New Era for Translational Research in Cardiac Arrhythmias

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Heart failure is a multifactorial syndrome of hemodynamic decompensation that is a final common pathway for a variety of cardiovascular disorders. More than 40% of patients with heart failure lose their lives because of sudden cardiac death. Thus, the prevention of life-threatening cardiac arrhythmia is one of the major goals in the treatment of heart failure. The Cardiac Arrhythmia Suppression Trial (CAST) study has shown that class I antiarrhythmic agents are not clinically beneficial for long-term treatment of arrhythmias in patients with previous myocardial infarction. Although β-adrenergic blockers and amiodarone are effective in reducing arrhythmic mortality, the underlying mechanisms are not fully understood. Thus, development of the experimental animal models and comprehensive studies for elucidation of pathophysiological characteristics of life-threatening cardiac arrhythmias in heart failure is of fundamental importance.

The electrophysiological substrates associated with life-threatening cardiac arrhythmias are varied and include impairment of conduction attributable to structural alterations, spatial and temporal inhomogeneity of action potential duration attributable to remodeling of ionic channels, and triggered activity. There are several studies describing changes in the functional expression of various ion channels and Ca2+-handling proteins/systems in cardiac myocytes isolated from failing hearts. In human and some animal models of heart failure, the protein level of the sarcoplasmic reticulum (SR) Ca2+ ATPase (SERCA) is reduced and that of Na+-Ca2+ exchanger (NCX) is increased. It has also been reported that the reduced SR Ca2+ uptake activity and enhanced Ca2+ extrusion via NCX results in a decrease of the Ca2+ content in the SR and of contractility. In addition to the downregulation of SERCA activity and upregulation of Na+-Ca2+ exchanger, downregulation of K+ currents and of the β-adrenergic receptor signaling pathway have been reported in late-stage heart failure. These fragmented reports, however, have not provided us with the integrative view of how these alterations cause lethal cardiac arrhythmias.

Delayed afterdepolarizations (DADs) can trigger fatal ventricular tachycardia. DADs are oscillations of membrane voltage elicited by SR Ca2+ release that activate several depolarizing currents, including forward-mode Na+-Ca2+ exchange. It is an enigma that despite the lower SR Ca2+ load in the failing heart, spontaneous Ca2+ releases of a magnitude sufficient to generate triggered activity, such as DADs, can occur.

In this issue of Circulation Research, Pogwizd et al. give a fascinating answer to this paradox. Cardiac hypertrophy and, ultimately, decompensated heart failure are established in rabbits by destroying the aortic valve and constricting the aorta. The rabbits often die suddenly because of ventricular tachycardia and fibrillation. By studying the cardiac myocytes isolated from rabbit ventricles, Pogwizd et al. showed, as in previous studies, an upregulation of NCX proteins, downregulation of Iκ1 current, and downregulated but still residual activity of β-adrenergic signaling system. They demonstrated that even though the SERCA2 activity and the β-adrenergic receptor signaling pathway are downregulated in failing ventricular myocytes, the residual β-adrenergic receptor/protein kinase A activity is still able to enhance SR Ca2+ uptake. Their data fit well with the higher risk of fatal arrhythmias and sudden death in less severe stages of heart failure. The L-type Ca2+ channel current density was not altered; therefore, stimulation of the myocytes in the presence of β-adrenergic receptor agonists was able to load the SR with Ca2+ sufficient to induce spontaneous Ca2+ release. The released Ca2+ was extruded from the cell via an upregulated NCX, thus producing substantial inward current. The enhanced NCX current in the setting of a reduction of Iκ1 density was sufficient to generate DADs. Pogwizd et al. quantitatively analyzed the relationship between the reduction of Iκ1 and depolarization in response to current injection and demonstrated that the Ca2+-dependent ion channels other than NCX, such as ICa(Ca) and I(Ca,L), are not required to produce DADs in their heart failure model.

The study by Pogwizd et al. not only confirms the results of previous studies on human heart failure and animal models that altered cellular Ca2+ handling may be a final common pathway in both contractile dysfunction and arrhythmogenesis but also provides a novel integrative...
view on the quantitative relationships among the alterations in the Ca\(^{2+}\)-handling mechanisms and ionic currents in generation of lethal cardiac arrhythmias. Thus, this study may have opened another door for the translational approach for treating heart failure.

This study identifies multiple targets for the treatment of heart failure. Although Pogwizd et al\(^9\) emphasized the rationale for the β-blocking agent in treatment of the lethal cardiac arrhythmia in heart failure, the possibilities for controlling function of other targets may be examined additionally in future studies. The study by Pogwizd et al\(^9\) raises the interesting possibility that therapeutic modulation of β-adrenergic signaling in the failing heart may be possible by increasing the activity of G protein–mediated pathways, for example, by applying A\(_1\)- or m\(_2\)-receptor agonists.\(^{14,15}\) This work should initiate future experiments aimed at the mechanistic understanding and treatment of the lethal cardiac arrhythmias in heart failure. In this regard, several points relevant to future studies should be emphasized. First, although the study by Pogwizd et al\(^9\) is integrative, it is not completely comprehensive. The alterations of many more proteins in cardiac myocytes, which might be involved in the generation of lethal arrhythmias, should be examined to reach a final view on the mechanisms and thus evidence-based development of treatment. The candidates may include various cytokines, cytoskeletal and contractile proteins, ion channels, and transporters other than I\(_{Kr}\), and NCX, such as stretch-activated channels and Na\(^+-\)H\(^+\) exchanger. Second, the results obtained in their rabbit model may represent an important but not the only mechanism of arrhythmogenesis in multifactorial heart failure syndrome. Lethal cardiac arrhythmias can be generated by different mechanisms, depending on the etiology and stage of heart failure. Although DADs seem to be the predominant cause of nonreentrant ventricular arrhythmias in this model, reentrant mechanisms, for instance, seem to be responsible for many fatal arrhythmias in ischemic cardiomyopathy.\(^{16,17}\) Furthermore, downregulation of I\(_{Kr}\), found in the study by Pogwizd et al\(^9\), may only occur in specific types of human heart failure.\(^{18}\) Third, a major unanswered question is how compensated cardiac hypertrophy devolves into decompensated. Are the alterations in Ca\(^{2+}\)-handling proteins of cardiac myocytes in the heart failure causative or merely the result of decompensation?

We anxiously await future studies that move us closer to the development of evidence-based therapeutic approaches to the failing heart.

**References**

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