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Post-operative Atrial Fibrillation at the Start of Atrial Fibrillation Burden

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Abstract

Atrial Fibrillation (AF) is the most common persistent arrhythmia with adverse clinical outcomes. AF ectopic firing and re-entry depends on several mechanisms: (1) ion channel dysfunction; (2) Ca^{2+}-handling abnormalities; (3) structural remodelling; (4) autonomic neural dysregulation. The oxidized CAMKII enzyme pathway establishes a connexion between redox imbalance and the electrical and functional cardiomyocyte properties altered in AF patients. Postoperative atrial fibrillation (PoAF) is the most common complication after cardiac surgery and a subtype of AF, associated with increased time spent in the intensive care unit (ICU), in-hospital stay, stroke incidence and 30-day and long-term mortality. Recent studies have implicated oxidative stress in AF pathophysiology including mechanisms such as an imbalance in reactive oxygen species (ROS) production, decreased endothelial nitric oxide synthase (eNOS) activity and nitric oxide unavailability. Indeed, NADPH oxidase enzymes (NOX) are largely responsible for this imbalance, which is supported by the beneficial effect of statins in early atrium electrical remodelling. Epicardial adipose tissue has a direct contact with the myocardium, located between the myocardium and visceral pericardium, and it has been established a clinical relationship between EAT and the development of AF. In this review, we explore pathophysiological mechanisms of AF and POAF, as well as its implications for management.

Keywords: Atrial fibrillation • Arrhythmia • Pathophysiology

Introduction

Atrial fibrillation prevalence, impact and pathophysiology

Atrial Fibrillation (AF) is the most common persistent arrhythmia with adverse clinical outcomes [1]. The Framingham Heart Study cohort has shown that, over the last fifty years, age-adjusted prevalence of AF increased from 20.4 to 96.2 and 13.7 to 49.4 per 1000 persons-years for men and women, respectively [2]. Additionally, AF related health costs increased overtime and it is estimated that AF patients spend 73% more than their healthy counterparts [3].

AF ectopic firing and re-entry depends on several mechanisms: (1) ion channel dysfunction; (2) Ca^{2+}-handling abnormalities; (3) structural remodelling; (4) autonomic neural dysregulation. Regarding ion channel dysfunction, cardiomyocytes return to their resting potential after depolarization through an equilibrium between I_f (pacemaker) and I_{k1} (inward rectifier k^+) currents, which might be dysfunctional in AF. In addition, early afterdepolarizations (EADs) and delayed after depolarizations (DADs), most likely related to Ca^{2+}-handling abnormalities, may contribute significantly to AF pathogenesis [4]. Structural and electrical remodelling is core to most forms of AF, especially in the more permanent ones [5]. Concerning structural remodeling, atrial fibrosis is key and alters cardiomyocyte electrical coupling due to misplacing and changing the structure of connexins, thus inducing a fragmented electrical conduction [6]. Several other mechanisms are present in the pathophysiology of the arrhythmia, including redox imbalance, genetic and anatomic abnormalities, not forgetting the distinct role of the right and left atrium, as well as the pulmonary veins. These holistic changes in the atrium are revealed through a contractile dysfunction which contributes to the enlargement observed in echocardiographic studies and sometimes persistent after cardioversion to sinus rhythm [4,7]. At the myocyte level, atrial dysfunction is characterized by a decrease in the maximum velocity of tension generation and in the maximum developed active tension. The increased calcium sensitivity possibly results from increased myofilament protein phosphorylation (e.g. cMyBP-C) through kinases such as PKA and CAMKII (ser282 residue). Additionally, AF atria show decreased stiffness, as assessed by passive tension, probably due to the increase in the N2BA/N2B titin ratio [7].

Atrial fibrillation: The role of oxidative stress in CAMKII-RyR dysfunction and Ca^{2+} leaks

The key factor in generating DADs is the diastolic calcium leak of the RyR (ryanodine receptor), which promotes Na^+-Ca^{2+} exchanger function, resulting in membrane depolarization due to an increase in intracellular sodium (I_{ti} – transient inward current) [4]. CAMKII increased activity functionally modifies phospholamban, RyR and L-type Ca^{2+} channels, regulating normal and reserve cardiac pacemaker function [8]. Recently, this enzyme was implicated in sinus node dysfunction, myocardial rupture and adverse remodelling following myocardial infarct. Angiotensin-II-induced NOX activation promotes a post-transcriptional oxidative change in the CAMKII 281/282 methionines, constitutively activating the enzyme, thus being independent of Ca^{2+}/calmodulin complex. Consequently, Ca^{2+} sparks and DADs increase mainly due to the phosphorylation of the serine 2814 residue of the RyR2 receptor [9]. Thus, oxidized CAMKII enzyme potentially explains the connexion between redox imbalance and the electrical and functional cardiomyocyte properties altered in AF patients.

Postoperative atrial fibrillation: The role of inflammation

Postoperative atrial fibrillation (PoAF) is the most common complication after cardiac surgery– occurring in 30-60% of cases and recurring in about 40% of patients [8,9]. Recent studies reported an increase in the time spent in the intensive care unit (ICU), in-hospital stay, stroke incidence and 30-day and long-term mortality [10]. PoAF is a secondary form of AF with a marked impact in the short- and long-term prognosis of patients submitted to cardiac surgery. Several pathways underlie the pathophysiology of PoAF and inflammation has been implicated both as cause and consequence of the arrhythmia. Figure 1 represents the common inflammatory pathway associated both with AF and the PoAF subtype. Inflammatory conditions such as obesity, pulmonary and arterial hypertension, coronary artery disease and also pericarditis correlate

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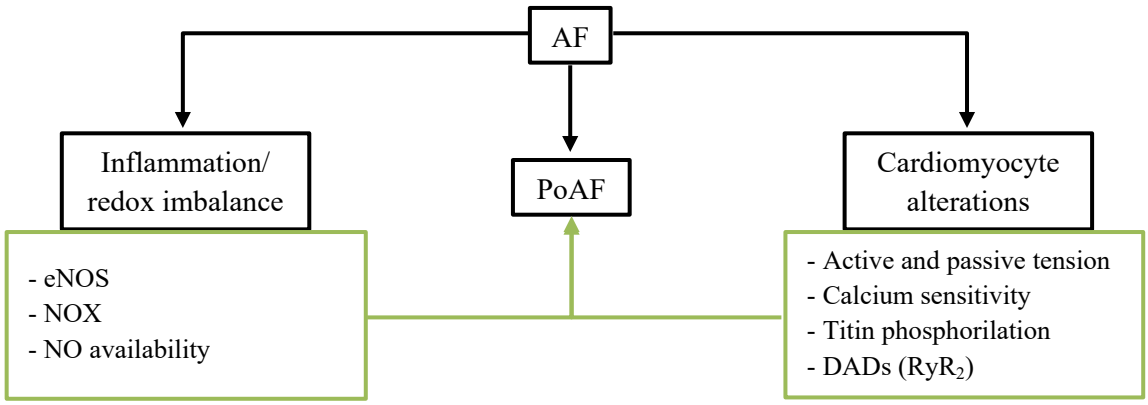

Figure 1. Molecular and functional cardiac alterations associated with both AF and the PoAF sub-type.

Table 1. Clinical, echocardiographic/electrocardiographic and analytical factors associated with PoAF occurrence [25,31-35].

PoAF Prediction Factors		
Clinical	**Echocardiographic/EKG**	**Analytical**
Age, obesity, tobacco use	Enlarged atria	Plasminogen Activator Inhibitor-1 (PAI-1)
Pulmonary and arterial hypertension	Left atrial reservoir strain	Type-B natriuretic peptide (BNP)
Heart failure	Ejection fraction	CRP
Myocardial infarction, inotropic requirement	Prolonged PR interval	Neutrophil/lymphocyte ratio
Epicardial adipose tissue	Thickness	*IL-6, IL-1B, IL-8, TNF-*α, Activin A

with AF occurrence [11]. Additionally, other clinical, echocardiographic/electrocardiographic and analytical variables have been associated with the arrhythmia (Table 1). In the randomized trial Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery (ARMYDA-3), plasma levels of C-reactive protein (CRP) were associated with an increased risk of developing PoAF [12]. Along with inflammation, recent studies have implicated oxidative stress in AF pathophysiology including mechanisms such as an imbalance in reactive oxygen species (ROS) production, decreased endothelial nitric oxide synthase (eNOS) activity and nitric oxide unavailability. Indeed, NADPH oxidase enzymes (NOX) are largely responsible for this imbalance, which is supported by the beneficial effect of statins in early atrium electrical remodelling [13,14]. PoAF risk is greater when NOX-induced superoxide anion levels are increased in the right atrium tissue and reduced when patients are supplemented with n-3 polyunsaturated fatty acids and vitamin C [15]. The latter effect is explained by the upregulation of antioxidant enzymes [16]. Concerning structural pre-existing remodelling, SERCA2A and sarcolipin expression are reduced in the arrhythmia [17]. In a model of sterile pericarditis, IL-17A-induced inflammation and fibrosis contributed to the development of PoAF [18]. Vacuolization and nuclear derangement of myocytes, myocytolysis and lipofuscin levels also correlated with the occurrence of this arrhythmia [19-21]. Additionally, the collagen III/I ratio is lower in heart surgery patients with PoAF when compared to the control subjects [22].

Epicardial adipose tissue and atrial fibrillation

Epicardial adipose tissue has a direct contact with the myocardium, located between the myocardium and visceral pericardium [23]. It has been established that there is a clinical relationship between EAT and the development of AF. Adipose tissue is an endocrine organ that is responsible for the secretion of adipocytokines with pro- and anti-inflammatory properties. It has been well described in the literature that EAT has an important role in the development of POAF [24]. Gunturk EE et al. showed EAT thickness is an independent and strong predictor of POAF development. Indeed, EAT is different from the subcutaneous adipose tissue, being more metabolically active and having a predilect anatomy location to influence cardiac muscle [25,26]. Several mechanisms have been proposed to explain this relationship. On one hand, inflammatory cytokines secreted by EAT have powerful profibrotic effects, such as Activin A, which is significantly increased in POAF patients [27]. One the other hand, gelsolin is an anti-inflammatory adipokine secreted by EAT which has protective effects against POAF. The underlying mechanism is based on its ability to bind with actin filaments or bind actin monomers preventing its disorganized assembly. Actin is released by damaged cells activating inflammatory mediators, with gelsolin acting as a scavenger of proinflammatory actin filaments. Additionally, L-type Ca^{2+} channels are in direct relationship with the cytoskeleton and its changes. Gelsolin decreases the probability of Ca^{2+} channels opening, reducing myocardium excitability, thus protecting against AF [28-30].

Postoperative atrial fibrillation: Implications for management

In a recent nationwide population-base study from Sweden involving 24,523 patients who underwent isolated CABG, POAF was associated with a moderately increased long-term risk of ischemic stroke, any thromboembolism and heart failure, changing the perception of POAF from the previously thought transient and benign arrhythmia [31-36].

POAF patients should be managed with β-blockers as the first line of treatment, unless contraindicated. These act through downregulation of adrenergic receptors and inhibition of sympathetic stimulation [37]. As a second line treatment, amiodarone is indicated to reverse AF rhythm [38]. The use of intravenous magnesium as an alternative to beta-blockers and amiodarone is still debatable. Furthermore, the use of anticoagulants is uniformly suggested, although there is no consensus within cardiac societies about the duration of treatment. An alternative non-pharmacologic option is the use of bi-atrial pacing with colchicine being considered as a last resource, because of its capacity to inhibit the process of microtubule self-assembly, blocking the movement of intercellular granules and the secretion of several cytokines. Consequently, leukocyte functions are impaired, prompting an anti-inflammatory action [39-44].

Conclusion

As an established common complication after cardiac surgery associated with severe short- and long-term cardiovascular events, identification of at-risk patients is key, even though there is no optimal strategy for the prevention of POAF. This allows the physician to start prophylaxis treatment and early management of POAF, preventing adverse outcomes. Moreover, selecting POAF patients that present with increased risk of long-term AF can facilitate early treatment and prevention of more advanced AF subtypes, with increased remodeling and myocardial fibrosis. In addition, the setting of POAF is a unique opportunity to study the pathophysiology of AF at its onset, with access to

tissue samples otherwise unavailable, contributing to the discovery of new molecular pathways and targeted therapeutics.

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