Prevention of atrial fibrillation following cardiac surgery: Basis for a novel therapeutic strategy based on non-hypoxic myocardial preconditioning

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Abstract

Atrial fibrillation is the most common complication of cardiac surgical procedures performed with cardiopulmonary bypass. It contributes to increased hospital length of stay and treatment costs. At present, preventive strategies offer only suboptimal benefits, despite improvements in anesthesia, surgical technique, and medical therapy. The pathogenesis of postoperative atrial fibrillation is considered to be multifactorial. However oxidative stress is a major contributory factor representing the unavoidable consequences of ischemia/reperfusion cycle occurring in this setting. Considerable evidence suggests the involvement of reactive oxygen species (ROS) in the pathogenic mechanism of this arrhythmia. Interestingly, the deleterious consequences of high ROS exposure, such as inflammation, cell death (apoptosis/necrosis) or fibrosis, may be abrogated by a myocardial preconditioning process caused by previous exposure to moderate ROS concentration known to trigger survival response mechanisms. The latter condition may be created by *n-3* PUFA supplementation that could give rise to an adaptive response characterized by increased expression of myocardial antioxidant enzymes and/or anti-apoptotic pathways. In addition, a further reinforcement of myocardial antioxidant defenses could be obtained through vitamins C and E supplementation, an intervention also known to diminish enzymatic ROS production. Based on this paradigm, this review presents clinical and experimental evidence supporting the pathophysiological and molecular basis for a novel therapeutic approach aimed to diminish the incidence of postoperative atrial fibrillation through a non-hypoxic preconditioning plus a reinforcement of the antioxidant defense system in the myocardial tissue.

Keywords: Postoperative atrial fibrillation; Myocardial preconditioning; Oxidative stress; *n*-3 PUFA; Vitamin E; Vitamin C

Abbreviations: ACE, Angiotensin-1 converting enzyme; AF, Atrial fibrillation; BH_4, Tetrahydrobiopterin; CABG, Coronary artery bypass graft; CHF, Chronic heart failure; CM, Cardiomyocyte; CRP, C-reactive protein; Cx40(43), connexin 40(43); DHA, Docosahexaenoic acid; eNOS, Endothelial nitric oxide synthase; EPA, Eicosapentaenoic acid; ERK, Extracellular signal-regulated kinase; ERP, Effective refractory period; H_2O_2, Hydrogen peroxide; hs-CRP, High sensitive C-reactive protein; HSP, Heat shock proteins; IL-6(8, 1β), Interleukin-6(8, 1β); IP_3, Inositol 1,4,5-trisphosphate; JAK2, Janus kinase 2; LA, Left atrium; LDL, Low-density lipoprotein; MAPKs, Mitogen activated protein kinases; M3-mAChR, M3 subtype of muscarinic acetylcholine receptors; *n-3*, Omega-3; NF-κB, Nuclear factor kappa-B; NO, Nitric oxide; $O_2^{\cdot -}$, Superoxide anion; $OH^{\cdot}$, Hydroxyl radical; POAF, Postoperative atrial fibrillation; PUFA, Polyunsaturated fatty acids; PVs, Pulmonary veins; ROS, Reactive oxygen species; SR, Sinus rhythm; STAT-3, Signal transducer and activator of transcription-3; TNF-α, Tumor necrosis factor-α; VLDL, Very low-density lipoprotein.

Contents

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1. Introduction

Although atrial fibrillation (AF) is the most common sustained arrhythmia in the adult population (Lloyd-Jones et al., 2004), it remains challenging to treat, prevent, or cure (Van Wagoner, 2007). It is associated with increased mortality (Kannel et al., 1998; Vidaillet et al., 2002) and significant morbidity, including heart failure and stroke (Wolf et al., 1991; Wang et al., 2003). The disorganized atrial activity itself affects cardiac function, metabolic demand, and quality of life (Andrews & Nelson, 2006). The problem of AF is now widely appreciated, but the underlying mechanisms that lead to onset and persistence of arrhythmia have been difficult to elucidate (Van Wagoner, 2007). The AF frequently occurs as a complication of cardiac surgical procedures performed with cardiopulmonary bypass (i.e. postoperative AF, POAF), which has been associated with length of hospital stay, intensive care unit readmission, persistent congestive heart failure increased stroke risks, overall costs, and mortality (Borzak et al., 1998; Maisel et al., 2001; Stanley et al., 2002; Mathew et al., 2004; Villareal et al., 2004). Despite improvement in anesthesia, surgical techniques, and medical therapy (Maisel et al., 2001), POAF occurs in 20–40% of patients, even when proven and recommended preventive drug therapies such as beta-blockers and amiodarone are used (Mathew et al., 2004; Mitchell, 2007). Numerous studies have demonstrated that when POAF develops, patients are at increased risk of developing hemodynamic instability and cerebrovascular complications. It is likely that these complications contribute to the increased length of hospital stay and treatment costs observed in patients with POAF (Mathew et al., 2004; Gillespie et al., 2005; Gillespie et al., 2006). The pathogenesis of POAF is considered to be multifactorial. The factors include patient's preoperative status and preexisting electrocardiogram abnormalities. In addition

intraoperative stress plays a key role due to occurrence of reperfusion, inflammation, or hemostasis (Mathew et al., 1996a, Mathew et al., 1996b; Zaman et al., 2000). The pathophysiological mechanism whereby these complex processes cause POAF remains poorly understood. Accumulating evidence suggests a link between AF and myocardial oxidative processes, since the latter may contribute to atrial remodelling (Korantzopoulos et al., 2003; Van Wagoner, 2003). Oxidative stress triggers pro-inflammatory signalling pathways that activate NF-κB and AP-1 transcription factors (Bowie & O'Neill, 2000). Marked inflammatory infiltrates, myocyte necrosis, and fibrosis have been demonstrated in the atrial biopsies of patients with lone AF refractory to antiarrhythmic drug therapy, but not in control patients (Frustaci et al., 1997). As a result oxidative stress is unavoidably present in all cardiac surgeries with extracorporeal circulation and the atrial tissue is subjected to an oxidative challenge participating in the mechanism of AF. A search for preventive alternative measures is needed and it is reasonable to assume that a reinforcement of antioxidant defense system of cardiac tissue should be a strategy to protect the heart from the oxidative damage. Recent experimental and clinical studies have shown that polyunsaturated fatty acids (PUFA) may be effective in preventing cardiac arrhythmias and sudden death (Jouven et al., 2001; Christensen et al., 2005; Jahangiri et al., 2006), although the mechanism remains to be established. In addition, vitamin C was reported to attenuate electrical remodelling to decrease the incidence of POAF (Carnes et al., 2001), although these data could not be reproduced by other authors (Shiroshita-Takeshita et al., 2004). Recently, a well documented overview of preventive strategies for POAF was presented (Baker & White, 2007a). The aim of the present review is to provide the pathophysiological and molecular basis supporting an antiarrhythmic cardioprotection by therapeutic approaches based on exposure to moderate ROS concentration followed by antioxidant vitamin supplementation in patients scheduled for cardiac surgery with cardiopulmonary bypass. Thus, *n-3* PUFA supplementation, known to trigger survival response mechanisms, followed by a reinforcement of the myocardial non-enzymatic antioxidant defense through vitamin C and E supplementation, is expected to lower the incidence of AF, a frequent complication of cardiac surgery, thereby improving the clinical outcome of these patients.

2. Etiology of atrial fibrillation

Atrial fibrillation usually occurs in the context of an atrial substrate produced by alterations in atrial tissue properties referred to as remodeling. Atrial tachycardias (particularly rapid tachyarrhythmias such as atrial flutter and atrial fibrillation) cause ionic remodelling, which decreases the atrial refractory period and promotes atrial re-entry. An understanding of AF mechanism has been developed on the basis of the notion that it is caused by rapidly discharging, spontaneously active atrial ectopic foci (Nattel, 2002). The atria have areas of slow conduction and heterogeneous refractoriness such that atrial ectopic activity in the "vulnerable" phase results in multiple wavelet re-entry (Kecskeméti et al., 1985; Ramanna et al., 2000). Multiple wave fronts propagate through the atria in a chaotic fashion, constantly colliding, reinitiating, and reforming. A critical mass of atrial tissue is required to sustain the multiple simultaneous wave fronts that perpetuate the rhythm (Hashimoto et al., 1991; Dell'Orfano et al., 1998; Nattel, 2002).

The current theories regarding the initiation and maintenance of atrial fibrillation are presented below.

2.1. Rapid firing focus

Rapidly firing foci, usually from within the pulmonary veins, drive the surrounding atrial tissue to produce atrial fibrillation. The rhythm is then maintained by the multiple re-entrant wavelets even after the burst of automaticity has ceased (Wijffels et al., 1995; Jaïs et al., 1996, Haïssaguerre et al., 1998; Gong et al., 2007).

Numerous studies have highlighted the importance of ectopic activity from the region of pulmonary veins in initiation of AF particularly in patients with lone, paroxysmal AF (de Bakker et al., 2002; Jaïs et al., 2002; Van Wagoner, 2007). AF can be initiated and perhaps perpetuated by focal discharges of atrial tissue located in the sleeves of pulmonary vein ostia. Focal pulmonary vein discharges can initiate longer lasting rapid re-entrant activity within the pulmonary veins. These waves can propagate and collide with normal activation wavefronts in susceptible atria, leading to wave breaks and multiple wavelets of electrical activation throughout the atria, initiating AF (Takahashi et al., 2006; Van Wagoner, 2007).

2.2. Electrical remodelling

Atrial fibrillation itself, once initiated, results in electrophysiologic changes (ie, shortening of the refractory period) that make atrial fibrillation more likely to sustain itself or reinitiate after termination. (Wijffels et al., 1995; Nattel et al., 2005; Nattel et al., 2007). This may result in a lengthening of paroxysms of atrial fibrillation until it becomes persistent. Sinus bradycardia and pauses between episodes of atrial fibrillation further enhance the ability of ectopic beats to become manifest and reinitiate atrial fibrillation.

2.3. Structural remodelling

Structural remodeling, so-called "second factor", is the dominant factor that facilitates the maintenance of AF (Everett et al., 2000). The ultrastructural changes result in an inhomogeneous conduction and electrical uncoupling, and the enlarged atrium is able to accommodate more circulating wave fronts that stabilize the AF. (Allessie et al., 2002). Progression to persistent AF is probably related to an AF substrate, which is undergoing progressive structural remodeling owing to heart disease and other factors and is now suddenly capable of sustaining prolonged or multiple ATs. (Saksena et al., 2007).

Left atrial (LA) enlargement has been widely related to AF both in patients with underlying heart disease and those with idiopathic lone AF (Thamilarasan & Klein, 1999; Sitges et al., 2007). In addition, left atrial size reduction improves sinus rhythm conversion rate after radiofrequency ablation for

continuous AF in patients undergoing concomitant cardiac surgery (Scherer et al., 2007). This pathophysiologic mechanism has been confirmed in clinical settings also, concluding that the probability to succeed in sinus rhythm restoration is inversely related to atrial size (Villa et al., 2007).

Enlargement of the left atrium during atrial fibrillation can help perpetuate the arrhythmia (Manning et al., 1994; Manning et al., 1989). Although this is reversible to some extent with maintenance of sinus rhythm, patients who have undergone valvular operation often have enlarged atria at baseline.

The occurrence of paroxysmal atrial fibrillation in patients with high C-reactive protein (CRP) levels are associated with enlargement of the left atrium, depression of its contractile function and is independent of left ventricular hypertrophy and function. The mechanisms linking these variables remain undefined (Dernellis & Panaretou, 2006a; Dernellis & Panaretou, 2006b).

2.4. Neurohormonal activation

High sympathetic tone as a result of fluid shifts, pain, pressors, and inotropes are largely universal in the postoperative state. Patients undergoing cardiothoracic surgery with cardiopulmonary bypass have increased plasma norepinephrine and epinephrine concentration that correlate with increases in mean blood pressure (Baker & White, 2007b). In addition, sympathetic and parasympathetic activation of atrial tissue reduces atrial effective refractory period and an increase in automaticity of ectopic foci both predispose to the initiation of atrial fibrillation (Kalman et al., 1995; Maisel & Stevenson, 2003). This notwithstanding, studies showing sympathetic activation before the initiation of atrial fibrillation are somewhat discordant (Tisdale et al., 2006; Baker & White, 2007b).

3. Postoperative atrial fibrillation

3.1. Risk factors

3.1.1. Preoperatives

Age correlates very well with the incidence of POAF and is the strongest independent predictor (Hogue & Hyder, 2000; Zaman et al., 2000; Dogan et al., 2007). In fact, the AF incidence increases by 50% with each decade of life with approximately one-third of the patients over the age of 70 years developing AF postoperatively (Almassi et al., 1997; Rossano et al., 2007). AF was also associated to postoperative infection and renal dysfunction (Elahi et al., 2003). Not surprisingly, a history of AF (Mathew et al., 2004; Burgess et al., 2006) and the presence of valvular disease (Creswell et al., 1993; Auer et al., 2005; Osranek et al., 2006) also predispose patients to arrhythmia because the conditions that contribute to the initiation and perpetuation of the rhythm are already present.

In addition, ageing and intraoperative fluid balance, are also associated with the onset of AF after cardiac surgery with cardiopulmonary bypass (Hosokawa et al., 2007). Other identified risk factors have been less consistent including; hypertension (Mathew et al., 2004; Hilleman et al., 2005), angina (Yousif et al., 1990; Kernis et al., 2004), left-ventricular dysfunction (Levy et al., 2006), noncardiac comorbidities (Vaporciyan et al., 2004), male sex (Zaman et al., 2000; Mathew et al., 2004), previous congestive heart failure (Banach et al., 2006), elevation of left-ventricular diastolic pressure (Hashimoto et al., 1991; Scapellato et al., 2000) and preoperative transthoracic left atrial volume (Osranek et al., 2006).

Recently, a regression model with 14 significant indicators was developed. Indicators showing the greatest predictive influence were the patient age, the need for prolonged ventilation (24 h or more), use of cardiopulmonary bypass, and preoperative arrhythmias. These factors show acceptable concordance with POAF and the algorithm may be used preoperatively to appropriately target high-risk patients for aggressive prophylactic treatment (Magee et al., 2007).

3.1.2. Intraoperative considerations

Several studies have addressed whether certain surgical techniques are more apt to result in AF in the postoperative period. Myocardial protection is designed to decrease metabolic demands of the myocardium during cardiopulmonary bypass, when the heart is deprived of blood flow (Mathew et al., 2004; Baker & White, 2007a). Since hypothermia has been implicated as a contributing factor in the development of postoperative dysrhythmias in noncardiac surgery (Frank et al., 1995) it was hypothesized that temperature affects the incidence of POAF during cardiac surgery. It was performed a randomized, controlled trial to analyze the effect of mild hypothermia (*ie*, 34 °C) vs moderate hypothermia (*ie*, 28 °C) in a group of 65 patients undergoing cardiac surgery (Adams et al., 2000). Accordingly, AF guidelines published by the American College of Chest Physicians have recommended mild hypothermia as possible option for reducing the incidence of POAF (Creswell et al., 2005), what has been corroborated recently (Augoustides et al., 2007).

3.1.3. Postoperative factors

Postoperative administration and/or withholding of several medications were associated with an alteration in the occurrence of AF (Baker & White, 2007a). Withdrawal of β-blocker therapy in the immediate postoperative period resulted in a 91% increase in risk of developing atrial fibrillation (Connolly et al., 2003). The guidelines recommending early postoperative administration of β-blockers should be considered a standard therapy for the prevention of atrial fibrillation (Eagle et al., 2004; Valtola et al., 2007). Similarly, angiotensin-converting enzyme therapy initiated before and after the surgery was associated with a lower risk for AF, while its withdrawal was associated with increased risk (Mathew et al., 2004; Coleman et al., 2007). Atrial expression of angiotensin-converting enzyme increased in patients with AF (Goette et al., 2000), possibly leading to angiotensin II-dependent atrial fibrosis and regulation of angiotensin II-receptor subtypes (Boldt et al., 2003).

On the other hand, it is difficult to distinguish the cause and effect relationship in assessing the contribution of respiratory dysfunction to POAF. Pneumonia (Manganas et al., 2007), prolonged ventilation (Hilleman et al., 2005; Magee et al., 2007), and chronic obstructive lung disease (Van Belleghem

et al., 2003a, 2003b; Mathew et al., 2004), have all been associated with a higher incidence of atrial fibrillation. Recent clinical studies are in agreement with the success and extent to which postconditioning, defined as brief intermittent cycles of ischemia alternating with reperfusion applied after the ischemic event, reduces infarct size and myocardial injury, even in the presence of multiple co-morbidities (Vinten-Johansen et al., 2007).

At present, the incidence of this arrhythmia remains high despite the currently available measures for the attenuation of pre-, intra- and postoperative risk factors involved in the development of POAF.

4. Pathophysiology

Re-establishment of blood flow in the ischemic myocardium is a common situation in cardiovascular surgery. Experimental studies have shown that reperfusion itself is associated with structural and functional derangement (Jennings & Reimer, 1983; Becker & Ambrosio, 1987; Mihm et al., 2001). Although the underlying mechanisms accounting for these effects have been extensively debated, they still remain unknown. However, it has become evident that oxidative stress and ROS may have more subtle effects, for example the highly specific modulation of intracellular signaling pathways and proteins, which stimulate ROS production by various highly specific enzymes. The pathophysiological effects of ROS depend upon the type, concentration and specific site of production and involve three broad types of action. When the local levels of ROS are high, they tend to react with numerous proteins, DNA, cell membranes and other molecules, causing significant cellular damage. At lower concentrations, however, local targeted production of ROS serves as a second messenger system that transmits biological information by highly specific modulation of intracellular signaling molecules, enzymes and proteins. The latter process includes an adaptive response to enhance antioxidant defenses, mainly by up-regulating antioxidant enzymes expression and/or anti-apoptotic pathways. In contrast, high ROS levels could give rise to pathological effects of oxidative stress characterized by oxidative damage, resulting in cell dysfunction, apoptosis and/or necrosis. Structural effects involving cardiomyocyte (CM) function may contribute to the pathophysiological remodeling underlying the cardiac rhythm impairment. A wide mechanistic survey of AF is beyond the scope of the present review, but it is discussed in detail in a recent article focused on new aspects of pathophysiology of AF (Van Wagoner, 2007). This section is devoted to present the experimental and clinical evidence to show the role of ROS in the pathogenesis of AF following cardiac surgery, as well as in the protection of cardiomyocytes against the ischemia/reperfusion cycle.

4.1. Oxidative stress

Multiple lines of evidence have strongly suggested a link between oxidative stress and cardiac arrhythmias, especially AF (Neuman et al., 2007; Iravanian & Dudley, 2006). Interestingly, cardiac surgery has also been reported to increase oxidative stress as measured by thiol ratios in the plasma and myocardium (De Vecchi et al., 1998), and supplementing postoperative patients with ascorbate, a known antioxidant, cuts rates of AF more than 2-fold (Carnes et al., 2001). Although the latter data need to be confirmed, it could be suggested that oxidative stress markers may have predictive value in AF management. Thus, it was demonstrated a reduction in the activity of myofibrillar creatine kinase, which is redox sensitive, and an increase in immunodetectable 3-nitrotyrosine, a marker for the presence of peroxynitrite, in right atrial appendage taken from patients with AF compared to patients in normal sinus rhythm (Mihm et al., 2001).

Interestingly, recent studies have demonstrated the implication of oxidative stress within the atrial tissue during AF suggesting a potential role in the remodeling phenomenon. (Korantzopoulos et al., 2007; Van Wagoner, 2003).

Atrial fibrillation induced by rapid atrial pacing in pigs is characterized by increased nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity and superoxide production in the left atrium (Dudley et al., 2005). Right human atrial appendages of patients with AF exhibit higher levels of the oxidative markers 3-nitrotyrosine and protein carbonyls compared with patients with sinus rhythm (Mihm et al., 2001). In addition, left atria of patients with AF exhibit up-regulation of Rac1, and positive correlation with NADPH oxidase activity (Adam et al., 2007). In mice, chronic cardiac overexpression of Rac1 represents a novel model for AF. Rac1 GTPase contributes to the pathogenesis of AF and might represent a target for the prevention and treatment of AF.

4.2. Myocardial ischemia/reperfusion

The myocardium can tolerate brief periods (up to 15 min) of severe and even total myocardial ischemia without resultant CM death. This is observed in clinical settings like coronary vasospasm, angina and balloon angioplasty, and is therefore not associated with concomitant myocyte death (Kloner & Jennings 2001a; Kloner & Jennings 2001b). It was suggested that endothelial dysfunction occurs early during reperfusion of a previously ischemic tissue and that it will be present for long time (Lefer & Lefer, 1996). In a clinical setting, reperfusion injury after revascularization of the ischemia-related artery is manifested by myocardial stunning, reperfusion arrhythmia, myocyte death, and endothelial- and microvascular dysfunction including the no-reflow phenomenon (Moens et al., 2005). Early reperfusion is an absolute prerequisite for the survival of ischemic myocardium. However, reperfusion has been referred as the double edged sword because reperfusion may itself lead to accelerated and additional myocardial injury beyond that generated by ischemia alone (Braunwald & Kloner, 1985). This results in a spectrum of reperfusion-associated pathologies, collectively called reperfusion injury (Yellon & Baxter, 2000). These observations are consistent with the notion that reintroduction of abundant oxygen at the onset of reperfusion evokes a burst of ROS within the first few minutes of reflow as demonstrated in experimentally and in patients with acute

myocardial infarction undergoing thrombolysis (Béard et al., 1994) or percutaneous coronary intervention (Roberts & Yoon, 2002), and patients undergoing open heart surgery (Kim et al., 1994).

4.3. Reactive oxygen species (ROS)

ROS are oxygen-based chemical species characterized by their high reactivity and include free radicals (ie, species with one or more unpaired electrons, such as superoxide ($O_2^{\cdot -}$) and hydroxyl ($OH^{\cdot}$) and non-radicals capable of generating free radicals (eg, hydrogen peroxide (H_2O_2). Under normal conditions 95% of the oxygen consumed by the myocardium is reduced to water via mitochondrial electron transport chain, whereas the remaining 5% is partially reduced to form ROS. If present in excess, free radicals can induce oxidative damage to DNA, membranes, proteins and other macromolecules. Cells are not passive to increased oxygen radical production but rather up-regulate protective responses. The ability of tissues to tolerate ROS is partly conditioned by the activity of their antioxidant defense system to scavenge and degrade ROS to non-toxic molecules, which include antioxidant enzymes (catalase, superoxide dismutase and glutathione peroxidase), mainly located in the intracellular space, and, the antioxidant molecules both within the intra- and extracellular spaces. The balance between ROS production and their removal by antioxidant systems describes the "redox state" of a cell; a pathological imbalance in favor of excess ROS is termed oxidative stress. The setting of an ischemia/reperfusion cycle alters this homeostasis giving rise to a prevalence of prooxidants over antioxidant activity (oxidative stress). Consequently, the increased ROS concentration at the steady state causes direct damage to lipids, proteins and DNA. A large body of experimental evidence supports the notion that ROS-generated reperfusion injury occurs when oxygen is reintroduced to the ischemic tissue (Hess & Manson, 1984; Weisfeldt et al., 1988; Opie, 1991; Kilgore & Lucchesi, 1993; Zughaib et al., 1994; Park & Lucchesi, 1999; Ambrosio & Tritto, 1999). Previously, it has been proposed that the beneficial effects of ROS occur at moderate concentrations and involve physiological roles in cellular responses (Martindale & Holbrook, 2002; Valko et al., 2007). Several lines of evidence suggest an association between oxidative stress and AF. It is of interest to mention that $O_2^{\cdot -}$ is able to react with nitric oxide (NO) via a high rate constant non-enzymatic reaction to form peroxynitrite, a highly peroxidant molecule responsible for additional structural changes, such as nitrotyrosine derivatives formation, nitrosylation and oxidation of thiol groups. Redox signaling processes are involved in the activation of many signal transduction protein kinases and transcription factors, the stimulation of DNA synthesis and expression of growth-related genes and the regulation of myocardial excitation-contraction coupling. The third general ROS-related pathophysiological mechanism involves the reaction of $O_2^{\cdot -}$ with the signaling molecule NO, which plays a central role in vascular homeostasis as well as in modulating cardiac function. The reaction between $O_2^{\cdot -}$ and NO leads to the inactivation of NO and loss of its biological activity as well as the generation of peroxynitrite ($ONOO^-$) species. This reaction is likely to occur when both $O_2^{\cdot -}$ and NO levels are high and antioxidant activity is low. Interestingly, while high levels of $ONOO^-$ may induce nonspecific toxic effects, at lower levels it is capable of modulating signaling events in vivo indicating an additional level of complexity. NO synthase normally generate NO but may instead generate $O_2^{\cdot -}$ if they become "uncoupled", a state that may occur from deficiency of NOS cofactor tetrahydrobiopterin (BH_4) or the NOS substrate L-arginine (Verhaar et al., 2004).

4.4. NADPH oxidases

These enzymes catalyze electron transfer from NADPH to molecular oxygen, resulting in the formation of $O_2^{\cdot -}$. Interestingly, ROS produced by NADPH oxidases can promote ROS generation by other sources thereby amplifying total levels of ROS. For example, $O_2^{\cdot -}$ from NADPH oxidase may oxidize and degrade BH_4, thereby leading to NOS uncoupling, as in diabetes and experimental hypertension. Similarly, NADPH oxidase-derived ROS may also activate xanthine oxidase (Li & Shah, 2004). NADPH oxidases are of particular interest because they appear to be the only enzymes specifically designed for ROS production. Furthermore, the complexity of their regulation suggests that they may be attractive targets for novel therapies. These oxidases are specifically activated by diverse stimuli that are important in cardiovascular pathology, eg, angiotensin II, endothelin-1, cytokines, growth factors, oxidized LDL, shear stress, mechanical stretch and others (Li & Shah, 2004; Lambeth, 2004; Murdoch et al., 2006). All NADPH oxidases contain a core catalytic subunit called Nox. Five distinct Nox isoforms each encoded for by separate genes, of which Nox2 is abundantly expressed in endothelial cells, fibroblasts and CM (Kim et al., 2005). In turn, Nox4 is also expressed in endothelial cells (Ago et al., 2004) and in CM and fibroblasts (Cave et al., 2005). The evidence indicates that the primary source of $O_2^{\cdot -}$ production in the human atrial myocardium is an NADPH oxidase. NADPH-stimulated $O_2^{\cdot -}$ release from right atrial appendange homogenates was significantly increased in patients with AF compared with matched patients in sinusal rhythm. In addition, enhanced NADPH oxidase activity can either be attributable to increased expression or post-translational modifications of oxidase subunits, due to the absence of changes in mRNA expression of the p22phox and gp91phox subunits of the NADPH oxidase (Kim et al., 2005). In addition, these authors demonstrated that uncoupled NOS contributes to $O_2^{\cdot -}$ production in the presence of AF, although they did not specify whether the NOS isoform involved was eNOS, iNOS and/or nNOS. Adam et al., reported that AF was associated with a 4-fold increase of Rac1 total protein and membrane expression as well as up-regulation of Rac1 activity (Adam et al., 2007). Possible mechanisms of Rac1 activation include increased Ang II receptor activation, or increased cytosolic Ca^{2+} (Wassmann et al., 2001; Ito et al., 2004; Cook-Mills et al., 2004). Finally, other enzyme systems such as xanthine oxidase (Dudley et al., 2005) could contribute also to the increased $O_2^{\cdot -}$ production.

5. Atrial remodeling by ROS

Compelling evidence shows that AF development and perpetuation depends on the electrophysiological and structural substrates of the atria (Allessie et al., 2002; Nattel et al., 2007). The structural substrates refer to abnormalities in atrial architecture such as atrial dilatation (Kojodjojo et al., 2007), fibrosis (Everett & Olgin, 2007), apoptosis phenomena, tissue dedifferentiation etc. (Shiroshita-Takeshita et al., 2005). The altered morphology, as well as the diminished functionality, is a reflection of transitions that take place at the molecular level. The CM has to cope with new circumstances and consequently change the expression and organization pattern of proteins involved in activation, conduction, and contraction.

5.1. Triggers of AF in the post-operative period

Extensive investigations aiming at the identification of risk factors for the initiation of POAF have been developed; however, the pathogenesis has remained unresolved. Factors involved in its induction and maintenance include aging (Koutlas et al., 2000), premature beats (Pak et al., 2006), autonomic nervous system activity (Dimmer et al., 1998), atrial stretch (Wijffels et al., 1997; Osranek et al., 2006), anisotropic conduction (Chung et al., 2007), prolonged aortic cross-clamping (Hkala & Hedman, 2003) and atrial ischemia and local inflammation (Mueller et al., 2001; Feringa et al., 2007). Analysis of heart rate variability indicated that a moderate increase in sympathetic tone and a loss of excessive vagal tone before the onset of POAF were important triggering factors (Steinberg et al., 1993; Dimmer et al., 1998). Furthermore, the withdrawal of preoperative β-blocker and/or angiotensin I converting enzyme inhibitor was associated with an increased incidence of POAF (Mathew et al., 2004; Budeus et al., 2007). These changes could be triggered by several factors including atrial ischemia (Zangrillo et al., 2004), probably secondary to poor myocardial protection because of the rapid rewarming of the atria after coronary artery bypass surgery (Fearon et al., 1997).

In addition, an elevated preoperative plasma brain natriuretic peptide level is a strong and independent predictor of POAF. This finding has important implications for identifying patients at higher risk of POAF who could be considered for prophylactic antiarrhythmic or β-blocker therapy (Wazni et al., 2004).

It has been shown an enhancement of arrhythmic activity in arrhythmogenic contexts such as chronic atrial tachypacing and thyroid hormone exposure (Chen et al., 2001; Chen et al., 2002). Atrial Na^+–Ca^{2+} exchanger activity is enhanced in cardiac heart failure (Li et al., 2000), providing a further potential basis for triggered activity-related tachyarrhythmias (Stambler et al., 2003; Fenelon et al., 2003).

5.2. Triggers and oxidative stress

Ions like Ca^{2+}, Na^+ and K^+ are important players in the excitation–contraction cycle, and the expression patterns of their channels and other proteins involved in ion homeostasis have been extensively studied. The decreased level of L-type calcium channel expression was correlated with the shortening of the atrial effective refractory period but was not influenced by atrial dilatation.

Oxidative membrane damage has been found to be of great pathological importance in ischemia/reperfusion of myocardial tissue injury. At the molecular level, membrane functions may be modified by direct attack of ROS on its related components. ROS exposure influences the physical properties of membranes, and hence ion transport mainly due to changes in the dielectric constant, which is enhanced by lipid peroxidation (Killig & Stark, 2002). This effect is caused by the accumulation of polar products of lipid peroxidation, or secondary reactive species, in the membrane interior. Consequently, membrane barrier, experienced by the charged species throughout their translocation across the membrane, would be further reduced (Stark, 2005) giving rise to many of the activation phenomena of membrane transport described in the literature. Ion channels (contrary to ion carriers) provide polar pathways for ions across the hydrophobic membrane barrier. For their proper functioning, the structural element forming the polar pathway must be inserted into the membrane, a process which is substantially facilitated by increased dielectric constant. Membrane proteins have a natural lipid environment and are therefore particularly exposed to an eventual attack of secondary reactive species.

In addition, it should be considered that both ROS and the highly reactive products of lipid peroxidation react and modify structure and function of membrane proteins and thus influence their functional efficiency. The oxidative modification of (Na + K)-ATPase has been studied considering the direct and the indirect inactivation pathways (Shao et al., 1995). In agreement with this view it was reported that erythrocyte (Na + K)-ATPase activity correlated negatively with 8-isoprostane (in vivo index of lipid peroxidation) in hypertensive and normotensive subjects (Rodrigo et al., 2007a).

6. Signaling pathways induced by ROS in POAF

ROS and reactive nitrogen species (e.g. nitric oxide, $NO^{\cdot}$) are well recognized for playing both deleterious and beneficial roles (Valko et al., 2007). ROS are produced in the heart by ischemia/reperfusion injury, myocardial infarction and cardiomyopathy. However, potential sources for ROS generation also include NADPH oxidase (Heymes et al., 2003), dysfunctional mitochondrial electron-transport chain (Halestrap et al., 2007), arachidonic-acid metabolism (Caro & Cederbaum, 2006), neutrophil infiltration and activation, xanthine oxidase, and catecholamines (Cai & Harrison, 2000).

Molecular mechanisms through which oxidized lipids and their electrophilic decomposition products mediate redox cell signalling are not well understood. This may involve direct modification of signal-transduction proteins or the secondary production of reactive oxygen or nitrogen species in the cell (Levonen et al., 2004). The deleterious consequences of high ROS exposure, such as inflammation, cell death (apoptosis/necrosis) or fibrosis, may be abrogated by myocardial preconditioning caused by previous exposure to moderate ROS concentration known to trigger survival response mechanisms. The preconditioning is thought

to result in activation of mitochondrial (and membrane) ATP-sensitive K+ channels, rather than calcium-sensitive K+ channels (Fruehauf & Meyskens, 2007; Valko et al., 2007).

The occupancy of surface receptors during the preconditioning ischemia has been suggested to result in the opening of calcium-sensitive potassium channels which causes the mitochondria to release ROS. The ROS would then act as second messengers, activating protein kinase C survival pathway (Cohen et al., 2006).

6.1. Role of transcriptional factors in POAF

The mechanistic basis of AF remains incompletely understood, although active research promises to provide new insights that may lead to improved therapeutic options (Allessie et al., 2001; Nattel, 2002). A variety of animal models have been used to assess AF pathophysiology under controlled conditions. The molecular basis of AF is not well elucidated and novel strategies have been developed to improve the understanding of the underlying mechanisms involved in this arrhythmia. Accordingly, analysis of cardiac gene expression changes has been attempted through gene microarray technology and has been applied to compare AF patients with those in sinus rhythm (Barth et al., 2005). Microarray technology identifies differentially expressed genes with high sensitivity and fidelity and can correctly predict expression of corresponding proteins (Kim et al., 2003). This technology offers a broader and unbiased approach to identify the genes participating in pathophysiologically relevant pathways, involving transcript of the extracellular matrix compartment (Kim et al., 2003; Nakano et al., 2004), ionic channels (Gaborit et al., 2005) and signal transduction molecules (Goette et al., 2002). Since oxidative stress is thought to cause AF, novel evidence for previously unknown patterns of gene expression events that are related to oxidative stress of AF patients has been presented. The most interesting results of the array study were upregulation of genes involved in facilitating oxidative stress and downregulation of genes involved in protecting against oxidative stress and oxidative damage repair (Kim et al., 2003). Other investigators have confirmed these findings and reported changes in genes related to cell signalling, inflammation, oxidation and cellular respiration (Ohki-Kaneda et al., 2004; Ohki et al., 2005).

During reperfusion injury following cardiopulmonary bypass enhancement of ROS leads to their interaction with some survival signalling pathways. In this point, modulation in mitochondrial ROS production is relevant (Becker, 2004). Increases in cellular Ca^{2+} and ROS, initiated in ischaemia and then amplified upon reperfusion, are thought to be the main causes of reperfusion injury. Mitochondria are involved both in the production of ROS and as targets for the damaging action of both ROS and Ca^{2+} (Halestrap et al., 2004; Solaini & Harris, 2005; Halestrap, 2006). One model proposed for H_2O_2 induction of apoptosis is the upregulation of Fas–FasL system, leading to the activation of caspase-8 and downstream caspases. Extracellular H_2O_2 is associated with an increase in $O_2^{\cdot -}$ production by the mitochondria caused by an increase in Ca^{2+} influx through L-type Ca^{2+} channels. This effect persists because of a positive feedback in increased basal channel activity, elevated intracellular Ca^{2+}, and $O_2^{\cdot -}$ production by the mitochondria (Viola et al., 2007). Also, H_2O_2 can cause the release of cytochrome c from the mitochondria into the cytosol. Cytochrome c binding to Apaf-1 in the cytosol is a critical step in the formation of the apoptosome which activates caspase 9, which then activates caspase 3. Also, H_2O_2 may activate nuclear transcription factors such as NF- κB, AP-1, and P53, which may up-regulate death proteins or produce inhibitors of survival proteins (Chandra et al., 2000).

6.1.1. Nuclear factor Kappa B

A key role for the transcriptional regulation of proinflammatory cytokines has been attributed to the ubiquitous transcription nuclear factor-kappa B (NF-κB) and p38 mitogen-activated protein kinase (MAPK) signalling pathway (Valen et al., 2001). Triggered by ischemia–reperfusion and proinflammatory cytokines themselves, phosphorylation of the inhibitory protein of NF-κB (inhibitory kappa-B alpha [IκBα]), and p38 MAPK promotes gene expression of potential myocardial damaging mediators such as TNFα, IL-1β, and IL-6 (Liakopoulos et al., 2007).

It has been indicated that NF-κB may play important roles in cardiac hypertrophy and remodeling besides promoting inflammation. Also, NF-κB has been shown to be activated in the failing human heart (Wong et al., 1998; Grabellus et al., 2002), where expression of proinflammatory cytokines is exacerbated (Torre-Amione et al., 1996; Kubota et al., 2000) and blockade of NF-κB improves cardiac function and survival after myocardial infarction (Kawano et al., 2006). A role of NF-κB in POAF has not been demonstrated; however, it is reasonable to propose its participation, due to its importance in the activation of inflammatory genes (Ishida et al., 2006). This activation increases cytokine production, such as IL-6, acute phase proteins (eg. CRP) and procoagulant elements (eg. fibrinogen). In addition, elevation leukocyte recruitment which enhances the inflammatory systemic state, leading to the genesis and persistance of AF. In proinflammatory state, tumor necrosis factor (TNF)-α exacerbates myocardial ischemia/reperfusion injury at an early stage of reperfusion by activating NF-κB, thereby inducing chemokines and adhesion molecules and facilitating leukocyte infiltration (Maekawa et al., 2002). Collectively, from the available data it should be noted that further studies on the participation of NF-κB in the pathophysiology of AF are still needed.

6.1.2. STAT3

The inflammatory mediators produced by myocardium in response to ischemia–reperfusion injury (Wang et al., 2006a, 2006b) contribute to myocardial functional depression and cardiomyocyte apoptosis. Since STAT3 signaling has been reported to play critical roles in the regulation of inflammatory response pathways (Hilfiker-Kleiner et al., 2005), it is therefore assumed that the STAT3 pathway may be involved in this response. Indeed, accumulated evidence has indicated that STAT3 can be activated by ischemic-oxidative stress. This signaling pathway plays an important role in myocardial functional recovery following ischemia–reperfusion injury by maintaining capillary integrity, thus protecting the myocardium from apoptosis (Hilfiker-Kleiner et al., 2004). It is unclear how the

JAK-STAT pathway affects cardioprotection after early-phase preconditioning. After late-phase preconditioning, JAK-STAT signaling may promote cell survival by diminishing myocyte apoptosis (Bolli, 2000).

The network of intracellular signal transduction activated by interleukin-6 (IL-6) has been studied intensely and the JAK/STAT pathway is critical for IL-6 signaling. STAT 3 binds to (IL-6) response elements identified in the promoter region of various acute-phase protein genes in response to IL-6 (Akira, 1997; May et al., 2003). Several studies have indicated that ischemia activates JAK2 and that STAT 3 activation via JAK2 transduces cytoprotective and survival signals in infarcted heart. In vitro studies have demonstrated that STAT 3 potentiates antiapoptotic signals through the induction of bcl-2 or bcl-xL genes (Schwarze and Hawley, 1995). Early phase of ischemic preconditioning potentiates JAK/STAT signalling by activating STAT3 which transmits a survival signal to the myocardium (Hattori et al., 2001). In addition, selective activation of a set of STAT proteins underlies mobilization of gene activation program intrinsic to post-ischemic myocardial remodelling (El-Adawi et al., 2003).

6.1.3. Heat shock proteins

Patients with low preoperative atrial heat shock proteins (HSP) expression have a significantly greater incidence of postoperative atrial fibrillation. Heat shock proteins (HSP) expression is increased in both experimental (Vitadello et al., 2001) and clinical AF (Schäfler et al., 2002). There is evidence suggesting that HSP may protect against clinical AF. HSP expression did not, however, correlate with the onset of atrial fibrillation and the resistance to administered medications (St Rammos et al., 2002). HSP70, one of these proteins, has been shown to act as a chaperone and is associated with cytoprotection against DNA damage caused by environmental stresses. (Yang et al., 2007). Intracellular, but not serum, HSP70 level is negatively correlated with postoperative atrial fibrillation. This suggests a cardioprotective and an anti-arrhythmic role for intracellular HSP70. (Mandal et al., 2005). It was found that a mutation in hsp70-Hom gene is associated with higher incidence of POAF, suggesting that patients harbouring this substitution will have less endogenous myocardial protection against AF in stressful situations (Afzal et al., 2007). These findings advance our understanding of the biochemical determinants of AF and suggest the possibility that HSP induction may be an interesting novel approach to prevent clinical AF (Brundel et al., 2006).

6.2. Inflammation in POAF

New etiologic mechanisms of AF have been proposed in recent years. The first study documenting elevated CRP was reported in non-postoperative arrhythmia patients (Chung et al., 2001). In particular, there is increasing evidence of a link between AF and inflammation (Tselentakis et al., 2006), as shown by the association between AF and a variety of inflammatory markers, such as high-sensitivity C-reactive protein (hs-CRP), IL-6, TNF-α, and white blood cell count (Boos et al., 2006; Roldan et al., 2005; Abdelhadi et al., 2004; Conway et al., 2004; Sata et al., 2004; Dernellis & Panaretou, 2004). Furthermore, it would seem that hs-CRP may relate to the clinical burden of AF (Chung et al., 2001). Atrial biopsy specimens from subjects with lone AF have shown the presence of inflammatory infiltrates. (Boos et al., 2006; Frustaci et al., 1997). In contrast, it has been considered that CRP is not only associated with the presence of AF but may also predict patients at increased risk for future development of AF. (Aviles et al., 2003).

Collectively, these data provide additional evidence to support an association between inflammatory response and POAF (Amar et al., 2006; Lamm et al., 2006).

6.2.1. Proinflammatory cytokines

Proinflammatory cytokines, such as TNF-α, IL-6, and IL-8, play a pivotal role in the upstream of inflammatory cascade. TNF-α stimulates the secretion of other proinflammatory cytokines including IL-6 and IL-8 (Wan & Yim, 1999). IL-6, a multifunctional proinflammatory cytokine, plays an important role in ischemia/reperfusion injury (Sawa et al., 1998). IL-8 induces neutrophil migration and activation, which results in neutrophil-mediated organ injury. Systemic inflammatory response after on-pump coronary artery bypass grafting participates in the pathogenesis of POAF (Ishida et al., 2006).

6.2.2. C-reactive protein

Elevated IL-6 and CRP levels in patients with AF suggest a role of inflammation in the pathogenesis and recurrence of AF (Gaudino et al., 2003; Hatzinikolaou-Kotsakou et al., 2006; Ucar et al., 2007). It is of interest to note that in contrast to findings from studies that have included mostly men, preoperative CRP concentrations are not associated with risk for atrial fibrillation after cardiac surgery for women (Hogue et al., 2006).

6.2.3. Leukocytosis

Cardiac surgery is associated with an elevated postoperative leukocyte count that represents a common marker of inflammation and predicts the development of POAF. These data provide evidence supporting the association between the inflammatory response and POAF. (Lamm et al., 2006). Monocyte CD11b upregulation perioperatively was significantly associated with POAF (Fontes et al., 2005). CD11b is the ß2-integrin that mediates leukocyte adhesion to vascular endothelial cells and leukocyte migration from the vasculature into tissues (Smith et al., 1989).

The long circulation half-life for monocytes and their ability to transform into long-lived tissue macrophages may also have a role in the inflammatory response leading to postsurgical AF.

6.2.4. Inflammation and oxidative stress in POAF

Although the relative strength of the association of inflammation and oxidative stress markers with AF remains unclear, currently the role of inflammation and oxidative stress on electrical remodeling is under investigation.

Studies of animal and human samples have shown increased myocardial oxidative stress associated with AF (Dudley et al., 2005; Kim et al., 2005). Increased concentration of the inflammatory marker CRP was found to be associated with AF in some studies (Aviles et al., 2003) and has been suggested to be a predictor of the incidence of AF after cardioversion (Watanabe et al., 2006) or cardiac surgery (Lo et al., 2006).

It is of interest to remark that although both oxidative stress and inflammation could be separately involved in the mechanism of POAF, there is an interplay between the 2 processes (inflammation induces oxidative stress and vice versa).

A schema accounting for the mechanism involved in the pathophysiology of postoperative atrial fibrillation with the contribution of oxidative stress and inflammatory response is depicted in Fig. 1.

7. Prevention of postoperative atrial fibrillation

7.1. Myocardial protection by ischemic preconditioning

Cardiac ischemic preconditioning was first described in 1986 in dogs subjected to brief, intermittent episodes of ischemia that causes a protective effect on the myocardium that is later subjected to a sustained bout of ischemia (Murry et al., 1986). A single brief ischemic interval was found to be as effective as preconditioning with multiple ischemic periods (Li et al., 1990). Brief ischemia of the myocardium initiates a cascade of biochemical events in CM that protects the heart muscle during subsequent ischemic insults (Rezkalla & Kloner, 2007). Ischemic preconditioning lowers the incidence of cardiac arrhythmias in various clinical settings and its benefits have been suggested for solid organ transplantation (Ambros et al., 2007). This response is associated with remarkable attenuation of cell death, suggesting that ischemic cell death may be a regulated event. In addition, recent reports confirm the efficacy of pre- and postconditioning in cardiac surgery and percutaneous coronary interventions in humans (Rezkalla & Kloner, 2007). Regular exercise shows benefits of preconditioning in patients with coronary artery disease, particularly elderly. Nevertheless, the protective effect of preinfarction angina is preserved in elderly patients with a high level of physical activity (Abete et al., 2001). The exact cellular mechanism of preconditioning is still a question for debate, however, among several other mediators, $NO^{\cdot}$, $^{\cdot}OH$, and $ONOO^{-}$ that play a role in both ischaemia/reperfusion injury and in the development of the cardioprotective effects of preconditioning (Bolli, 2001). Oxidant stress contributes to cell death in ischemia/reperfusion; which is attenuated by physiological levels of $NO^{\cdot}$ (Iwase et al., 2007). $NO^{\cdot}$ has been considered a cardioprotective agent during ischemia/reperfusion, and a mediator of preconditioning but the mechanism remians unknown. However, whether $NO^{\cdot}$ plays a protective or detrimental role in myocardial ischaemia–reperfusion injury or preconditioning remains controversial (Ferdinandy & Schulz, 2003; Cohen et al., 2006). In addition, species difference in the effectiveness of endogenous $NO^{\cdot}$ to protect hearts against arrhythmia has been reported. Thus, in vitro studies in primate hearts showed a lack of antiarrhythmic cardioprotection by endogenous $NO^{\cdot}$ (Pabla & Curtis, 2007). In case of prolonged ischemia and reperfusion, the mechanisms appear to require activation of protein kinase C-epsilon, either by receptor-mediated events or through transient increases in ROS. Other signalling pathways may show cross-talk with this primary mechanism, but

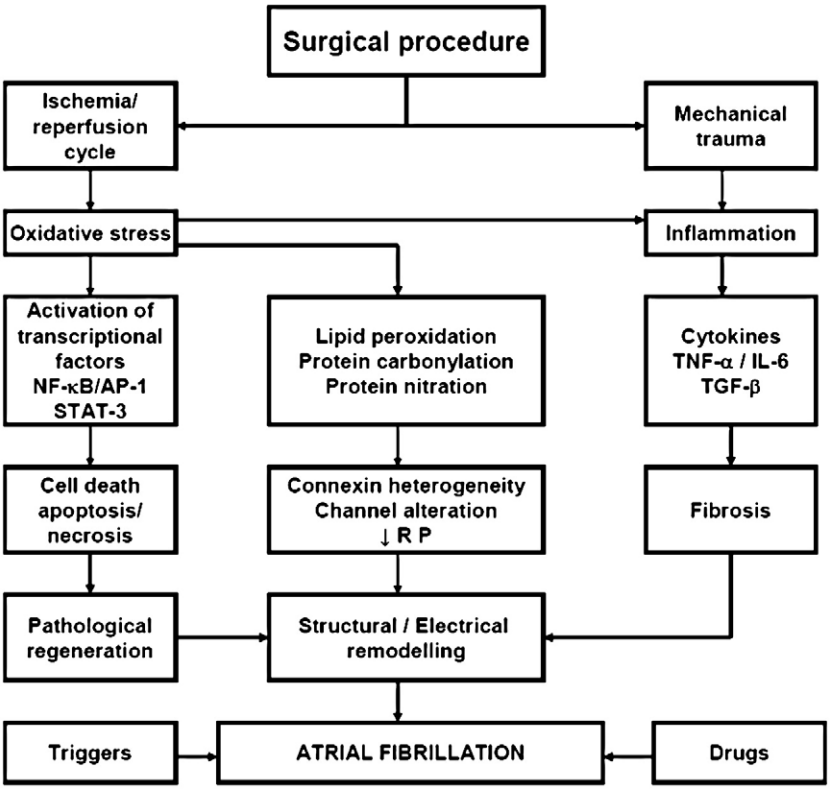

Fig. 1. Proposed hypothesis for the role of oxidative stress and inflammation in the pathophysiology of postoperative atrial fibrillation in patients scheduled for cardiac surgery with cardiopulmonary bypass. NF-κB, nuclear factor Kappa B; AP-1, transcriptional factor activating protein-1; STAT 3, signal transducer and activator of transcription-3; TNF-α, tumoral necrosis factor-α; IL-6, interleukin-6; TGF-β, transforming growth factor-β; RP, refractory period.

a role for mitochondrial potassium channels was suggested to be unlikely (Halestrap et al., 2007). Midkine, a heparin-binding growth factor involved in diverse biological phenomena, was recently reported to have a protective action against ischemia/reperfusion injury in the heart, because of its cytoprotective effects in cultured neurons and tumor cells (Horiba et al., 2006).

To our knowledge, at present there is no clinically useful preconditioning tool that is routinely utilized during on-pump bypass surgery. On the other hand, the performance of cross clamping always carries a risk of causing embolic stroke during the surgery, and is unlikely to be popular, particularly in elderly patients with significant aortic atherosclerosis. Concerning the clinical setting of coronary artery bypass grafting, a survey of current myocardial protection practices in a study of 160 surgeons reported that ischemic preconditioning is not commonly practised (Karthik et al., 2004). Alternatively, pharmacological preconditioning has been attempted, although most of such agents have no proven clinical benefit in myocardial ischemia and it is discussed below.

7.2. Non pharmacological therapy

Several investigators have studied the effects of various non pharmacological methods of myocardial protection on the frequency of postoperative atrial arrhythmias (Auer et al., 2004). However, no convincing benefit for any one particular protection strategy has been identified in retrospective reports, either in terms of POAF or other conduction abnormalities (Creswell et al., 2005). It deserves to be mentioned that some previously used measures such as mild hypothermia, potassium myocardial stunning (cardioplegia) or posterior pericardiotomy could be applied to diminish the occurrence of cardiac arrhythmia during the surgical procedures (Ekim et al., 2006). Cardioplegia is a very important component during cardiopulmonary bypass surgery, for providing bloodless field for the surgeon and also decreasing myocardial injury from ischemia/reperfusion cycle (Valen et al., 2004). Metabolic substrate enhancement with glucose or other energy sources (eg., aspartate, glutamate, taurine, L-carnitine) during periods of myocardial ischemia and reperfusion has been proposed as one strategy to limit myocardial necrosis (Becker, 2004; Pauly & Pepine, 2004).

Used of above methods in association could produce enhanced benefits to prevent mycocardial necrosis. Cold blood cardioplegia enriched with potassium–magnesium aspartate is beneficial on reducing reperfusion injury (Ji et al., 2006). However mortality and morbidity of myocardial ischemia/reperfusion injury include intracellular calcium overload (Park & Lucchesi, 1999). Potassium–magnesium aspartate can be effective in stimulating myocardial metabolism and producing antiarrhythmic effect (Kühn et al., 1991). In addition, magnesium is a natural blocker of the L-type calcium channels and therefore prevents the rise in intracellular calcium during ischemia. Thus, it is likely to reduce myocardial energy demands and preserve intracellular metabolites (Ataka et al., 1993; Yang et al., 2002).

It should be noted that the non pharmacological preventive strategies of POAF are based on a relatively small number of studies and on only single randomized controlled trials.

The following pharmacological agents have been studied according to their ability to protect the heart against POAF.

7.3. Pharmacological agents

7.3.1. β-blockers

The effectiveness of beta blockers for preventing postoperative AF has been shown in several trials, and a recent meta-analysis has confirmed the value of these drugs (Crystal et al., 2002; Zimmer et al., 2003). Although many studies are small with variable methodology, an attempt at a meta-analysis was made on 24 randomized, controlled trials involving a total of 1549 patients (Andrews et al., 1991; Baker & White, 2007a). Sympathovagal imbalance and withdrawal of β-blocker therapy can increase the risk of POAF. Moreover, continuous β-blocker therapy reduces POAF risk especially in patients with a sympathovagal imbalance and should always be practiced (Budeus et al., 2007).

Carvedilol, a nonselective beta- and alpha-1 adrenergic receptor blocker, has been shown to prolong survival in heart failure and postmyocardial-infarction settings (Poole-Wilson et al., 2003; Dargie, 2001). Recent data also indicate that carvedilol has a pharmacologic profile somewhat different from that of other beta blockers and might be more effective for preventing AF in various clinical settings (Katritsis et al., 2003; Merritt et al., 2003), likely arising from a triple protection provided by its antioxidant, anti-inflammatory and β-blocker effects (Acikel et al., 2007). The drug significantly increases myocardial levels of the antioxidant enzymes superoxide dismutase and glutathione peroxidase, whereas the beta-1-selective blocker metoprolol does not (Arumanayagam et al., 2001). Besides its antioxidant properties, carvedilol also has been shown to reduce CRP (Yasunari et al., 2004). The antioxidant and possible anti-inflammatory properties of carvedilol, which are not present in other betablockers, might be important in preventing AF after bypass surgery. In a prospective study oral carvedilol administration was well tolerated when started before and continued after the surgery. In addition, it was reported carvedilol is more effective than oral metoprolol in the prevention of POAF (Haghjoo et al., 2007). However, further prospective studies are needed to clarify this issue. These data suggest that use of β-blockers preoperatively is more effective than postoperatively and that β-blocker therapy reduces the incidence of POAF (Coleman et al., 2004).

7.3.2. Amiodarone

A handful of trials have examined amiodarone as a prophylactic agent against POAF (Hohnloser 1991; Butler et al., 1993; Daoud et al., 1997; Guarnieri et al., 1999; Dunning et al., 2004). These trials differed by dosage, timing of initiation, whether β-blockers were used concomitantly, and duration of therapy. Another study initiated an oral dose 7 days before the operation and found that the rate of POAF decreased by 45% (Daoud et al., 1997). Similar results were found with post-operative administration of intravenous amiodarone in some studies. Although short-term use of amiodarone is very safe and appears to be effective in many studies at preventing AF, several things need to be pointed out. Firstly, only a single trial compared amiodarone with β-blockers (propranolol) (Solomon

et al., 2001). Amidarone was more effective than β-blockers for preventing POAF (incidence of POAF: 16% vs 33%), and there was no difference in the length of hospital stay (8.8 vs 8.4 days). Secondly, potentially serious adverse effects including pulmonary toxicity may become more evident if this strategy is adopted widely. Finally, bradycardia and other adverse effects would likely be more evident with the use of amiodarone in patients on full doses of β-blockers. There is no compelling reason at this time to recommend amiodarone over β-blockers.

At present, optimal treatment strategies for reducing POAF are not well established (Mitchell, 2007). Therefore novel therapeutic approaches, such as omega-3 fatty acid and antioxidant vitamins, have been suggested and experimental and clinical studies supporting their benefits are discussed below.

7.4. Novel strategies for POAF prevention

7.4.1. Statins

Statin drugs, which have both antioxidant and antiinflammatory properties, may attenuate POAF development and constitute a potential preventive approach (Chello et al., 2006). Patients with preoperative statins undergoing cardiac surgery demonstrated a lower incidence of POAF (Marín et al., 2006; Ozaydin et al., 2007; Patti et al., 2006; Mariscalco et al., 2007).

Studies on animal models of ischemia and reperfusion have demonstrated reduction in infarct size with prior statin administration (Merla et al., 2007). Clinical studies have shown preventive effects of statins on the basis of diminished later recurrence of POAF after electrical cardioversion (Tveit et al., 2004; Ozaydin et al., 2006; Humphries et al., 2007). Simvastatin attenuates AF promotion by atrial tachycardia in dogs and could be potentially interesting new pharmacological approach to prevent the consequences of atrial tachycardia remodelling (Shiroshita-Takeshita et al., 2004). In addition, observational evidence suggests that patients with previous statin therapy have a lower incidence of POAF (Patti et al., 2006; Humphries et al., 2007).

7.4.2. Corticosteroids

Perioperative corticosteroid use may reduce the incidence of AF and length of hospital stay in patients undergoing cardiothoracic surgery, thus supporting the role of inflammation in the pathophysiology of POAF and the benefits from agents that attenuate inflammatory response (Baker et al., 2007; Baker & White, 2007a). Intermediate doses of corticosteroids caused the highest reduction in the occurrence AF. Since evidence to support corticosteroids to other proven therapies, such as β-blockers and amiodarone is scarce, as well as potential safety concerns, routine use of corticosteroids to reduce POAF risk is not recommended at this time (Prasongsukarn et al., 2005). Patients at high risk for developing AF after cardiothoracic surgery should be treated with proven therapies (e.g. β-blockers, amiodarone, statins) barring any contraindication. Prednisone prevents the electrophysiological and atrial fibrillation-promoting effects of atrial tachycardia-remodeling, possibly by an anti-inflammatory action, whereas the less potent anti-inflammatory ibuprofen and the calcineurin inhibitor cyclosporine-A are without effect (Shiroshita-Takeshita et al., 2006). However, a prospective, randomized, double-blind, placebo-controlled trial demonstrated that dexametasone despite modulating the release of several inflammatory and acute-phase response mediators associated with adverse outcomes, did not affect the incidence of AF in patients undergoing cardiac surgery with cardiopulmonary bypass (Yared et al., 2007). Large randomized, controlled trials are needed to support corticosteroid therapy.

7.4.3. Polyunsaturated omega-3 fatty acids

Omega-3 polyunsaturated fatty acids (*n-3* PUFA) are essential substances for the proper development and function of human organism. They cannot be synthesized in humans thus acquired from food, mainly from fish. *n-3* PUFA occurs as alpha-linolenic acid in the diet. The main forms are eicosapentaenoic acid (EPA, 20:5 *n-3*) and docosahexaenoic acid (DHA, 22:6 *n-3*) and they are believed to have a protective action against cardiovascular diseases. Although mammals are able to synthesize EPA and DHA from linolenic acid, the lack of effectiveness of the precursor fatty acids in cardiovascular disease has been recently reviewed (Wang et al., 2006a, 2006b). The view that *n-3* fatty acid administration could create a moderate ROS concentration has been previously documented and it is based on the susceptibility of these compounds to lipid peroxidation (Alexander-North et al., 1994; van Ginkel & Sevanian, 1994). Despite it could be assumed that this heightens the level of oxidative stress, thereby diminishing the antioxidative capacity of the heart, it is also possible that the *n-3* PUFA-induced oxidative stress may function to potentiate the defense system and stimulate upregulation of the antioxidant enzymes themselves. The latter has been demonstrated in CM, in a rat model (Jahangiri et al., 2006). In addition, DHA supplementation at 25, 50 and 75 M to C6 glial cells, resulted in enhancement of the cellular antioxidant defense system and decreased levels of lipid peroxidation at the lowest doses (Leonardi et al., 2007). The results of prospective cohort studies indicate that consuming fish or fish oil containing *n-3* PUFA may provide cardiovascular health benefits (von Schacky 2007; von Schacky & Harris 2007; Biscione et al., 2007; Wang et al., 2006a, 2006b; Breslow, 2006). Accordingly, the mechanistic explanations of the reduced risk for sudden cardiac death and cardiac disease induced by *n-3* PUFA have been attributed to their effects on decrease in VLDL and, thereby, in plasma triglyceride levels, improvement in endothelial function, cell membrane stabilization, platelet aggregation inhibition, suppression of smooth muscle cell proliferation and prevention of calcium overload (Alberte & Zipes, 2003; Boriani et al., 2007). An epidemiological study of Frost and Vestergaard (2005) found that consumption of *n-3* fatty acids from fish was not associated with a reduction in risk of AF. However this study was based on estimation from a food-frequency questionnaire and not based on an accurate daily dose. On the other hand, supplementation of daily doses of 2 g *n-3* PUFA, containing ethyl esters in the average ratio of EPA/DHA 1:2 since five days before surgery until 36 h in the immediate postoperative period, has successfully reduced the incidence of AF after coronary bypass grafting (Calò et al., 2005). Acute effects of *n-3* PUFA may be due to the attenuation of the effects of acute atrial tachypacing over the electrophysiological properties of the atrial

myocardium (da Cunha et al., 2007). Supplementation with fish-oil capsules containing *n-3* PUFA or placebo, decreased free radical-catalyzed isoprostane formation (Nälsén et al., 2006). The results of studies on humans and animal models on the effect of *n-3* PUFA on cardiac arrhythmia are discussed below.

7.4.3.1. Recent epidemiologic findings. During the last two years the field of *n-3* PUFA benefits in cardiovascular medicine has gained major importance. The findings of epidemiologic studies have substantiated the consumption of fish rich in EPA and DHA with low incidence of fatal or nonfatal cardiovascular events (von Schacky, 2007). EPA and DHA affect cardiac rhythm at the supraventricular and the ventricular levels. EPA and DHA (1 g/day) intake was found to be associated with a reduction in heart rate by 2.3 beats/min (Mozaffarian et al., 2006). The omega-3 index has been proposed as a biomarker that reflects the status of EPA and DHA in an individual and to monitor compliance throughout studies. It is defined as the percentage of EPA and DHA in red-cell fatty acids (Harris & Von Schacky, 2004). At present, work is in progress to prospectively validate the omega-3 index as a risk factor for sudden cardiac death. The cardiovascular health study found that consumption of tuna or other broiled or baked fish (1–4 times/week) is associated with a 28% lower risk of AF compared with intake of less than once per month (Mozaffarian et al., 2004). The observational studies show a strong relationship of *n-3* PUFA with fatal heart disease and sudden cardiac death, but not with nonfatal myocardial infarction, this is consistent with possible antiarrhythmic effects of these fatty acids (Mozaffarian et al., 2003). However, it was pointed out that the antiarrhythmic effect of fish oil remains unproven although the idea is still viable and is being actively tested in further trials (Brouwer et al., 2006).

7.4.3.2. Mechanistic studies. Epidemiologic studies have provided an association between *n-3* PUFA and protection against cardiovascular disease, but large-scale long-term randomized clinical trials, are relatively few. These findings have been recently presented in excellent reviews (Breslow, 2006; von Schacky, 2007; Boriani et al., 2007; Biscione et al., 2007). Proposed mechanisms to explain beneficial effects of *n-3* PUFA include the prevention of arrhythmias (Leaf et al., 2003), diminution of triacylglicerols (Harris et al., 1997; Sacks & Katan, 2002), blood pressure (Geleijnse et al., 2002), and platelet aggregation (Knapp, 1997; Hornstra, 2001), improvement of endothelial function (Harris et al., 1997; Goodfellow et al., 2000; von Schacky, 2003; Harris, 2005; Morgan et al., 2006), diminution of inflammation (Calder, 2001) and stabilization of atherosclerotic plaques in the coronary circulation (Thies et al., 2003). After ingestion of EPA and DHA there is evidence of a reduced heart rate, a faster return to resting heart rate after exercise, and increased heart rate variability (Christensen, 2003; Mozaffarian et al., 2004; O'Keefe et al., 2006). These results demonstrate the antiarrhythmic effect of these compounds in humans. Recently, it was shown that the induction of glutathione synthesis by human fibroblasts is triggered by docosahexaenoic methyl ester (Arab et al., 2006). The antioxidant response enhanced by human fibroblasts triggered with DHA-met, was associated with increased production of ROS (Rossary et al., 2007). Although many studies have been addressed to the understanding of the molecular mechanisms underlying the effects of PUFA on gene expression in the liver (Nakamura et al., 2004), little is known in the heart, and the effects of EPA and DHA on the whole genome have not been investigated in CM (Hulbert et al., 2005). Recent studies suggest that the beneficial effects of fish oil are due, in part, to the generation of various free radical-generated non-enzymatic bioactive oxidation products from *n-3* PUFAs, although the specific molecular species responsible for these effects have not been identified. It is of interest to note that the beneficial effects of EPA and DHA could arise from both direct short-term or long-term effects mediated by changes in some intracellular pathways, is discussed below.

7.4.3.3. Direct effects. Direct actions of *n-3* PUFA alter the excitability of the cardiac sarcolemmal membrane, thus preventing asynchronous contractile activity in the isolated cell model and myocardial arrhythmias in vivo by exerting effects on cell excitability to prevent the generation of aberrant action potentials and re-entrant circuits (Leifert et al., 1999a; Leifert et al., 1999b). Direct actions have been confirmed by experimental studies in a reliable dog model of sudden cardiac death, showing that these compounds electrically stabilize heart cell membranes through the modulation of the fast voltage-dependent Na^+ currents and the L-type Ca^{2+} channels. As a consequence, heart cells become resistant to arrhythmias (Leaf et al., 2005; Jahangiri et al., 2000). Moreover, it has been pointed out that *n-3* PUFA can exert a reversible effect to modulate the electrophysiological kinetics of several ion channels, by binding to specific sites on channel proteins and by non-specifically incorporating into lipid cell membranes (Xiao et al., 2005). Fish oil supplementation is associated with a reduction in the susceptibility of CM to ROS-induced injury and this may be related to membrane incorporation of *n-3* PUFA, increased antioxidant defenses, changes in CM membrane fluidity, and the ability to prevent increase in cellular Ca^{2+} in response to ROS (Leifert et al., 2000; McMurchie et al., 1999; Jahangiri et al., 2006). The identity of the molecular mechanism(s) responsible for *n-3* fatty acid mitigation in these adverse effects has represented an important and intriguing question. Oxidative stress is a common factor in the etiology of diseases impacted by *n-3* PUFA. Interestingly, these *n-3* fatty acids are very susceptible to free radical oxidation, exceeding that of arachidonic acid (Fam et al., 2002). Studies have shown that EPA and DHA supplementation reduced urinary F_2-isoprotane levels, a biomarker for oxidative stress, as well as enhanced cellular antioxidant defense systems (Iraz et al., 2005). These compounds have been shown to prevent acute atrial electrophysiological remodelling during high rate activity, thus minimizing the self-perpetuation of AF in adult dogs (da Cunha et al., 2007). Although the latter study could not be extrapolated to the clinical settings of AF, it is in agreement with a significant reduction of the incidence of POAF in patients undergoing coronary artery bypass graft surgery (Calò et al., 2005). These patients received a daily therapy with EPA/DHA (1:2) in the

immediate postoperative period (24 to 36 h) until hospital discharge.

7.4.3.4. Mediated effects. Long-term studies have demonstrated that dietary feeding of fish oil to rats results in increased *n-3*/*n-6* PUFA ratio in the sarcoplasmic reticulum, associated with a reduction of Ca^{2+}`-ATPase activity (Taffet et al., 1993; O'Neill et al., 2002). Consequently, it is likely that the severity of ventricular arrhythmias may be reduced by inhibiting the accumulation of intracellular Ca^{2+} following ischemia by modulating other mechanisms responsible for Ca^{2+} extrusion such as the Na^{+}/Ca^{2+} exchanger. The contractile activity of myocardium is controlled by intracellular Ca^{2+} that is increased by the release of the second messenger inositol 1,4,5-trisphosphate (IP_3) from the sarcolemma.

Dietary fish oil supplementation, which increases composition of *n-3* fatty acids in myocardial membrane phospholipids, exerts an antiarrhythmic effect by preventing the reperfusion-induced rise in IP3 and significantly suppresses reperfusion arrhythmias (Anderson et al., 1996; Leifert et al., 1999a). Cardiomyocytes isolated from fish oil-fed pigs had higher levels of *n-3* PUFA and lower levels of IP3 released after stimulation with epinephrine and phenylephrine (Nair et al., 2000). Fish oil diet increases *n-3* PUFA content in the ventricular sarcolemma, decreases L-type Ca^{2+} current and Na^{+}–Ca^{2+} exchange current, and increases inward and slow delayed rectifier K^{+} currents, resulting in action potential shortening. Incorporation of *n-3* PUFA in the sarcolemma may have consequences for arrhythmias independent of circulating *n-3* PUFA (Verkerk et al., 2006). Therefore, it could be expected that EPA and DHA supplementation may prevent IP_3-induced Ca^{2+} oscillations and the development of subsequent arrhythmias following an ischemic challenge caused by cardiac surgery with extracorporeal circulation. It is of interest to note that experimental data have reported that DHA inhibits L-type calcium channel while preserving contraction in the same cardiomyocytes (Ferrier et al., 2002), giving rise to differential actions on Ca^{2+}-induced Ca^{2+} release and the voltage-sensitive release mechanism. These actions of *n-3* PUFA may explain their protective effects to preserve the myocardial function.

In cardiac cells the effects of *n-3* PUFA on the whole genome are still unknown despite their recognized cardioprotective effects and ability to modulate gene expression. A study of *n-3* PUFA supplementation on the global gene expression profile in cultured neonatal rat CM showed that many of the down regulated genes appeared related to inflammation, cell growth, extracellular and cardiac matrix remodelling, calcium movements and ROS generation. From these data, it was speculated that the cardioprotective effect of *n-3* PUFA is related to a modulation of genes in cardiac cells (Bordoni et al., 2007). The beneficial effects of *n-3* PUFA are due, in part, to the generation of various free radical-generated non-enzymatic bioactive oxidation products although the specific molecular species responsible for these effects have not been identified. Nevertheless, it is likely, that the mechanism of antioxidant enzyme activation occurs through activation of the pathway for antioxidant response element (ARE) driven phase II detoxification gene induction. The transcription factor Nrf2 binds to ARE sites in the promoter regions of many detoxification and antioxidant genes, leading to the coordinate up-regulation of downstream targets that boost cellular detoxification processes and antioxidant potential (Itoh et al., 1999; Lee et al., 2005). Nrf2 is sequestered in the cytoplasm by Keap1, and ARE activation signals (i.e., protein kinase pathways and electrophiles) disrupt the Nrf2-Keap1 complex leading to nuclear translocation of Nrf2. It should be noted that DHA and EPA are more susceptible to auto-oxidation than arachidonic acid, because they possess more double bonds. Oxidized *n-3* PUFA could react directly with the negative regulator of Nrf2, Keap1, initiating Keap1 dissociation with Cullin3, thereby inducing Nrf2-directed gene expression (Gao et al., 2007). Use of liquid chromatography-tandem mass spectrometry analyses of oxidized EPA demonstrated the presence of novel cyclopentenone-containing molecules termed J3-isoprostanes in vitro and in vivo to induce Nrf2-directed gene expression. Furthermore, these studies show that J3-IsoPs stabilize Nrf2 levels and induces Nrf2-directed gene expression. Whereas, arachidonic acid-derived 15-deoxy-12, 14-prostaglandin J2 was hypothesized to activate Nrf2-directed gene expression via dissociation of Nrf2 from adducted Keap1 (Levonen et al., 2004), thereby supporting an alternative mechanism: dissociation of Cullin3 from oxidized Keap1. These experiments provide a molecular basis for the hypothesis that formation of J-ring compounds generated from the oxidation of EPA and DHA in vivo can reach concentrations high enough to induce Nrf2-based cellular defense systems. ROS level was related to DHA dose and supplementation time. At the lowest dose no significant increase in ROS values was observed. Low doses of DHA strengthened the cellular antioxidant defense system as highlighted by a raise in both glutathione peroxidase and catalase activity, and the decreased levels of lipid peroxidation. Therefore, the final effect of DHA on cellular redox status is dependent on dose and time supplementation. (Leonardi et al., 2007).

7.4.4. Ascorbic acid and α tocopherol

Vitamin C (ascorbic acid) and Vitamin E (generic name for biologically active lipid soluble compounds, the tocopherols and tocotrienols, of which in humans α-tocopherol is the most abundant in plasma) are key antioxidants which in humans are obtained exclusively from the diet (Levine et al., 1999; Wang & Quinn, 2000; Benzie, 2003). Vitamin C and vitamin E protect water-soluble or lipid-soluble components of the body from oxidation, respectively. Biological membranes are particularly sensitive to oxidative stress damage due the abundance of PUFA which, account for increased lipid peroxidation. This process may result from either increased ROS and/or α-tocopheroxyl. Ascorbic acid may reduce α-tocopheroxyl radical, thereby abrogating lipid peroxidation (Heller et al., 2004; Heller et al., 2006) and further supporting the synergism between vitamins C and E. Combined administration of antioxidant vitamins C and E protects the myocardium from oxidative stress injury following ischemia/reperfusion cycles in isolated CM (Rinne et al., 2000; Qin et al., 2003) and against AF in animal models (Poliukhovich et al., 1991; Carr et al., 2000; Shite et al., 2001; Qin et al., 2006).

7.4.4.1. Recent epidemiologic findings. It was found that vitamin C reduced the incidence of POAF in patients subjected

to coronary artery bypass (2 g of vitamin C, given orally, one day before surgery followed by 500 mg twice daily until the fifth postoperative day) (Carnes et al., 2001). Also, these authors demonstrated that ascorbate reverses atrial electrical remodeling and effectively reduces the accumulation of peroxynitrite by preserving intracellular ascorbate levels in a tachy-pacing dog model. Nevertheless, other study also performed in a dog model could not observe the effectiveness of vitamin C, alone or in combination with vitamin E, in preventing effective refractory period or AF-promoting effects of 7-day atrial tachycardia (Shiroshita-Takeshita et al., 2004). This discrepancy may be attributed to the marked differences in body weight, race and timing of the protocols used in both experimental models. Unfortunately, there are no further studies in humans about the use of ascorbate in the prevention of POAF. It should be noted that the first of these studies (Carnes et al., 2001) was a small uncontrolled not randomised trial. Instead, the authors just gave ascorbate supplements perioperatively to 43 patients and matched them with retrospective controls. Although this study reported a diminution of the incidence of POAF it is necessary for these results to be confirmed by a larger randomized placebo controlled trial.

7.4.4.2. Mechanistic studies. The association of vitamins C and E used in diminishing the incidence of POAF would be recommended because both vitamins may act synergistically in abrogating lipid peroxidation and providing optimal conditions for endothelial $NO^{\cdot}$ formation and bioavailability under oxidative stress (Heller et al., 2004). Both vitamin C and E not only behave as ROS-scavengers, but also are able to induce down-regulation of NADPH oxidase and up-regulation of eNOS (Attia et al., 2001; Ulker et al., 2003), thereby further supporting their antiarrhythmic effects.

In addition, the effect of vitamin C on the early recurrence rates and inflammatory indices after successful cardioversion of persistent AF was recently investigated (Korantzopoulos et al., 2005). Forty-four carefully selected patients with successfully restored sinus rhythms by electrical cardioversion received standard treatment and were randomized to either oral vitamin C administration or no additional therapy. Patients were closely followed-up for 7 days performing successive measurements of simple inflammatory indices. AF recurred in 4.5% of patients in the vitamin C group compared to 36.3% in the control group. While inflammatory indices decreased after cardioversion in patients receiving vitamin C, but not in the control group. In addition, in the vitamin C group, CRP levels were significantly lower on the seventh day. These findings suggest that vitamin C reduces the early recurrence rates after cardioversion of persistent AF and attenuates the associated low-level inflammation (Boos et al., 2006; Rodrigo et al., 2007b). It should be noted that a deficiency of appropriate reductants, which recycle vitamin E radicals back to its antioxidative active form, causes an irreversible degradation of vitamin E leading to tocopheryl quinone derivatives that may induce pro-oxidative and antioxidative effects depending on the distribution in the heart tissue and the interacting redox system (Gille et al., 2001).

The beneficial effect of the iron chelator deferoxamine on iron-associated mortality is well documented in heart affection. It was reported that ascorbic acid improves the biochemical and histopathological changes in comparison to those rats administered deferoxamine individually (Emara et al., 2006) likely due to the attenuation of Fenton reaction.

In turn, high dosages of vitamin E may displace other fat-soluble antioxidants (Huang & Appel, 2003), disrupting the natural balance of antioxidant systems and increasing vulnerability to oxidative

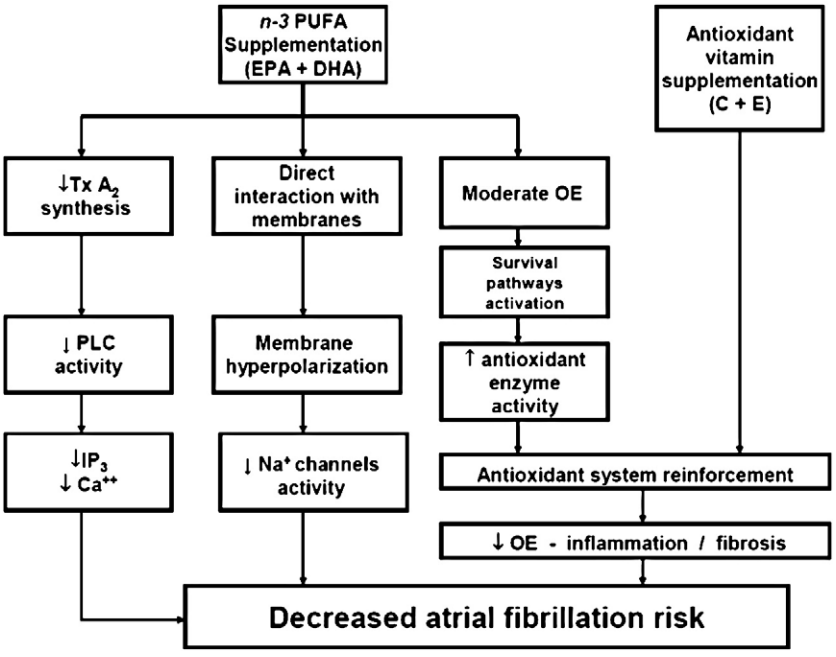

Fig. 2. Mechanism for the protective effect of *n-3* PUFA and antioxidant vitamin administration against postoperative atrial fibrillation in patients scheduled for cardiac surgery with cardiopulmonary bypass. EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; PLC, Phospholipase C; Tx A_2, Thromboxane A_2; IP_3, Inositol trisphosphate; Ca^{++}, cytosolic calcium; OE, oxidative stress; Na^{+}, sodium channels.

damage. Vitamin E may also inhibit human cytosolic glutathione S-transferases, which help detoxify drugs and endogenous toxins (van Haaften et al., 2003).

A schema depicting the hypothesis of a mechanism of non hypoxic preconditioning responsible for the protective effect of *n-3* PUFA and antioxidant vitamin administration against POAF in patients scheduled for cardiac surgery with cardiopulmonary bypass is shown in Fig. 2.

8. Proposed hypothesis for the prevention of POAF by non hypoxic preconditioning

At present, the available data could provide the basis to postulate that oxidative stress is an important event in myocardial dysfunction. In fact, oxidative stress contributes in the pathophysiology of postoperative AF by mediating processes such as inflammation (via NF-κB activation), cell death (through apoptotic and necrotic pathways) or even survival response (through anti-apoptotic pathways), according to the time-course activation and concentration of ROS. It should be emphasized that oxidative stress is commonly present in all cardiac surgeries with extracorporeal circulation and the atrial tissue is expected to be subjected to an oxidative challenge which participates in the mechanism of AF. Therefore, it is reasonable to assume that reinforcement of the antioxidant defense system in cardiac muscle should result in a protective effect on myocardium against oxidative damage. On the basis of this paradigm, it could be hypothesized that benefits of an intervention based on antioxidant enzyme induction plus antioxidant vitamin administration is based on two main effects. First, moderate ROS production could be induced by pre-treatment of the cardiovascular patients with *n-3* PUFA (daily doses of 2 g containing EPA and DHA as ethyl esters in the average ratio of EPA/DHA 1:2) from 7 days prior to surgery until hospital discharge, to enhance the enzymatic antioxidant defenses and/or anti-apoptotic pathways. Second, the administration of antioxidant vitamins (500 mg/12 h of ascorbic acid+400 IU α-tocopherol) from 2 days prior to surgery until hospital discharge, would further reinforce the antioxidant defense system. Consequently, the deleterious effects of the unavoidable myocardial ischemia occurring during coronary artery bypass graft surgery and other surgical procedures performed with cardiopulmonary bypass could be attenuated (Rodrigo et al., 2007b).

9. Concluding remarks and future perspectives

Atrial fibrillation is the most common complication associated with cardiac surgery with cardiopulmonary bypass. This setting is accompanied of ischemia/reperfusion cycle, a clinically relevant problem occurs as damage to the myocardium following blood restoration after a critical period of ischemia. The unavoidable generation of reactive oxygen species (ROS) during surgery presents an oxidative challenge to myocardial tissue that can activate cellular signaling pathways leading to a wide range of effects. While high levels of ROS can promote deleterious processes such as inflammation, cell death (apoptosis/necrosis), or fibrosis, moderate ROS concentration triggers cell survival pathways (preconditioning), and thus abrogating further oxidative bouts of ischemia. The latter condition may be reached by *n-3* PUFA supplementation. Clinical observations and results from animal studies suggest a cardioprotection of *n-3* PUFA through their antiarrhythmic effects exerted either directly or by modulating intracellular survival pathways. In turn, antioxidant vitamin supplementation could play a major role to reinforce the myocardial antioxidant defense system by abrogating the contribution of ROS in ischemia/reperfusion tissue damage that could contribute in the mechanism of atrial fibrillation. At present, the pharmacological resources available for the prevention of postoperative atrial fibrillation offer only suboptimal benefits; therefore, alternative novel potential therapies to diminish AF should be attempted. Accordingly, polyunsaturated omega-3 fatty acids and antioxidant vitamins deserve special consideration, based on the clinical and experimental studies supporting their cardioprotection and a lack of secondary effects. The present review analyzes the molecular basis supporting a novel therapeutic approach to prevent postoperative atrial fibrillation on the basis of direct or mediated antiarrhythmic effects of EPA and DHA and the reinforcement of the myocardial antioxidant system by antioxidant vitamin supplementation.

The role of antioxidants in counteracting the effects of oxidative stress could be limited because it is difficult to scavenge the ROS once their formation has been triggered. The schema here proposed to diminish the risk of POAF is based on a reinforcement of the antioxidant system prior to the occurrence of ischemia/reperfusion in the myocardial tissue. Therefore it should be expected a diminished vulnerability to ROS attack, in part due to the induction of antioxidant enzymes caused by *n-3* fatty acid exposure and to the enhancement of the non enzymatic antioxidant capacity due to the administration of antioxidant vitamins.

Interestingly, the pathophysiological principles and molecular basis discussed here could also find future relevant clinical applications, such as the optimization of survival conditions of allografts. Since the protective effect of both *n-3* PUFA and antioxidant vitamins is known to be exerted systemically, it could be used for preconditioning of any organ, such as kidney or liver, including those to be removed from a donor. Recently, it was pointed out the convenience to address the potential therapeutic application of preconditioning in the prevention of ischemia/reperfusion damage specially aimed at clinical transplantation. To our knowledge, these interventions have not been attempted in living donors prior to transplantation. Future research should aim to find the experimental and clinical support for this proposal.

Acknowledgment

This work is supported by the Fondo Nacional de Investigación Científica y Tecnológica (FONDECYT), grant no. 1070948.

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