Non-antiarrhythmic drugs for the prevention of cardiac arrhythmias

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It is noteworthy that drugs having a significant impact in preventing arrhythmias (atrial or ventricular) are those with no direct specific antiarrhythmic electrophysiologic properties. Specifically, drugs able to interfere with the renin-angiotensin system and the n-3 fatty acids seem to play a relevant role as antiarrhythmics, even if they do not act in the typical manner. Angiotensin-converting enzyme (ACE) inhibitors decrease the incidence of arrhythmias in patients with decreased left ventricular function. The main reduction is linked to a decrease of ventricular arrhythmias, while several studies have suggested that ACE-inhibitors may also decrease the burden of atrial fibrillation. Furthermore, many of angiotensin receptor blockers and spironolactone have been shown to have antiarrhythmic properties.

n-3 polyunsaturated fatty acids (PUFAs) are known to be antiarrhythmic as well. Their effects on the fast voltage-dependent sodium current I_{NA}, inhibition of $I_{Ca^{2+}}$ and the K^+ channel modulation explain their antiarrhythmic properties. For these reasons the renin-angiotensin system blockade and the n-3 PUFA intake may provide simple and safe protection from cardiac arrhythmias.

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Introduction

It is of growing interest that drugs having a significant impact in preventing arrhythmias (atrial or ventricular) are those with no direct specific antiarrhythmic electrophysiologic properties.

Atrial fibrillation (AF) is the most common sustained arrhythmia. To date there is still uncertainty regarding the management of this arrhythmia in patients who fail to respond to or do not tolerate antiarrhythmic drugs. Non-pharmacological strategies, such as atrioventricular ablation, pulmonary vein ablation, pacemakers and atrial defibrillators, have recently attracted a great deal of attention and are destined to play an increasing role in the treatment of patients refractory to medications. Nonetheless pharmacological therapy remains a mainstay for the management of AF and there is an ongoing need to find new pharmacological therapies.

On the other hand, it is worth noting that drug reduction in sudden cardiac death has been obtained from the use of non-antiarrhythmic drugs. In particular, drugs able to interfere with the renin-angiotensin system and n-3 fatty acids seem to play a relevant role as antiarrhythmics, even if they do not act in the common manner.

Renin-angiotensin system blockade

Angiotensin-converting enzyme inhibitors. Although angiotensin-converting enzyme (ACE) inhibitors are not classified as antiarrhythmics, they reduce the incidence of arrhythmias in patients with decreased left ventricular function[1]. The major reduction is due to a decrease of ventricular arrhythmias, while several studies have suggested that ACE-inhibitors may also decrease the burden of AF.

Angiotensin-converting enzyme inhibitors and atrial fibrillation. There is a growing evidence that ACE-inhibitors have antiarrhythmic effects on AF, since several studies have shown a significant reduction in the incidence of AF in patients treated with ACE-inhibitors. A retrospective analysis of the SOLVD patients treated with enalapril indicated that they were less likely to be hospitalized for atrial tachyarrhythmias than patients treated with placebo[2]. In patients with left ventricular dysfunction due to acute myocardial infarction, trandolapril was associated with a 47% relative risk reduction in the incidence of AF compared to placebo[3].

The exact mechanism by which ACE-inhibitors exert this antiarrhythmic effect is

uncertain. It has been suggested that this mechanism involves an effect on atrial electrical and structural remodeling with changes in the refractory period of the atrial muscle and a reduction of atrial fibrosis responsible for intra-atrial conduction disturbances[4,5]. Shi et al.[6] demonstrated the ability of the ACE-inhibitor enalapril to regress atrial fibrosis and reduce associated AF promotion in the setting of congestive heart failure.

There is evidence suggesting a role for the renin-angiotensin system in the pathophysiology of AF. Angiotensin II has been shown to increase atrial pressure and stretch, which are associated with electrophysiologic and structural changes[7]. Angiotensin II is also a potent promoter of fibrosis leading to cardiac myoblast proliferation and reduced collagenase activity[8]. In addition to its role in atrial structural remodeling, angiotensin II has also been shown to modify electrophysiologic remodeling. Inhibition of endogenous angiotensin II prevents atrial effective refractory period shortening and loss of atrial effective refractory period rate adaptation during rapid atrial pacing[7].

ACE-inhibitors may carry out antiarrhythmic activity by means of other mechanisms. These include decrease of wall stress, improvement of left ventricular systolic function, decrease of end-diastolic left ventricular pressure and subsequently of left atrial pressure, beta-blocking properties, and stabilization of electrolyte concentrations.

Angiotensin-converting enzyme inhibitors and ventricular arrhythmias. The use of ACE-inhibitors in preventing arrhythmic death has been evaluated by several clinical trials which analyzed patients with recent myocardial infarction as well as heart failure. In the CONSENSUS trial enalapril showed a 27% reduction in total mortality compared to the control group, but with no differences in terms of sudden cardiac death[9]. In the SOLVD study, patients belonging to the enalapril group had a significant 22% risk reduction in mortality due to heart failure or arrhythmias[10].

The V-HeFT II study showed a 39% risk reduction of sudden cardiac death[11]. SAVE[12], AIRE[13], and TRACE[14] trials evaluated ACE-inhibition in post-infarction patients with or without overt heart failure. In all the three trials there was a risk reduction of mortality, including sudden cardiac death.

Various mechanisms have been postulated to explain the potential antiarrhythmic effects of these medications on ventricular arrhythmias:
- sympatholytic activity: treatment with ACE-inhibitors reduces the amount of circulating norepinephrine, as well as angiotensin II, and enhances vagal tone. ACE-inhibitors modify the autonomic balance and decrease the risk of ventricular arrhythmias[15,16];
- reduction of local norepinephrine release due to prostacyclin synthesis[15];
- local accumulation of bradykinin[17];
- improvement in the hemodynamic status by reducing sympathetically-mediated vasoconstriction;
- reverse remodeling process in heart failure. This can be considered as an indirect antiarrhythmic effect;
- reduction in cardiac systolic and diastolic volumes caused by ACE-inhibition decreases the extension and progression of infarct scar areas[18];
- reduction of hypertrophy in hypertension with concomitant reduction in wall stress[19];
- electrophysiologic effect: ACE-inhibitors prolong the action potential by reducing the I_k current and enhancing the L-type calcium current[20,21].

Angiotensin receptor blockers. Another group of pharmacological agents involved in the renin-angiotensin system with potential antiarrhythmic properties are the angiotensin receptor blockers. Their potential antiarrhythmic effect has been suggested in the ELITE trial[22], where losartan showed a reduction in mortality compared with captopril, due primarily to the prevention of sudden cardiac death.

Many angiotensin receptor blockers have been shown to have potentially useful ACE-inhibitor-like effects. Several studies have proven their favorable hemodynamic and neurohormonal effects.

The potential antiarrhythmic benefit has been explained by blockade of the AT_1 receptors.

Angiotensin receptor blockers and atrial fibrillation. The angiotensin II receptor blocker candesartan was found to prevent the promotion of AF by suppressing the development of structural remodeling (fibrosis) in a dog rapid pacing model[23]. A randomized study prospectively compared irbesartan plus amiodarone with amiodarone alone in the treatment of patients with an episode of persistent AF. The study showed that patients receiving irbesartan were significantly less likely to develop AF[24].

Irbesartan could prevent or modify atrial remodeling by decreasing atrial stretch, lowering left ventricular diastolic pressure and subsequently left atrial pressure, preventing atrial fibrosis, modifying the sympathetic tone, or modulating ion currents or refractoriness.

Angiotensin receptor blockers and ventricular arrhythmias. Several studies (ELITE[18], ELITE II[25], OPTIMAAL[26]) have demonstrated the non-inferiority of losartan in comparison with captopril in terms of total mortality and sudden cardiac death prevention. The LIFE study[27] compared losartan with atenolol as an antihypertensive treatment. There was a significant reduction in the primary composite endpoint of cardiovascular morbidity and mortality.

The addition of valsartan in the treatment of heart failure was evaluated in the Val-HeFT study[28]. Similar

overall mortality including sudden death was observed in both valsartan and placebo groups; a significant benefit from valsartan was observed in the subgroup not taking ACE-inhibitors.

The mechanisms by which angiotensin receptor blockers could explain their benefit may include antagonism toward markers involved in the pathophysiology of heart failure such as tumor necrosis factor-alpha and interleukin-6[29], suppression of sympathetic tone and decrease of myocardial hypertrophy with a reduction of left ventricular mass[27].

Spironolactone

Aldosterone induces cell proliferation and myocardial fibrosis, possibly due to an increase of AT_1 receptors, and enhances local expression of the ACE. Moreover, it appears to promote inflammation and oxidative stress and the proposal has been made that it may induce baroreceptor dysfunction with autonomic imbalance[30].

In the RALES study[31] the aldosterone receptor blocker spironolactone caused a 30% mortality reduction in patients with severe heart failure. The mechanisms which may explain the beneficial effects obtained with spironolactone therapy could include its antifibrotic cardiac effect and the increase of cardiac norepinephrine uptake, indicating rapid metabolism and inactivation of arrhythmogenic catecholamines in the cardiac cells[32].

n-3 fatty acids

n-3 fatty acids enter the food chain and become abundant in marine foods through the ingestion of marine phytoplankton by fish, thus yielding the most biologically active elongated products: the eicosapentaenoic acid (EPA) and the docosahexaenoic acid. The low mortality rate of the people of Greenland from ischemic heart disease led to the suggestion that, despite the high total fat intake of the Eskimos, this low mortality rate was due to the abundance in their diet of n-3 fatty acids from seafood. This hypothesis initiated studies by various investigators into the possible antiatherogenic effects of n-3 polyunsaturated fatty acids (PUFAs).

Cardiovascular health benefits of n-3 fatty acids arise from their effect on atherogenesis, inflammation and thrombosis. n-3 PUFAs are known to have antiarrhythmic properties too.

The increasing awareness of their health benefit has led to further investigations. Three important trials, the DART trial[33], the Lion Heart study[34] and the GISSI-Prevenzione study[35], led to the belief in the preventive effect of n-3 fatty acids on cardiac death.

The DART trial[33] was a randomized, multifactorial study of patients with a recent acute myocardial infarction. At 2-year follow-up, patients eating fatty fish intake, at least two fish meals weekly, had a significantly lower mortality (29%).

The Lion Heart Study[34] evaluated the effect of a Mediterranean alpha-linolenic acid-rich diet in post-infarction patients and showed a 70% reduction in all-cause mortality and morbidity, included sudden death.

In the GISSI-Prevenzione study[35] the n-3 fatty acid dietary supplementation significantly reduced total death by 20%, cardiovascular death by 30%, and sudden death by 45%.

Mechanisms of antiarrhythmic effects. Experimental evidence of prevention of *in vitro*-induced arrhythmias by n-3 fatty acids supported the idea that they exert an important antiarrhythmic effect. Leaf et al.[36] demonstrated that, when n-3 EPA was added first in a cultured neonatal rat cardiomyocyte preparation, it prevented the expected arrhythmias induced by the toxic concentrations of extracellular calcium concentration or ouabain. In this study, if the fatty acid was added first to the superfusate, the subsequent addition of any type of cardiotoxic agent would fail to elicit the expected arrhythmias; on the other hand, if arrhythmias were established, subsequent addition of n-3 fatty acid would terminate it. In conclusion, this suggested that n-3 fatty acids must affect the excitability/automaticity of the heart.

Electrophysiologic effects of n-3 polyunsaturated fatty acids.

• Effects on fast-voltage-dependant sodium current $I_{NA.}$ Voltage-gated sodium current I_{NA} elicits action potentials in most cardiac myocytes. PUFAs increased the magnitude of depolarizing stimulus required to elicit an action potential. PUFAs inhibit I_{NA} in a concentration-dependent manner. n-3 fatty acids stabilize the inactive state of the channel accelerating the transition from the resting to the inactivated state, thereby prolonging the effective refractory period of the cardiac cycle.

• Many serious arrhythmias can be triggered by excessive cytosolic-free Ca^{2+}. Ca^{2+} overload produces a number of arrhythmogenic electrophysiologic derangements including depolarization of the resting membrane potential, increase in automaticity and occurrence of delayed afterdepolarizations with triggered activity. Xiao et al.[37] examined the effects of PUFAs on the voltage-gated L-type Ca^{2+} current and sarcoplasmic reticulum Ca^{2+} release events. PUFAs produced a reversible concentration-dependent inhibition of $I_{Ca^{2+}}$. This inhibition reduced sarcoplasmic reticulum Ca^{2+} release, thereby preventing cytosolic Ca^{2+} overload.

• Evidence of K^+ channel modulation has also been provided. Repolarizing outward K^+ current I_{to}, fast outward K^+ current and delayed rectifier current are inhibited in cardiomyocytes by PUFAs, while inward K^+ current is activated and acts to stabilize the resting membrane potential of the myocyte[36].

It is clear that relevant regulations of cardiac function exist and may provide simple and safe protection from ischemia-induced and possibly other serious cardiac arrhythmias.

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