Could Plugging the Oxidation-Mediated Ca\textsuperscript{2+} Leak Stem the Tide of the Atrial Fibrillation Epidemic?

Peter H. Backx

As the most common sustained arrhythmia, atrial fibrillation (AF) afflicts >2 million patients in the United States alone, and this number is predicted to double by the year 2050. Although AF is not life-threatening, it is linked to a 2-fold increase in mortality when present as a comorbidity in heart disease patients. AF can have devastating consequences, such as stroke, impaired cardiac performance, and promotion of cardiomyopathy. The treatment of AF can also produce life-threatening side effects, such as ventricular arrhythmias and hemorrhage. AF patients are generally classified as paroxysmal (episodes lasting <7 days), persistent (lasting >7 days but treated to restore sinus rhythm), or permanent (no attempt to restore sinus rhythm). AF is usually secondary to other conditions such as hypertension, heart failure, valvular disease, sleep apnea, hyperthyroidism, and diabetes. Most of these AF-inducing conditions are associated with elevated atrial pressure and atrial stretch, as well as increased oxidative stress and inflammation, which lead to structural and electric changes (remodeling) that create a substrate for supporting AF induction and maintenance.

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Although the majority of AF patients have preexisting cardiovascular disease, an important subpopulation do not and are therefore referred to as “lone AF” patients. Besides the obvious increase in stroke risk, a major concern with lone AF patients is their predisposition to develop persistent or permanent AF, because bouts of AF appear to promote more AF (ie, AF begets AF). AF is usually secondary to other conditions such as hypertension, heart failure, valvular disease, sleep apnea, hyperthyroidism, and diabetes. Most of these AF-inducing conditions are associated with elevated atrial pressure and atrial stretch, as well as increased oxidative stress and inflammation, which lead to structural and electric changes (remodeling) that create a substrate for supporting AF induction and maintenance.

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of calstabin2 from RYR2 channels may be sufficient to treat the oxidation-mediated induction of AF, opening up exciting new approaches for treating AF.

Shan et al23 also concluded that neither protein kinase A nor CaMKII activation plays a notable role in the enhanced sensitivity of CPVT mice to pacing-induced AF susceptibility. Their conclusion is supported by the absence of differences between CVPT mice and wild-type mice in phosphorylation of RYR2 channels at either position S2808 (the protein kinase A/CaMKII site) under baseline conditions or position S2814 (the CaMKII site) after rapid pacing. Furthermore, treatment with β-blockers did not reduce AF incidence in the 3 CPVT mouse models. At first glance, these observations are somewhat unexpected, because ventricular arrhythmias in humans and mice with CPVT are usually initiated by exercise or acute emotional stress, which causes rhythmias in humans and mice with CPVT are usually initiated by exercise or acute emotional stress, which causes

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presence of R2474S-RYR2 channels create a subclinical elevation in oxidative stress (presumably in atria only), and could structural changes induced by the R2474S mutation increase the susceptibility of RYR2 channels to oxidation (as seen in S2808D-RYR2 channels)?25  Do both wild-type and mutant RYR2 channels become oxidized in CPVT patients, who typically express both mutant and wild-type RYR2 channels? As already mentioned, results from R176Q-RYR2/S2814A mice suggest increased phosphorylation of both mutant and wild-type channels can occur in CPVT.18  Definitive answers to these questions will require biochemical methods for separating R2474S-RYR2 channels from wild-type RYR2 channels in the CPVT atria, possibly by incorporation of an antigenic tag into the mutant channels. Alternatively, measuring susceptibility to oxidation by use of heterologous expression of R2474S or other CPVT channels might also be informative.

The observation that CPVT mutations of RYR2 cause AF could provide unique opportunities for further investigation of the cellular and ionic mechanisms underlying AF, especially the contribution of abnormal Ca\(^{2+}\) handling in the setting of lone AF. These types of studies are sorely needed, because most previous mechanistic studies have relied on tissues and myocytes isolated from atria that have already undergone electric and structural remodeling. It will be interesting to explore whether AF shares features of ventricular arrhythmias seen in CPVT mutations. For example, bidirectional and polymorphic ventricular tachycardia could be explained by the appearance of regular delayed afterdepolarizations after pacing.33  Previous studies have also shown that enhanced Ca\(^{2+}\) release properties of RYR2 channels predispose to the development of pacing-induced Ca\(^{2+}\) alternans, which leads to the appearance of electric alternans and increases dispersion of repolarization.34  Ca\(^{2+}\) alternans might be particularly important in atrial myocytes because of their distinct Ca\(^{2+}\)-handling ultrastructure compared with ventricular myocytes.35  Taking advantage of these CPVT models for understanding AF mechanisms will require detailed analyses of surface and intracardiac ECGs during bouts of AF, as well as optical mapping of voltage and Ca\(^{2+}\) levels in right atrial cardiac tissue of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines: developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. J Am Coll Cardiol. 2011;57:e101–e198.


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