

Mini Review

New Insights into the Mechanisms and Risk Factors of Postoperative Atrial Fibrillation following Cardiac Surgery

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Abstract

Postoperative atrial fibrillation (POAF) following cardiac surgery represents a common, potentially morbid, and often misunderstood complication. Patients who develop POAF incur an increased cost of care, a prolonged hospital stay, and are at a higher risk for numerous adverse outcomes, including renal and respiratory failure, cardiac arrest, stroke, and death. The etiology of POAF is multifactorial and likely involves interplay between individual characteristics and predispositions, cardiac remodeling, and postoperative inflammation. This Mini Review summarizes the known risk factors for POAF and describes recent breakthroughs in the understanding of the pathophysiology of this complication.

INTRODUCTION

Postoperative atrial fibrillation (POAF) is a common and potentially serious complication following surgery. Around 35% of patients undergoing cardiac surgery develop POAF, while the incidence of POAF following non-cardiac surgery ranges from 1-30% depending upon the procedure [1,2]. There are many detrimental operative outcomes that are associated with POAF including infection, increased postoperative bleeding, renal and respiratory failure, cardiac arrest, a two- to four-fold increased risk of stroke, and a two-fold increase in all-cause 30-day and 6-month mortality [1-8]. While POAF may not be the primary etiology of these adverse events, it is likely contributory in some cases and is certainly responsible for increased morbidity and mortality following cardiac surgery [5].

Patients who develop POAF incur on average \$10,000-\$20,000 in additional hospital treatment costs, 12-24 hours of prolonged ICU time, and an additional 2 to 5 days in the hospital [2,3,9,10]. Healthcare costs related to the care of patients with POAF in the US are estimated at over \$1 billion annually [11]. Due to the incompletely understood etiology and pathophysiological mechanisms of POAF, clinical interventions aimed at preventing this complication after cardiac surgery have thus far been less than optimal and the incidence of POAF has not changed over the past several decades [3,12].

This Mini Review summarizes the known risk factors for POAF and describes the most current understanding of the pathogenesis of POAF following cardiac surgery.

RISK FACTORS FOR POAF**Age**

The most widely accepted risk factor of POAF is advanced age [1,3,7,11,13]. Aging results in the loss of myocardial fibers and increased fibrosis and collagen deposition in the atria, particularly near the sinoatrial node [1,11,14]. These changes may lead to alterations in the refractory and dispersion properties of atrial electrical impulses as well as increased wavelet reentrance and propagation [11]. Age-related physiological changes provide the physical changes necessary for arrhythmias to develop, while surgical trauma and inflammation likely provide the inciting factors that allow for the induction of POAF [7,14].

However, the odds of developing POAF do not increase linearly with age [3,11]. A large single-institution retrospective study of 14,960 patients undergoing cardiac surgery over two decades found a non-linear trend between age and POAF incidence [3,11]. This study showed that the patients aged 72 or older are around 5 times more likely to develop POAF than patients younger than 55, and that the probability of developing POAF increases at a higher rate past the age of 55 [3].

Cardiovascular risk factors

Certain cardiovascular factors have been identified as risk factors for POAF, including hypertension, congestive heart failure (CHF), coronary artery disease (CAD), left atrial enlargement, and left ventricular dysfunction [1-3,5, 6,11,15]. Patients with chronic atrial fibrillation or a history of other arrhythmias are also at a

higher risk of developing POAF, likely because the physiological factors necessary for the development and maintenance of arrhythmias already exist in these patients [1,9,11,16].

Non-cardiovascular risk factors

Other risk factors for POAF include Caucasian race, male gender, chronic obstructive pulmonary disease (COPD), high cholesterol, hyperthyroidism, chronic kidney disease, diabetes, obesity, and high body surface area (BSA) [1-3,5,11,13,14,16]. Greater BSA has been associated with enlarged atria and altered intrathoracic pressure, which may result in alterations in atrial electrical conductivity and, therefore, increased susceptibility to POAF [14].

Some patients undergoing cardiac surgery also have a chronic inflammatory state that can become exacerbated following surgery, thereby increasing the probability of developing POAF [4,11]. A genetic predisposition towards postoperative inflammation has recently been identified as a risk factor for POAF, but more research is needed to elucidate this [1,4,11,17].

PATHOGENESIS OF POAF

A number of physiological changes occur during and immediately after cardiac surgery: the immune and complement systems are activated, releasing pro-inflammatory cytokines and promoting intrathoracic and systemic inflammation; the composition of the pericardial fluid (PCF) is drastically altered and the heart itself must recover from ischemia and trauma; and serum electrolyte levels fluctuate [4,6,15,18,19]. Each of these may contribute to POAF.

Systemic inflammation and oxidative stress

Inflammation and oxidative stress likely play a major role. Surgical trauma, ischemia from the initiation and prolonged use of CPB, and reperfusion lead to oxidative stress and the production of pro-inflammatory molecules. These changes trigger a systemic response consisting of endothelial and leukocyte activation, the release of NADPH oxidases, nitrous oxide production, and reactive oxygen species generation [4,6,7,17,20]. The association between the development of POAF and systemic inflammation and oxidative stress has been demonstrated by cohort studies examining postoperative inflammation in cardiac surgery patients and further support has been demonstrated by multiple studies, which found decreased rates of POAF in patients who receive anti-inflammatory prophylaxis using corticosteroids [1,4,6,15,17,20-23].

Local inflammation and oxidative stress

Upon disruption of the pericardium to access the heart during surgery, a local inflammatory response ensues, leading to the accumulation of inflammatory cells within the pericardial cavity and an increase in PCF volume [2,11]. Postoperative PCF is highly oxidative and contains blood, hemolyzed blood cells, free hemoglobin, and high levels of inflammatory markers reflective of leukocyte and platelet activation [15,21]. Pro-inflammatory molecules produced by the myocardium itself also contribute to local inflammation and can directly impair cardiac function [4]. Contact between inflammatory cells and cardiac tissue likely plays a role in the pathogenesis of POAF but the mechanisms of this interaction remain to be described [15].

Inflammation within the pericardial space leads to cardiomyocyte apoptosis and altered electrical activity, primarily due to damaged sodium and calcium channels, which allows heterogeneous action potentials and arrhythmias to form and propagate [4,11,20]. Animal models have illustrated that the incidence of POAF is directly correlated to the degree of inflammation of the atria and around the heart [15,20,21].

Electrolytes

Electrolyte level fluctuations following surgery may also play a role in POAF [13,24,25]. The association between hypomagnesemia in particular and/or hypokalemia and oxidative stress, cardiac arrhythmias, and sudden cardiac arrest has been extensively studied, but their reported effects on POAF have been varied [26-28].

Some studies have identified postoperative hypomagnesemia as a predictor of POAF [11,25]. The primary roles of magnesium include the regulation of calcium mobility and the regulation of cardiomyocyte contractility, particularly during the plateau and final repolarization phases of the cardiac cycle [27,28]. Hypomagnesemia has been shown to increase sinus node automaticity, while hypermagnesemia prolongs atrioventricular node conduction time and is thought by many to help prevent oxidative damage [2,26,29]. Magnesium is also widely considered to have anti-arrhythmic properties. However, recent evaluation has called this into question by showing that high serum magnesium levels were associated with a higher incidence of POAF in a dose-dependent manner [19].

Hypokalemia causes cell membrane hyperpolarity and higher a resting potential, and in the heart causes increased automaticity, excitability, and ventricular arrhythmias [7,24]. It has been widely assumed that low serum potassium levels contribute to POAF, but recent data does not support this long-held dogma [16,30]. Our group recently reported that hypokalemia was not associated with an increased risk of developing POAF, while high serum potassium levels were not protective [19]. Further investigation is clearly warranted.

CONCLUSION

Postoperative atrial fibrillation occurs in around 35% of cardiac surgery patients and has been associated with greatly increased treatment costs and duration, and is an independent predictor of numerous detrimental complications such as infection, cardiovascular complications, and higher rates of postoperative mortality. The risk factors for POAF include advanced age, cardiovascular factors (i.e. hypertension, coronary artery disease, and cardiac remodeling), and non-cardiovascular factors (i.e. male gender, Caucasian race, COPD, obesity). The pathogenesis of POAF has remained elusive for several decades, but recent work has shown that POAF likely arises due to a combination of preexisting cardiac conditions, individual characteristics, and local and systemic inflammation caused by surgery. Additional research centered around the exact mechanisms of POAF is still needed to provide a greater understanding of this widespread complication and to yield effective treatment modalities.

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