

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).^{1,2,7,8,10,11,17,18} 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.^{2–4,6,10,12,13,24,28,30–33}

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

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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,³² 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 pre-disposing 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.^{5,34} Mathew *et al.*³ 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%).³ Another example that stresses the importance of patient demographics is the identification of Caucasian race as an independent predictor of POAF in several studies.^{17,34} 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.*¹¹ 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.¹¹ 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.⁹ On the other hand, in a large retrospective study Shen *et al.*¹⁷ 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.¹⁷ 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.^{7,16}

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%.^{4,6,8,9,11–17} The incidence is higher after valve surgery and highest after a combination of CABG and valve surgery.^{1,2,7,10,11,17,18} Remarkably, after heart transplantation the incidence of post-operative atrial arrhythmias is reported to be very low (4%).³⁵ 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.^{36,37} In non-cardiac, non-thoracic surgery, POAF occurs relatively infrequently (0.37% for ophthalmic surgery up to 13% for large colorectal surgery).^{25–30} After thoracic surgery POAF is more frequent, with reported incidences of 9–29%.^{20,21,23,24,38–42} Some studies report no differences in incidence between more invasive and less invasive types of thoracic surgical procedures,^{20,21} although other studies do.^{22,38–40}

The time course of the onset of POAF after cardiac surgery is very typical, with 70% of the patients developing POAF in the first 4 post-operative days and only 6% developing AF after the 6th day.^{4,7,43} Post-operative atrial fibrillation has its peak incidence on the 2nd post-operative day and recurrence of POAF is highest on the 3th post-operative day, with only 22% of the patients experiencing >2 episodes of POAF.^{3,8}

Different risk factors for development of POAF after cardiac surgery have been identified. The strongest predictor of POAF is advancing age.^{1,2,4,6–9,15–18,44–48} Association with other risk factors shows a large degree of variability between different studies (Table 2). For example, Zacharias *et al.*⁴⁷ found body mass index to be an important determinant of POAF, while other studies failed to show this.^{6,7,15} Furthermore, left atrial enlargement is a predictor of POAF in some studies.^{15,46} However, 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.^{3,48}

In 2002, Ferguson *et al.*⁴⁹ 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.¹ Other studies, however, failed to identify an increase or even reported a trend towards a decreasing prevalence.^{9,10,17,50,51} 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.*,¹⁷ 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.¹⁷

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.^{52–57} 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	Fuller et al.	Leitch et al.	Creswell et al.	Aranki et al.	Almassi et al.	Siebert et al.	Mahoney et al.	Mathew et al.	Villareal et al.	Banach et al.	Mariscalco et al.	Ahlsson et al.	Shen et al.
Year of publication	1989	1990	1993	1996	1997	2001	2002	2004	2004	2006	2009	2009	2010
n (% male)	1666 (88.6)	5807 (NS)	3983 (66.7)	570 (69)	3855 (98.4)	821 (74.4)	10550 (71)	4657 (79.8)	6477 (73.8)	1200 (66.6)	9495 (73.2)	571 (78)	10390 (65)
Age (overall)		NS	62.2 ± 12.3	67	63.7 ± 9.6	NS	NS			61 ± 2.4	66.2 ± 9.5		62.3 ± 12.9
Age (AF group)	60.9 ± 7.3			71	66.8 ± 8.3			67.8	67.9 ± 9.6	66 ± 7.8		69.2 ± 7.6	
Study type	Prospective	Prospective	Prospective	Prospective	Prospective	Prospective	Retrospective	Prospective	Retrospective	Prospective	Retrospective	Prospective	Retrospective
Multicentre (number)	No	No	No	No	Yes (14)	No	No	Yes (70)	No	Yes(12)	No	No	No
Definition of POAF	AF detected by continuous telemetry	detected by continuous monitoring (48 h) or by clinical symptoms and signs	New onset AF, AFL, PAT	AF requiring medication/pacing	NS	Any AF detected via continuous ECG monitoring (only) during intensive care unit stay	NS	Entry in case report form/AF detected by ECG	AF of any duration, any time based on ECG	NS	AF-AFL > 15 min	ECG verified episode > 1 min during first 7 days	AF(L) during post-operative recovery period and requiring treatment
CPB (% of patients)	100	100	100	100	100	85.6 (703/821)		100	NS	87.5	100	93.9	NS
History of AF	None	None	None	None	None	None	None	0.09% (424/4657)	None	NS (28% arrhythmias)	None	None	None
Incidence of POAF (%)	28.4	17.2	34.6 (1378/3983)	33	29.6 (1143/3885)	NS	NS	32.3 (1503/4657)	16	23.2	26.7	28.9	30
CABG Alone	28.4 (476/1666)	17.2	31.9 (905/2833)	33	27.6	9.8 (64/650)	17.7	30.9 (1349/4371)	16 (994/6477)	23.2 (278/1200)	22.9	28.9 (165/571)	29 (2098/7284)
OPCAB						10.2 (12/118)							
CABG+AVR			60.1 (95/158)		36.4	25.0 (9/36)							
CABG+MVR			63.1 (65/103)		60	17.6 (3/17)							
AVR			48.8 (83/170)		32.9								
MVR			44.3 (43/97)		48.8								
Transplantation			11.0 (15/136)										

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.	Almassi 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	1997	2000	2002	2004	2005	2005	2006	2010
Number of Patients	1666	5807	3983	570	3855	326	88	4657	253	8051	1200	10390
Risk Factors												
Age	$P = 0.0001$	OR = 1.7, $P < 0.001$ (10 yr decile)	$P < 0.001$	OR = 2.0 $P = 0.002$ (age 70 to 80 yr)	OR = 1.61 $P = 0.0001$ (10 yr decile)	OR = 1.53 $P < 0.0005$ (per 5 yr increase)	OR = 1.07, $P = 0.02$ (each increasing yr above lower border)	OR = 1.75 $P < 0.001$ (10 yr decile)	OR = 2.6, $P < 0.01$ (above vs. below median)	OR = 1.52 $P < 0.001$ (10 yr decile)	OR = 2.6 $P < 0.001$ (age > 70 yr)	OR = 5.34 (age > 72 yr)
History of AF								OR = 2.11, $P < 0.001$			OR = 6.1, $P < 0.002$	
COPD		OR = 1.5, $P = 0.006$	$P < 0.001$	ns	OR = 1.37, $P = 0.0016$		ns	OR = 1.43, $P = 0.009$		OR = 1.28, $P < 0.001$	ns	ns
Hypertension	ns	ns	ns	OR = 1.6, $P = 0.03$	OR = 1.19, $P = 0.027$		ns	ns	ns	ns	ns	OR = 1.15
Male gender	$P = 0.02$		ns	OR = 1.7, $P = 0.01$	ns	OR = 2.88, $P = 0.009$	ns	ns	ns	OR = 1.24, $P = 0.001$	ns	ns
Diabetes	ns		ns	ns	ns		ns	ns	ns	ns	ns	ns
Prior MI	ns	ns		OR = 1.6, $P = 0.01$	ns		ns	ns		ns		ns
CHF				ns				ns	ns	ns	OR = 4.8, $P < 0.005$	OR = 1.28
BMI				ns			ns		ns	OR = 1.36, $p < 0.001$ BMI = > 30–35 kg/m ²	ns	
No pre-operative β -blocker therapy	ns	OR = 1.2, $P = 0.011$	ns	ns	ns	ns		ns	OR = 1.7, $P < 0.05$	OR = 1.17, $P = 0.005$	OR = 0.79, $P < 0.01$	ns
Left atrial enlargement						ns	OR = 1.29, $P = 0.01$	ns				
RCA stenosis						ns	ns	ns	ns			
Mitral valve surgery					OR = 2.86, $P = 0.0001$			OR = 1.74, $P < 0.001$	OR = 2.8, $P < 0.01$	OR = 2.42, $P < 0.001$		OR = 1.91
Postoperative withdrawal of β -blocker						ns		OR = 1.91, $P < 0.001$				
Postoperative withdrawal of ACE-I								OR = 1.69, $P < 0.001$				
(No) post-operative β -blocker therapy	$P = 0.001$					ns		OR = 0.32, $P < 0.001$			OR = 0.79, $P < 0.01$	
Postoperative ACE-I therapy								OR = 0.62, $P < 0.001$				

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, 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,⁵² interleukin-2,⁵⁸ and interleukin-6.⁵³ 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.^{56,59} Furthermore, patients developing POAF have up-regulated monocyte activation and higher monocyte and neutrophil levels post-CPB.^{60,61}

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.⁶² However, several studies failed to show statistical association between OPCAB and a

lower incidence of POAF.^{11,63–68} 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.^{69–72} For example, Panesar *et al.*⁷³ 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.^{1–4} 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.^{74,75} 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.*⁷⁶, showing lymphomononuclear infiltrates compatible with atrial myocarditis in atrial tissue of 66% of patients with lone AF.⁷⁶ Also Chen *et al.*⁷⁷ 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.*⁷⁸ 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.⁷⁹ 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 43.⁸⁰ 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).^{81,82} Administration of prednisone inhibited tissue inflammation and reduced serum CRP and AF inducibility.⁸¹ Also atorvastatin, an HMG-CoA reductase inhibitor, significantly reduced CRP levels and AF duration, and attenuated perimyocarditis.⁸² 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.⁸³

Atrial inflammation is known to cause conduction disturbances. For example, in a study with mongrel canines, Ishii *et al.*⁸⁴

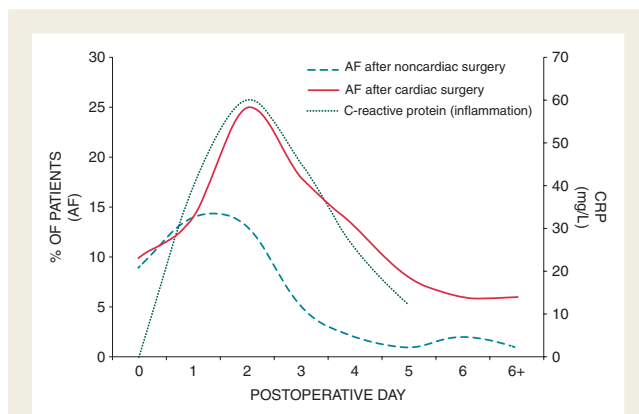


Figure 1 Time course of atrial fibrillation incidence after cardiac and non-cardiac surgery and time course of C-reactive protein after cardiac surgery. Atrial fibrillation incidence after non-cardiac surgery peaks at post-operative day 1 and then rapidly declines to 2% at day 6, while atrial fibrillation incidence after cardiac surgery peaks at post-operative day 2 and slowly declines to around 6% at day 6. This suggests a 'cardiac factor', related to the specific setting of cardiac surgery. The time course of C-reactive protein is surprisingly similar to that of atrial fibrillation incidence after cardiac surgery, supporting the role for inflammation in the mechanism of post-operative atrial fibrillation (modified from references ^{4,30,52}).

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.⁸⁴ In another canine study, acute inflammation provoked by arachidonic acid produced slowing and enhanced anisotropy of conduction but did not affect atrial refractoriness.⁸⁵

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 and predicts patients at risk of developing future non-surgical AF.^{54,55} This chronic inflammation might also predispose to the occurrence of POAF. Some studies found elevated pre-operative CRP levels to be associated with an increased risk of the arrhythmia after CABG.^{32,96} Others, on the contrary, failed to find an association between pre-operative CRP and POAF.^{60,97,98} This controversy suggests that the induction of inflammation during surgery, rather than a pre-existing inflammation process, contributes more to the development of the arrhythmia.

Sympathetic activation

In the heart, sympathetic stimulation is mediated by β -adrenoreceptors and leads to an increase in heart rate and contractile force, but also to enhanced excitability and automaticity.⁹⁹ Several findings support a role for sympathetic activation in the pathogenesis of atrial arrhythmias after cardiac surgery. Advanced age, the most important risk factor for POAF, is associated with increasing circulating norepinephrine levels.¹⁰⁰ Patients who develop POAF also have significantly elevated norepinephrine levels post-operatively compared with patients without POAF.¹⁴ This association is further reflected by the fact that the onset of POAF is preceded by an increase in sinus rate and atrial ectopic activity. Also, studies on post-operative heart rate variability (HRV) showed an increase in time- and frequency-domain parameters of HRV prior to the onset of POAF, consistent with increasing sympathetic activity.^{101,102} However, controversy remains if this sympathetic activation is accompanied by either increased activity or loss of vagal tone.^{101–103} Finally, sympathetic

activation has been reported to shorten atrial refractoriness non-uniformly, thereby favouring the perpetuation of the arrhythmia.¹⁰⁴ On the other hand, there is a slight discrepancy between the peak of sympathetic activation, which occurs within 24 h post-operatively, and the onset of POAF, mostly developing between 48 and 72 h after surgery.¹⁰⁵

If sympathetic activation plays an important role in onset of POAF, one would expect that cardiac denervation reduces the incidence of the arrhythmia. This was first studied by Melo et al.¹⁰⁶ They performed ventral cardiac denervation in 207 patients undergoing low-risk CABG, and indeed found that this intervention significantly reduced the incidence and severity of POAF.¹⁰⁶ It should be noted, however, that only 15% of the patients in their study underwent telemetric monitoring and some patients with asymptomatic AF might not have been identified. Other studies failed to show the benefit of cardiac denervation or found even an increase in POAF.^{107–109} 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_{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_{Ks})) and increased ectopic activity.^{114–116}

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.^{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.¹⁰⁵ 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.¹²⁰ 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 develop POAF.⁵⁰ 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.⁵⁰

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.¹²¹ However, oral β -blocker therapy started at least 1 week before surgery remains the first choice in preventing POAF after cardiac surgery.⁹¹

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.^{122,123}

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.¹²⁴ 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).¹²⁴ In another canine RAP study, AF promotion after 7 days of RAP was attenuated by simvastatin but not by antioxidant vitamins C and E.¹²⁵ 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 remodelling 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.¹²⁶

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.¹²⁷ 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.¹²⁸ Nicotinamide adenine dinucleotide phosphate oxidase is known to be an important source of reactive

oxygen species in human atrial myocytes.¹²⁸ 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.^{129,130}

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.^{129,130} Secondly, Ramlawi *et al.*¹³¹ 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.*¹³² 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.*¹³³ 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.*¹²⁴ 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.¹³⁴ Another example is the administration of the antioxidant *N*-acetylcysteine. *N*-acetylcysteine lowered the incidence of POAF after CABG and/or valve surgery significantly.¹³⁵ By scavenging reactive oxygen species with *N*-acetylcysteine, myocardial oxidative stress is attenuated in patients undergoing CABG with CPB and cardioplegic arrest.¹³⁶ Furthermore, nitric oxide (NO) gas has been reported to significantly inhibit oxidative stress when administered to patients undergoing CABG.¹³⁷ Sodium nitroprusside (SNP), an NO donor, significantly lowered the incidence and duration of post-CABG AF in a recent pilot study.¹³⁸ Finally, also statins are known to lower the incidence of POAF, presumably in part through their antioxidative properties.⁸⁸

Another argument supporting a causative relation between oxidative stress and POAF is the higher occurrence of the arrhythmia in the elderly.⁴ Ageing hearts are more susceptible for ischaemia/reperfusion injury.¹³⁹ 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.⁶² Furthermore, inflammation seems to be at least as important as ischaemia/reperfusion in producing oxidative radicals during on-pump surgery.^{132,133} Indeed, some studies indicate that off-pump surgery is associated with less oxidative stress. For example, Fontaine et al.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.¹⁴¹ In another study, Orhan et al.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.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.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.,¹⁴⁴ 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 surgery¹⁴ 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.¹⁴⁴ However, a more recent and very detailed study by Workman et al.⁵⁰ 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

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_{CaL} measured at the time of surgery and the occurrence of POAF.
Brandt (2000)	Alteration in ion channels	Human	No difference in I_{to} and a non-significant trend towards a decrease in I_{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_{K1} and I_{KACH} .
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_{CaL} , I_{to} , I_{K1} , and I_{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.

earlier report¹⁴⁴ suggest that changes in L-type Ca^{2+} channel might have contributed to POAF initiation in some patients, but certainly not in all.

Potassium (K^+) channels, which are altered in patients with persistent AF, are apparently not involved in the occurrence of POAF. First, Brandt *et al.*¹⁴⁵ reported that the ultra-rapid delayed rectifier K^+ current (I_{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_{Kur} and no difference in the transient outward K^+ current (I_{to}) were detected compared with patients without POAF.¹⁴⁵ Dobrev *et al.*^{146,147} found the larger basal inward rectifying K^+ current in patients with persistent AF to consist of increased activity of the inward rectifier K^+ current (I_{K1}) and constitutive activity of the acetylcholine-activated K^+ current (I_{KACH}). Again, both I_{K1} and I_{KACH} were not altered in non-AF patients developing POAF compared with patients not having AF after surgery. Thirdly, Workman *et al.*⁵⁰ found no differences in I_{to} , in I_{K1} , or in the sustained outward K^+ current (I_{SUS}) between patients who did and did not develop POAF. These findings are consistent with unaltered APD or ERP in their study⁵⁰ and with results in other reports.^{145,147} Finally, a recent study of Swartz *et al.*¹⁴⁸ confirmed the lack of difference in K^+ 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^{2+} and K^+ 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 Dolber¹⁴⁹ 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.¹⁴⁹ Such an alteration in conduction is often associated with the presence of extensive collagenous septa and favours reentry.¹⁴⁹ The relationship between this age-dependent remodelling and the occurrence of POAF is strengthened by several studies. First, Ad *et al.*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 *et al.*,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.*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.*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.¹⁵³ Finally, a larger amount of fibrosis was found in left atria of patients developing POAF.¹⁴⁸ On the other hand, one study reported no differences in right atrial histology between patients who do and do not develop POAF.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.⁴⁵ 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 terminalis 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'¹⁶¹ 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^{162,163} 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 fibrosis^{151,153,164} 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,^{2,4,17} 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 regurgitance, *prolongation* rather than shortening of AERP is seen in the left atrium.¹⁶⁹ Moreover, a line

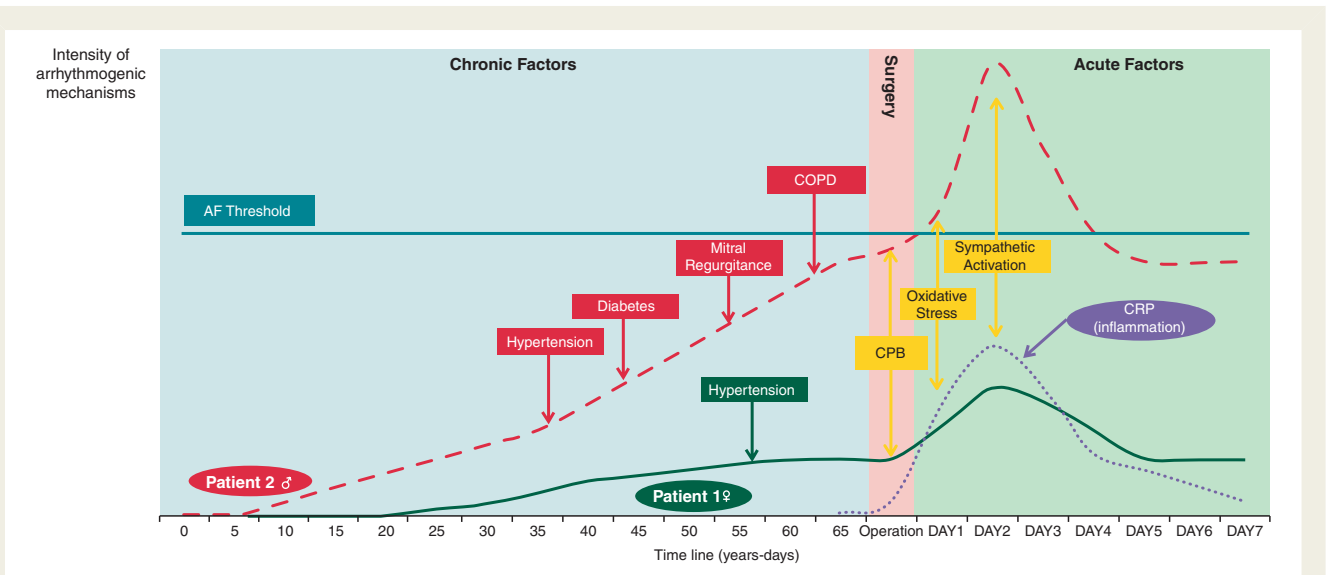


Figure 2 Time course of substrate development and surgery-related factors in the occurrence of atrial fibrillation. Time course of pro-arrhythmic mechanisms is depicted in two hypothetical patients undergoing cardiac surgery. Both chronic as well as acute factors related to the operation on day 0 are shown. When the intensity of pro-arrhythmic factors reaches a certain threshold,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.

of conduction block runs vertically between the pulmonary veins in the posterior left atrium.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.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.¹⁷¹ Histological analysis of these atria revealed areas of chronic inflammation and increased interstitial fibrosis.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.^{172,173}

Hypertension

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

History of atrial fibrillation

High propensity to POAF in patients with previous episodes of AF is not surprising^{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'.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.^{162,163,177,178} Also in POAF, the predictive value of diabetes for the incidence of the arrhythmia is low.^{1-4,6-8,15,17,47} In a recent meta-analysis reviewing 100 217 patients, no difference in POAF incidence was found between patients with and without diabetes.¹⁷⁹ Furthermore, men have a 1.5 times greater likelihood of developing new onset AF compared with women.¹⁶² The mechanism behind the higher AF susceptibility remains unclear. In POAF, male gender fails to reach significance in many studies,^{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.^{4,8,47,48} Association between chronic obstructive pulmonary disease (COPD) and new onset AF is still under discussion.^{162,178} COPD has been identified

as an independent predictor of AF progression.¹⁸⁰ In the occurrence of POAF, COPD is often identified as a risk factor.^{1–3,9,47} The pathogenesis of AF in patients with COPD is unclear,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.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^{4,7,43} 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,^{50,117–119} while reducing oxidative stress,^{124,135} or inflammation^{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.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.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)¹⁵⁹ and more profound atrial structural changes like fibrosis^{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.^{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.^{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^{1,2,4,6–9,15–18,44–48} and cardiac surgery nowadays is performed in older patients,⁴⁹ one would expect POAF incidence to rise over time. The fact that recent epidemiological studies^{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.

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