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In the Spotlight: Cardiovascular Engineering

Natalia Trayanova

Department of Biomedical Engineering, The Johns Hopkins University, Baltimore, MD 21224 USA

Natalia Trayanova: ntrayanova@jhu.edu

Over the past year several cardiovascular engineering studies have been published in top scientific journals such as *Science*, *Nature*, and *Proceedings of the National Academy of Science (PNAS)*. This brief report reviews these significant advances in cardiovascular engineering.

The article by Wong *et al.* [1] in the August issue of *Science Translational Medicine* presents research that utilizes Electrocardiographic Imaging (ECGI) to noninvasively map human ventricular arrhythmias. ECGI methodology combines body surface electrical potentials and heart-torso anatomical geometry reconstructed from computed tomography (CT) or magnetic resonance imaging (MRI) scans, to noninvasively determine, i.e., calculate, the local electrical signals of the heart (electrograms) over the entire surface of the ventricles. Using the relative timing of the constructed electrograms, activation sequences (isochrones) can be constructed, providing information about the electrical patterns of ventricular tachycardia (VT). The method was applied in a series of 25 patients undergoing catheter ablation procedures for various forms of VT. ECGI was used to characterize each VT on the basis of analysis of isochrones, potential, local electrogram, and wavefront propagation information. A three-step process was used for each patient: (i) localize the site of origin of the arrhythmia from isochrone and potential maps; (ii) evaluate the mechanism by observing the three-dimensional propagation pattern and its relationship to the myocardial substrate; and (iii) approximate the myocardial depth of the origin with local electrograms. The results reveal diverse activation patterns, mechanisms, and sites of initiation of human VT. Over a wide range of VT locations and mechanisms, the noninvasive ECGI results were consistent with those of invasive catheter mapping. ECGI overcomes the limitations of the standard body surface 12-lead ECG by providing high spatial resolution maps of ventricular arrhythmias on the heart surface. Where the 12-lead ECG requires interpretation of body surface data in terms of cardiac activity, assuming a “standard” heart shape and size in a “standard” torso, ECGI uses the patient’s specific heart-torso geometry to identify the location of the arrhythmia and map its sequence on the heart. Additionally, ECGI offers distinct advantages over invasive catheter mapping. These advantages include its noninvasive nature and the ability to map the entire tachycardia in a single beat. The spatial resolution and ability to image continuously and simultaneously the activation sequences over the entire ventricular surfaces allowed the researchers to make observations beyond the ability of current tools regarding VT initiation and maintenance, and regarding the relationship of the VT activation wavefronts to the ventricular substrate.

The same issue of *Science Translational Medicine* published another cardiovascular engineering study, this one focused on the pharmacological approach to the management of lethal cardiac rhythms. Pharmacological management of cardiac arrhythmia has failed in the past because it has not been possible to predict how drugs target cardiac ion channels; drugs have intrinsically complex dynamic interactions with ion channels, altering the emergent electrical behavior generated at the level of the organ (the heart). The study by Moreno *et al.* [2] presented a computational approach for predicting the effects of anti-arrhythmic therapy, which was informed and validated with experimental data that defined key measurable

parameters necessary to simulate the interaction kinetics of the anti-arrhythmic drugs flecainide and lidocaine with cardiac sodium channels. Flecainide is a prototypical class 1C drug that carries a warning from the FDA, while lidocaine is a class 1B anti-arrhythmic drug not known to cause conduction block. The model incorporated a Markovian representation of the cardiac sodium channel. To model drug binding, any discrete state in the drug-channel model was assumed to be drug-free or drug-bound. Experimental data was used to determine access, diffusion, and channel conformation-specific affinity for charged and neutral fractions of these common anti-arrhythmic drugs. After conducting channel-level simulations that informed the determinants of pharmacokinetics, the model was used to predict the effects of these drugs at varied drug concentrations and pacing frequencies on normal human ventricular cellular and tissue electrical activity in the setting of a common arrhythmia trigger, spontaneous ventricular ectopy. Simulation results, including those in an MRI-based human ventricular model, demonstrated that in the models with high clinical doses of flecainide but not in the models with high clinical doses of lidocaine, a premature stimulus administered within the vulnerable window induced unidirectional block and retrograde propagation that resulted in persistent reentry. This difference in action was found to be due to flecainide's strong use-dependent block that reduced excitability and slowed conduction velocity to reduce the wavelength of reentry. The model forecasted the clinically relevant concentrations at which flecainide and lidocaine exacerbate, rather than ameliorate, arrhythmia. Experiments in rabbit hearts validated the model predictions. This computational framework initiated the first steps toward development of a virtual drug-screening system that models drug-channel interactions and predicts the effects of drugs on emergent electrical activity in the heart.

The past year has seen a surge in the studies of cardiac de-fibrillation, typically considered a mature research subject. This surge in research has been motivated by the desire to develop new, low-voltage methodology for termination of lethal arrhythmias or to apply defibrillation in novel, less damaging ways. The article by Luther *et al.* [3] published in the July issue of the journal *Nature* offers a method for low-voltage control of electrical turbulence in the heart. Controlling the complex spatiotemporal dynamics underlying life-threatening cardiac arrhythmias such as fibrillation is extremely difficult because of the nonlinear interaction of excitation waves in a heterogeneous anatomical substrate. In the absence of a better strategy, strong electrical shocks have remained the only reliable treatment for cardiac fibrillation. This study used a sequence of five low-energy electric field pulses (termed low-energy antifibrillation pacing, LEAP) and compared the energy used to successfully terminate atrial fibrillation to that for standard atrial defibrillation using a single, high-energy shock. A substantial reduction was demonstrated in 56 episodes in seven *in vivo* experiments, in which an average energy reduction of 84% was found. The differences in LEAP effectiveness between *in vivo* and *in vitro* atrial preparations were then assessed, in which three of the five *in vitro* atrial preparations were derived from the hearts used in the *in vivo* experiments. The overall energy reduction in the *in vitro* experiments was 91%. To elucidate the mechanism of defibrillation by LEAP, the authors studied the response of quiescent atrial and ventricular tissue to a pulsed electric field using optical mapping. The heart has heterogeneities of all sizes, and the authors hypothesized that these heterogeneities become sources of activation following a series of low-voltage shocks; the many pulses of the field recruit many such activation sites. The density of sources was found to increase with increasing field strength for both the ventricle and the atrium. The article demonstrated that the geometric structure of the coronary vasculature (one type of heterogeneities in the heart) resulted in characteristic activation dynamics in response to the pulsed electric field. The heterogeneity of the vascular structure allowed the recruitment of the corresponding density of wave sources inside the myocardium that effectively terminated the wavefronts of fibrillation. These distributed wave sources acted as non-invasive, intramural multi-site pacing, which was key to the novel approach of LEAP.

The second out-of-the-box defibrillation study, by Tandri *et al.* [4], was published in the September issue of *Science Translational Medicine Research*. The premise of the study is based on the fact that sustained kilohertz-range alternating current (AC) fields have been known to block electrical conduction in nervous tissue; this conduction block is instantaneous and completely reversible upon cessation of the stimulus. The study by Tandri *et al.* hypothesized that electric fields, such as those used for neural block, when applied to cardiac tissue, would similarly produce reversible block of cardiac impulse propagation and lead to successful defibrillation, and that this methodology could potentially be a safer means for termination of life-threatening reentrant arrhythmias. The article provided proof of the concept for conduction block in cardiac tissue during high-frequency AC field stimulation in cell monolayers and animal models (guinea pig and rabbit). During field application over a broad frequency range (50 to 1000 Hz), the transmembrane potential of cells remained at a field-dependent, elevated (partially depolarized) voltage throughout the preparation, and pacing-initiated waves were completely blocked. Conduction block was significantly more likely at field strengths 5 V/cm for the frequencies between 50 Hz and 1 kHz than at frequencies outside this range or field strengths lower than this voltage. Computer simulations using a bidomain rabbit heart model were used to dissect the underlying mechanisms. The data revealed a previously unrecognized capacity for myocardial cells to be placed in an extended, yet immediately reversible, state of refractoriness by an applied electric field. The imposed refractory state blocked all wave propagation and resulted in termination of reentrant arrhythmias, without impairment of subsequent cellular electrical function or initiation of postshock fibrillatory activity.

Finally, imaging methodologies also made substantial contributions this year in uncovering the structure-function relationships in the cardiovascular system. Two studies were particularly notable. The first, by Liu *et al.* [5], published in *Nature Medicine*, presented a new form of optical coherence tomography, termed micro-optical coherence tomography (μ OCT). The μ OCT system utilized a very broad bandwidth light source and common-path spectral-domain OCT technology to provide 1- μ m axial resolution and a lateral resolution of 2 μ m, maintained over an extended focal depth. These technical advances enabled the researchers to conduct cross-sectional imaging of human tissue (cadaver coronary arteries) with resolutions that are approximately an order of magnitude better than those of conventional OCT systems. The μ OCT images provided clear pictures of cellular and subcellular features associated with atherogenesis, thrombosis and responses to interventional therapy. These results suggested that μ OCT could complement existing diagnostic techniques for investigating atherosclerotic specimens, and that it could become a useful tool for cellular and subcellular characterization of the human coronary wall *in vivo*.

The second study, by Luther *et al.*, [6] published in the journal *PNAS* used electron tomography of rapidly-frozen and freeze-substituted muscle to provide a direct evidence that the myosin-binding protein C bridges myosin and actin filaments in intact muscle. Myosin-binding protein C (MyBP-C) is a thick filament protein playing an essential role in muscle contraction. MyBP-C mutations cause heart and skeletal muscle disease in millions worldwide, however the mechanism of MyBP-C function has remained unknown. It has been hypothesized that MyBP-C regulates contraction in a unique way—by bridging thick and thin filaments, however evidence supporting this hypothesis *in vivo* has been lacking. The authors used electron tomography to obtain such evidence. The bridging of myosin and actin filaments in intact muscle implied a mechanism for communicating the relative sliding between thick and thin filaments, which could modulate the contractile process.

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