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In the Spotlight: Cardiovascular Engineering

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It has been an exciting year of novel advancements in cardiovascular engineering. New molecular mechanisms have been discovered, and relationships leading to emergent behavior in the heart have been ascertained. Below is a brief review of these new developments.

The article by Rutherford *et al.* [1] published in the journal *Circulation Research* examined the impact of structural remodeling in the infarct border zone on electrical activation. The authors aimed to determine whether structural remodeling alone in the infarct border zone could provide a substrate for reentrant arrhythmia by characterizing the three-dimensional (3-D) structure of the myocardium surrounding a rat healed myocardial infarction at high spatial resolution and using the data to construct a model of electric activation. Analysis of the structural data revealed that myocyte tracts traversed the border zone, and that there was a heavy infiltration of collagen into the adjacent myocardium. When the structure was incorporated into a model of electrical activation, unidirectional propagation occurred in the border zone, with rate-dependent slowing and conduction block, and occasional reentry. Activation times were prolonged because of tract path length and local slowing. The results of the study indicate that highly-detailed image based models offer unprecedented opportunity to examine the role of structural heterogeneity in the dynamic substrate for reentrant arrhythmias.

The structural substrate for reentrant arrhythmias was the subject of another publication in the same journal. Ashihara *et al.* [2] used computer simulations to investigate the role of fibrosis in permanent/persistent atrial fibrillation and the formation of complex fractionated atrial electrograms (CFAEs). The study hypothesized that electrotonic interactions between atrial myocytes and fibroblasts in the fibrotic regions play an important role in arrhythmogenesis. The study used a human atrial tissue model in heart failure, in which coupling of fibroblasts to atrial myocytes was represented, resulting in shorter action potential duration, slower conduction velocity, and lower excitability. Heterogeneous fibroblast proliferation in the myocardial sheet resulted in frequent spiral wave breakups, and the bipolar electrograms recorded at the fibroblast proliferation area exhibited CFAEs. The simulations demonstrated that ablation targeting such fibroblast-derived CFAEs terminated AF, indicating that fibroblast proliferation in atria might be responsible for the genesis of CFAEs during persistent/permanent AF.

The optical mapping technique was used to study conduction remodeling and the electrophysiological substrate for arrhythmia in human end-stage nonischemic left ventricular cardiomyopathy in the paper by Glukov and co-workers [3] published in the journal *Circulation*. Coronary-perfused left ventricular wedge preparations from ten human

hearts with end-stage nonischemic cardiomyopathy and ten nonfailing hearts were optically mapped and the remodeling examined. Heart failure produced heterogeneous prolongation of action potential duration resulting in the decrease of transmural action potential duration dispersion. In the failing hearts, transmural activation was significantly slowed from the endocardium to the epicardium. Failing hearts demonstrated spatially discordant conduction velocity alternans, which resulted in nonuniform propagation discontinuities and wave breaks. The authors concluded that conduction disorders resulting from the anisotropic downregulation of Cx43 expression, the reduction of Cx43 phosphorylation, and increased fibrosis is likely to be a critical component of the arrhythmogenic substrate in patients with nonischemic cardiomyopathy.

The study by Ng *et al.* [4] published in the *Journal of American College of Cardiology* sought to test the hypothesis that “virtual” electrophysiological simulation studies with a 3-D magnetic resonance imaging reconstruction of the left ventricle can reproduce the reentrant circuits of induced ventricular tachycardia in a porcine model of myocardial infarction. Myocardial infarction by coronary artery occlusion was induced in eight pigs, and *in vivo* cardiac magnetic resonance images acquired. Normal areas, gray zones, and infarct cores were classified based on voxel intensity. In the computer model, the different zones were assigned different electrophysiological properties. Virtual electrophysiological studies was performed and compared with results of actual *in vivo* programmed stimulation and noncontact mapping. This initial study demonstrated the feasibility of using a computational model reconstructed from magnetic resonance images of the left ventricle to predict ventricular tachycardia circuits. Such approach could be helpful to plan catheter ablation strategies or to identify patients who are at risk of future episodes of ventricular tachycardia.

In an exciting development published in the journal, *Science*, Previs *et al.* [5] presented research on interactions of actomyosin molecular motors, and specifically on the ability of cardiac myosin-binding protein C (cMyBP-C) to regulate these motors. Using single-particle fluorescence imaging techniques, transgenic protein expression, proteomics, and modeling, we the authors found that cMyBP-C slowed actomyosin motion generation in native cardiac thick filaments. This mechanical effect was localized to sites where cMyBP-C resides within the thick filament, the C- zones, i.e., cMyBP-C modulates cardiac contractility despite being restricted to the C-zone. The mechanical effect was modulated by phosphorylation and site-specific proteolytic degradation. These results provide molecular insight into why cMyBP-C should be considered a member of a tripartite complex with actin and myosin that allows fine-tuning of cardiac muscle contraction.

Finally, the journal *Nature* published a breakthrough in the utilization of human embryonic-stem-cell-derived cardiomyocytes (hESC-CMs) to improve the function of infarcted hearts. The study by Shiba *et al.* [6] focused on hESC-CMs’ electro-physiological behavior *in vivo*, and specifically, on the risk of arrhythmias following hESC-CM transplantation, and on the electromechanical integration of hESC-CMs in injured hearts. The authors used a guinea-pig model to show that hESC-CM grafts in injured hearts protect against arrhythmias and can contract synchronously with host muscle. Infarcted hearts with hESC-CM grafts show improved mechanical function and a significantly reduced incidence of both spontaneous and induced ventricular tachycardia. To assess the activity of hESC-CM grafts *in vivo*, hESC-CMs expressing the genetically encoded calcium sensor, GCaMP3 were transplanted in the infarcted hearts. By correlating the GCaMP3 fluorescent signal with the host ECG, the authors found that grafts in uninjured hearts had consistent 1:1 host-graft coupling. Grafts in injured hearts were more heterogeneous and typically included both coupled and uncoupled regions. Thus, human myocardial grafts were shown to meet physiological criteria for true

heart regeneration, providing support for the continued development of hESC-based cardiac therapies for mechanical and electrical cardiac repair.

We look forward to new discoveries in cardiovascular engineering in the year to come.

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