Medical management of atrial fibrillation: Future directions

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Atrial fibrillation is the most common arrhythmia that requires treatment, and although ablation is appropriate in many cases, antiarrythmic drug therapy remains the first and most appropriate therapy in most patients. Currently available antiarrhythmic drugs are limited by modest efficacy and significant toxicity. Cardiac toxicity realtes to effects on the ventricle, especially in prolonging the QT interval and causing torsades de pointes. Amiodarone, an agent with multiple antiarrhythmic effects, is unique in its relative lack of proarrhythmia, although its non-cardiac toxicities limit its use. Some investigational agents are directed at multiple ion channels, or are designed to be analogs of amiodarone. The other line of investigation focuses on the antiarrhythmic action of agents that affect novel ion channel targets. Basic and early clinical studies show promise for drugs that provide atrial antiarrhythmic effects without ventricular proarrhythmia by affecting the atrium preferentially or selectively (inhibiting the I_{TO} and I_{Kur} currents, respectively). Future drugs may possess preferential effects on the remodeled atrium (and as such would be selective for patients with atrial fibrillation). It is hoped that efforts to develop new drugs, including those with preferential effects on the atrium, will provide therapy with greater efficacy and safety.

KEYWORDS Atrial fibrillation; Antiarrhythmic medications; Investigational drugs

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Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice.[1] Although a strategy of rate control with anticoagulation is safe and appropriate in many cases, patients often suffer from significant symptoms that prompt efforts to maintain sinus mechanism. Ablation cannot be attempted in all patients and is not universally effective, so drug therapy remains an important option for atrial stabilization. Antiarrhythmic drug therapy has been disappointing because of limited efficacy and potential toxicity.[2] In this manuscript, I will discuss antiarrhythmic drug therapy, including current options and novel ion channel targets. Developments regarding targets other than ion channels for treatment of AF are described elsewhere within this journal.

Mechanisms of AF

Reentry within the atria, consisting of multiple wavelets, has long been seen as a mechanism for AF. While this holds true in many cases, it is now recognized that initiation and perpetuation of AF usually result from some combination of triggers and a fibrillation-prone atrium. The triggers have been identified as typically originating in the pulmonary veins, although other sites may be responsible.[3] Further triggers to AF may include other supraventricular tachycardias (including atrial flutter). In addition, consistent with the long-identified relationship between cardiac enlargement and AF, stretch-related triggers have been identified.[4]

Both the triggers and reentry may be amplified by the process of remodeling. Remodeling, first demonstrated in goats and dogs subjected to long-term high-rate atrial pacing, results in shortening of the atrial action potential duration (APD) and refractoriness such that the atria become even more prone to perpetuating the AF.[5] Inflammation also contributes to the occurrence of AF.[6]

Current antiarrhythmic therapy

As described above, multiple reentrant circuits meandering throughout the atria often perpetuate AF such that atrial tissue is depolarized almost immediately after recovery from the previous impulse. When the wavelength (defined as the product of conduction velocity and refractory period) is prolonged, as with increasing the refractory period, the activating wave may collide on itself and extinguish. On the other hand, slowing of conduction is also effective (even though this shortens the wavelength and potentially could stabilize reentry), presumably through causing primary reentry waves to extinguish.

The Vaughn Williams classification allows a general mechanism for categorizing the currently available antiarrhythmic agents, although it oversimplifies the complex distinction among these agents and does not account for overlap among the various classes. Many of these agents were developed for ventricular arrhythmias, and none were designed to be specific to the atria, so the same properties that allow for salient atrial effects can lead to ventricular proarrhythmia.

Class I agents are grouped together on the basis of sodium channel blockade, although there are important dis-

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tinctions among the subcategories. Class Ia agents, including quinidine, procainamide, and disopyramide, prolong the action potential and as such can precipitate the polymorphic ventricular tachycardia that results from QT prolongation, that is, torsades de points. Recent guidelines deemphasize the use of these agents due to proarrhythmia and limited efficacy.[1] Class Ic agents (flecainide, propafenone) have a greater slowing effect on cardiac conduction and do not significantly prolong the QT interval. These are first-line agents for AF in structurally normal hearts but are contraindicated otherwise because of the risk of ventricular proarrhythmia.[1]

Class III agents constitute the remainder of our current options for atrial stabilization. Since these prolong refractoriness and APD, they can be associated with QT prolongation and torsades. Dofetilide is a pure I_{Kr} blocking agent and has been shown to be relatively safe and effective in patients with structural heart disease, including heart failure and coronary artery disease. Sotalol combines beta-adrenergic blocking properties with I_{Kr} blockade; it is indicated in patients with coronary artery disease and with heart failure but carries the risk of torsades. Amiodarone, which combines properties of all the Vaughn Williams classes, is the most effective drug for AF and is unique in its relative lack of proarrhythmia, although its noncardiac toxicities (pulmonary, ocular, thyroid, skin, and hepatic) limit its utility.[6]

New ion channel targets for the treatment of AF

An ideal potassium channel–blocking drug would have selective block in the atria, which would treat AF but not prolong the QT and lead to torsades. The "ultrarapid" delayed rectifier potassium current I_{Kur}[7] may allow such atrial selectivity. Because I_{Kur} has not been reported in the human ventricle[8] and the potassium channel gene that encodes for I_{Kur} is expressed much more extensively in atrium than in ventricle, ventricular proarrhythmia should not result from I_{Kur} blockade. The gene is expressed in extracardiac sites (pancreas, central nervous system) so noncardiac side effects are a concern.

Another potassium current that could allow for atrial selectivity is the transient outward current, I_{TO}, which provides for the earliest phase of repolarization. Although the current is present in ventricular tissue, I_{TO} blockade may contribute more to atrial refractoriness because of the minimal plateau in the atrial action potential.[9]

The acetylcholine-dependent K^+ current I_{KACh} may represent a novel atrial-specific target for AF therapy. Vagal influence on the atria, which results in hyperpolarization and shortening of the atrial action potential, has been implicated in precipitation of AF, so inhibition of this current could potentially treat AF. Even more important for this target is the potential to affect the remodeled atrium. A constitutively active (independent of vagal influence) form of I_{KACh}, also called I_{KH}, is evident in canine atrial tissue[10] and human myocytes[11] that have been subjected to experimental atrial tachycardia and fibrillation, respectively. A highly selective antagonist to this current has been shown to prolong atrial refractoriness and suppress tachyarrhythmias in the canine remodeled atrium, without affecting ventricular electrophysiology[12]; this may provide a model for future atrial-specific drug development. Several standard antiarrhythmic agents, including amiodarone, flecainide, and quinidine, inhibit I_{KACh}, possibly accounting in part for their effectiveness in AF.[11]

Stretch-activated ion channels (SACs) have been described, with both selective and nonselective conduction of Ca^{++}, K^+, and Na^+. Atrial stretch is implicated as both a cause of and a result of AF; furthermore, computer models suggest that SACs could generate fast arrhythmias.[4] Thus, the SAC might represent a novel target for the treatment of AF.

Drugs in development

Nonselective ion channel–blocking drugs

Dronedarone is a noniodinated benzofuran derivative of amiodarone that has been shown to have similar electrophysiological effects, despite deletion of iodine.[13] The hope in designing this compound was to replicate the clinical efficacy of amiodarone but reduce toxicity. In a study of 270 patients with AF that required cardioversion, dronedarone (800, 1,200, or 1,600 mg daily) was compared with placebo.[13] The endpoint was timed to recurrent AF, and a significant prolongation was observed only in the 800 mg group (median time to relapse 60 days vs. 5.3 days; $P = .001$). Higher doses resulted in more frequent discontinuation, often for gastrointestinal symptoms. Dronedarone slowed the ventricular rate in recurrent AF by 13 bpm at the 800-mg dose. Two other trials have been reported with similar findings of efficacy and no significant toxicity.[14] However, another study that included patients with heart failure was discontinued in 2003 after an interim safety analysis raised concern for potential increased mortality in treated patients.[15] A further study of the safety in higher-risk patients is ongoing.

SSR149744 is a follow-up compound to dronedarone that also shares the electrophysiological properties of all four Vaughn Williams drug classes.[16] The agent showed efficacy in animal models for AF, with a potency that was equal to or greater than that of amiodarone and dronedarone. A clinical dose-ranging, placebo-controlled phase II study for conversion of AF and flutter has been completed, although the results are not available.[17]

KB130015 is another amiodarone derivative that inhibits Na^+, K^+, and Ca^{2+} currents[18] but also interacts with thyroid hormone nuclear receptors (acting as a thyroid antagonist). It is unique also in slowing the inactivation of voltage-dependent sodium channels, which raises concern for prolongation of the APD.[19] In addition, KB130015 inhibits I_{KACh} and I_{KATP} by direct drug-channel interaction.[20] Clinical data are not available.

Azimilide is a class III antiarrhythmic agent that blocks not only I_{Kr} (like dofetilide) but also I_{Ks}. The addition of the I_{Ks} blockade was postulated to allow for reduced risk of torsades de pointes; however, torsades has been reported. A study of survival in high-risk postinfarct patients showed no