Atrial Fibrillation in Heart Failure
Steady Progress but Still a Long Way to Go
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Management of atrial tachyarrhythmias, especially atrial fibrillation (AF), in patients with congestive heart failure (CHF) remains a major challenge. It is widely recognized that CHF promotes AF and that AF worsens CHF. An individual with either condition who develops the other has higher morbidity and poorer prognosis. The prevalence of AF and CHF is expected to increase as the population ages. Therefore, it remains just as likely as it was more than a decade ago that the emerging epidemic of AF and CHF will continue to be both a challenge and an opportunity.

Contrary to popular belief, there is strong mechanistic evidence that CHF promotes AF and that AF worsens CHF. Atrial fibrillation in CHF results in a higher cardiovascular mortality rate, CHF, or stroke by attempting to maintain sinus rhythm with current AAD therapy (primarily amiodarone). Newer nonpharmacological therapies, including pulmonary vein (PV) isolation and cardiac resynchronization therapy, are generating considerable interest; however, their rates of efficacy in patients with AF and CHF have not been established definitively. Thus, continued progress toward an enhanced understanding of upstream mechanisms that promote AF and contractile dysfunction in CHF and development of innovative therapeutic approaches based on fundamental, mechanistic insights is of paramount importance.

In this context, the study by Yeh et al in this issue of Circulation: Arrhythmia and Electrophysiology provides important new insights into the role of atrial calcium dysregulation in promoting atrial arrhythmias and contractile dysfunction in the CHF substrate. This report comes from the Nattel laboratory, which has been a major driving force in improving our understanding of arrhythmogenic mechanisms in a variety of AF substrates, including CHF.

CHF-induced atrial remodeling plays a significant role in genesis and maintenance of atrial tachyarrhythmias in this setting. Much new information has become available in recent years describing effects of CHF on structural, electrical, and functional properties of atrial tissue, some of which may have important pathophysiological and therapeutic implications. Cardiac remodeling in the failing heart is highly complex, involving a host of pathways and multiple, dynamic processes that operate at many levels. Determining those alterations that are critical and causally related to atrial arrhythmogenesis or contractile dysfunction in CHF is challenging but certainly crucial to development of a target-specific, therapeutic approach.

The mechanisms that underlie the electrophysiological basis of AF continue to be studied in experimental models and in humans undergoing ablation procedures. Although it is well substantiated that electrical activity originating in the pulmonary and thoracic veins is intimately involved in the initiation and perpetuation of AF, the long-debated controversy as to whether this repetitive activity has its mechanism based on reentry (macro or micro), triggered activity, or automaticity has not been resolved conclusively. Studies utilizing frequency analysis and activation mapping have shown that the AF in a canine CHF model is characterized by discrete stable, high-frequency areas in the PVs, as well as the left atrium (LA) and right atrium. Both reentry and focal drivers have been shown to promote and sustain atrial arrhythmias in failing hearts. It is important to note, however, that effective therapy (other than ablation) has not been developed that can specifically suppress PV and non-PV triggers that initiate and maintain AF in CHF.

Altered cellular calcium homeostasis is a major hallmark of contractile dysfunction and is increasingly recognized as an important contributor to ventricular arrhythmogenesis in CHF. However, limited data are available with regard to atrial intracellular calcium handling and its role in arrhythmogenesis in CHF, which is the focus of the study by Yeh et al. Some relevant insights are available from prior studies in the failing ventricle. At the cellular level, calcium dysregulation in the failing ventricle can be attributed, in part, to impaired calcium release and reuptake from the sarcoplasmic reticulum (SR). Abnormalities of calcium dysregulation are associated with a significant incidence of nonreentrant arrhythmias that occur as a result of early or delayed afterdepolarizations (DADs) due to nonelectrically driven SR calcium release. In addition to abnormalities of impulse formation, calcium dysregulation can also play a direct role in development of reentrant ventricular arrhythmias. A mechanistic relationship exists between abnormal calcium handling and repolarization alternans, a potent substrate for reentrant arrhythmias. Thus,
there is growing appreciation for calcium-mediated arrhythmogenesis in the failing ventricle. Are we headed down the same path for the atria?

The results presented by Yeh et al suggest a magnitude of calcium dysregulation in the atria similar to that in the ventricles. Notably, reduced cell shortening and triggered activity mediated by DADs in isolated myocytes were demonstrated, suggesting that altered calcium regulation may be a mechanism of atrial mechanical and electrical dysfunction in CHF. The expression and function of calcium regulatory proteins are, however, where differences between the ventricles and atria become apparent. Typically, ventricular calcium transients are smaller and have a slower decay phase in myocytes from failing hearts than in myocytes from normal hearts. In contrast, Yeh et al report that atrial calcium transient amplitude is larger, with a similar decay phase, in cells from canines with CHF as compared with normal cells, even though cell shortening is reduced. As elegantly shown by the authors, the mechanism for reduced cell shortening in the presence of enhanced calcium release probably is due to atrial contractile protein dysfunction attributed to reduced PKA phosphorylation of myosin-binding protein C, an important mediator of contraction. Altered expression of calcium regulatory proteins can explain some of the calcium transient changes, but it’s not obvious whether this is the case. Even though Yeh et al report reduced atrial ryanodine receptor expression in CHF, calcium release is larger than normal. This is probably due to enhanced calcium entry ($I_{\text{L,Ca}}$) caused by longer action potentials that increase SR calcium content. Interestingly, SR content was larger in the LA than in the right atrium, which may explain a higher occurrence of ectopy in the LA. Yeh et al also report increased calcium/calmodulin-dependent protein kinase II, which may enhance SR calcium uptake, but SR Ca(2+) ATPase is decreased. This may explain why no significant change in the decay phase of the calcium transient was observed. Calcium/calmodulin-dependent protein kinase II may also contribute to enhanced calcium entry.11

The authors suggest that enhanced SR calcium content and a reduced expression of calsequestrin promote initiation of DAD-mediated triggered activity. In this CHF model, it is not clear if the ryanodine receptor in the atrium is impaired as in the ventricle. If not, then the mechanisms of DAD activity may be purely calcium overload in the presence of normal ryanodine receptor. Thus, there are ways to explain the contractile and electrical dysfunction on the basis of protein expression; however, the mechanisms of arrhythmogenesis are not exactly the same as in the failing ventricle.

Mechanisms of atrial tachyarrhythmias vary according to the substrate, such as remodeling during rapid atrial rates (ie, AF begets AF) and changes in autonomic tone. In either case, calcium dysregulation may be playing an important role. Atrial remodeling caused by rapid rates can alter calcium-sensitive currents and thus the substrate for AF.12,13 Cytosolic calcium as well as atrial ectopy increase during acetylcholine administration after a period of rapid pacing.14 A novel hypothesis of calcium-mediated triggered activity in the atria has been suggested, whereby the calcium transient far outlasts an acetylcholine-shortened action potential, such that the sodium–calcium exchanger becomes active in the forward mode and depolarizes the membrane.15 Studies utilizing optical mapping of calcium and voltage in the atria have shown that DADs and triggered activity can be initiated in the LA during autonomic changes and calcium dysregulation can play an important role in arrhythmias originating from the PVs.16,17 The extent to which these mechanisms play a role in atrial arrhythmogenesis in the intact, failing heart is not clear, and additional studies are required. In addition to spontaneous ectopy and repetitive activity mediated by triggered activity, calcium dysregulation may also play a role in development of reentrant atrial arrhythmias that are mediated by repolarization alternans. In a canine chronic myocardial infarction model, atrial alternans is enhanced.18 Therefore, calcium dysregulation in the atrium may promote a broad range of arrhythmia mechanisms.

Also notable in the study by Yeh et al is that isolated CHF atrial myocytes displayed reduced contractility over a range of stimulation frequencies $\approx$2 Hz attributed to alterations in calcium-handling contractile proteins. Pacing-induced CHF also upregulates $\beta$-myosin heavy chain in the LA free wall, which reduces LA contraction velocity in the intact heart as an adaptation to chronic LA pressure and volume overload.19 In severe CHF, compensatory LA contraction is decreased as a result of increased LV diastolic wall stress and intrinsic LA systolic dysfunction. LA systolic failure contributes to the transition from moderate to advanced CHF. If contractile dysfunction is present in the atria during physiological rates in CHF, what might this imply for patients who develop AF in this setting? During AF, LA contractile function is severely depressed, contributing to reduced cardiac output, decreased exercise capacity, and increased thromboembolism risk. Although intuitively one might expect that restoration of sinus rhythm therefore would improve the adverse hemodynamics associated with AF, this may not always be the case. A small study in patients with AF and CHF who underwent electrical cardioversion found no benefit in peak oxygen consumption, exercise duration, LV size, or neurohormone levels even with maintenance of sinus rhythm after cardioversion.20 Furthermore, administering AADs that prolong atrial APD theoretically could worsen calcium overload by prolonging atrial repolarization time. Thus, even if sinus rhythm is restored and maintained with current AADs, intrinsic atrial contractile dysfunction and cellular calcium overload may persist. Viewed from this perspective, it may not be entirely surprising that current rhythm control strategies may not benefit patients with AF and CHF. Moreover, this also implies that other therapies (such as ablation) that do not address the underlying atrial contractile dysfunction in CHF may not be associated with sustained improvement in important clinical outcomes.

Treatment of patients with AF in the setting of CHF is no less daunting an endeavor today than it was in the prior century. Despite some important advances in our understanding of the mechanisms that promote CHF-related AF, many questions remain to be answered. More needs to be done to define the culprit mechanisms that promote atrial arrhythmias and contractile dysfunction in CHF and to use these critical insights to develop novel and more effective therapeutic
approaches. The study by Yeh et al and others like it in the future may help to continue the steady progress made thus far and ultimately to lessen the impact of this major source of cardiovascular morbidity and mortality.

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References

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