Early outcomes in the elderly: a meta-analysis of 4921 patients undergoing coronary artery bypass grafting—comparison between off-pump and on-pump techniques. Heart 2006;92:1908–16.

74. Stamou SC, Dangas G, Hill PC, Pfeister AJ, Dullum MKC, Boyce SW et al. Atrial fibrillation after beating heart surgery. Am J Cardiol 2000;86:64–67.

75. Scherer M, Sirat A, Dogan S, Aybek T, Moritz A, Wimmer-Greinecker G. Does early outcome after off-pump versus on-pump techniques for coronary artery bypass grafting performed off pump does not result in lower in-hospital morbid-ity than coronary artery bypass grafting performed on pump. Circulation 2004;109:887–92.

76. Frustaci A, Chimenti C, Bellocci F, Morgante E, Russo MA, Maseri A. Histological analysis of pericardial arteries prevents atrial fibrillation by inhibiting inflammation in a canine sterile pericarditis model. J Int Cardiol 2010; online publish ahead of print 15 September 2010, doi:1016/j.ijcard.2010.08.024.

77. Ishi Y, Schuessler RB, Gaynor SL, Yamada K, Fu AS, Boineau JP et al. Inflammation of atrium after cardiac surgery is associated with inhomogeneity of atrial conduction and atrial fibrillation. Circulation 2003;111:2881–8.

78. Tselentakis EV, Woodward E, Chandy J, Gaudette GR, Saltman AE. Inflammation effects on the electrical properties of atrial tissue and inducibility of postoperative atrial fibrillation. J Surg Res 2010;153:68–75.

79. Ho KM, Tan JA. Benefits and risks of corticosteroid prophylaxis in adult cardiac surgery: a dose-response meta-analysis. Circulation 2009;119:1853–66.

80. Bourbon A, Vionnet M, Leprince P, Vaissier E, Copeland J, McDonagh P et al. The effect of methylprednisolone treatment on the cardiopulmonary bypass-induced systemic inflammatory response. Eur J Cardio-Thorac Surg 2006;29:332–38.

81. Liakopoulos GJ, Choi Y-H, Kuhn EW, Witteborn T, Boys M, Madesharhan N et al. Statins for prevention of atrial fibrillation after cardiac surgery: a systematic literature review. J Thorac Cardiovasc Surg 2009;138:678–86.e1.

82. Chello M, Anselmi A, Spadaccio C, Patti G, Goffredo C, Di Sciascio G et al. Sim- vastatin increases neutrophil apoptosis and reduces inflammatory reaction after coronary surgery. Ann Thorac Surg 2007;83:1374–80.

83. Wagner AH, Kohler T, Ruckschloss U, Just I, Hecker M. Improvement of nitric oxide-dependent vasodilatation by HMG-CoA reductase inhibitors through attenuation of endothelial superoxide anion formation. Arterioscler Thromb Vasc Biol 2005;20:61–69.

84. Camm AJ, Kirchhof P, Lip GYH, Schotten U, Savelieva I, Ernst S et al. Guidelines for the management of atrial fibrillation. Europace 2010;12:1360–420.

85. Calò L, Bianconi L, Colivichci F, Lambert F, Loriochic ML, de Ruvo E et al. N-3 fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a randomized, controlled trial. J Am Coll Cardiol 2005;45:1723–28.

86. Mariscalco G, Sarzi Braga S, Banach M, Bornani P, Bruno VO, Napoleone M et al. Preoperative n-3 polyunsaturated fatty acids are associated with a decrease in the incidence of early atrial fibrillation following cardiac surgery. Angiology 2010;61:643–50.

87. Saravanan P, Bridgewater B, West AL, O’Neill SC, Calder PC, Davidson NC. Omega-3 fatty acid supplementation does not reduce risk of atrial fibrillation after coronary artery bypass surgery: a randomized, double-blind, placebocontrolled clinical trial. Circ Arrhythm Electrophysiol 2010;3:46–53.

88. Heidarzadavar R, Armar DO, Skuladottir GV, Torfason B, Edvardsson V, Gottskallsson G et al. Does treatment with n-3 polyunsaturated fatty acids prevent atrial fibrillation after open heart surgery? Europace 2010;12:356–63.

89. Kaireviucute D, Blain AD, Balakrishnan B, Lane DA, Patel JV, Uzdavines G et al. Characterisation and validity of inflammatory biomarkers in the prediction of post-operative atrial fibrillation in coronary artery disease patients. Thromb Haemost 2010;104:122–7.

90. Ahlsson AJ, Bodin L, Lundblad OH, Englund AG. Postoperative Atrial Fibrillation Is Not Correlated to C-Reactive Protein. Ann Thorac Surg 2007;83:1332–37.

91. Gaudio M, Nasso G, Andreotti F, Minniti G, Iacoello L, Donati M et al. Preoperative C-reactive protein level and outcome following coronary surgery. Eur J Cardiothorac Surg 2002;22:521–6.

92. Workman A. Cardiac adrenergic control and atrial fibrillation. Naunyn-Schmiedeberg’s Arch Pharmacol 2010;381:235–49.

93. Hoekstra DS, Cilmi KM. Effects of aging on catecholamine metabolism. J Clin Endocrinol Metab 1985;60:479–84.

94. Dimmer C, Tavernier R, Gjorgj N, Van Nooten G, Clement DL, Jordans L. Variations of autonomic tone preceding onset of atrial fibrillation after coronary artery bypass grafting. Am J Cardiol 1998;82:22–25.

95. Armar D, Zhang H, Miodownik S, Kadih AH. Competing autonomic mechanisms precede the onset of postoperative atrial fibrillation. J Am Coll Cardiol 2003;42:1262–68.

96. Hogue CW Jr., Hyder ML. Atrial fibrillation after cardiac operation: risks, mech- anisms, and treatment. Ann Thorac Surg 2000;69:300–6.

97. Mela J, Voigt P, Sonnmez B, Ferreira M, Abecasis M, Rebocho M et al. Ventral cardiac denervation prevents inducible atrial flutter in the canine sterile pericarditis model. Eur J Cardio-Thorac Surg 2004;25:101–11.

98. Zhang Z, Zhang C, Wang H, Zhao J, Liu L, Lee J et al. n-3 polyunsaturated fatty acids prevents atrial fibrillation by inhibiting inflammation in a canine sterile pericarditis model. J Int Cardiol 2010; online publish ahead of print 15 September 2010, doi:1016/j.ijcard.2010.08.024.
Post-operative atrial fibrillation

108. Cummings JF, Gill I, Akhrass R, Dery M, Biblo LA, Quan KJ. Preservation of the anterior fat pad paradoxically decreases the incidence of postoperative atrial fibrillation in humans. J Am Coll Cardiol 2004;43:994–1000.

109. Omran AS, Karimi A, Ahmadi H, Yazdanifard P, Sheikh Fahrooli M, Tazik M. Prophylactic ventral cardiac denervation: Does it reduce incidence of atrial fibrillation after coronary artery bypass grafting? J Thorac Cardiovasc Surg 2010;140:106–13.

110. Levy MN. Brief reviews: sympathetic-parasympathetic interactions in the heart. Circ Res 1971;29:437–45.

111. Fleming GA, Murray KT, Yu C, Byrne JG, Greetleh JP, Petracel MR et al. Mibrinone use is associated with postoperative atrial fibrillation after cardiac surgery. Circulation 2008;118:1619–25.

112. Feneck RO, Sherry KM, Withington PS, Oduro-Dominah A. Comparison of the hemodynamic effects of mibrinone with dobutamine in patients after cardiac surgery. J Cardiotorac Vasc Anesth 2001;15:306–15.

113. Argaliou M, Mota P, Khandwala F, Samuel S, Koch CG, Gillinov AM et al. Renal dose dopamine is associated with the risk of new-onset atrial fibrillation after cardiac surgery. Crit Care Med 2005;33:1327–32.

114. Sampson KJ, Terrenoire C, Cervantes DO, Kaba RA, Peters NS, Kass RS. Adrenergic regulation of a key cardiac potassium channel can contribute to atrial fibrillation. Circ Res 2003;93:231–9.

115. Eslami M, Badkoubeh RS, Mousavi M, Radmehr H, Salehi M, Takavoli N et al. 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. Tex Heart J 2007;34:268–74.

116. Tossios P, Bloch W, Huebner A, Raji MR, Dodos F, Klass O et al. N-acetylcysteine prevents reactive oxygen species-mediated myocardial stress in patients undergoing cardiac surgery: results of a randomized, double-blind, placebo-controlled clinical trial. J Thorac Cardiovasc Surg 2003;126:1513–20.

117. Elahi MM, Wonmer M, Khan JS, Matata BM. Inspired nitric oxide and modulation of oxidative stress during cardiac surgery. Curr Drug Saf 2009;4:188–98.

118. Cavioli R, Kaya K, Asian A, Emiroglu O, Erturk S, Korkmaz O et al. Does sodium nitroprusside decrease the incidence of atrial fibrillation after myocardial revascularization?: a pilot study. Circulation 2008;118:476–81.

119. Lesenejs EJ, Lundergan CF, Hodson JM, Nair R, Reiner JS, Greenhouse SW et al. Increased left ventricular dysfunction in elderly patients despite successful surgical bypass: the GUSTO-I angiographic experience. J Am Coll Cardiol 1996;28:331–37.

120. Fontaine D, Pradier O, Haquebark E, Stefanis C, Carpentier Y, de Canteire D et al. Oxidative stress produced by circulating macrophages in on-pump but not off-pump coronary surgery. Acta Cardiol 2009;64:715–22.

121. Matata BM, Sosnowski AW, Gallianos M. Off-pump bypass graft operation significantly reduces oxidative stress and inflammation. Ann Thorac Surg 2000;69:785–91.

122. Orhan G, Sargin M, Senay S, Yuksel M, Kurec TA, Tansdemir M et al. Systemic and myocardial inflammation in traditional and off-pump cardiac surgery. Tex Heart J 2007;34:160–5.

123. Yue L, Feng J, Gao R, Li-GW, Wang Z, Nettel S. Ionic remodeling underlying action potential changes in a canine model of atrial fibrillation. Circ Res 1997;81:512–25.

124. Van Wagner DR, Pond AL, Lamorgese M, Rossie SS, McCarthy PM, Nerbonne JM. Atrial L-type Ca(2+) currents and human atrial fibrillation. Circ Res 1999;85:428–36.

125. Brandt MC, Priebre L, Bothe L, Sidkamp M, Beekelmann DJ. The ultrarapid and the transient outward K+ current in human atrial fibrillation, their possible role in postoperative atrial fibrillation. J Mol Cell Cardiol 2002;32:1885–96.

126. Dobrev D, Friedrich A, Voigt N, Jost N, Wettwer E, Christ T et al. The G protein-gated Potassium current gKATP is constitutively active in patients with chronic atrial fibrillation. Circulation 2003;111:3697–704.

127. Doebrev D, Wettwer E, Kortner A, Knaut M, Schuler S, Ravens U. Human inward rectifier potassium channels in chronic and postoperative atrial fibrillation. Circ Res 2002;94:407–49.

128. Szwarc MF, Fink GW, Lutz CJ, Taffs SM, Berenberg O, Vikstrom KL et al. Left versus right atrial difference in dominant frequency, (K(+)) channel transcripts, and fibrosis in patients developing atrial fibrillation after cardiac surgery. Heart Rhythm 2009;6:1415–22.

129. Spach MS, Dolber PC. Relating extracellular potentials and their derivatives to anisotropic propagation at a microscopic level in human cardiac muscle. Evidence for electrical uncoupling of side-to-side fiber connections with increasing age. Circ Res 1986;58:356–71.

130. Ad N, Snir E, Vidne BA, Golomb E. Histologic atrial myolysis is associated with postoperative atrial fibrillation related to cardiopulmonary bypass. J Thorac Cardiovasc Surg 2005;131:1970–75.

131. Gotte 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. Circ Cardiovasc Res 2002;54:390–6.

132. Cozgrave J, Folley JB, Flavin R, O'Brien DS, Fitzpatrick E, Bennett K et al. Proopective atrial histopathological changes are not associated with postoperative atrial fibrillation. Circulation Pathol 2006;15:213–17.

133. Anné W, Willems R, Raskams T, Sergeant P, Herigers P, Holemans P et al. Matrix metalloproteinases and atrial remodeling in patients with mitral valve disease and atrial fibrillation. Cardiovasc Res 2005;67:653–66.
156. Asher CR, Miller DP, Grimm RA, Cosgroveli DM, Chung MK. Analysis of risk factors for development of atrial fibrillation early after cardiac valvular surgery. Am J Cardiol 1998;82:892–95.

157. Kanagaratnam P, Kojojiro P, Peters NS. Electrophysiological abnormalities occur prior to the development of clinical episodes of atrial fibrillation: observations from human epicardial mapping. Pacing Clin Electrophysiol 2008;31:443–53.

158. 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;103:842–9.

159. Steinberg JS, Zelenkofske S, Wong SC, Gelernt M, Sciacca R, Menchavez E. Value of the P-wave signal-averaged ECG for predicting atrial fibrillation after cardiac surgery. Circulation 1993;88:2618–22.

160. Chandy J, Nakai T, Lee RJ, Bellows WH, Dzankic S, Leung JM. Increases in P-wave dispersion predict postoperative atrial fibrillation after coronary artery bypass graft surgery. Anesthesia Analgesia 2004;98:303–10.

161. Schotten U, Verheule S, Kirchhof P, Goette A. Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. Physiol Rev 2011;91:263–325.

162. Benjamin EJ, Levy D, Vaziri SM, D’Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort: the Framingham heart study. JAMA 1994;271:840–44.

163. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D’Agostino RB Sr et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. Lancet 2009;373:739–45.

164. Nakai T, Chandy J, Nakai K, Bellows WH, Flachsbart K, Lee RJ et al. Histologic assessment of right atrial appendage myocardium in patients with atrial fibrillation after coronary artery bypass graft surgery. Cardiology 2007;108:90–96.

165. Kojojiro P, Kanagaratnam P, Markides V, Davies DW, Peters N. Age-related changes in human left and right atrial conduction. J Cardiovasc Electrophysiol 2006;17:120–27.

166. Brembilla-Perrot B, Burger G, Beurrier D, Houriez P, Nippert M, Miljoen H et al. Influence of age on atrial fibrillation inducibility. Pacing Clin Electrophysiol 2004;27:287–92.

167. Renzsa PL, Alesiss MA, Lammers WJ, Bonke FL, Schalij MJ. Length of excitation wave and susceptibility to reentrant atrial arrhythmias in normal conscious dogs. Circ Res 1998;82:395–410.

168. Vaziri SM, Larson MG, Benjamin EJ, Levy D. Echocardiographic predictors of nonrheumatic atrial fibrillation. The Framingham Heart Study. Circulation 1994;89:724–30.

169. Roberts-Thomson KC, Stevenson I, Kistler PM, Haqqani HM, Spence SJ, Goldblatt JC et al. Role of chronic atrial stretch and atrial fibrillation on posterior left atrial wall conduction. Heart Rhythm 2009;6:1109–17.

170. Roberts-Thomson KC, Stevenson IH, Kistler PM, Haqqani HM, Goldblatt JC, Sanders P et al. Anatomically determined functional conduction delay in the posterior left atrium: relationship to structural heart disease. J Am Coll Cardiol 2008;51:856–62.

171. Verheule S, Wilson E, Everett TIV, Shanbhag S, Golden C, Ollign J. Alterations in atrial electrophysiology and tissue structure in a canine model of chronic atrial dilatation due to mitral regurgitation. Circulation 2003;107:2615–22.

172. Barasch E, Gottsdener JS, Aurigemma G, Kitzman DW, Han J, Kop WJ et al. Association between elevated fibrosis markers and heart failure in the elderly: clinical perspective. Circulation: Heart Fail 2009;2:303–10.

173. Li D, Fareh S, Leung TK, Nattel S. Promotion of atrial fibrillation by heart failure in dogs: atrial remodeling of a different sort. Circulation 1999;100:87–95.

174. L’Allier PL, Ducharme A, Keller P-F, Yu H, Guertin M-C, tardich C. Angiotensin-converting enzyme inhibition in hypertensive patients is associated with a reduction in the occurrence of atrial fibrillation. J Am Coll Cardiol 2004;44:159–64.

175. Shariff N, Zelenkofske S, Eid S, Weiss M, Mohammed M. Demographic determinants and effect of pre-operative angiotensin converting enzyme inhibitors and angiotensin receptor blockers on the occurrence of atrial fibrillation after CABG surgery. BMC Cardiovasc Disorders 2010;10:7.

176. White CM, Kluger J, Lertabura K, Faheem O, Coleman CI. Effect of preoperative angiotensin converting enzyme inhibitor or angiotensin receptor blocker use on the frequency of atrial fibrillation after cardiac surgery: a cohort study from the atrial fibrillation suppression trials II and III. Eur J Cardio-Thorac Surg 2007;31:817–20.

177. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol 1998;82:2N–9N.

178. Rush B, Friberg J, Scharling H, Lange P, Prescott E. Reduced lung function and risk of atrial fibrillation in The Copenhagen City Heart Study. Eur Respir J 2003;21:1012–16.

179. Zhang X, Wu Z, Peng X, Wu A, Yue Y, Martin J et al. Prognosis of diabetic patients undergoing coronary artery bypass surgery compared with nondiabetics: a systematic review and meta-analysis. J Cardiothorac Vasc Anesth 2010;25:288–98.

180. de Vos CB, Pisters R, Nieuwlaat R, Prins MH, Tieleman RG, Coenen RJ et al. Progression from paroxysmal to persistent atrial fibrillation: clinical correlates and prognosis. J Am Coll Cardiol 2010;55:725–31.

181. Lopez CM, House-Fancher MA. Management of atrial fibrillation in patients with chronic obstructive pulmonary disease. J Cardiovasc Nurs 2005;20:133–40.