Fading Sodium Channels in Failing Hearts

John R. Bankston, Robert S. Kass

Heart failure (HF) affects over 5 million Americans with 550,000 new cases diagnosed each year. Despite advances in understanding and treatment, the mortality rate remains extremely high with up to 50% of the patients dying suddenly. Ventricular arrhythmias are frequently the cause of sudden death in these heart failure patients. The mechanisms for these arrhythmias remain the focus of fervent research, but ion channel remodeling in the heart with prolongation of the action potential is one of the best documented changes in heart failure that lead to these fatal arrhythmias. Prolongation of the cardiac action potential can occur through a decrease in outward current or an increase in inward current during the plateau phase of the action potential. Reduction in outwardly conducting potassium channels during heart failure has been well documented. The role of the inwardly conducting cardiac sodium channel (NaV1.5) in sudden death in heart failure patients is much less clear. In this issue of Circulation Research, Shang et al report a novel contribution of altered gene transcription in failing hearts to the expression of potentially arrhythmogenic dysfunctional sodium channels expressed in the heart.

Sodium Channels and Channelopathies
During excitation, opening of the cardiac sodium channel produces a large and rapid inward current that underlies membrane depolarization and conduction of electrical impulses in the heart. The precise timing of ion channel opening and closing can be altered under pathological conditions or during drug treatment, resulting in changes in cellular action potentials that can eventually affect heart function. Dysfunctional sodium channel gating or functional expression levels has been found in many cases to be responsible for several cardiac electrical diseases such as Long QT syndrome, Brugada syndrome, and sick sinus syndrome, all of which predispose the affected individuals to increased risk of lethal arrhythmias.

Gain of Function Alterations of Sodium Channels in Failing Hearts
Multiple reports suggest now that the behavior of the cardiac sodium channel changes in failing hearts. In healthy hearts, the sodium channel opens rapidly and then transitions into a nonconducting inactive state. Multiple reports have now shown that, in failing hearts, there is a significant increase in the fraction of channels that fail to enter an absorbing inactivated state resulting in small, persistent Na+ current (\(I_{NaL}\)) during the action potential plateau phase. Given the small membrane conductance during the plateau phase of the action potential, a persistent inward current can result in marked impact on the action potential, delaying repolarization and Mechanisms underlying this “gain of function” alteration of Na+ channels in failing hearts remains to be fully understood, although evidence is surfacing suggesting Ca2+/CaM modulation of Na+ channel function may be at least one posttranslational pathway in failing hearts.

In addition to changes in action potential duration, multiple studies have found that altered conduction through the myocardiuni greatly contributes to the risk of sudden death in HF patients. One of the principal determinants of conduction in ventricular myocardium is availability of sodium (Na) current. Loss of sodium current can lead to failed or slowed conduction and can produce an enhanced dispersion of recovery in failing ventricles facilitating reentry and ventricular tachyarrhythmias.

Loss of Sodium Channel Function in Failing Hearts Through Altered Gene Transcription
In this issue, Shang et al explore a new role for the cardiac sodium channel that may contribute to an increase in the risk of arrhythmia in HF. The authors focused on altered transcript levels for NaV1.5 in ventricular tissue from heart failure patients and found a reduction in WT channel mRNA along with an increase in mRNA levels for 3 previously undiscovered truncated transcripts. Shang et al found a total of 6 mRNA variants in human heart including WT SCN5A, 2 variants that differ only in the length of the poly-A tail, and 3 novel truncated transcripts that result in channels that are missing segments from domain IV S3 or S4 through the C terminus. These truncated transcripts, when tested in HEK cells, were shown to not pass current when transfected alone and shown to reduce peak current when transfected into a stable cell line expressing the full length channel. The authors more closely examined the relative levels of these transcripts during development as well as in patients with heart failure. Adult hearts showed higher levels of all 3 truncated transcripts relative to those of fetal heart tissue. More interestingly, ventricular tissue from failing hearts showed a 25% decrease in WT transcript levels as well as a 4- and 14-fold rise in 2 of the 3 truncated mRNAs. The authors were also able to confirm that this led to a reduction of NaV1.5 protein levels in the ventricular tissue. To look at the physiological effects of these truncations the authors attempted to create a gene-targeted mouse model with a stop codon inserted near the location where the various truncations cause premature death.

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stops in vivo, but this mutation was embryonic lethal. They were, however, able to differentiate mouse embryonic stem cells that were heterozygous for this channel truncation into cardiomyocytes and found that peak sodium current was reduced by 86% and that action potentials, recorded in current clamp, showed a slowing of beat frequency as well as a reduction in the rate of rise of the action potential.

These results shed light on the observation that frequently patients with heart failure present with conduction system abnormalities and nearly 50% show intraventricular conduction delay (IVCD) and left bundle branch block. This causes the signal from the atrium to be distributed through the ventricles in a cell to cell manner instead of via the usual fast-conduction pathway (ie, the bundle branches). The results from Shang et al suggest that a reduction in sodium channel levels attributable to changes in the transcription of the SCN5A gene may underlie many of the clinical features, such as IVCD and left bundle branch block, in patients with HF that often lead to reentrant arrhythmias and contribute to the high risk of fatal arrhythmias. In fact, previous reports have shown that HF patients that have IVCD, potentially because of a loss of expressed functional sodium channels, show an increased mortality compared with HF patients that do not present with those symptoms.

This work adds to the growing literature that suggests that changes in mRNA transcript levels lead to altered functional expression of ion channels which may underlie changes in the cardiac action potential or changes in impulse conduction that are observed in failing hearts. Reports, often contradictory in nature, have suggested that NCX, SERCA, RyR, L-type Ca channels, and several of the cardiac potassium channels show changes in mRNA levels in failing hearts. The results of this study further the idea that altered regulation of transcription during heart failure contributes significantly to ion channel remodeling in the heart that in turn can lead to fatal arrhythmias. The authors here discover a new twist on that well established mechanism: during heart failure, changes in mRNA levels of alternatively spliced variants of ion channels, not just a change in the transcript levels of the normal channel, can alter the important cellular currents that drive action potentials in the heart.

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Disclosures
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