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EDITORIAL COMMENT

Proarrhythmic Remodeling of Atrial Myocyte Ca^{2+} Handling in Atrial Fibrillation*

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Atrial fibrillation (AF) is the most common arrhythmia in the United States and other Western nations. It is increasing in prevalence in our aging society and represents a major health problem. In general terms, AF occurs when abnormal spontaneous electrical activity in atrial myocytes, usually residing near or within pulmonary veins, overrides the normal sinus pacemaker.[1] The resulting electrical activity is rapid and chaotic such that atrial myocyte contraction is disrupted.

AF is a complex cardiac arrhythmia that can be intermittent (paroxysmal AF) or persistent. It results in the loss of coordinated atrial contractile function and can lead to serious symptoms including exercise intolerance, stroke, and heart failure. AF severity (paroxysmal to persistent) is often progressive, and it can be difficult to return persistent AF patients to a normal sinus rhythm. A better understanding of AF mechanisms that promote AF progression should guide novel strategies for more effective treatments.

AF often starts with brief bursts of AF that can revert spontaneously to normal sinus rhythm. These periods of paroxysmal AF often become more frequent, and eventually a persistent AF phenotype ensues. Disruption of atrial myocyte structure and function become more severe with the progression from paroxysmal to permanent AF, and these changes are thought to be contributors to the progression of the AF phenotype.[1] Therefore, understanding the cellular and molecular bases of the alterations in atrial myocyte function with AF progression could identify therapeutic targets to prevent or reverse the progression of AF.

AF induces increases in atrial myocyte Ca^{2+}, largely as a result of the increased beating rate with this arrhythmia. The increased beating frequency with AF results in increased Ca^{2+} influx through voltage regulated L-type Ca^{2+} channels. The resultant Ca^{2+} stress induces remodeling of atrial myocyte Ca^{2+} handling that can promote spontaneous electrical activity, which is thought to exacerbate AF. The current notion is that the changes in myocyte Ca^{2+} handling induced by AF result in structural and functional atrial remodeling that exacerbates AF.[1,2]

AF-induced changes in atrial myocyte Ca^{2+} handling have been fairly well studied in AF patients.[1,2] During many types of cardiac surgery, small pieces of right atrial cardiac tissue are removed. These tissue samples can be used to define AF-induced changes in atrial tissue structure, molecular remodeling and atrial myocyte function, including Ca^{2+} handling processes.

Previous studies with myocytes and tissues from patients with AF have shown that AF induces changes in the atrial myocyte Ca^{2+} current (I_{Ca}), sarcoplasmic reticulum (SR) Ca^{2+} uptake, and SR Ca^{2+} release through the ryanodine receptor (RyR2).[1,2] The molecules that determine these Ca^{2+} handling processes can change in abundance, and/or their activity can be altered by phosphorylation. The results of these previous studies show that AF leads to changes in the

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activity of Ca^{2+} handling in a fashion that promotes spontaneous SR Ca^{2+} release through the RyR.[1,2] The spontaneously released SR Ca^{2+} can be transported out of the cell via the electrogenic Na/Ca exchanger (NCX) or transported back into the SR via the SR Ca^{2+} ATPase (SERCa2). The relative amounts of released Ca^{2+} that are transported by these 2 mechanisms is likely determined by the location of the spontaneous release sites and their proximity to SR uptake or surface membrane NCX-mediated Ca^{2+} efflux. Importantly, Ca^{2+} transported out of the cell via electrogenic NCX induces membrane depolarization that can be sufficient to cause arrhythmic action potentials (APs).

In this issue of *JACC: Basic to Translational Science*, Tarifa et al[3] have studied the cellular and molecular bases for the increased ability of spontaneous SR Ca^{2+} release events (termed *sparks*) to induce membrane depolarization and spontaneous APs in atrial myocytes from AF patients. It is known that spontaneous SR Ca^{2+} release events are more frequent in AF atrial myocytes and that these events cause greater depolarizations and spontaneous APs,[1,2] but the underlying mechanisms are not well known. In a series of elegant experiments, Tarifa et al[3] have shown that spontaneous SR Ca^{2+} release events in AF atrial myocytes are more likely to occur just below the surface membrane, whereas spontaneous SR Ca^{2+} release events in non-AF myocytes were more likely to occur within the interior of the cell, at an increased distance from the surface membrane. Given the fact that the electrogenic NCX is localized to the surface membrane, the spontaneous SR Ca^{2+} release in AF myocytes is more likely to cause membrane depolarization and arrhythmic beating. Interestingly, the location and abundance of key molecules involved in SR Ca^{2+} release, including RyR2, were not found to be substantially disrupted in AF myocytes. Key experiments using a newly developed image analysis methodology showed that the increases in Ca^{2+} sparks at or near the sarcolemma in AF myocytes was likely caused by increased RyR2 phosphorylation at serine 2808 and a lower amount of calsequestrin-2 in the SR. Modeling analysis showed that these 2 changes, in combination, could reproduce the changes in spontaneous SR Ca^{2+} release events observed in AF myocytes. Because RyR-S2808 phosphorylation is thought to result from activation of G-protein coupled receptors that alter cAMP and the activity of protein kinase A, Tarifa et al[3] speculate that the alterations in spontaneous SR Ca^{2+} release in AF myocytes could be reduced or prevented by drugs that alter these signaling cascades. Collectively, these results help to explain the known proarrhythmic properties of atrial myocytes from AF patients.

As with most studies, this one leaves unanswered questions and opportunities for the next set of studies that could generate new insights leading to paradigm shifting AF treatments.

Unanswered questions in the Tarifa et al[3] study include why enhanced phosphorylation of well-known CaMKII target proteins, including RyR-S2814 and phospholamban-T17, were not observed. Hyperphosphorylation of these sites in AF has been observed by others and would be expected, because the rapid beating rate in AF is known to produce an increase in cellular Ca^{2+} and activation of CaMKII signaling.[1,2] It is unclear that Ca^{2+} regulatory protein phosphorylation, in situ, can be reliably inferred from observations made in isolated myocyte preparations. Atrial myocyte protein phosphorylation status in situ is likely to change in isolated myocytes because: 1) single myocytes are isolated from right atrial tissue in Ca^{2+}-free solutions; and 2) these myocytes are removed from rapid pacing rates and the presence of neurohormones that are known to regulate the phosphorylation of the proteins involved in spontaneous SR Ca^{2+} release. Comparing Ca^{2+} regulatory protein phosphorylation in freshly isolated atrial tissue and in atrial myocytes from the same or similar tissues could address these questions in the future.

Another unanswered question from the Tarifa et al[3] study is whether there are critical differences in the processes that determine spontaneous SR Ca^{2+} release between patients with paroxysmal and persistent AF. Both types of AF patients were included in this study, and data shown in Supplemental Figure 2 in that study suggest that Ca^{2+} spark distribution is significantly different in these 2 forms of AF. Defining those processes that drive the transition from paroxysmal to permanent AF[1,2] is important because therapies to convert permanent AF to normal sinus rhythm are not well established.

Tarifa et al[3] suggest that changes in the activity of G-protein coupled receptors that alter cAMP and the activity of protein kinase A may explain their results. A missed opportunity in this study was to compare results from AF patients that were or were not being treated by β-blockers. These comparisons might give insight into the utility of this therapy as

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a strategy to slow arrhythmogenic substrate evolution in AF.

In summary, the study by Tarifa et al[3] shows that changes in the spatial distribution of Ca^{2+} sparks in AF myocytes result from increases in RyR-S2808 phosphorylation and reduced calsequestrin 2 abundance, and these changes can explain the proarrhythmic properties these myocytes exhibit. Understanding the causes and consequences of these changes could provide clues regarding AF progression and novel AF therapies.

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