Atrial fibrillation: Is NO an answer for refractoriness?

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The progressive nature of atrial fibrillation (AF) has been attributed to alteration in the electrophysiological properties of the atrial myocardium. As a net effect, a shortening in the refractory period contributes to the substrate, allowing ectopic complex arising and re-entry [1]. Transmembrane ion channel activity determines atrial action potential (AP) shape. Whereas Na⁺ and Ca²⁺ channels are responsible for depolarizing currents, K⁺ channels are responsible for repolarizing currents and therefore shortening of the AP duration. The refractory period is directly correlated to the AP duration. Class III antiarrhythmic drugs are predicted to lengthen AP duration and to prevent subsequent AF.

In human atrium, three components contribute to the late repolarizing K⁺ current: an ‘ultra-rapid’ component (\(I_{Ku}\)), a ‘rapid’ component (\(I_{Kr}\)), and a ‘slow’ component (\(I_{Ks}\)), referring to their voltage-dependent activation kinetics. Among the genes encoding the proteins underlying these currents, HERG codes for the K⁺ channel generating \(I_{Kr}\), the target of class III antiarrhythmic drugs. Since this gene is also expressed at the ventricular level, pharmacological intervention on \(I_{Kr}\) may be responsible for ventricular AP lengthening and potentially for ventricular arrhythmias. Inversely, \(I_{Ku}\) is specific to the atrium in humans and is carried by Kv1.5 channels [2,3]. Kv1.5 appears to be an appealing and specific target for pharmacological treatment of atrial tachyarrhythmias. Indeed, recent in vivo studies of Kv1.5 blockers in animal models support the antiarrhythmic efficacy of this approach [4–6].

However, considering Kv1.5 as a potential target for AF management may be questioned. Indeed, the Kv1.5-related current has been reported as being decreased in atrial cells from patients with chronic AF [7]. If so, inhibiting a weak current could be ineffective. A second study discriminating the electrical remodeling induced by paroxysmal or permanent AF showed decreased Kv1.5 protein levels in both groups [8]. Inversely, in a rat model with paroxysmal AF there was no modification of Kv1.5 protein levels [9]. In another study performed in cells from patients in AF, neither Kv1.5 gene expression nor \(I_{Ku}\) current density was altered [10]. These discrepancies could be due to different clinical profiles of the AF patients. Grammer et al. [10] studied cells from patients undergoing aortocoronary bypass surgery, whereas patients in the Van Wagoner et al. study [7] underwent Maze procedures or mitral valve replacement and generally had dilated atria. Potential efficacy of Kv1.5 inhibition may therefore be pondered depending on the clinical status of the AF patient.

In this issue, Núñez et al. further investigated the physiological regulation of human Kv1.5 [11]. This work, conducted on mouse fibroblasts stably expressing human Kv1.5 channels, characterizes the channel regulation by nitric oxide (NO). Testing acute treatment with NO or various NO donors or precursors, the authors showed that NO inhibits the K⁺ current with an IC₅₀ of about 350 nM. This is in the range of physiological NO concentration (200–800 nM) [12]. Dissecting the effects of NO, Núñez et al. also showed that these effects are partially mediated by the activation of the soluble guanylate cyclase/cGMP-dependent kinase pathway. In addition, further data suggest that the channel undergoes NO-dependent S-nitrosylation within the same delay as for current inhibition. The NO-mediated inhibition of the Kv1.5-related current \(I_{Kslow1}\) was confirmed in isolated mouse ventricular myocytes where the channel is expressed.

The interest in NO in AF was raised a few years ago when Cai et al. observed a decreased expression of endocardial NO
synthase and NO availability in an experimental AF model [13]. In addition, plasma levels of NO are reduced in AF patients and restored after cardioversion to sinus rhythm [14]. AF is associated with thrombosis formation in the appearance of the dysfunctional left atrium, resulting in increased risk of systemic embolism. The anti-thrombotic effects of NO are well documented, and it is proposed that the loss of such a mechanism could contribute to AF morbidity.

In addition to its anti-thrombotic effects, NO has multiple effects on vascular and cardiac physiology. NO levels are reduced in AF, and Rubart and Zipes have extensively discussed the negative effects of NO deficiency [15]. These authors suggested that maintaining normal NO levels could limit alterations due to AF. In line with this, Núñez et al proposed that the ‘tonic’ I\textsubscript{Kur} inhibition by NO in physiological conditions may be released when NO is decreased in AF. Consequently, I\textsubscript{Kur} may be larger than previously expected in AF [7], which may facilitate the maintenance and recurrence of the arrhythmia.

The work by Núñez et al. stimulates further interest in Kv1.5 as a potential target for AF treatment. In addition, this work adds another brick to the hypothesis that the control of NO levels may be a key factor for AF treatment.

However, the effects of NO on cardiac ion channels are not only limited to I\textsubscript{Kur} but also concern, for example, the L-type calcium current I\textsubscript{Ca,L}. [15]. AF-induced electrical remodeling is associated with reduced transient outward current (I\textsubscript{to}) and I\textsubscript{Ca,L} [16] and with increased inward rectifier current (I\textsubscript{K1}) [17], each effect having opposite consequences for the AP shape. Since the AP is a dynamic system governed by current–voltage feedback loops, the effects of NO on the atrial AP shape should be considered in an integrated system rather than as a sum of single effects. For this purpose, computer simulations of human atrial AP have tremendous value for inferring the consequences of subtle, complex changes in ion current characteristics due to the pathological status or the use of specific blockers [18]. To implement such models, further studies like the one by Núñez et al. are greatly needed.

References