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Commentary

Atrial fibrillation (AF) is the most common sustained arrhythmia disease. Current drug- and surgical-based therapies are ineffective in about 40% to 50% of AF patients; therefore, there is a great need to better understand the underlying mechanisms of this disease and identify potential therapeutic targets. In this issue of the *JCI,* Greiser and coworkers discovered that atrial remodeling in response to sustained tachycardia silences Ca$^{2+}$ signaling in isolated rabbit and human atrial myocytes. This Ca$^{2+}$ release silencing was attributable to a failure of subcellular propagated Ca$^{2+}$ release due to an increased cytosolic buffering strength. The results from this study challenge the current paradigm that Ca$^{2+}$ release instability underlies AF. Instead, Ca$^{2+}$ silencing could be protective against the massive cellular Ca$^{2+}$ loading that occurs during chronic AF.

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Calcium in atrial fibrillation — pulling the trigger or not?

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Atrial fibrillation (AF) is the most common sustained arrhythmia disease. Current drug- and surgical-based therapies are ineffective in about 40% to 50% of AF patients; therefore, there is a great need to better understand the underlying mechanisms of this disease and identify potential therapeutic targets. In this issue of the JCI, Greiser and coworkers discovered that atrial remodeling in response to sustained tachycardia silences Ca2+-signaling in isolated rabbit and human atrial myocytes. This Ca2+-release silencing was attributable to a failure of subcellular propagated Ca2+ release due to an increased cytosolic buffering strength. The results from this study challenge the current paradigm that Ca2+ release instability underlies AF. Instead, Ca2+-silencing could be protective against the massive cellular Ca2+ loading that occurs during chronic AF.

Atrial fibrillation: arrhythmogenic atrial remodeling and unstable Ca2+ handling

Atrial fibrillation (AF) is the most common sustained arrhythmia disease, affecting 1% to 2% of the US population (1). Because current therapy — either with drugs or surgical ablation — remains ineffective in about 40% to 50% of AF patients (2), there is a great need to understand the underlying mechanisms of AF and identify better therapeutic targets. Previous work has shown that a rapid atrial activation rate induces electrical remodeling of the atria, which in turn increases the risk for AF (3). The remodeling consists of L-type Ca2+ current reduction (4), sodium-calcium exchanger upregulation, reduced Ca2+-transients (5), and altered sarcoplasmic reticulum (SR) function, which is characterized by increased spontaneous Ca2+ sparks and waves and has been attributed to hyperactive RyR2 channels, possibly as the result of increased phosphorylation at residues Ser2808 and Ser2815 (5–7). These so-called “leaky” RyR2 channels and increased Ca2+ waves are capable of triggering delayed afterdepolarizations and focal atrial electrical activity (8); therefore, hyperactive RyR2 channels are thought to be important contributors to the induction and maintenance of AF in humans (9).

Rapid arterial pacing induces paradoxical Ca2+ signaling silencing

It remains unclear whether the Ca2+ signaling remodeling observed in myocytes isolated from humans with AF is a consequence of a rapid activation rate or due to concomitant heart disease. In this issue of the JCI, Greiser et al. (10) attempt to answer this question by characterizing subcellular Ca2+ signaling in atrial myocytes harvested from rabbits that underwent 5 days of rapid atrial pacing (RAP) and compared them with atrial myocytes harvested from patients with chronic AF. Surprisingly, Greiser et al. did not observe changes in Ca2+ sparks, Ca2+ waves, or Ca2+ release instability, but rather they found that Ca2+ release was strongly suppressed in the center of rabbit atrial myocytes. Greiser and colleagues have termed this suppression “Ca2+ signaling silencing,” and a similar central Ca2+ release silencing also occurred in atrial myocytes harvested from patients with chronic AF. What causes the loss of central Ca2+ release? Because the density of transverse tubules is much lower than that of ventricular myocytes, atrial myocytes rely on Ca2+ diffusion to activate Ca2+ release in the myocyte core (11); consequently, the Ca2+ signal that is generated in the subsarcolemmal region from Ca2+ release triggered by L-type Ca2+ channels is propelled to the cell center by repetitive release from intracellular RyR2 clusters (Figure 1A). Greiser et al. determined that cytosolic Ca2+ buffering strength is markedly increased in RAP myocytes. This increased Ca2+ buffering capacity could be the consequence of reduced troponin I phosphorylation, which in turn would increase Ca2+ binding to troponin C in the myofilaments. Hence, increased Ca2+ binding to myofilaments may reduce the free Ca2+ available to activate neighboring RyR2 clusters. Together with the observed reduction in RyR2 expression, increased cytosolic buffering likely explains the failure in the centripetal Ca2+ propagation of RAP myocytes (Figure 1B), because SR Ca2+ content, RyR2 channel activity, and peripheral L-type current-induced Ca2+ release were all preserved.

Greiser and colleagues (10) also report that, consistent with previous studies, the remaining RyR2 clusters were hyper-phosphorylated at the protein kinase A (PKA) phosphorylation site (Ser2808), which may compensate for the reduction in RyR2 protein expression and help sustain subsarcolemmal Ca2+ release despite reduced L-type Ca2+ currents (Figure 1B). However, RAP myocytes exhibited reduced RyR2 phosphorylation at the calmodulin-dependent protein kinase II (CaMKII) phosphorylation site (Ser2815) and no changes in CaMKII activity. This finding contrasts with previous studies that reported increased atrial CaMKII activity and CaMKII-dependent RyR2-Ser2815 phosphorylation in human AF (5). Moreover, other studies have shown that treatment with CaMKII inhibitors or selective disruption of the Ser2815...
CaMKII phosphorylation site prevented AF in animal models through a reduction of SR Ca²⁺ leak (12). One explanation for this discrepancy could be the limited duration of pacing in the rabbit model used by Greiser and colleagues, in which none of the animals exhibited spontaneous AF after the 5 days of rapid pacing. It remains unclear whether the effects observed in response to limited atrial pacing are just transient changes due to the short period of this protocol, or whether, as suggested by Greiser et al., Ca²⁺ signaling silencing represents a maintained response of atrial myocytes to chronic rapid activation. Strikingly, but consistent with the unaltered CaMKII activity, Greiser et al. did not observe changes in phospholamban activity. Rather, they found decreased expression of the SR Ca²⁺ ATPase (SERCA), despite the fact that the Ca²⁺ load in the SR was also unchanged. This reduction in SERCA expression with no changes in SR Ca²⁺ load can be explained by the reduction in Ca²⁺ release from the SR due to Ca²⁺ release silencing; however, the role of SERCA remodeling during AF remains unclear. Recent studies suggest that in atrial muscle, SERCA activity is also regulated by sarcolipin (13, 14), and it remains to be tested whether changes in sarcolipin contribute to altered SERCA activity in the rabbit model of RAP.

**Ca²⁺ signaling silencing: counteracting arrhythmogenic atrial remodeling?**

The study by Greiser et al. (10) elegantly provides evidence of altered atrial Ca²⁺
Commentary

The role of Ca2+ signaling silencing in the AF will be needed to better understand Studies in the intact atria during and after or in preventing AF triggering is not clear. It is well established that Ca2+-dependent signaling affects atrial remodeling: cellular Ca2+ loading during rapid pacing activates calcineurin, which in turn dephosphorylates, for example, nuclear factor of activated T cells (NFAT) and promotes its translocation to the nucleus. In the nucleus, NFAT regulates several targets at the transcriptional level, including the L-type Ca2+ channel, which is reduced by NFAT (15). In this regard, it would be interesting to further analyze whether atrial Ca2+ signaling silencing reduces NFAT translocation to the nucleus and thus limits the electrical and structural remodeling that occurs after the Ca2+ overload in AF. This structural remodeling contributes to the reinduction of AF. Although it takes place after the electrical remodeling, the Ca2+ overload induced by rapid atrial activation rates is one of the main signals that triggers the remodeling process (16). Thus, while the Ca2+ signaling silencing discovered by Greiser et al. (10) appears to help limit the consequence of rapid pacing–induced Ca2+ overload, the extent of this protective effect in the intact organ during AF or in preventing AF triggering is not clear. Studies in the intact atria during and after AF will be needed to better understand the role of Ca2+ signaling silencing in the pathophysiology of AF.

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