A Surprising New Arrhythmia Mechanism in Heart Failure

Dan M. Roden

Heart failure is the most common discharge diagnosis in the United States, with a prognosis worse than many cancers. Patients with heart failure die for two reasons: advanced circulatory insufficiency or sudden death. We know that continuous online monitoring of cardiac rhythm from patients with advanced heart failure is inevitably abnormal and often shows long runs of irregular and/or polymorphic ventricular tachycardia. Unlike patients with ventricular tachycardia due to healed myocardial infarction, those with heart failure rarely have ventricular tachycardia inducible by programmed stimulation, and when it is, its prognostic importance is uncertain. Therapy with conventional antiarrhythmics is no more successful in patients with heart failure than in those with serious ventricular arrhythmias due to healed infarction.

Arrhythmias, Disordered \([\text{Ca}^{2+}]_i\), Homeostasis, and \(K^+\) Current Downregulation in Heart Failure

Given the huge public health impact of the problem and the failure of current pharmacological therapies, one obvious way forward in attacking the problem of sudden death in heart failure is to understand the basic molecular mechanisms underlying arrhythmia susceptibility in this setting. The disordered contractility that characterizes heart failure naturally suggests abnormal intracellular calcium homeostasis, a well-recognized feature of the heart failure phenotype, as a candidate arrhythmia mechanism, and experimental studies support this idea. Pogwizd and colleagues have used three-dimensional activation mapping in rabbits with volume-overload heart failure to identify focal triggers and repetitive focal activity as a major mechanism underlying VT in this model, behaviors that are highly reminiscent of afterdepolarization-related triggering due to intracellular calcium overload. Indeed, their further studies indicated that heart failure–related upregulation of the sodium-calcium exchanger, in the setting of downregulation of the inward rectifier and maintained \(\beta\)-adrenergic responsiveness, markedly increases the propensity for triggered arrhythmias due to intracellular calcium overload. More upstream mechanisms implicated as drivers of the “hypertrophy/heart failure” phenotype in cellular, animal, and human models include calcium-mediated activation of transcriptional programs, a leaky calcium release channel, and increased CaM kinase activity.

Another common electrophysiological finding both in animal models and in patients with heart failure is reduction in a range of potassium currents, including \(I_{\text{To}}, I_{\text{Kr}}\), and the delayed rectifier components. Indeed, this effect, which in at least some cases has been definitively attributed to decreased ion channel gene transcription, contributes to action potential prolongation and disordered QT regulation, another characteristic finding in heart failure. Marbán, Tomasselli, and colleagues proposed in the mid-1990s that such action potential prolongation would be linked to arrhythmogenesis, in effect that a torsades de pointes–like mechanism (at the time not well defined) might be linked to the problem of serious arrhythmias in heart failure. In this issue of Circulation Research, Akar and Rosenbaum provide evidence for that link, by reporting striking similarities in the electrophysiological properties of “wedge preparations” isolated from dogs with pacing-induced heart failure, compared with those from animals treated with drugs causing torsades de pointes.

The Wedge Preparation and Transmural Heterogeneity of Repolarization

Seminal observations from the laboratory of Antzelevitch over the past decade have documented the existence of a previously unrecognized cell type in the midmyocardium whose unusual response to electrophysiological stressors such as proarrhythmic drugs is an important contributor to long QT–associated arrhythmias. Indeed, M cells may constitute up to 40% of the bulk of the ventricular myocardium. The left ventricular “wedge” preparation, originated and popularized by the Antzelevitch laboratory, has identified marked drug-induced action potential prolongation in the M-cell layer as a key contributor to increased transmural heterogeneity of repolarization that, in turn, appears to generate the substrate for reentry that is now thought to underlie typical torsades de pointes. The concept that heterogeneity, or “dispersion,” of action potential durations creates a substrate for reentry is an older one, but the concept that this heterogeneity might extend to sites across the ventricular wall, rather than between adjacent sites located in the same cell layer, is newer.

In the heart failure wedge preparation, as in the drug-treated wedge preparation, there was marked prolongation of action potential durations among M cells, with much less prolongation in endocardial and epicardial cell types, leading to increased dispersion of repolarization. Further, in both settings, stimulation from the epicardium (the site with the shortest action potentials) generates conduction block at the...
epicardial-midmyocardial junction with polymorphic arrhythmias arising as a result of conduction around this region of functional block. Extending the link to heart failure are studies in the wedge and other preparations that have implicated disordered intracellular calcium homeostasis as a potential contributor to drug-induced torsades de pointes.22,23

M cells display long basal action potentials, suggesting reduced net inward current, and this may underlie their susceptibility to display such marked prolongation with QT-prolonging drugs (or pacing-induced heart failure). However, it is not yet established why M cells display long action potentials under normal conditions; suggested possibilities include reduced K+ current, increased inward current, altered intracellular calcium handling, or altered gap junction protein function.17,24,25 Most importantly, we have yet to understand how a disease like heart failure, however defined, engenders changes in expression or function of not only these candidate proteins, but a myriad of others that together make up the complex signaling pathways that we call normal electrophysiology. Even more fundamentally, we do not understand the signals that tell a cell to become an M cell or the mechanisms that determine their unusual, and not totally homogeneous, distribution within the midmyocardium; obviously, their location and their electrophysiological properties will be linked in some as yet poorly understood fashion. Indeed, a difficulty with this field is an exact definition of what constitutes a normal M cell. It is a cell with a long action potential, like those in the endocardium, but with a prominent phase 1 notch, as in the epicardium. These gross morphological descriptors of action potential configuration reflect balancing acts among a multitude of inward and outward currents, but how big a notch constitutes a notch or how long an action potential one must have before an M cell becomes an M cell and is no longer an epicardial cell is not so clear. The gradients described by Akar and Rosenbaum17 suggest that these distinctions are continuous rather than abrupt, and thus we should expect gradients of expression of channels and other proteins important for electrogenesis in the same fashion.

Implications for Heart Failure Research and Patient Care

Any investigator studying heart failure or any clinician caring for patients with heart failure will immediately recognize that the diagnosis of “heart failure” itself represents a highly heterogeneous mixture of clinical diagnoses, presentations, and responses to therapies. Thus, an interesting and important question raised by the present study is how commonly increased transmural dispersion of repolarization occurs in heart failure and to what extent it contributes to generating the associated arrhythmia-prone substrate. As a corollary, one can turn the question around: having implicated heterogeneity of repolarization as an important mechanism in clinically important polymorphic tachycardias such as classical torsades de pointes and ventricular tachycardia in heart failure, how often does this mechanism underlie other polymorphic tachycardias?

Many insults cause the contractile dysfunction/arrhythmia phenotype we call heart failure. Intervening once this pheno-

References


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