International Journal of Cardiology 138 (2010) 221–228

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Use of vitamins C and E as a prophylactic therapy to prevent postoperative atrial fibrillation

Ramón Rodrigo [a,*], José Vinay [a], Rodrigo Castillo [a], Mauricio Cereceda [b], René Asenjo [b], Jaime Zamorano [b], Julia Araya [c], Rodrigo Castillo-Koch [b], Juan Espinoza [b], Ernesto Larraín [b]

[a] Molecular and Clinical Pharmacology Program, Institute of Biomedical Sciences, Faculty of Medicine, University of Chile, Santiago, Chile
[b] Cardiovascular Center, University of Chile Clinical Hospital, Santiago, Chile
[c] Department of Nutrition, Faculty of Medicine, University of Chile, Santiago, Chile

ARTICLE INFO

Article history:
Received 14 August 2008
Received in revised form 7 April 2009
Accepted 23 April 2009
Available online 15 May 2009

Keywords:
Postoperative atrial fibrillation
Ischemia/reperfusion
Oxidative stress
Vitamin C
Vitamin E

ABSTRACT

Oxidative stress has been strongly involved in the underlying mechanism of atrial fibrillation, particularly in the arrhythmia occurring in patients undergoing cardiac surgery with extracorporeal circulation (postoperative atrial fibrillation). The ischemia/reperfusion injury thus occurring in the myocardial tissue contributes to the development of tissue remodeling, thought to be responsible for the functional heart impairment. Consequently, structural changes due to the cardiac tissue biomolecules attack by reactive oxygen and/or nitrogen species could account for functional changes in ion channels, transporters, membrane conductance, cytosolic transduction signals, and other events, all associated with the occurrence of arrhythmic consequences. The lack of success and significant side effects of anti-arrhythmic drugs have given rise to attempts aimed to develop alternative novel pharmacologic treatments. On this line, the biological properties of the antioxidant vitamins C and E suggest that they could decrease the vulnerability of the heart to the oxidative damage. Nevertheless, very few studies to assess their anti-arrhythmic effects have been reported in humans. The clinical and experimental evidence supporting the view that the pharmacological use of antioxidant vitamins could contribute to prevent postoperative atrial fibrillation is presented.

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia occurring in the general population [1,2], as well as in patients undergoing cardiac surgery (postoperative atrial fibrillation, POAF). Epidemiologic studies suggest that the number of patients with AF will triple in the next 30 years, and therefore, its impact on medical and economic issues will further increase [3]. Although considerable effort has been devoted to study the genesis, pathophysiology, risk factors and complications of this arrhythmia for many years [4,5], there is no relative risk-free treatment available to successfully prevent and control its occurrence. Despite improvement in anesthesia, surgical techniques, and medical therapy [6], POAF occurs in 20–40% of patients, even when proven and recommended preventive drug therapies such as beta-blockers and amiodarone are used [7,8]. The lack of success and significant side effects of anti-arrhythmic drugs have given rise to efforts to develop novel alternative pharmacologic treatments aimed to prevent or interfere, at a molecular level, the alterations involved in atrial remodeling [9]. Several studies have suggested a pathophysiological link between POAF and oxidative stress, being the latter substantially present in the unavoidable ischemia/reperfusion cycle of this setting [1,10–12], thus giving rise to the involvement of reactive oxygen species (ROS) as pathogenic factors of the functional and structural myocardial impairment. This new paradigm has been used as a starting point by a number of authors trying to assess the molecular pathways underlying POAF. Since ROS may be involved in the genesis and perpetuation of POAF, the use of antioxidants, such as vitamins C and E, appears to be a coherent therapeutic and prophylactic strategy, as further supported by the results of some clinical studies.

Available data are consistent with the view that vitamins C and E, through their biological properties, could decrease the vulnerability of the heart to the oxidative damage caused by the exposure to the ischemia/reperfusion injury known to occur in patients undergoing cardiac surgery with extracorporeal circulation. Therefore, it has recently been hypothesized that this antioxidant effect should be reflected in a diminution of the incidence of atrial arrhythmias [13,14]. The aim of the present review was to provide a rational basis supporting the potential benefit of the use of vitamins C and E as therapeutic tools against the occurrence of POAF.

2. Pathophysiology of POAF

Atrial fibrillation results in high-rate asynchronous atrial electrical activation with loss of atrial contractility. The resulting tachycardia-

* Corresponding author. Molecular and Clinical Pharmacology Program, Institute of Biomedical Sciences, Faculty of Medicine, University of Chile, Independencia 1027, Casilla 70058, Santiago 7, Chile. Tel.: +56 2 9786126; fax: +56 2 7372783.
E-mail address: rrodrigo@med.uchile.cl (R. Rodrigo).

0167-5273/$ – see front matter
doi:10.1016/j.ijcard.2009.04.043

mediated cardiopathy can precipitate ventricular dysfunction and heart failure. Nevertheless, the underlying etiology of AF is likely different in quite different patient subpopulations. In the postoperative state, a number of mechanisms play a pivotal role in its genesis and perpetuation; among them, the increase of adrenergic tone [15], the activation of the renin–angiotensin system (RAS) [16,17], inflammation, fibrosis and the pre-operative injuries associated with cardiac diseases (ventricular hypertrophy, atrial dilatation, hypertension and necrotic zones secondary to atherosclerotic injuries) are the most significant elements underlying atrial remodeling. Specific mechanisms involved in long-term structural remodeling include activation of calcium dependent proteases [18,19], phosphatases or kinases and/or inflammatory mechanisms [20].

The appearance of ectopic rapidly discharging foci, usually near the pulmonary veins, generates extrasystoles that lead to AF in the presence of the mentioned risk factors [21,22]. The perpetuation is helped by multiple re-entrant wavelets that appear in the injured atria, secondary to the existence of heterogeneous electrophysiological properties, such as atrial zones with differential conduction velocities [23,24].

The remodeling has two faces, for one hand the atria suffers an electric remodeling based on electrophysiological changes, like shortening of the refractory period, calcium overloading of cardiomyocytes, leading to the diminution of the L-type calcium current, and activation of cardiomyocytes automatism properties; thereby contributing to the continuation of the re-entry process [1,25,26]. On the other hand, the atria suffers a structural remodeling, represented by atrial dilation and fibrosis (extracellular matrix remodeling secondary to the intracellular effects of angiotesin II, transforming growth factor beta 1 and tumor necrosis factor alpha 1) leading to changes in the conduction properties of the heart, and therefore in the configuration of new re-entry foci [27–29].

3. Oxidative stress in the pathogenesis of POAF

3.1. ROS, free radicals and the antioxidant system

In the last years, oxidative stress (OE) has been found to play a crucial role in the pathophysiology of cardiovascular diseases such as essential hypertension and rhythm related disorders. Postoperative atrial fibrillation, being the most common postoperative arrhythmia, has been specially studied [10–12,30,31]. There is evidence for oxidative injury in atrial tissues from AF patients [32]. In fact, a clinical model involving oxidative stress may accompany some kind of surgeries when ischemia/reperfusion cycles occur. Thus, it has been reported that patients undergoing coronary artery bypass graft surgery have increased plasma lipid peroxidation and decreased cardiac glutathione levels following release of the cross clamp, changes that persist for at least 24 h following cardiac surgery [33]. In addition, there is direct evidence of increased free radical production in canine hearts subjected to rapid ventricular pacing [34], and evidence that antioxidants can improve cardiac function in animals with pacing-induced failure [35].

Oxidative stress arises from an imbalance between pro-oxidants and antioxidants in favor of the pro-oxidants [36]. Among the pro-oxidant agents there are highly reactive molecules such as free radicals (molecules having an unpaired electron), which are formed physiologically in low concentrations. However when they are heavily produced the balance is broken, and we are in the presence of OE. Among pro-oxidant molecules, oxygen and nitrogen reactive species can be found. In addition to free radicals, other molecules can be found that, though they do not have an unpaired electron, they are highly reactive. Hence, the terms reactive oxygen species and reactive nitrogen species have been applied to all the molecules of oxygen and nitrogen that can shift the balance in favor of the oxidative state. Among these reactive species, the most studied are superoxide, hydrogen peroxide, hydroxyl radical and peroxynitrite [37].

The main source of superoxide of the cardiovascular system is the enzyme reduced nicotine adenine dinucleotide phosphate (NAD(P)H) oxidase that has been found in leucocytes, endothelial cells, vascular smooth muscle cells and cardiomyocytes [38–40]. Other important superoxide source (especially in presence of OE) is the uncoupled nitric oxide synthase (NOS). This enzyme physiologically produces the molecule nitric oxide (NO) that plays a critical role in maintaining the tone of smooth muscle cells in the cardiovascular system, but in the presence of high concentrations of peroxynitrite (such as in OE), NO reacts with the NOS co-factor tetrahydrobiopterin (BH4) [41,42], generating a conformation change that induces a shift from the production of NO to the production of superoxide. Hence the OE grows through a positive feedback mechanism [31,38,43].

The antioxidant system, which gathers enzymatic and non-enzymatic components, offsets ROS. Among the first, we found the enzymes superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and catalase. The non-enzymatic antioxidants are molecules that can neutralize the action of ROS through direct and indirect mechanisms; within this group we find vitamins C and E [44–46]. While, antioxidant enzymes can be regulated through transcriptional and post-transcriptional effects, non-enzymatic antioxidants have to be incorporated through the diet. Some studies have demonstrated that these two sub-systems are not independent, but on the contrary, several bridges between them are activated in the presence of ROS [47].

3.2. Oxidative stress in the genesis and perpetuation of POAF

Following cardiac surgery, and particularly after the use of extracorporeal circulation, ischemic phenomena are mandatory. This leads to the production of high concentration of ROS that play an important role in a number of injuries affecting not only the heart but also other organs [11,33]. Specifically at the heart, ROS are involved in various molecular cascades of pathological processes that can produce and maintain POAF. Many studies have shown increased levels on serum myocardial oxidation markers (peroxide, derivatives of reactive oxidative metabolites) in AF patients in relation to non-AF patients [10,32,48]. The main source of superoxide in the atria is NAD(P)H oxidase, found at higher levels in POAF developing patients than in those who do not develop this arrhythmia [39]. At the same time, it was shown that cardiac myocytes of POAF patients had increased levels and expression of the NAD(P)H subunit Nox2 and in Nox-derived superoxide generation. Consequently, it could be hypothesized that ROS production is a complex process involving mechanisms of pre- and post-transcriptional regulation. Together with NAD(P)H oxidase, it has been found that other pro-oxidative enzymes are up-regulated in POAF, this is the case of xanthine oxidase and uncoupled NOS [38].

3.2.1. Transcriptional effects and mitochondrial DNA damage

Mitochondrial DNA (mtDNA) oxidative damage, has been measured through quantitative PCR technique, showing that mtDNA of AF patients has more deletions than the mtDNA of patients in sinus rhythm, based on the high concentration of 8-hydroxy-2-deoxyguanosine, the most frequent product of oxidative DNA damage found in those patients [2]. These findings demonstrate that ROS produce damage in intracellular structures, particularly in organelles involved in energy processes, which may lead to a higher rate of ROS formation. Consequently, a positive feedback is activated, thus enhancing ROS production. Many trials have reported effects of ROS in redox-sensitive gene expression. The occurrence of OE in AF patients results in changes accounting for a shift from antioxidant proteins to pro-oxidant ones [49]. Trials studying patients undergoing coronary artery bypass grafting or valve procedure described significant differences in genomic response between the patients that presented POAF and the ones that maintained in sinus rhythm; the first also showing the

highest OE related parameters [48]. Microarray studies have demonstrated the existence of genes specifically associated with both AF and sinus rhythm, among the first, the authors described molecules related to antioxidant power, inflammation and ion channels [50]. In total, there are over 100 genes modulated between AF and sinus rhythm specific genes, and it is plausible to believe that ROS are involved in the modulation cascade of the AF intracellular transcriptional events. Nevertheless, more studies aimed to analyze the function of these genes are still lacking.

3.2.2. Oxidative stress and inflammation nexus

Inflammation is another heavily studied pathophysiological process implicated in the POAF [1,17,51]. Thus, it was shown that white cell count [52], as well as the levels of C-reactive protein on postoperative day 2 [53], is more elevated in the postoperative period in patients that experience POAF than in those who do not. The role of cytokines, chemokines, leukocytes and acute-phase proteins, like high-sensitivity C-reactive protein (hsCRP) in the pathogenesis of POAF has been described in several studies [20,54]. Indeed the role of inflammation response in the intra and extracellular mechanisms implicated in this disorder cannot be separated from that of OE. The biochemical nexus between these two processes represents an essential piece in the puzzle. It is of interest to mention that the transcriptional factor nuclear factor-kappa B (NF-κB) was found to play a pivotal role in this connection [55].

It has been found that this transcriptional factor responds to changes of the cellular oxidative status [56]. When NF-κB is activated, by phosphorylation of an inhibitory co-factor, it bonds to a DNA response element and promotes the transcription of genes coding to inflammation mediators such as hsCRP, interleukin-6 and fibrinogen, among others [57]. NF-κB activation has been associated with cardiac dysfunction, ventricular hypertrophy and maladaptive cardiac growth [27]. Increased levels of several inflammation markers were found in serum and atria biopsies of AF and POAF patients [1,10,17,20]. Therefore it is reasonable to assume that OE and inflammation response act in a synergic way in the underlying mechanisms of POAF, giving the foundation for studies involving anti-inflammatory AF therapy [58,59].

3.2.3. Electric remodeling and mechanical impairment

One of the most important mechanisms behind POAF is the ROS-mediated electrical remodeling. Fibrillating atria is characterized by a diminished action potential and effective refractory period, due to changes in several currents that normally maintain the cardiomyocyte electric potential [25]. Among those, the majority of studies have been the L-type voltage-gated Ca2+ current that is diminished in cells extracted from fibrillating atria. This diminution could be a consequence of cardiomyocytes calcium overloading [1,25]. The real nexus between ROS and calcium overloading has been difficult to find [60]. Calcium influx into the cytosolic space is mediated largely by the ryanodine receptor Ca2+ channel (RyRC), which moves calcium between the sarcoplasmic reticulum into the cytosol. Experiments using canine sarcoplasmic reticulum vesicles demonstrated the existence of a superoxide activated calcium release from RyRC [61]. These authors hypothesized that ischemia–reperfusion ROS could activate the RyRC and produce calcium overloading, which reduces the L-type current thus leading to electrical changes involved in the initiation and perpetuation of POAF. Cardiac electric remodeling is a complex phenomenon which involves multiple pathological processes, such as the effect of ROS in the disruption of cardiomyocytes connexins. Connexins are a set of proteins assembled between two adjacent cardiac cells, forming the structure known as gap junction. This structure participates in the efficient and rapid conduction of the electric potential through the cardiac tissue. Reduced levels of connexin 43 in mice cardiac tissue leads to a reduction in cardiomyocytes conduction velocity [62]. Disruption of connexin 43 has also been correlated with increased propensity for tachyarrhythmias [63]. In addition, it has been argued that connexin 43 densities could not be significantly altered, but rather dispersed away from the intercalated discs to account for these alterations [64]. Under conditions of OE, following an ischemia/reperfusion cycle, increased ROS directly interact with the connexins, particularly with connexin 43, thereby disrupting its organization, leading to electrical remodeling and therefore to propensity to present AF [65,66]. The exact molecular mechanism whereby ROS disrupt normal connexin morphology has not been completely identified; however the ROS-mediated activation of protein kinase C gamma, unique isoform present only in neural and optic tissue, leads to the phosphorylation and posterior disassembly of connexin 43 [67].

Mechanical impairment is also present in fibrillating atria; it was hypothesized that oxidative damage could act on myofibrillar creatine kinase (MM-CK), molecule playing an important role in cardiomyocyte contractility, and consequently impairing atrial contractility. This functional impairment was associated with an increased MM-CK protein oxidation and reduction of its activity in AF patients undergoing Maze procedure in relation to non-AF patients undergoing cardiac surgery. Consequently, contractile dysfunction and energetic impairment may also be involved in the pathophysiology of POAF [32]. A schematic representation of the events associated with POAF genesis and perpetuation is presented in Fig. 1.

4. Prevention of POAF by antioxidant vitamin supplementation

Based on the growing evidence supporting the hypothesis that oxidative stress is a cornerstone in the underlying POAF mechanism, it could be noted that the use of antioxidants as therapeutic tools appears to be a rational line of study. Substances with antioxidant properties such as statins and N-acetylcysteine have probed to be efficient not only in decreasing the serum oxidative levels in patients undergoing cardiac surgery, but also in diminishing the occurrence of POAF [68–70]. Furthermore it has been hypothesized that one of the mechanisms by which classic anti-AF drugs act is related with the ability to ROS scavenging and protection against membrane lipid peroxidation [71]. However, Vitamin C (ascorbate) and Vitamin E (α-tocopherol) deserve special mention among other antioxidants, gathering several biochemical and empiric evidence that makes them excellent candidates to be used in the treatment and/or prevention of POAF [72,73].

Despite the history of vitamins C and E studied in randomized clinical trials in humans has been so recurrently disappointing when having endpoints such as prevention of atherosclerosis or hypertension [74], the available data so far account for a beneficial effect in POAF at least for vitamin C supplementation and no negative results have been reported for antioxidant vitamins in humans. It should be noted that the available data collected from trials involving a specific antioxidant agent should not be expected to represent the real potential of all antioxidants in preventing or treating POAF. Likely, some antioxidants may not prevent the development of POAF, but this should not rule out the paradigm by which a reinforcement of the antioxidant defense system diminishes the vulnerability of myocardium to the effect of increased ROS as expected to occur in an ischemia–reperfusion cycle. In support of this view, prevention of POAF by classic antioxidants such as N-acetylcysteine and statins has been reported [68–70]. In the last years, other antioxidant agents, such as xanthophyll carotenoids have demonstrated biological properties useful in the prevention of several ROS-mediated diseases, although studies in POAF models have not been performed. In addition, it has been documented that carotenoids could play a role in preventing the development of certain types of cancer and ocular diseases. Also, carotenoids could be protective against coronary vascular disease [75]. These agents have shown specific anti-inflammatory and anti-injury

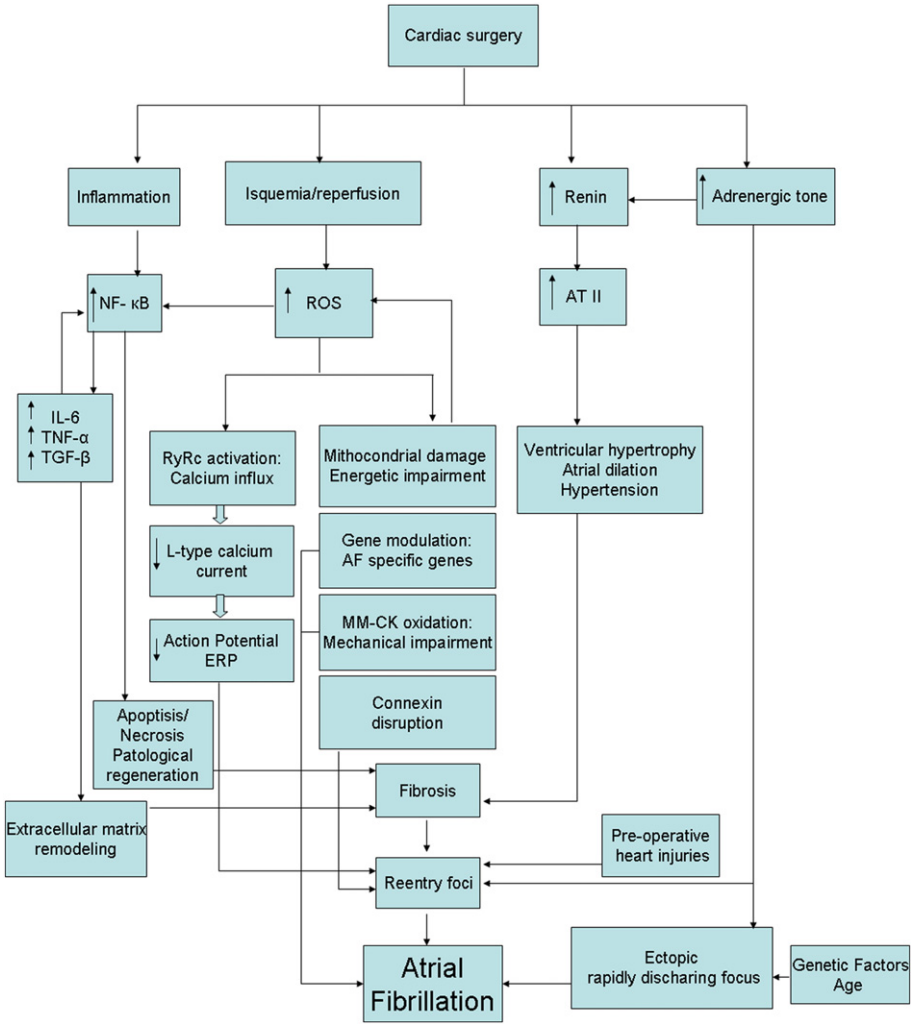

Fig. 1. Schematic diagram illustrating the main contributory factors involving the genesis and perpetuation of postoperative atrial fibrillation. NF-kB, nuclear factor-kappa B; TNF-α, tumor necrosis factor alpha; TGF-β, transforming growth factor beta; ROS, reactive oxygen species; AT II, angiotensin II; IL-6, interleukin-6; RyRc, ryanodine receptor Ca^{2+} channel; ERP, effective refractory period; MM-CK, myofibrillar creatine kinase.

properties, attenuating complement activation and diminishing infarct size in an ischemia–reperfusion rabbit model [76].

The above mentioned studies showing different responses for individual antioxidant molecules are consistent with the fact that structural and molecular differences between antioxidants lead to critical differences involving metabolism, solubility, and physicochemical interactions with biological membranes; properties that subsequently could influence the efficacy and safety of these compounds [77,78]. Therefore, diverse antioxidants could perform its action through different molecular pathways. The consideration of these factors when analyzing the data of trials involving an individual compound used as antioxidant is of pivotal importance.

4.1. Biological properties and synergism of vitamins C and E

Vitamin C and vitamin E are essential antioxidants that perform their roles in different cell locations. While the first acts in water-soluble components the second one does it in lipid-soluble zones (mainly biological membranes). Thus, when both vitamins are used together, all cell components could be protected against the oxidative damage [79,80]. The most studied mechanism whereby they act is partly based on their ability to directly reduce ROS. In addition to its ROS scavenging functions, these two antioxidants exert their action in a synergistic way: when α-tocopherol losses an electron and is left as α-tocopheroxyl radical, vitamin C reduces it at the level of the lipid–water interphase, so that it can thus recover its antioxidant properties [72,73]. In contrast, in the absence of efficient reducers, vitamin E cannot be recycled into its antioxidant form, leading to the formation of tocopheryl quinone, molecule that could compete in mitochondrial respiratory chain reactions. Hence, the therapeutic strategy presented in this review is based in the associated administration of both ascorbate and α-tocopherol, ensuring the efficient recycling of vitamin E radicals [81,82].

4.2. Endothelial modulation

Besides their ROS scavenging actions, vitamins C and E exert a complex modulation of numerous enzymes involved in ROS production, endothelial function, platelet aggregation, inflammation and smooth muscle cell tone regulation [46,47,83].

NAD(P)H oxidase, the most important superoxide source in the cardiovascular system, can be directly down-regulated by vitamins C and E. The mechanism behind this effect has not been completely elucidated. It has been described that ascorbate and α-tocopherol could be involved in NAD(P)H oxidase transcriptional and post-transcriptional modulation. At the same time, studies describing a possibly direct effect to the NAD(P)H oxidase synthesis have also been presented. Vitamin E could be involved in inhibiting the enzyme subunits aggregation, based in the location (membranous organelle) in which this process takes place [84].

In the presence of OE, endothelial NOS is mainly encountered in its uncoupled form, participating in ROS production and NO synthesis impairment, all which leads to endothelial dysfunction. In this context, antioxidant vitamins have shown to increase eNOS activity, by enhancing the intracellular availability of BH4 and by inhibiting the p47phox subunit expression. Therefore, ascorbate and α-tocopherol increase NO synthesis, reduce ROS formation and contribute to improve the vascular tone regulation [84–87].

Previously the existence of molecular bridges between enzymatic and non-enzymatic antioxidants was mentioned. Accordingly, studies have demonstrated a positive correlation between antioxidant vitamin concentration and the activity of the antioxidant enzyme, especially SOD. The mechanisms underlying these findings are not well elucidated, but it is plausible to hypothesize the existence of transcriptional and post-transcriptional events involved in the up-regulation of those antioxidant enzymes [47].

Vitamin E also modulates the vascular prostanoid synthesis by up-regulating phospholipase A2 expression and arachidonic acid release; and downregulating cyclooxygenase-2 expression. The final result is a net increase in vasodilator prostanoids, which contribute to the regulation of the vascular tone [88].

4.3. Empiric evidence

4.3.1. In-vitro studies and animal trials

Vitamins C and E have demonstrated intrinsic abilities in preventing cell apoptosis, necrosis and cardiac dysfunction. Several studies have established their pivotal role in preventing oxidative damage in in-vitro cardiomyocytes. Thus, when isolated cardiomyocytes were exposed to singlet oxygen oxidative damage, which lead to irreversible hypercontracture of 95% of the cells, the pre-treatment with vitamins C and E reduced the hypercontracture percentage in a vitamin concentration-dependent manner. This effect was enhanced when using both vitamins simultaneously [89]. Cardiomyocyte apoptosis has also been prevented by administration of antioxidant vitamins, which was also correlated with the diminution of oxidative markers [90,91]. Electrophysiological changes, secondary to hypoxia mediated injuries in guinea pig cardiomyocytes, were prevented upon ascorbate administration. Vitamin C generated an important attenuation in the hypoxia related sodium current disturbance [92]. But ascorbate and α-tocopherol have been involved not only in cardiomyocyte apoptosis, contracture and current disturbance studies, since there are also available data supporting vitamin anti-arrhythmic specific properties. On this line, in isolated rat hearts undergoing ischemia–reperfusion injuries, vitamin E showed an effective prevention in the appearance of reperfusion arrhythmias [93].

Furthermore, several animal models have been used to assess the favorable effects of vitamins C and E in the prevention of necrosis–apoptosis pathways, oxidative damage, calcium overloading and cardiac dysfunction [94–96]. Antioxidant vitamins anti-necrosis properties were established considering that cardiomyocytes necrosis, of rats submitted to stimulation of myocardial infarction, was prevented by the administration of vitamins C and E [91].

Myocardium fibrosis and remodeling play an important role in POAF genesis and perpetuation, in this respect, α-tocopherol has shown important effects in preventing cardiac remodeling in spontaneously hypertensive rats, based in the inhibition of cardiomyocyte hypertrophy [97]. Vitamin based cardiac dysfunction attenuation was demonstrated using rabbit models. Antioxidant vitamins were administered after pacing-induced cardiac dysfunction. Subsequently, a decrease in myocardial oxidation markers, an attenuation of the pacing-induced cardiac dysfunction and a reduction in cardiomyocytes necrosis markers were found [90,95].

Both in-vitro studies and animal trials have opened the path to understand the real potential that antioxidant vitamins could have in preventing POAF. Although the molecular basis and the in-vitro evidence that supports the use of antioxidant vitamins has been accumulating over the last years (evaluating cardiomyocyte contractility, apoptosis, electrophysiology, and isolated hearts arrhythmia appearance), it is necessary to gather all efforts in performing studies based on POAF models, which has not been done so far. The lack of studies in this specific field has a great impact in the subsequent conduction of POAF clinical trials.

4.3.2. AF clinical trials

Antioxidant vitamins and AF related clinical trials, have not been heavily studied; in the paragraphs below the advances made in this direction are presented.

A study was conducted to test not only the effects of vitamin C supplementation in POAF incidence, but also to assess the biochemical changes in oxidative and electric status after canine atrial pacing. In the first part, 43 patients subjected to coronary artery bypass were given 2 g of vitamin C the day before the surgery, followed by 500 mg daily until the fifth postoperative day. Postoperative atrial fibrillation incidence in the ascorbate treated group was 16% vs 35% in the control group. In the other part of the study, eleven dogs were subjected to rapid atrial pacing, which lead to shortening of the effective refractory period, associated with accumulation of 3-nitrotyrosine, a peroxynitrite oxidative marker, and decreased levels of ascorbate compared with non-paced controls. Ascorbate treatment attenuated the

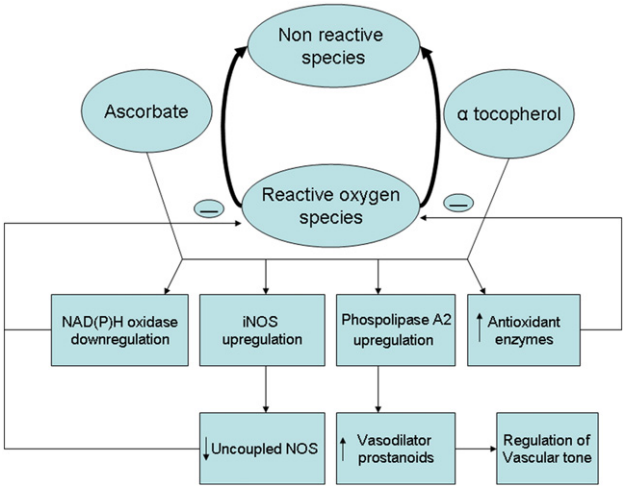

Fig. 2. Schema with the proposed effect of antioxidant vitamins in the reinforcement of the myocardial antioxidant defense system. NAD(P)H oxidase, reduced nicotine adenine dinucleotide phosphate oxidase; NOS, nitric oxide synthase; iNOS, inducible nitric oxide synthase.

effective refractory period shortening and diminished the 3-nitrotyrosine concentration found after atrial pacing [98].

The effects of ascorbate administration in relation to AF have been tested under different contexts. A trial studied 44 patients subjected to electrical cardioversion of persistent AF. All patients received standard treatment, but one group received, additionally, vitamin C during 7 days. Within a week, AF recurred in 4.5% of the ascorbate treated group and in 36% of the control group [99]. Also, antioxidant vitamins have been tested in the prevention of post-thrombolysis AF. When comparing the two groups subjected to therapeutic alteplase thrombolysis, one receiving antioxidant vitamins and the other placebo, the results showed that the first one developed AF after reperfusion in 6% while the placebo group presented the arrhythmia in 44% [100].

Recently, it was shown that oral vitamin C in association with beta-blockers was more effective in preventing POAF than beta-blockers alone (100 patients undergoing coronary artery bypass grafting were separated into a beta-blockers group and a beta-blockers/ascorbate group, which received ascorbic acid at a dose of 2 g on the night prior to the surgery and 2 g daily for 5 days following surgery). The POAF incidence was 4% in ascorbate group and 26% in the control group [101]. Consequently, antioxidant vitamins not only have shown favorable anti-arrhythmogenic results compared with non-vitamin patients, but also with patients receiving classical anti-AF drug treatment.

A schema with the proposed effect of antioxidant vitamins in the reinforcement of the myocardial antioxidant defense system is depicted in Fig. 2.

4.3.3. Other pharmacological agents

Antioxidant vitamins administration could be considered as potential pharmacological intervention against POAF. First, abundant evidence has supported the paradigm that oxidative stress plays a pivotal role in the genesis and perpetuation of AF and POAF. Second, the innocuousness of vitamins administration, compared to the numerous classic anti-arrhythmic drugs having undesirable side effects, suggests their use alone or in combination with other anti-arrhythmics. Third, some studies emerged in the last years, reporting that vitamin C shows a satisfactory anti-arrhythmic effect, together with its antioxidant properties. There are two POAF-specific clinical trials involving ascorbate [98,101]. When comparing the effects of vitamin C with those of other anti-arrhythmic agents or antioxidants in POAF treatments, some conclusions could be drawn.

In a study with 115 patients undergoing coronary artery bypass and/or valve surgery, 58 patients received pre-operative N-acetylcysteine and 57 received placebo (both groups received also standard medical therapy, including beta-blockers); POAF incidence was 5.2% in the N-acetylcysteine group and 21.1% in the placebo group [70]. When comparing the results of this study with the ascorbate trials described previously, it highlights the similar outcome when using antioxidants vs beta-blockers in the prevention of POAF, being vitamin C slightly more effective achieving this purpose than N-acetylcysteine. However, further conclusions cannot be drawn, since the conditions in which the trials were performed were different, especially in terms of the pre- and postoperative drugs included in the standard medical therapy used in the latter study.

Several studies have demonstrated that statins, which have both antioxidant and anti-inflammatory properties, may attenuate the incidence of POAF [102–104] A meta-analysis of over 30,000 patients showed that POAF incidence when using pre-operative statins diminished from 29.3% (in the no-statins groups) to 24.9% [104]. Hence, when compared with vitamin C, statins seemed to show a lower capacity to attenuate POAF incidence. However, more studies in this field are still lacking to probe this hypothesis.

Between all beta-blockers, accumulated evidence indicates that carvedilol could be the most effective in preventing POAF. However, in those clinical trials, POAF incidence in the different carvedilol treated groups fluctuated between 8% and 16%, exceeding vitamin C results [105–107]. However, a comparative carvedilol–ascorbate trial could determine the real effects of these pharmacological agents (used separately or together) in preventing POAF. Finally, the most broadly use anti-arrhythmic drug, amiodarone has to be discussed. Despite its universal use in the prevention of POAF, amiodarone has important disadvantages, such as serious side effects (pulmonary fibrosis) and several pharmacological interactions. Moreover, amiodarone effectiveness in preventing POAF is comparable to carvedilol, being both better than classic beta-blockers such as atenolol or propanolol [108]. Although vitamins C and E have demonstrated to be as effective as other therapies in preventing AF, the evidence regarding specifically POAF is quite limited. Their innocuousness makes them suitable to be incorporated in different animal and clinical trials, to assess their real potential in preventing the appearance and perpetuation of POAF.

5. Conclusions

Available pharmacological treatments for AF based on ion channel blockade have demonstrated limited efficacy, underlining the relevance of the development of a prophylaxis for this disorder. In the light of the current advances, the future of antioxidant vitamins based POAF preventive therapy looks promising. The studies made in this field, that gathers in-vitro, animal and clinical trials, all point to potential benefit of the antioxidant vitamins to at least prevent or likely treat oxidative stress related disorders. Among these disorders POAF highlights due to its high incidence, complications and lack of effective and low risk treatments. On this basis, it could be suggested that the pharmacological use of vitamins C and E may not only minimize the risk of POAF, but also increase the success in atrial fibrillation treatment. Moreover, since there are very few studies in humans on the beneficial effects of these antioxidant vitamins for this setting, it could be remarked that they could and should be heavily tested under different protocols to assess their real potential benefit for POAF prevention.

Acknowledgments

The authors wish to thank FONDECYT (grant number 1070948, Chile Government), Procaps Laboratory (Colombia) and Gynopharm CFR Laboratory (Chile) for their financial support of this study.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [109].

References

[1] Korantzopoulos P, Kolettis T, Siogas K, Goudevenos J. Atrial fibrillation and electrical remodeling: the potential role of inflammation and oxidative stress. Med Sci Monit 2003;9:225–9.
[2] Lin PH, Lee SH, Su CP, Wei YH. : Oxidative damage to mitochondrial DNA in atrial muscle of patients with atrial fibrillation. Free Radic Biol Med 2003;35:1310–8.
[3] Fuster V, Rydén LE, Cannom DS, et al. Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation 2006;114:e257–354.
[4] Hogue Ch, Hyder M. Atrial fibrillation after cardiac operation: risks, mechanisms, and treatment. Ann Thorac Surg 2000;69:300–6.
[5] Wu ZK, Iivainen T, Pehkonen E, Laurikka J, Zhang S, Tarkka MR. Fibrillation in patients subjected to coronary artery bypass grafting. J Thorac Cardiovasc Surg 2003;126:1477–82.
[6] Maisel WH, Rawn JD, Stevenson WG. Atrial fibrillation after cardiac surgery. Ann Intern Med 2001;135:1061–73.
[7] Mathew JP, Fontes ML, Tudor IC, et al. Multicenter study of Perioperative Ischemia Research Group. A multicenter risk index for atrial fibrillation after cardiac surgery. J Am Med Assoc 2004;291:1720–9.
[8] Mitchell LB. Prophylactic therapy to prevent atrial arrhythmia after cardiac surgery. Curr Opin Cardiol 2007;22:18–24.
[9] Hammwöhner M, Smid J, Lendeckel U, Goette A. New drugs for atrial fibrillation. J Interv Card Electrophysiol 2008;23:15–21.

[10] Neuman RB, Bloom HL, Shukrullah I. Oxidative stress markers are associated with persistent atrial fibrillation. Clin Chem 2007;53:1652–7.
[11] Korantzopoulos P, Kolettis TM, Galaris D, Goudevenos JA. The role of oxidative stress in the pathogenesis and perpetuation of atrial fibrillation. Int J Cardiol 2007;115:135–43.
[12] Corradi D, Callegari S, Maestri R, et al. Heme oxygenase-1 expression in the left atrial myocardium of patients with chronic atrial fibrillation related to mitral valve disease: its regional relationship with structural remodeling. Hum Pathol 2008;39:1162–71.
[13] Rodrigo R, Castillo R, Cereceda M, Asenjo R, Zamorano J, Araya J. Non-hypoxic preconditioning of myocardium against postoperative atrial fibrillation: mechanism based on enhancement of the antioxidant defense system. Med Hypotheses 2007;69:1242–8.
[14] Rodrigo R, Cereceda M, Castillo R, et al. Prevention of atrial fibrillation following cardiac surgery: basis for a novel therapeutic strategy based on non-hypoxic myocardial preconditioning. Pharmacol Ther 2008;118:104–27.
[15] Olshansky B. Interrelationships between the autonomic nervous system and atrial fibrillation. Prog Cardiovasc Dis 2005;48:57–78.
[16] Dilaveris P, Giannopoulos G, Synetos A, Stefanadis C. The role of renin angiotensin system blockade in the treatment of atrial fibrillation. Curr Drug Targets Cardiovasc Haematol Disord 2005;5:387–403.
[17] Boos CJ, Anderson RA, Lip GY. Is atrial fibrillation an inflammatory disorder? Eur Heart J 2006;27:136–49.
[18] Goette A, Arndt M, Röcken C, et al. Calpains and cytokines in fibrillating human atria. Am J Physiol Heart Circ Physiol 2002;283:264–72.
[19] Brundel BJ, Ausma J, van Gelder IC, et al. Activation of proteolysis by calpains and structural changes in human paroxysmal and persistent atrial fibrillation. Cardiovasc Res 2002;54:380–9.
[20] Chung MK, Martin DO, Sprecher D, et al. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. Circulation 2001;104:2886–91.
[21] de Bakker JM, Ho SY, Hocini M. Basic and clinical electrophysiology of pulmonary vein ectopy. Cardiovasc Res 2002;54:287–94.
[22] Van Wagoner DR. Recent insights into the pathophysiology of atrial fibrillation. Semin Thorac Cardiovasc Surg 2007;19:9–15.
[23] Aslan O, Güneri S. [Electrophysiological mechanisms of atrial fibrillation]. Anadolu Kardiyol Derg 2002;2:244–52.
[24] Platonov PG. Interatrial conduction in the mechanisms of atrial fibrillation: from anatomy to cardiac signals and new treatment modalities. Europace 2007;9 (Suppl 6):vi10–6.
[25] Van Wagoner DR. Electrophysiological remodeling in human atrial fibrillation. Pacing Clin Electrophysiol 2003;26:1572–5.
[26] Van Wagoner DR. Molecular basis of atrial fibrillation: a dream or a reality? J Cardiovasc Electrophysiol 2003;14:667–9.
[27] Opie LH, Commerford PJ, Gersh BJ, Pfeffer MA. Controversies in ventricular remodelling. Lancet 2006;367:356–67.
[28] Everett TH, Olgin JE. Atrial fibrosis and the mechanisms of atrial fibrillation. Heart Rhyth 2007;4:24–7.
[29] Polizio AH, Balestrasse KB, Yannarelli GG, et al. Angiotensin II regulates cardiac hypertrophy via oxidative stress but not antioxidant enzyme activities in experimental renovascular hypertension. Hypertens Res 2008;31:325–34.
[30] Murray KT, Mace LC, Yang Z. Nonantiarrhythmic drug therapy for atrial fibrillation. Heart Rhythm 2007;4(3 Suppl):S88–90.
[31] Förstermann U. Oxidative stress in vascular disease: causes, defense mechanisms and potential therapies. Nat Clin Pract Cardiovasc Med 2008;5:338–49.
[32] Mihm MJ, Yu F, Carnes CA, et al. Impaired myofibrillar energetics and oxidative injury during human atrial fibrillation. Circulation 2001;104:174–80.
[33] De Vecchi E, Pala MG, Di Credico G, et al. Relation between left ventricular function and oxidative stress in patients undergoing bypass surgery. Heart 1998;79:242–7.
[34] Ide T, Tsutsui H, Kinugawa S, et al. Direct evidence for increased hydroxyl radicals originating from superoxide in the failing myocardium. Circ Res 2000;86:152–7.
[35] Ukai T, Cheng CP, Tachibana H, et al. Allopurinol enhances the contractile response to dobutamine and exercise in dogs with pacing-induced heart failure. Circulation 2001;103:750–5.
[36] Sies H, editor. Oxidative stress: oxidants and anti-oxidants. London Academic Press; 1991.
[37] Nagano T. Chemical and biochemical studies on reactivities, formations and toxicities of reactive oxygen species. Yakugaku Zasshhi 1991;111:103–19.
[38] Kim YM, Guzik TJ, Zhang YH, et al. A myocardial Nox2 containing NAD(P)H oxidase contributes to oxidative stress in human atrial fibrillation. Circ Res 2005;97:629–36.
[39] Kim YM, Kattach H, Ratnatunga C, Pillai R, Channon KM, Casadei B. Association of atrial nicotinamide adenine dinucleotide phosphate oxidase activity with the development of atrial fibrillation after cardiac surgery. J Am Coll Cardiol 2008;51:68–74.
[40] Paravicini TM, Touyz RM. NADPH oxidases, reactive oxygen species, and hypertension: clinical implications and therapeutic possibilities. Diabetes Care 2008;31(Suppl 2):S170–80.
[41] Heller R, Unbehaun A, Schellenberg B, Mayer B, Werner-Felmayer G, Werner ER. L-ascorbic acid potentiates endothelial nitric oxide synthesis via a chemical stabilization of tetrahydrobiopterin. J Biol Chem 2001;276:40–7.
[42] Werner ER, Gorren AC, Heller R, Werner-Felmayer G, Mayer B. Tetrahydrobiopterin and nitric oxide: mechanistic and pharmacological aspects. Exp Biol Med 2003;228:1291–302.
[43] Förstermann U, Münzel T. Endothelial nitric oxide synthase in vascular disease: from marvel to menace. Circulation 2006;113:1708–14.
[44] Kim HY, Kim OH, Sung MK. Effects of phenol-depleted and phenol-rich diets on blood markers of oxidative stress, and urinary excretion of quercetin and kaempferol in healthy volunteers. J Am Coll Nutr 2003;22:217–23.
[45] Aviram M, Kaplan M, Rosemblat M, Fuhrman B. Dietary antioxidants and paraoxonases against LDL oxidation and atherosclerosis development. Handb Exp Pharmacol 2005;170:263–300.
[46] Newaz MA, Yousefipour Z, Nawal NN. Modulation of nitric oxide synthase activity in brain, liver, and blood vessels of spontaneously hypertensive rats by ascorbic acid: protection from free radical injury. Clin Exp Hypertens 2005;6:497–508.
[47] Guney M, Oral B, Demirin H, Karahan N, Mungan T, Delibas N. Protective effects of vitamins C and E against endometrial damage and oxidative stress in fluoride intoxication. Clin Exp Pharmacol Physiol 2007;34:467–74.
[48] Ramlawi B, Otu H, Mieno S, et al. Oxidative stress and atrial fibrillation after cardiac surgery: a case–control study. Ann Thorac Surg 2007;84:1166–72.
[49] Kim YH, Lim DS, Lee JH, et al. Gene expression profiling of oxidative stress on atrial fibrillation in humans. Exp Mol Med 2003;35:336–49.
[50] Ohki R, Yamamoto K, Ueno S, et al. Gene expression profiling of human atrial myocardium with atrial fibrillation by DNA microarray analysis. Int J Cardiol 2005;102:233–8.
[51] Aviles RJ, Martin DO, Apperson-Hansen C, et al. Inflammation as a risk factor for atrial fibrillation. Circulation 2003;108:3006–10.
[52] Abdelhadi RH, Gurm HS, Van Wagoner DR, Chung MK. Relation of an exaggerated rise in white blood cells after coronary bypass or cardiac valve surgery to development of atrial fibrillation postoperatively. Am J Cardiol 2004;93:1176–8.
[53] Bruins P, te Velthuis H, Yazdanbakhsh AP, et al. Activation of the complement system during and after cardiopulmonary bypass surgery: postsurgery activation involves C-reactive protein and is associated with postoperative arrhythmia. Circulation 1997;96:3542–8.
[54] Lamm G, Auer J, Weber T, Berent R, Ng C, Eber B. Postoperative white blood cell count predicts atrial fibrillation after cardiac surgery. J Cardiothorac Vasc Anesth 2006;20:51–5.
[55] Pavlović D, Đorđević V, Kocić G. A "cross-talk" between oxidative stress and redox cell signalling. Med Biol 2002;2:131–7.
[56] Chandra J, Samali A, Orrenius S. Triggering and modulation of apoptosis by oxidative stress. Free Radic Biol Med 2000;29:323–33.
[57] Liakopoulos OJ, Schmitto JD, Kazmaier S, et al. Cardiopulmonary and systemic effects of methylprednisolone in patients undergoing cardiac surgery. Ann Thorac Surg 2007;84:110–8.
[58] Halonen J, Halonen P, Järvinen O, et al. Corticosteroids for the prevention of atrial fibrillation after cardiac surgery: a randomized controlled trial. JAMA 2007;297:1562–7.
[59] Goldstein RN, Ryu K, Khrestian C, van Wagoner DR, Waldo AL. Prednisone prevents inducible atrial flutter in the canine sterile pericarditis model. J Cardiovasc Electrophysiol 2008;19:74–81.
[60] Bukowska A, Schild L, Keilhoff G, et al. Mitochondrial dysfunction and redox signaling in atrial tachyarrhythmia. Exp Biol Med 2008;233:558–74.
[61] Kawakami M, Okabe E. Superoxide anion radical-triggered Ca2+ release from cardiac sarcoplasmic reticulum through ryanodine receptor Ca2+ channel. Mol Pharmacol 1998;53:497–503.
[62] Eloff BC, Lerner DL, Yamada KA, Schuessler RB, Saffitz JE, Rosenbaum DS. High resolution optical mapping reveals conduction slowing in connexin43 deficient mice. Cardiovasc Res 2001;51:681–90.
[63] Peters NS, Coromilas J, Severs NJ, Wit AL. Disturbed connexin43 gap junction distribution correlates with the location of reentrant circuits in the epicardial border zone of healing canine infarcts that cause ventricular tachycardia. Circulation 1997;95:988–96.
[64] Sawaya SE, Rajawat YS, Rami TG, et al. Downregulation of connexin40 and increased prevalence of atrial arrhythmias in transgenic mice with cardiac-restricted overexpression of tumor necrosis factor. Am J Physiol Heart Circ Physiol 2007;292:H1561–7.
[65] Severs NJ, Bruce AF, Dupont E, Rothery S. Remodelling of gap junctions and connexin expression in diseased myocardium. Cardiovasc Res 2008;80:9–19.
[66] Duffy HS, Wit AL. Is there a role for remodeled connexins in AF? No simple answers. J Mol Cell Cardiol 2008;44:4–13.
[67] Ramachandran S, Xie LH, John SA, Subramaniam S, Lal R. A novel role for connexin hemichannel in oxidative stress and smoking-induced cell injury. PLoS ONE 2007;2:e712.
[68] Korantzopoulos P, Kountouris E, Kolettis T, Siogas K. Anti-inflammatory and antioxidant actions of statins may favorably affect atrial remodeling in atrial fibrillation. Am J Cardiol 2004;93:1200.
[69] Liu T, Li G, Korantzopoulos P, Goudevenos JA. Statins and prevention of atrial fibrillation in patients with heart failure. Int J Cardiol 2009;134:336–41.
[70] Ozaydin M, Peker O, Erdogan D, et al. N-acetylcysteine for the prevention of postoperative atrial fibrillation: a prospective, randomized, placebo-controlled pilot study. Eur Heart J 2008;29:625–31.
[71] Das KC, Misra HP. Antiarrhythmic agents. Scavengers of hydroxyl radicals and inhibitors of NADPH-dependent lipid peroxidation in bovine lung microsomes. J Biol Chem 1992;267:19172–8.
[72] Heller R, Werner-Felmayer G, Werner ER. Alpha-tocopherol and endothelial nitric oxide synthesis. Ann N Y Acad Sci 2004;1031:74–85.
[73] Heller R, Werner-Felmayer G, Werner ER. Antioxidants and endothelial nitric oxide synthesis. Eur J Clin Pharmacol 2006;62:21–8.
[74] Rodrigo R, Guichard C, Charles R. Clinical pharmacology and therapeutic use of antioxidant vitamins. Fundam Clin Pharmacol 2007;21:111–27.
[75] Krinsky NI, Johnson EJ. Carotenoid actions and their relation to health and disease. Mol Aspects Med 2005;26:459–516.

[76] Lauver DA, Lockwood SF, Lucchesi BR. Disodium Disuccinate Astaxanthin (Cardax) attenuates complement activation and reduces myocardial injury following ischemia/reperfusion. J Pharmacol Exp Ther 2005;314:686–92.
[77] Mason RP. Molecular basis of differences among statins and a comparison with antioxidant vitamins. Am J Cardiol 2006;98:34–41.
[78] McNulty H, Jacob RF, Mason RP. Biologic activity of carotenoids related to distinct membrane physicochemical interactions. Am J Cardiol 2008;101:20–9.
[79] Levine M, Rumsey SC, Daruwala R, Park JB, Wang Y. Criteria and recommendations for vitamin C intake. JAMA 1999;281:1415–23.
[80] Wang X, Quinn PJ. The location and function of vitamin E in membranes. Mol Membr Biol 2000;17:143–56.
[81] Gille L, Staniek K, Nohl H. Effects of tocopheryl quinone on the heart: model experiments with xanthine oxidase, heart mitochondria, and isolated perfused rat hearts. Free Radic Biol Med 2001;30:865–76.
[82] Gille L, Gregor W, Staniek K, Nohl H. Redox-interaction of alpha-tocopheryl quinone with isolated mitochondrial cytochrome bc1 complex. Biochem Pharmacol 2004;68:373–81.
[83] Pignatelli P, Sanguigni V, Paola SG, Lo Coco E, Lenti L, Violi F. Vitamin C inhibits platelet expression of CD40 ligand. Free Radic Biol Med 2005;38:1662–6.
[84] Ulker S, McKeown PP, Bayraktutan U. Vitamins reverse endothelial dysfunction through regulation of eNOS and NAD(P)H oxidase activities. Hypertension 2003;41:534–9.
[85] Taddei S, Virdis A, Ghiadoni L, Salvetti A. Endothelial dysfunction in hypertension: fact or fancy? J Cardiovasc Pharmacol 1998;32(Suppl 3):S41–47.
[86] Newaz MA, Nawal NN, Rohaizan CH, Muslim N, Gapor A. Alpha-tocopherol increased nitric oxide synthase activity in blood vessels of spontaneously hypertensive rats. Am J Hypertens 1999;12:839–44.
[87] Wu F, Schuster DP, Tyml K, Wilson JX. Ascorbate inhibits NADPH oxidase subunit p47phox expression in microvascular endothelial cells. Free Radic Biol Med 2007;42:124–31.
[88] Wu D, Liu L, Meydani M, Meydani SN. Vitamin E increases production of vasodilator prostanoids in human aortic endothelial cells through opposing effects on cyclooxygenase-2 and phospholipase A2. J Nutr 2005;135:1847–53.
[89] Rinne T, Mutschler E, Wimmer-Greinecker G, Moritz A, Olbrich HG. Vitamins C and E protect isolated cardiomyocytes against oxidative damage. Int J Cardiol 2000;75:275–81.
[90] Qin F, Shite J, Liang CS. Antioxidants attenuate myocyte apoptosis and improve cardiac function in CHF: association with changes in MAPK pathways. Am J Physiol Heart Circ Physiol 2003;285:822–32.
[91] Guaiquil VH, Golde DW, Beckles DL, Mascareno EJ, Siddiqui MA. Vitamin C inhibits hypoxia-induced damage and apoptotic signaling pathways in cardiomyocytes and ischemic hearts. Free Radic Biol Med 2004;37:1419–29.
[92] Zhou H, Ma JH, Zhang PH, Luo AT. Vitamin C pretreatment attenuates hypoxia-induced disturbance of sodium currents in guinea pig ventricular myocytes. J Membr Biol 2006;211:81–7.
[93] Walker MK, Vergely C, Lecour S, Abadie C, Maupoil V, Rochette L. Vitamin E analogues reduce the incidence of ventricular fibrillations and scavenge free radicals. Fundam Clin Pharmacol 1998;12:164–72.
[94] Poliukhovich GS, Vasil'eva LP, Maslova GT, Boboriko TL, Speranskiĭ SD. [Efficacy of various antioxidants in experimental ischemia and myocardial infarct in the rat]. Vopr Med Khim 1991;37:54–6.
[95] Shite J, Qin F, Mao W, Kawai H, Stevens SY, Liang C. Antioxidant vitamins attenuate oxidative stress and cardiac dysfunction in tachycardia-induced cardiomyopathy. J Am Coll Cardiol 2001;38:1734–40.
[96] Qin F, Yan C, Patel R, Liu W, Dong E. Vitamins C and E attenuate apoptosis, beta-adrenergic receptor desensitization, and sarcoplasmic reticular Ca2+ ATPase downregulation after myocardial infarction. Free Radic Biol Med 2006;40:1827–42.
[97] Costa VA, Vianna LM, Aguila MB, Mandarim-de-Lacerda CA. Alpha-tocopherol supplementation favorable effects on blood pressure, blood viscosity and cardiac remodeling of spontaneously hypertensive rats. J Nutr Biochem 2005;16:251–6.
[98] Carnes CA, Cheng MK, Nakayama T, et al. Ascorbate attenuates atrial pacing-induced peroxynitrite formation and electrical remodeling and decreases the incidence of post-operative atrial fibrillation. Circ Res 2001;89:32–8.
[99] Korantzopoulos P, Kolettis TM, Kountouris E, et al. Oral vitamin C administration reduces early recurrence rates after electrical cardioversion of persistent atrial fibrillation and attenuates associated inflammation. Int J Cardiol 2005;102:321–6.
[100] Hicks JJ, Montes-Cortes DH, Cruz-Dominguez MP, Medina-Santillan R, Olivares-Corichi IM. Antioxidants decrease reperfusion induced arrhythmias in myocardial infarction with ST-elevation. Front Biosci 2007;12:2029–37.
[101] Eslami M, Badkoubeh RS, Mousavi M, et al. Oral ascorbic acid in combination with beta-blockers is more effective than beta-blockers alone in the prevention of atrial fibrillation after coronary artery bypass grafting. Tex Heart Inst J 2007;34:268–74.
[102] Marín F, Pascual DA, Roldán V, et al. Statins and postoperative risk of atrial fibrillation following coronary artery bypass grafting. Am J Cardiol 2006;97:55–60.
[103] Patti G, Chello M, Candura D, et al. Randomized trial of atorvastatin for reduction of postoperative atrial fibrillation in patients undergoing cardiac surgery: results of the ARMYDA-3 (Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery) study. Circulation 2006;114:1455–61.
[104] Liakopoulos OJ, Choi YH, Haldenwang PL, et al. Impact of preoperative statin therapy on adverse postoperative outcomes in patients undergoing cardiac surgery: a meta-analysis of over 30,000 patients. Eur Heart J 2008;29:1548–59.
[105] Merritt JC, Niebauer M, Tarakji K, Hammer D, Mills RM. Comparison of effectiveness of carvedilol versus metoprolol or atenolol for atrial fibrillation appearing after coronary artery bypass grafting or cardiac valve operation. Am J Cardiol 2003;92:735–6.
[106] Acikel S, Bozbas H, Gultekin B, et al. Comparison of the efficacy of metoprolol and carvedilol for preventing atrial fibrillation after coronary bypass surgery. Int J Cardiol 2008;126:108–13.
[107] Haghjoo M, Saravi M, Hashemi MJ, et al. Optimal beta-blocker for prevention of atrial fibrillation after on-pump coronary artery bypass graft surgery: carvedilol versus metoprolol. Heart Rhythm 2007;4:1170–4.
[108] Solomon AJ, Greenberg MD, Kilborn MJ, Katz NM. Amiodarone versus a beta-blocker to prevent atrial fibrillation after cardiovascular surgery. Am Heart J 2001;142:811–5.
[109] Coats AJ. Ethical authorship and publishing. Int J Cardiol 2009;131:149–50.