United We Stand; Divided We Fibrillate?

Barry London

The heart is an electric and biochemical syncytium with its cardiac myocytes coupled by gap junctions that allow the passage of both ionic current and small molecules. Electric coupling allows the rapid spread of depolarization through the atrium, ventricle, and specialized conduction system that is required for coordinated and efficient mechanical function. In addition, these low-resistance intercellular connections help to prevent arrhythmias in several ways. First, tight coupling leads to synchronization of repolarization across the cardiac chambers that decreases dispersion of repolarization and refractoriness and prevents functional reentry. Second, the flow of ions and metabolites minimizes the differences at the single cell level that could result from variations in ion channel expression and metabolic state, stabilizing electric propagation and preventing triggered activity. Third, if an aberrant action potential is triggered in a cell or small group of cells, the source–sink mismatch of the electric syncytium will often prevent propagation. In fact, both theoretical and experimental studies have estimated the number of synchronized myocytes required to initiate a premature ventricular beat.

Although coupling between cardiac myocytes is important, the absence of coupling is also critical in some circumstances. Electric isolation is required for pacemaker function in the sinoatrial and atrioventricular nodes, and limited coupling is required to overcome source–sink mismatch and prevent exit block as impulses leave the nodes. In addition, under pathophysiological conditions, such as myocardial infarction, damaged and dying myocytes must be isolated from the healthy tissue to prevent lethal arrhythmias.

Cardiac-specific deletion of connexin-43, the major cardiac connexin in gap junctions, increases arrhythmia susceptibility in mice. In experimental animal models and in humans, pathological conditions, such as heart failure, lead to gap junction remodeling and decreased intercellular conductance. Along with other types of electric remodeling, including decreased inward Na+ current (I_{Na}) leading to conduction slowing, increased late Na+ current (I_{Na,L}) leading to action potential duration prolongation, increased spontaneous Ca2+ release from the sarcoplasmic reticulum and increased expression of the sodium-calcium exchanger leading to increased transient inward current (I_{Na}) and afterdepolarizations, and decreased inward rectifier current (I_{K1}) leading to membrane depolarization, these changes increase the likelihood of both the initiation and propagation of ventricular arrhythmias.

The late Massachusetts Congressman and the 47th Speaker of the United States House of Representatives, Thomas Phillip (Tip) O’Neil, was famous for his statement that “All politics is local.” For the heart’s electric activity, this statement seems to hold some truth. In this issue of Circulation Research, Lang et al use high-resolution simultaneous voltage and calcium optical imaging to show that while hearts from wild mice have a small number of cells with spontaneous asynchronous calcium transients and no measurable depolarization, hearts from thoracic banded mice with heart failure have many more myocytes with both calcium waves and depolarization. They go on to show using calcein fluorescence recovery after photo-bleaching that cell-to-cell coupling is decreased in general in hearts from banded mice but to an even greater extent in myocytes with asynchronous calcium transients in those hearts.

Finally, they show that multiple asynchronous Ca2+ transients can interact, that asynchronous Ca2+ transients can disrupt synchronous Ca2+ transients, and that asynchronous Ca2+ transients can trigger action potentials. Putting everything together, there seems to be a subpopulation of cardiac myocytes with abnormal intercellular coupling that are responsible for a significant portion of arrhythmia initiation in this mouse model.

Several important questions remain. The specific mechanisms underlying the decrease in cellular coupling have not been ascertained in the affected population of cells. It is not clear whether the myocytes surrounding those with asynchronous transients have decreased coupling—that is are there actually islands of partially uncoupled cardiac myocytes, as the authors suggest? It is also not clear whether or to what extent the mechanisms underlying the increase in asynchronous Ca2+ transients are related to those underlying the change in coupling. Finally, there is no guarantee that all forms of heart failure will show the same electric phenotype or that the findings in mice will translate to large mammals including humans.

I wonder, though, whether the study reported here has even more far reaching implications than the authors suggest. Both nonischemic cardiomyopathies and the decompensation phase of ischemic cardiomyopathies involve structural remodeling with the death/dropout of cardiac myocytes accompanied by replacement fibrosis. In the electrically and metabolically coupled heart, which myocytes die when stressed and why? It is possible that the subpopulation of partially electrically uncoupled cardiac myocytes with asynchronous Ca2+ transients that Lang et al have identified is, in fact, the population destined for dropout. If true, the study of that group of cells could provide invaluable insights, beyond the confines of electrophysiology, into the pathophysiology of heart failure.

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progression. What is the molecular characterization of those cells, and why are they more vulnerable than others? Could we target treatments toward those cells to slow heart failure progression? Would increasing the coupling of those cells to their neighbors help to support them while other heart failure therapies take effect?

The lyrics of a popular Rock-and-Roll song from the 1970s stated “You can go your own way, Go your own way, You can call it, Another lonely day.” In the article by Lang et al., they seem to have identified a population of cardiac myocytes doing just that and increasing the electric vulnerability of the heart as a result. A major strength of the heart lies in its connectivity, mediated to a significant extent by gap junctions that can fail in the setting of diseases, such as heart failure. The whole is truly greater than the sum of its parts. Perhaps, a population of myocytes seceding from the syncytium has been identified, and now we can work to reunite and reconnect them for the benefit of the whole.

Disclosures
None.

References

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