Multi-channel blockers for treatment of atrial fibrillation: an effective strategy?

David R. Van Wagoner*

Department of Molecular Cardiology, NE-61, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA

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Atrial fibrillation (AF) is the most common arrhythmia and one of the most vexing cardiovascular conditions for patients and the physicians who care for them. AF is a primary cause of cardioembolic stroke and may account for more than 20% of all stroke cases in older individuals. While AF can easily be diagnosed by electrocardiography, many cases of AF are undetected due to the lack of symptoms. Lifetime risk for developing AF after an age of 40 years is ~25% for both men and women. The prevalence of AF has been increasing, due to both ageing of the population and an increased prevalence of risk factors such as obesity and sedentary lifestyle. The personal and societal economic consequences of AF are staggering.

Given the scope of the problem, efforts to better diagnose and manage AF are urgently needed. Although many cardiovascular conditions (hypertension, heart failure, etc.) can be managed with drugs, pharmacotherapy for the management of AF remains inadequate. Many of the available antiarrhythmic drugs have the potential for life-threatening ventricular proarrhythmia, coupled with a limited efficacy in maintaining sinus rhythm. Other drugs have less proarrhythmia, but are associated with systemic toxicity when used for long periods. From this perspective, it seems clear that additional efforts to develop drugs that safely and effectively treat AF are urgently needed. To achieve this goal, fundamental studies are needed to better understand the pathophysiology of AF, to identify the differences between atrial and ventricular physiology, and then to selectively target the atrial pathways that promote AF onset and/or increase its persistence. The studies by Wettwer et al. and Suzuki et al. help to advance us closer to this goal.

Suzuki et al. have compared the effects of amiodarone and mexiletine on atrial and ventricular conduction velocity (using optical mapping) and on sodium currents in atrial myocyte (AM) and ventricular myocyte (VM) isolated from rabbit hearts. They report that the IC50 for inhibition of Ina by amiodarone was much lower in AM than in VM, and that the steady-state inactivation curve was left-shifted much more in AM than in VM. In contrast, the IC50 values for mexiletine block of atrial and ventricular Ina were similar, and mexiletine shifted steady-state inactivation to a similar extent in both AM and VM, but with less impact than amiodarone on the steady-state inactivation curve in AMs.

The authors report on the effects of amiodarone but not mexiletine on action potentials (APs) in isolated atrial and VMs. They conclude that amiodarone does not significantly affect resting membrane potential or AP duration at 90% repolarization (APD90) in either cell type. Consistent with other studies, they note that resting potential was more negative in VM than in AM. Returning to the intact heart, the authors show that amiodarone had a greater impact on atrial (~18.9%) than ventricular (~3.7%) conduction velocity. In contrast, mexiletine slowed conduction to a similar extent in atrium (~19.4%) and ventricle (~24.1%). The reported functional results are rather expected, based on the atrial-ventricular difference in resting potential, the differences in IC50 for amiodarone block of Ina in atrial vs. VMs, and the amiodarone-induced shift in steady-state inactivation. However, they collectively point towards differential effects on atrial vs. ventricular sodium currents as an important element conferring atrial specificity. Suzuki et al. suggest that differences in atrial vs. ventricular sodium channel beta-subunit composition may underlie the reported differential responses of atrial vs. ventricular channels to amiodarone. The acute effects of amiodarone reported here are most relevant to the use of intravenous administration of amiodarone for AF cardioversion. Amiodarone is also one of the very few drugs with demonstrated efficacy as a treatment for recurrent AF. However, it is important to recognize the broad spectrum of targets (including ion channels) by which amiodarone affects the heart, and the presence of serious (if not life-threatening) side-effects associated with its long-term use.

Exploiting differences in atrial vs. ventricular gene expression is an appealing approach to enhance the safety of AF treatments by reducing the risk of ventricular proarrhythmia. Other targets that have been considered based on this logic include the delayed rectifier current, Ikur (encoded by KCNMA), and the acetylcholine-gated potassium current, IKACH (encoded by GIRK4). While highly atrial-specific Ikur blockers have been developed by several pharmaceutical firms, none of these have yet received regulatory approval in...
either Europe or the US markets. Several \( I_{Kur} \)-selective compounds remain in development. In both canine atria \(^6\) and in human atria, \(^8\) selective \( I_{Kur} \) blockade increases AP plateau height and thus calcium influx and contractility in preparations from subjects with no history of AF. As down-regulation of both \( I_{Kur}/\)KCNAS/Kv1.5 protein \(^9\) and L-type calcium current \(^10\) occur during the development of persistent AF, the therapeutic potential of highly selective \( I_{Kur} \) blockade remains unclear and perhaps unlikely. \(^7,11\)

In contrast to selective \( I_{Kur} \) blockade, multichannel blockers have progressed further. In addition to amiodarone, other recently approved multichannel blockers include ranolazine, dronedarone, and vernakalant. More multichannel blockers are still in the drug development pipeline. Wettwer et al. present an elegant analysis of the effects of vernakalant on APs and an array of the prominent ionic currents present in human AMs.\(^2\) The studies were performed over a wide range of drug concentrations, at rates spanning the physiologic range, using a combination of isolated trabeculae and isolated myocyte preparations, from patients with and without a history of AF. This careful combination of complementary approaches provides assurance that artefacts associated with myocyte isolation or ischaemia do not significantly affect the authors' interpretation of the primary effects of vernakalant on human atrial electrophysiology.

In intact atrial trabeculae from patients with no history of AF (sinus rhythm, SR), vernakalant affected early repolarization much more than terminal repolarization (APD\(_{90}\)), with no significant effect on APD\(_{90}\), but a reduction in AP upstroke velocity and plateau height. In trabeculae from AF patients, vernakalant increased both refractory period and APD\(_{90}\), but tended to increase refractory period more than AP duration (post-repolarization refractoriness), a characteristic typical of cardiac sodium-channel blockers.\(^12\)

Voltage-clamp studies on isolated myocytes showed that vernakalant blocked sodium current (\( I_{Na} \)) to a similar extent in AF and SR myocytes. As is typical of most sodium-channel blockers, the degree of block is affected by both resting potential and the frequency of stimulation, with a greater block at lower resting potentials and faster rates. In a manner similar to the effects on \( I_{Na} \), L-type calcium current (\( I_{Ca,L} \)) was partially blocked at higher concentrations of vernakalant, with a greater block at faster rates of stimulation. Vernakalant suppressed the transient outward (\( I_{TO} \)) and the ultrarapid delayed rectifier (\( I_{Kr} \)) potassium currents in both SR and AF myocytes. Vernakalant also effectively suppressed \( I_{K,ACH} \) (muscarinic potassium current) in SR and in some AF myocytes; variability reflected the presence of constitutive activation of this current in AF. A small block of \( I_{K1} \) was reported.

Owing to the significant impact of vernakalant on the AP upstroke and lack of impact on the plateau of APs in intact human atrial trabeculae, the authors conclude that the primary antiarrhythmic effects of vernakalant are likely due more to its effects on \( I_{Na} \) than its effects on \( I_{TO} \), \( I_{Kur} \), or \( I_{K,ACH} \). As noted above, in healthy hearts, the more negative resting potential of ventricular than AMs confers some atrial selectivity to sodium-channel blockers, and vernakalant block of \( I_{Na} \) would also be greater during the high rate activity during AF than during sinus rhythm. While this profile is encouraging from a safety perspective, the impact of vernakalant on patients with borderline CAD and regional ischaemia should be closely monitored.

In combination, studies by Wettwer et al.\(^2\) and Suzuki et al.\(^3\) reported that agents that block multiple atrial ionic currents can effectively prolong refractoriness and slow conduction. Efforts such as these to perform systematic, high-quality studies of ion-channel blocking antiarrhythmic drugs in human tissues and myocytes are critical for the development of more effective treatments for AF. However, it is unclear whether they will be sufficient to effectively manage AF. In many patients with AF, the presence of interstitial fibrosis promotes conduction heterogeneity and slowing. The abundance of atrial fibrosis increases with age and haemodynamic challenge (due to valvular dysfunction, impaired ventricular contractility, or heart failure). This group of patients is very often afflicted by AF. Thus, in future clinical studies, it will be important to specifically assess the efficacy of ion-channel blocking drugs such as amiodarone and vernakalant in the setting of extensive fibrosis. Only careful clinical monitoring will reveal whether multi-ion channel blockers are sufficient to either prevent AF recurrence or decrease the burden of AF enough that risk of stroke and heart failure are attenuated.

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