Post-operative atrial fibrillation: a maze of mechanisms

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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).12,13,16 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.2–4,6,10,12,13,24,28,30–33

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).14,15 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 (35.6%), Europe (34%), and the Middle East (41.6%), but a lower POAF incidence in South America (17.4%) and Asia (15.7%). Another example shows that 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 received continuous 24 h telemetry with arrhythmia-detection algorithms during their entire hospital stay. The difference in reported POAF incidence between these studies emphasizes that a more systematic ECG monitoring results in a better identification and thus a higher detected incidence. Finally, the definition of POAF also influences its reported incidence. For example, in one study POAF is defined as any documented AF >5 min, while in another study only episodes of >10 min are counted.

Despite the methodical differences between studies, the incidence of POAF could be shown to be strongly determined by the kind of surgery. In general, the reported incidence of POAF after CABG ranges between 16 and 50%. Remarkably, after heart transplantation the incidence of post-operative atrial arrhythmias is reported to be very low (4%). However, due to the surgical cut and sew lines in the atria during heart transplantation, the atrial surface is significantly reduced and pulmonary veins are isolated.

In the group of non-cardiac surgery, the incidence of POAF is higher after thoracic surgery than after non-thoracic surgical procedures. In non-cardiac, non-thoracic surgery, POAF occurs relatively infrequently (0.37% for ophthalmic surgery up to 13% for large colorectal surgery). After thoracic surgery POAF occurs more frequent, with reported incidences of 9–29%. Some studies report no differences in incidence between more invasive and less invasive types of thoracic surgical procedures, although other studies do.

The time course of the onset of POAF after cardiac surgery has been identified. The strongest predictor of POAF is advancing age. Association with other risk factors shows a large degree of variability between different studies (Table 2). For example, Zacharias et al. found body mass index to be an important determinant of POAF, while other studies failed to show this. Furthermore, left atrial enlargement is a predictor of POAF in some studies. Sometimes left atrial enlargement is not predictive even when mitral valve surgery in the same study is a risk factor. This might indicate a role for tissue trauma as a consequence of a more invasive procedure during mitral valve repair/replacement.

In 2002, Ferguson et al. confirmed the wide-spread perception among cardiac surgeons that the population of patients currently referred for isolated CABG are older, sicker, and have a higher surgical risk than a decade ago. As age represents an important risk factor for the onset of POAF, one would expect an increase in incidence of POAF over time which indeed in one study has been reported. Other studies, however, failed to identify an increase or even reported a trend towards a decreasing prevalence. Whether the lack of increase in POAF incidence over the past years is due to more frequent use of beta-blockers or amiodarone is currently unknown. In the study of Shen et al., the annual percentage of aortic and mitral valve procedures increased over two decades. Considering that these surgical procedures are associated with a higher risk of POAF, and that the incidence remained approximately 30%, the authors concluded that some progress in treating POAF has been made.

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>
<thead>
<tr>
<th>Author</th>
<th>Year of publication</th>
<th>n (% male)</th>
<th>Age (overall)</th>
<th>Study type</th>
<th>Multicentre (number)</th>
<th>Definition of POAF</th>
<th>History of AF</th>
<th>CPB (% of patients)</th>
<th>Incidence of POAF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fuller et al</td>
<td>1989</td>
<td>1666 (88.6)</td>
<td>62.2 ± 12.3 NS</td>
<td>Prospective</td>
<td>No</td>
<td>AF detected by continuous telemetry or by clinical symptoms and signs</td>
<td>None</td>
<td>100/100 100%</td>
<td>28.4 (703/2515)</td>
</tr>
<tr>
<td>Leitch et al</td>
<td>1990</td>
<td>5807 (NS)</td>
<td>67.9 ± 8.3</td>
<td>Prospective</td>
<td>No</td>
<td>AF detected by continuous ECG monitoring (48 h)</td>
<td>None</td>
<td>100/100 100%</td>
<td>17.2 (33/193)</td>
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<tr>
<td>Creswell et al</td>
<td>1993</td>
<td>3983 (66.7)</td>
<td>67 ± (69) NS</td>
<td>Prospective</td>
<td>No</td>
<td>New onset of AF, AFL, PAT</td>
<td>None</td>
<td>100/100 100%</td>
<td>26.9 (33/126)</td>
</tr>
<tr>
<td>Aranki et al</td>
<td>1996</td>
<td>570 (69)</td>
<td>63.7 ± 9.6</td>
<td>Prospective</td>
<td>No</td>
<td>AF requiring medication/pacing</td>
<td>None</td>
<td>100/100 100%</td>
<td>34.6 (1378/3983)</td>
</tr>
<tr>
<td>Almassi et al</td>
<td>2001</td>
<td>3853 (98.6)</td>
<td>71 ± 66.8 ± 8.3</td>
<td>Prospective</td>
<td>Yes (16)</td>
<td>Any AF detected via continuous ECG monitoring (only) during intensive care unit stay</td>
<td>None</td>
<td>100/100 100%</td>
<td>31.9 (29.6/103/4)</td>
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<tr>
<td>Siebert et al</td>
<td>2002</td>
<td>821 (74.4)</td>
<td>NS</td>
<td>Prospective</td>
<td>No</td>
<td>Entry in case report as AF detected by ECG</td>
<td>None</td>
<td>100/100 100%</td>
<td>36.4 (10.2/102)</td>
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<tr>
<td>Mathew et al</td>
<td>2004</td>
<td>10030 (71)</td>
<td>66.8 ± 8.3 NS</td>
<td>Prospective</td>
<td>No</td>
<td>Retrospective</td>
<td>None</td>
<td>100/100 100%</td>
<td>31.9 (29.6/103/4)</td>
</tr>
<tr>
<td>Mathew et al</td>
<td>2004</td>
<td>4637 (79.8)</td>
<td>NS</td>
<td>Prospective</td>
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<td>Retrospective</td>
<td>None</td>
<td>100/100 100%</td>
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<tr>
<td>Villareal et al</td>
<td>2004</td>
<td>6477 (73.8)</td>
<td>66 ± 9.6 NS</td>
<td>Prospective</td>
<td>No</td>
<td>Retrospective</td>
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<td>Barach et al</td>
<td>2006</td>
<td>1200 (66.6)</td>
<td>66 ± 7.8 NS</td>
<td>Retrospective</td>
<td>Yes (12)</td>
<td>AF of any duration, any time based on ECG</td>
<td>None</td>
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<td>36.4 (10.2/102)</td>
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<tr>
<td>Mariscalco et al</td>
<td>2009</td>
<td>9495 (73.2)</td>
<td>66.2 ± 9.5 NS</td>
<td>Retrospective</td>
<td>No</td>
<td>AF–AFL &gt;15 min</td>
<td>None</td>
<td>100/100 100%</td>
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<tr>
<td>Ahlsson et al</td>
<td>2009</td>
<td>571 (78)</td>
<td>62.3 ± 12.9 NS</td>
<td>Retrospective</td>
<td>No</td>
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<tr>
<td>Shen et al</td>
<td>2010</td>
<td>10390 (65)</td>
<td>65</td>
<td>Retrospective</td>
<td>No</td>
<td>AF–AFL &gt;15 min</td>
<td>None</td>
<td>100/100 100%</td>
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Table I Incidence of post-operative atrial fibrillation

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<th>Author</th>
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<th>n (% male)</th>
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<th>Study type</th>
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<td>67.9 ± 8.3</td>
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<td>None</td>
<td>100/100 100%</td>
<td>31.9 (29.6/103/4)</td>
</tr>
</tbody>
</table>

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

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</thead>
<tbody>
<tr>
<td>Fuller et al.</td>
<td>1989</td>
<td>1666</td>
<td>Age</td>
<td>P = 0.0001</td>
<td>OR = 1.7, P &lt; 0.001 (10 yr decile)</td>
<td>OR = 2.0, P = 0.002 (age 70 to 80 yr)</td>
<td>OR = 1.61, P = 0.0001 (10 yr decile)</td>
<td>OR = 1.53, P = 0.0005 (per 5 yr increase)</td>
<td>OR = 1.07, P = 0.02 (each increasing yr above lower border)</td>
<td>OR = 1.75, P &lt; 0.001 (10 yr decile)</td>
<td>OR = 2.6, P &lt; 0.01 (above vs. below median)</td>
<td>OR = 1.52, P &lt; 0.001 (10 yr decile)</td>
<td>OR = 2.6, P &lt; 0.01 (age &gt; 70 yr)</td>
<td>OR = 5.34 (age &gt; 72 yr)</td>
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<tr>
<td>Leitch et al.</td>
<td>1990</td>
<td>5807</td>
<td>History of AF</td>
<td>OR = 2.1, P &lt; 0.001</td>
<td>OR = 1.43, P = 0.009</td>
<td>OR = 1.28, P &lt; 0.001</td>
<td>OR = 6.1, P &lt; 0.002</td>
<td>ns</td>
<td>ns</td>
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<tr>
<td>Creswell et al.</td>
<td>1993</td>
<td>3983</td>
<td>COPD</td>
<td>OR = 1.3, P = 0.006</td>
<td>OR = 1.37, P = 0.0076</td>
<td>OR = 1.19, P = 0.027</td>
<td>OR = 2.88, P = 0.009</td>
<td>ns</td>
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<tr>
<td>Aranki et al.</td>
<td>1996</td>
<td>570</td>
<td>Hypertension</td>
<td>OR = 1.6, P = 0.03</td>
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<td>OR = 1.24, P = 0.001</td>
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<td>OR = 1.43, P = 0.009</td>
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<tr>
<td>Zaman et al.</td>
<td>2000</td>
<td>3855</td>
<td>Male gender</td>
<td>OR = 1.7, P = 0.01</td>
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<td>OR = 1.7, P = 0.01</td>
<td>OR = 2.86, P = 0.0001</td>
<td>OR = 1.74, P &lt; 0.001</td>
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<td>Hakala et al.</td>
<td>2002</td>
<td>326</td>
<td>Diabetes</td>
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<td>Mathew et al.</td>
<td>2004</td>
<td>88</td>
<td>Prior MI</td>
<td>OR = 1.6, P = 0.01</td>
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<td>Auer et al.</td>
<td>2005</td>
<td>4657</td>
<td>CHF</td>
<td>ns</td>
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<td>ns</td>
<td>OR = 1.7, P &lt; 0.001</td>
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<td>OR = 1.7, P &lt; 0.001</td>
<td>OR = 1.7, P &lt; 0.001</td>
<td>OR = 0.32, P &lt; 0.001</td>
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<td>253</td>
<td>BMI</td>
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<tr>
<td>Banach et al.</td>
<td>2006</td>
<td>8051</td>
<td>No pre-operative β-blocker therapy</td>
<td>ns</td>
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<td>OR = 1.2, P = 0.011</td>
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<td>OR = 1.29, P &lt; 0.01</td>
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<td>Shen et al.</td>
<td>2010</td>
<td>1200</td>
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<td>Postoperative withdrawal of ACE-I</td>
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<td>OR = 1.69, P &lt; 0.001</td>
<td>OR = 1.69, P &lt; 0.001</td>
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<td>Postoperative ACE-I therapy</td>
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<td>OR = 0.62, P &lt; 0.001</td>
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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; yr = year.
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.

For example, Panesar et al performed an extensive meta-analysis including 4921 patients aged 70 years and older and reported a significantly lower AF incidence in the OPCAB group compared with on-pump surgery. It could be argued that the influence of on-pump surgery compared with off-pump surgery on AF occurrence is rather small and that this effect only emerges in the older patient population, where the risk of POAF is known to be higher. 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.86,87 A recent meta-analysis of 17 643 patients undergoing cardiac surgery suggests that pre-operative use of statins significantly reduces POAF incidence.88 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,89 and also to attenuate myocardial reperfusion injury after cardiac surgery.90 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.91 Treatment with n-3 polyunsaturated fatty acids to prevent POAF has been reported with success in some studies;92,93 however, placebo-controlled, double-blinded, randomized trials have failed to reproduce this protective effect of fish oil.94,95

Finally, it is known that chronic inflammation in patients can cause atrial structural remodelling. C-reactive protein is associated with increased activity or loss of vagal tone.101 – 103 These findings, however, do not exclude a role for sympathetic activation in the arrhythmia substrate, as both sympathetic and parasympathetic activation alter atrial refractoriness.109,110 Hogue et al.103 detected a higher HRV in some patients, but a lower HRV in others in the hour before onset of POAF, suggesting the possibility of divergent autonomic conditions shortly before onset of the arrhythmia. Cardiac denervation obviously interrupts both sympathetic and parasympathetic regulation of heart function.

Drugs mimicking sympathetic activation are also pro-arrhythmic. 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.111 – 113 Activation of protein kinase A by cAMP can lead to stimulation of multiple cardiac currents, including the L-type calcium current (\(I_{\text{CaL}}\)), thereby promoting the occurrence of early and delayed afterdepolarizations.114,115 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 (\(I_{\text{Ks}}\))) and increased ectopic activity.114 – 116 In theory, blocking the sympathetic activation by β-adrenoceptor 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.50,117,118 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.106 The withdrawal of pre-operative β-blockade after CABG is associated with a more than two-fold increase in POAF.119 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.14 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.50 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 remodelling’, 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 β-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 aetiology 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 remodelling 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 remodelling (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 remodelling, but that it loses its protective effect during later stages of the electrical remodelling process. The fact that simvastatin attenuated AF promotion can be partly due to an anti-inflammatory mechanism. As discussed before, statins possess antioxidative properties 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, Ramli 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 perioperative 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 cardioplegic 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 relationship 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.\textsuperscript{62} Furthermore, inflammation seems to be at least as important as ischaemia/reperfusion in producing oxidative radicals during on-pump surgery.\textsuperscript{132,133} Indeed, some studies indicate that off-pump surgery is associated with less oxidative stress. For example, Fontaine et al.\textsuperscript{140} 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.\textsuperscript{141} In another study, Orhan et al.\textsuperscript{142} 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.\textsuperscript{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\textsuperscript{2+}) influx through the L-type Ca\textsuperscript{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 \(I_{\text{CaL}}\) which contributes to shortening of atrial refractoriness as a consequence of AF.\textsuperscript{143} 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.,\textsuperscript{144} \(I_{\text{CaL}}\) 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\textsuperscript{14} will further increase calcium influx through L-type Ca\textsuperscript{2+} channels. Enhanced calcium load might elicit triggered activity (e.g. delayed afterdepolarizations) potentially initiating POAF.\textsuperscript{144} However, a more recent and very detailed study by Workman et al.,\textsuperscript{50} could not confirm any differences in \(I_{\text{CaL}}\) between patients with and without POAF. This recent study and the significant overlap in the Ca\textsuperscript{2+} current density data for most patients in the

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<th>Author, year</th>
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<td>Frustaci (1997)</td>
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<td>Lymphomononuclear infiltrates compatible with atrial myocarditis in atrial tissue of 66% of patients with lone AF</td>
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<td>Inflammation/oxidative stress</td>
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<td>Workman (2006)</td>
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<td>Chronic (\beta)-blocker therapy is associated with reduced POAF incidence, unrelated to pre-operative ERP-prolonging</td>
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<td>Kim (2008)</td>
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<td>NADPH oxidase activity in right atrial appendage is the most important independent predictor of POAF.</td>
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<td>Treatment with N-acetylcysteine, an antioxidant, decreases the incidence of post-operative AF.</td>
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<td>Ho (2009)</td>
<td>Inflammation</td>
<td>Human</td>
<td>Corticosteroid prophylaxis is effective in reducing the risk of atrial fibrillation</td>
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earlier report\textsuperscript{444} 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 et al.\textsuperscript{445} reported that the ultra-rapid delayed rectifier K\textsuperscript{+} current (I\textsubscript{Kur}) 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{to}) were detected compared with patients without POAF.\textsuperscript{445} Dobrev et al.\textsuperscript{446,447} found the smaller 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 et al.\textsuperscript{50} found no differences in I\textsubscript{to}, 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{56} and with results in other reports.\textsuperscript{445,447} Finally, a recent study of Swartz et al.\textsuperscript{448} 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, pre-operative 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{449} were the first to report that progressive electrical uncoupling of the side-to-side connections between parallel-oriented 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{449} Such an alteration in conduction is often associated with the presence of extensive collagenous septa and favours reentry.\textsuperscript{449} The relationship between this age-dependent remodelling and the occurrence of POAF is strengthened by several studies. First, Ad et al.\textsuperscript{450} 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 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 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 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
example, Anné et al.155 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.156 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.155 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.,157 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.157 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.157 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.158 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.158

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.,159 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.159 In another study, increase in P-wave dispersion post-operatively predicted POAF after CABG.160

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.12 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’161 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 AF162,163 and POAF.1,2,4,6,9,15,18,44–48 Moreover, several arguments support that ageing enhances the development of a substrate capable of perpetuating AF.149 As discussed above, ageing goes along with fibrosis151,153,164 and is associated with slowing of conduction.165 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).166 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,167 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.162,163,168 Atrial structural remodelling consequent to these risk factors can predispose to the onset of POAF. Indeed, in large epidemiological studies,12,4,17 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.1,8,9,47 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.169 Moreover, a line
of conduction block runs vertically between the pulmonary veins in the posterior left atrium. 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. 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. Histological analysis of these atria revealed areas of chronic inflammation and increased interstitial fibrosis.

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.

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

History of atrial fibrillation
High propensity to POAF in patients with previous episodes of AF is not surprising. The fact that spontaneous episodes of AF already occurred shows that the activity of pro-arrhythmic mechanisms in these patients exceeded the ‘AF threshold’. 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. Also in POAF, the predictive value of diabetes for the incidence of the arrhythmia is low. In a recent meta-analysis reviewing 100,217 patients, no difference in POAF incidence was found between patients with and without diabetes. Furthermore, men have a 1.5 times greater likelihood of developing new onset AF compared with women. The mechanism behind the higher AF susceptibility remains unclear. In POAF, male gender fails to reach significance in many studies, and in studies that find male gender to be associated with POAF, the number of women included is often low. Association between chronic obstructive pulmonary disease (COPD) and new onset AF is still under discussion.
as an independent predictor of AF progression. In the occurrence of POAF, COPD is often identified as a risk factor. The pathogenesis of AF in patients with COPD is unclear, 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.

**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 un masks 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, while reducing oxidative stress or inflammation were less effective. In line with this the 2010 European Society of Cardiology guidelines recommend β-blocker treatment as first-line therapy of POAF.

(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 eight-fold increased risk of developing AF in the future. 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) and more profound atrial structural changes like fibrosis 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. However, the function of these ion channels is not altered in pre-operative atrial biopsies of patients developing AF after cardiac surgery. Therefore, subclassification 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.

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