Factors influencing post-coronary artery bypass grafting atrial fibrillation episodes

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INTRODUCTION

Although postoperative atrial fibrillation (AF) was first described in 1959 as a complication of mitral valvotomy, this arrhythmia still remains the most common complication following cardiac surgery [1–8]. Postoperative AF has significant adverse effects on patient recovery, affecting short- and long-term outcomes [4–19]. In addition, the impact of postoperative AF on hospital resources is substantial [14–23]. Therefore, intensive research has been carried out to address the issue of postoperative AF, its prevention and preoperative risk assessment. A common approach in previous studies was to look for preoperative means of stratification to enable novel preventive therapeutic strategies [4–10, 24]. Although several studies have analysed the risk factors for postoperative AF, the exact pathophysiology of this complication has not yet been elucidated [2]. Postoperative AF is the consequence of the interplay of different mechanisms, with patient-related factors and cardiopulmonary bypass (CPB) being major causes [2–4, 10].

A re-entry mechanism is considered as the main contributor to the onset of AF after cardiac surgery, resulting from an inhomogeneous distribution of atrial refractoriness [24–28]. Alterations of automaticity are considered to be other causative factors [29–31]. The phenomenon of altered automaticity requires an atrial substrate, which may reflect an association with multiple preoperative predisposing factors [25–31]. Operative and postoperative factors may also contribute to the development of this structural substrate [3–10, 24]. Therefore, several risk factors acting at pre-, intra-, and postoperative levels have been recognised [2, 3].

SEARCH STRATEGY

We searched using electronic databases [PUBMED/MEDLINE (1966–April 2013), EMBASE and SCOPUS (1965–April 2013), DARE (1966–April 2013)]. Additionally, abstracts from national and international cardiovascular meetings were searched. Where necessary, the relevant authors were contacted to obtain further data. Retrospective studies, as well as small studies with the number of patients below 100, were excluded from the review. The main data search terms were: ‘postoperative atrial fibrillation’, ‘postoperative AF’, ‘POAF’, ‘arrhythmias’, ‘risk factors’, ‘predictors’, and ‘clinical trials’.

PREOPERATIVE FACTORS

Clinical and demographic factors

Patient age has consistently been demonstrated to be one of the most important risk factors for AF, not only after cardiac surgery but in the general population as well [4–10, 21, 23, 32, 33]. It is not surprising that the incidence of postoperative AF increases with older age, with a rate of 18% when age is less than 60 years and 52% for patients older than 80 years, with an increase of 24% in the odds ratio of developing postoperative AF for every five-year increase in age and a plateau after the age of 80 [4, 5, 23]. Fibrosis and dilatation of the atria have been shown to increase with age, with a loss of side-to-side coupling among atrial myocardial fibres and consequent slow atrial electrical conduction [34]. Congestive heart failure and poor left ventricular (LV) function are associated with postoperative AF, because of the elevated LV end-diastolic pressure, left atrial (LA) dilatation due to increased atrial filling pressures secondary to decreased LV function, increased atrial fibrosis, and regional conduction abnormalities [30, 31]. Sex-based differences in AF occurrence include differences in the expression of ion channels, hormonal effects on autonomic tone, and in myocardial architecture or fibre orientation [35–38]. History of AF is another preoperative variable predisposing patients to this arrhythmia. The fact that spontaneous episodes of AF...
had already occurred shows that the activity of pro-arrhythmic mechanisms in these patients exceeded the ‘AF threshold’ [39]. Obesity predisposes to the development of postoperative AF, being associated with higher cardiac output requirement, higher LV mass, and larger LA size [40, 41]. Hypertension is present in 60% of patients affected by AF in the Framingham Study [33]. Hypertension leads to myocardial hypertrophy, with foci of myocardial fibrosis, and favours dispersion of atrial refractoriness [42–45]. Chronic obstructive pulmonary disease (COPD) determines arterial hypoxia because of the associated ventilation perfusion (V/Q) mismatch [46]. Patients with COPD have frequent premature atrial contractions that favour AF development [46–48]. Diabetes is another predictor of postoperative AF in the surgical population as well as in the general one [49]. Autonomic neuropathy seems to be responsible for AF in diabetic patients: it blunts parasympathetic activity, allowing for a higher sympathetic excess [49–51]. As a matter of fact, removal of parasympathetically innervated aortic fat has been demonstrated to increase the risk of developing AF [52]. Similarly, smoking interferes with the hyperadrenergic state registered after surgical trauma [53]. Smokers have a higher adrenergic tolerance and are protected against postoperative AF (Table 1) [53].

**Structural factors**

Fibrosis, myocyte vacuolisation (myolysis) and apoptotic nuclear derangement have clearly been shown to be associated with AF [54–58]. The ageing process associated with hypertension leads directly to the loss of myocardial fibres and an increase in fibrosis, which may act as a substrate for re-entry arrhythmias [59, 60]. The loss of myocyte fibrils with fibrotic remodelling interferes with cell-to-cell electrical coupling between atrial muscle fibres [57, 59]. This abnormal electrical coupling between atrial myocytes is also substantiated by the altered expression and distribution of gap junction proteins observed in atrial specimens of operated patients affected by AF [61, 62]. Nao et al. [63] reported that both the expression and distribution of the gap junction protein connexin 40 are significantly altered in the atrial appendage of patients with chronic AF. This abnormal cell-to-cell communication seems to play a relevant role in the initiation and/or perpetuation of AF [56]. Nuclear alterations of atrial myocytes such as apoptosis have also been observed in patients affected by postoperative AF, with coexisting myolysis [56, 59, 64]. Patients with increased atrial myocardial apoptosis are prone to develop postoperative AF [56, 59, 64]. Areas of chronic inflammation and increased interstitial fibrosis are also a characteristic element of patients affected by mitral regurgitation [65].

**ECG and echocardiographic factors**

It has been demonstrated that P-wave duration (cut-off values over 140 ms [66] or 155 ms [67]) is significantly longer in patients with a history of AF than in control subjects without a history of AF. The prolonged duration of the P-wave is an accurate marker of risk for the development of atrial arrhythmias, representing atrial conduction disturbances [68]. Buxton and Josephson [69] first reported that surface P-wave duration on the standard ECG was significantly longer in patients with atrial arrhythmias after coronary artery bypass grafting (CABG). The P-wave duration is directly related to LA pressure in fluid overload conditions such as congestive heart failure [70].

Echocardiographic parameters have been similarly associated with postoperative AF [71, 72]. Leung et al. [71], enrolling 300 patients undergoing elective CABG, investigated the relationship between echocardiographic parameters and AF occurrence. Larger LA area and lower LA ejection fraction pre-operatively were associated with AF occurrence, along with LV diastolic dysfunction postoperatively [71]. In addition, they observed that AF patients have an architecturally and functionally abnormal and remodelled left atrium prior to undergoing surgery [71]. Benedetto et al. [72], using tissue Doppler imaging techniques, showed that patients with an increased AF risk revealed functionally abnormal LA function. Prolonged atrial electromechanical intervals due to LA enlargement and atrial conduction delay have recently been adopted as new echocardiographic parameters for predicting AF after cardiac surgery [73].

**Genetic factors**

Postoperative AF seems to be related to altered gene expression, thus explaining the varying individual susceptibility and the time lag between the operation and the onset of arrhythmia [2, 63, 74].

Dupont et al. [61] analysed the expression of three atrial connexins (connexins 43, 40 and 45) at the mRNA and protein levels in the right atrial appendage of CABG patients. Connexin 40 transcript and protein were expressed at significantly higher levels in the AF patients [61]. Conversely, Gaudino et al. [74] investigated the −174G/C Interleukin-6 promoter gene variant in 110 primary isolated CABG patients. This gene variant modulates the inflammatory response to surgery and influences the development of postoperative AF, suggesting a clear genetic predisposition to this complication (Table 1).

**INTRAOPERATIVE FACTORS**

The predominant AF risk factor remains surgery and CPB use, with its unavoidable alterations related to inflammatory, haemodynamic, ischaemic, and mechanical phenomena (Table 1) [75–83].

**Mechanical and ischaemic factors**

Atrial manipulation because of venous cannulation, and pulmonary venous trauma due to LV venting, are well-recognised risk factors for AF [4–6, 10, 21]. Valve surgery presents a two-fold or three-fold risk of having postoperative AF, especially mitral valve surgery with its bicaval cannulation...
Table 1. Risk factors for postoperative atrial fibrillation in major published studies (> 5,000 patients)

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<td>No. patients</td>
<td>5,807</td>
<td>10,550</td>
<td>6,477</td>
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<td>19,620</td>
<td>7,347</td>
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<td>Age (overall)</td>
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<td>NR</td>
<td>65.1 ± 10.2</td>
<td>64 ± 11</td>
<td>64.7 ± 10.2</td>
<td>67</td>
<td>74</td>
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<td>Isolated CABG</td>
<td>100</td>
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<td>27.9</td>
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<td>5.9</td>
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<td>Incidence of AF (%):</td>
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<td>16</td>
<td>22.5</td>
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<td>Multivariable AF analysis for isolated CABG</td>
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<td>AUC</td>
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<td>0.68</td>
<td>NR</td>
<td>0.67</td>
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<td>Age</td>
<td>1.7 (per decade)</td>
<td>1.84 (per decade)</td>
<td>2.4 (age &gt; 65 years)</td>
<td>1.55 (per decade)</td>
<td>1.06 (y)</td>
<td>2.3 (60-69 y)</td>
<td>2.22 (&gt; 70 y)</td>
<td>1.77 (55-63 y)</td>
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<td>NS</td>
<td>1.26</td>
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<td>1.11</td>
<td>1.2</td>
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<td>NT</td>
<td>NT</td>
<td>1.14</td>
<td>1.12</td>
<td>NS</td>
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<td>CPB duration</td>
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<td>NS</td>
<td>1.82 (&gt; 3 h)</td>
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<td>Other (OR)</td>
<td>CRF (1.4)</td>
<td>Female (0.85)</td>
<td>Previous MI (0.87)</td>
<td>White race (1.34)</td>
<td>White race (1.55)</td>
<td>Female (0.8)</td>
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<td>Operation date</td>
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<td>EF &lt; 40% (1.16)</td>
<td>Smoker (1.10)</td>
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<td>BU (1.25)</td>
<td>Previous CABG (0.79)</td>
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<td>BMI ≥ 25</td>
<td>ACE inhibitors (1.12)</td>
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<td>Male (1.18)</td>
<td>Anticoagulants (0.91)</td>
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<td>Arrhythmia (0.76)</td>
<td>Prolonged ventilation (3.5)</td>
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* (BMI 22–25 as a reference); BMI ≥ 30, OR: 1.39; BMI ≥ 35, OR: 1.74; BMI > 40, OR: 2.38
* No atrial fibrillation/flutter
* CABG + valve
* (age, reference): Age 70-79 years, OR: 3.5; Age ≥ 80 years, OR: 5.0
* CABG + AVR
* (age 12–54 years as a reference); Age 64–71 years, OR: 3.28; Age ≥ 72 years, OR: 4.19
AF — atrial fibrillation; ACE — angiotensin converting enzyme; AVR — aortic valve replacement; AUC — area under the curve; BMI — body mass index; CABG — coronary artery bypass grafting; COPD — chronic obstructive pulmonary disease; CPB — cardiopulmonary bypass; CRF — chronic renal failure; CVA — cerebrovascular accident; EF — ejection fraction; HF — heart failure; IABP — intra-aortic balloon pump; MI — myocardial infarction; NI — not included; NR — not reported; NS — not significant; NT — not tested; OR — odds ratio; Preop — preoperative
and dissection in the interatrial groove [4–6, 10, 21]. Atrial ischaemia also plays an important role in the development of underlying substrate and triggering factors of AF [75]. In addition, the inadequate cardioplegic protection of atrial tissue with persistent electrical activity has been correlated with the arrhythmia [76].

**Inflammation**

The CPB-induced systemic inflammatory response is considered to be one of the relevant determinants of postoperative AF [74, 77–83]. As a matter of fact, the time course of AF after cardiac surgery closely follows the temporal activation of the complement system with the release of pro-inflammatory cytokines [79–83]. The interaction of blood cells with the extracorporeal circuits determines neutrophil and platelet activation [77–83]. Neutrophil-dependent inflammation increases the inhomogeneity of conduction and the refractory period in atrial myocytes, favouring re-entrant phenomena [84]. Frustaci et al. [85] demonstrated lymphomononuclear infiltrates in atrial tissue of 66% of patients with lone AF. Similarly, Chen et al. [86] found CD-45-positive cells to be significantly higher in right atrial appendages of patients affected by AF compared to those in sinus rhythm. The causative association between inflammation and postoperative AF has been demonstrated by several clinical studies designed to suppress inflammatory events following CPB use [87–94].

Therefore, as most of the inflammatory AF mechanisms are related to CPB use, its theoretical elimination could reduce its incidence. Wijesundera et al. [87] performed a meta-analysis of 37 small randomised controlled trials and 22 risk-adjusted observational studies, together encompassing more than 290,000 subjects, and demonstrated a statistically significant AF reduction in the off-pump group (odds ratio [OR] 0.59; 95% confidence interval [CI] 0.46–0.77). Identical results were achieved considering observational studies only (OR 0.78; 95% CI 0.74–0.82) [87]. Möller et al. [88] included in their review of meta-analyses 66 randomised trials of off-pump compared to on-pump CABG. Evaluating postoperative AF and considering a total of 3,634 patients, they confirmed that off-pump CABG was associated with a significant AF reduction (relative risk [RR] 0.69; 95% CI 0.58–0.83) [88].

Another approach is the use of anti-inflammatory drugs, both steroidal and non-steroidal [89, 90]. Ho and Tan [89] identified a total of 3,323 patients from 50 randomised controlled trials, demonstrating in their meta-analysis that corticosteroid prophylaxis significantly reduced the risk of AF (25.1% vs. 35.1%; RR 0.74; 95% CI 0.63–0.86). Conversely, Ruffin et al. [90] reported in the Atrial Fibrillation Suppression Trial (AFIST) that a non-steroidal anti-inflammatory drug is associated with significant reduction of arrhythmia (OR 0.54; 95% CI 0.32–0.90). Other drugs demonstrated effectiveness in reducing AF by their anti-inflammatory properties [91–94]. Anti-inflammatory markers such as cytokines or circulating adhesion molecules are attenuated in patients receiving statins after cardiac operations [91, 92]. Fang et al. [92] included in their meta-analysis 20 studies with 23,577 patients, observing that statin therapy was significantly associated with a decreased risk of the incidence and recurrence of AF (OR 0.49; 95% CI 0.37–0.65). Similar anti-inflammatory properties and a reduction in AF occurrence were demonstrated in patients subjected to preoperative n-3 polyunsaturated fatty acid (PUFA) therapy [94].

**Sympathetic activation**

The electrophysiological characteristics of atrial myocytes are all modulated differently by sympathetic and parasympathetic influences [95–101]. Operative trauma increases sympathetic activity, which is mediated by β-adrenoceptors and increases heart rate and contractile forces, enhancing excitability and automaticity [95, 96]. In this setting, sympathetic activation with an excess of catecholamine levels may constitute the mechanism that triggers the fibrillation process [3–8, 10–13, 95, 96]. Sympathetic activation also shortens atrial refractoriness in a non-uniform fashion, favouring perpetuation of AF [90]. In addition, older patients present increased circulating norepinephrine levels, and age is one of the most relevant risk factors for AF [97, 98]. In addition, patients affected by postoperative AF present higher norepinephrine levels than those who are unaffected [95].

As most AF mechanisms are related to sympathetic stimulation, its theoretical antagonism would reduce the incidence of the arrhythmia. As a matter of fact, cardiac denervation has been proven to be effective in reducing AF occurrence [102]. Melo et al. [102] enrolled more than 400 low-risk CABG patients, and among these 207 were subjected to ventral cardiac denervation (VCD). Patients submitted to VCD had fewer episodes of AF (7% vs. 27%); no patient had AF after discharge, and VCD was the most significant predictor of arrhythmia (OR 0.42; 95% CI 0.23–0.78) [97]. Blocking the sympathetic activity with β-adrenoceptor blocking agents (β-blockers) has also been demonstrated to reduce AF [102–108]. Various studies, including different meta-analyses, have reported that β-blockers reduce the incidence of AF in patients undergoing CABG from 40% to 20% and from 60% to 30% after valve surgery [95–108]. The beneficial effects of these drugs are documented when they are administered before or immediately after surgery, independently of their dose and type [103–108]. A significant prolongation of atrial cell action potential duration and atrial effective refractory period are the protective characteristics of these drugs in the cardiac surgery setting [109–111]. Starting β-blocker therapy at least one week before surgery is recommended, while their withdrawal after CABG is associated with a more than two-fold increase in postoperative AF [106, 109].

Conversely, drugs mimicking sympathetic activation are pro-arrhythmic, enhancing triggered activity and automatic-
ity, the triggers for the initiation of AF [10, 12, 53, 111–114]. In addition, catecholamines shorten atrial refractoriness in a non-homogeneous pattern [111–114]. Salaria et al. [114] first investigated the pro-arrhythmic AF effect of vasopressors (dopamine, dobutamine, and phenylephrine), enrolling 131 CABG patients. In their study, vasopressor use was an independent predictor of developing postoperative AF (OR 2.78, 95% CI 1.07–7.22). Among various vasopressor drugs, use of those with predominantly β1-adrenergic affinity was associated with a higher incidence of postoperative AF [113]. The pro-arrhythmic effects persist also when a ‘renal dose’ of dopamine is employed [113]. In a study population of 1,731 CABG patients, Argalious et al. [113] observed that the incidence of postoperative AF was 23% among patients who received a renal dose of dopamine, and 14% among those who did not receive it.

**Oxidative stress**

CPB is characterised by ischaemia-reperfusion injury phenomena [115–117]. During the reperfusion phase, increased production of reactive oxygen species develops, leading to myocardial stunning, tissue damage, and cell death [115–117]. Ramlawi et al. [118] reported that patients affected by postoperative AF have increased postoperative acute oxidative stress based on the presence of oxidised proteins. They collected right atrial samples before and after CPB for oxidative protein immunostaining, and serum samples preoperatively and postoperatively for microarray assessment of gene expression in order to quantify total peroxide levels [119]. Patients affected by AF had significantly more elevation in total peroxide levels in serum compared to patients unaffected, and more myocardial oxidation [118]. The authors demonstrated that patients with postoperative AF have a differential oxidative genomic response after CPB that may predispose them to oxidative stress [118]. Oxidation of polyunsaturated fatty acids of membrane phospholipids determines cellular membrane rupture, mitochondrial dysfunction, and abnormalities in calcium-handling proteins, leading to the electrical remodelling observed in postoperative AF [115–117].

The role of oxidative stress as a contributory mechanism in AF genesis has been investigated by administering several drugs to patients undergoing cardiac surgery [119–123]. Oral ascorbate in association with β-blockers is more effective in preventing AF than β-blocker alone [119]. Antioxidant N-acetylcysteine, by scavenging reactive oxygen species, attenuates myocardial oxidative stress in patients undergoing CABG with CPB use [120–121]. Baker et al. [122] reported a meta-analysis on the use of N-acetylcysteine, underlying a significant reduction of AF in patients using it. Statins and PUFA therapy are also beneficial in reducing AF, also due to their antioxidative properties [91–94, 123–126]. In addition, the relation between oxidative stress and postoperative AF is also documented by its reduced incidence in CABG patients undergoing off-pump surgery, with avoidance of ischaemia-reperfusion phenomena [87, 88].

**Electrolyte depletion**

Electrolytes such as potassium, magnesium, calcium and phosphate play important roles in cellular metabolism and energy transformation, and in the regulation of cellular membrane potential [127]. Depletion of these electrolytes can induce a wide range of clinical disorders, including supraventricular arrhythmias [128]. Hypermagnesemia and other electrolyte depletions are the result of haemodilution, preoperative and perioperative use of diuretics, and catecholamine discharge [129]. In addition, patients undergoing cardiac surgery are usually cooled to temperatures between 32°C and 34°C, in order to reduce tissue oxygen demand. The cooling phase is also characterised by electrolyte depletion [128]. Magnesium is a cofactor of Na-K adenosine triphosphatase, which regulates the myocardial transmembrane sodium and potassium gradients, and decreased levels of magnesium post-operatively are associated with a higher risk of AF occurrence after cardiac surgery [130, 131]. Burgess et al. [103], in their meta-analysis of 22 trials encompassing 2,896 patients, observed an overall reduction in AF in patients with magnesium supplementation (OR 0.57, 95% CI 0.42–0.77) (Table 1).

**POSTOPERATIVE FACTORS**

Several postoperative variables have been associated with postoperative AF: inotropes, intra-aortic balloon pump (IABP) need, blood transfusion, temporary ventricular pacing, prolonged ventilation, elevated central venous pressure, peri-carditis, postoperative cerebrovascular accidents, and acute kidney injury [3–24]. However, in some instances it is very difficult to distinguish whether AF occurs as a consequence of an observed complication or is a cause of that complication [6, 10]. The precise temporal correlation between the arrhythmia and postoperative complications has been investigated by a limited number of studies only (Table 1) [1, 2, 6].

**Inotropes**

Pharmacological and mechanical inotropic supports are frequently reported as risk factors for AF [3–24, 111–114]. Requirement for catecholamines and IABP in the immediate postoperative period can be assumed to mirror the preoperative LV function [5, 6, 10]. In addition, intraoperative factors such as inadequate myocardial protection, incomplete revascularisation, and technical problems, can exacerbate a pre-existing myocardial dysfunction [5, 6, 15, 20, 21]. The administration of catecholamines enhances triggered activity and automaticity, favouring the onset and maintenance of AF [111–114].

**Temporary pacing**

The transient loss of atrial synchrony, which happens in the immediate postoperative period, often requires atrial and/or
ventricular pacing [5, 10]. Atrial pacing is related to pre-existing sinus node dysfunction, and consequently with a higher susceptibility to the development of atrial tachyarrhythmias [5, 10]. The loss of atrioventricular pacing leads to a relevant change in atria, resulting in high atrial pressure due to atrial contraction against a closed atrioventricular valve with an acute rise in atrial pressure [5].

**Fluid balance**

Increased intravascular volume and pressure secondary to CPB priming and postoperative hydration increase the propensity to develop AF [5, 20, 132]. Frost et al. [132], investigating 120 consecutive CABG patients, noted a significant difference in central venous pressure at CPB weaning between patients affected by AF and those unaffected. A positive fluid balance can facilitate AF because of atrial distension and myocyte fibre distension [20].

**Blood transfusion**

Red blood cells (RBC) are associated with the development of AF after cardiac surgery [133]. The correlation seems to be justified through AF influence on inflammatory mediators [134, 135]. RBC transfusion elicits an inflammatory response by direct infusion of inflammatory mediators and through augmentation of the inflammatory process that further amplifies the intense inflammatory response that occurs as a consequence of CPB [134, 135]. Koch et al. [133] studied 5,841 patients undergoing isolated CABG with or without valve replacement, demonstrating that intensive care unit RBC transfusion increased the risk for AF (OR per unit transfused 1.18, 95% CI 1.14–1.23). After propensity matching analysis, the authors observed that RBC transfusions were associated with a significant increase in new-onset AF (46% vs. 38%) (Table 1) [133].

**CONCLUSIONS**

Postoperative AF is the most common postoperative complication, occurring in up to 35% of patients after CABG, and is characterised by a potential worsening course, being the consequence of the interplay of different pathophysiological mechanisms, with patient-related factors and CPB as major causes [3–24, 136–141]. An atrial substrate predisposing patients to the arrhythmia has been recognised, reflecting an association with multiple predisposing factors [1, 2]. Several risk factors acting at preoperative, intraoperative, and postoperative levels have been recognised [3–24].

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**References**

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