CARDIAC OPTOGENETICS

A move in the light direction

Computer simulations show how low-intensity illumination can be used to terminate cardiac arrhythmias.

EIKE M WÜLFERS AND FRANZISKA SCHNEIDER-WARME

For a human heart to pump blood through our circulatory system, billions of muscle cells, called cardiomyocytes, must contract in a well-orchestrated manner. Ordered contraction is achieved via sequential electrical excitation of cells. Cardiomyocytes are excited when a sufficiently strong electric stimulus causes them to depolarize; they then remain in their activated state for some time; and, lastly, they return to their resting state, ready to be activated again. For normal heartbeats, electrical excitation originates from specialized pacemaker cells in the sinus node of the heart, which depolarize automatically. This rhythmically generated electrical signal then propagates along cardiomyocytes throughout the heart. A short time after depolarization, cardiomyocytes contract. Thus, rhythmical electrical activity leads to a regular heartbeat.

Cardiac arrhythmias can be caused by various factors – such as diseased cells and scar tissue – and they are associated with serious clinical conditions, including myocardial infarction, heart failure, and sudden cardiac death. One specific mechanism responsible for cardiac arrhythmia is so-called re-entrant electrical activity: this happens when the electrical impulse that excites cardiomyocytes does not terminate after all cells have been activated. Instead, due to pathological changes in cell or tissue properties, the excitation wave finds a way to circle back and re-activate cells out-of-turn. Under certain conditions, a self-sustaining ‘rotor’ can form, where electrical activity keeps circling in the heart for extended periods of time. While rotating, it emits spiral waves of electrical excitation that override the normal heart rhythm (Pandit and Jalife, 2013; Figure 1A).

One elegant way to study mechanisms of cardiac arrhythmias is optogenetics. In cardiac optogenetics, light-sensitive proteins are expressed in heart cells and are used to monitor or steer their electrical properties and function (Schneider-Warme, 2018; Zgierski-Johnston and Schneider-Warme, 2021). For example, blue light can be used to activate an ion-channel protein called channelrhodopsin-2, which results in depolarization of cells. By activating this protein in cardiomyocytes, researchers have already successfully generated optical pacemakers (Arrenberg et al., 2010; Bruegmann et al., 2010) and conducted optical defibrillation in animal models (Bruegmann et al., 2018; Bruegmann et al., 2016; Crocini et al., 2016; Nyns et al., 2017). Now, in eLife, Stefan Luther and colleagues – including Sayedeh Hussaini as first author – report that low-intensity light may be used to steer rotors (Hussaini et al., 2021). Using a combination of cardiac optogenetics and computational modelling, they describe guiding rotors towards locations where re-entrant electrical activity is no longer possible, thereby terminating cardiac arrhythmias.

Related research article Hussaini S, Venkatesan V, Biasi V, Romero Sepúlveda J, Quiñonez Uribe R, Sacconi L, Bub G, Richter C, Krinski V, Parlitz U, Majumder R, Luther S. 2021. Drift and termination of spiral waves in optogenetically modified cardiac tissue at sub-threshold illumination. eLife 10: e59954. doi: 10.7554/eLife.59954
Computational modelling has long been used by cardiac researchers to explore how cellular (and sub-cellular) mechanisms act together in healthy or diseased heart tissue (Loewe et al., 2018). Hussaini et al. started with an established mathematical model of cardiomyocyte electrical activity (Petkova-Kirova et al., 2012) and added differential equations that describe light-activated currents mediated by channelrhodopsin-2 (Williams et al., 2013). A reaction-diffusion equation (the so-called monodomain model) was then used to couple multiple model cells in a two-dimensional tissue model.

Utilizing this model, the researchers – who are based at the Max Planck Institute for Dynamics and Self-Organization in Göttingen, the University of Göttingen and other institutions in Germany, France, Italy and Canada – first investigated the effect of illumination with intensities so low that the cardiomyocytes were slightly depolarized from their resting state, but were not excited. They found that increasing the intensity of such ‘sub-threshold’ illumination has two effects: it decreases the velocity at which electrical excitation is relayed from cell to cell, and it decreases the dominant frequency of spiral waves. Both results are in keeping with classically expected single-cell behaviour, but Hussaini et al. confirmed them in real tissue for the first time by performing ex vivo experiments with intact mouse hearts.

Next, Hussaini et al. simulated what could happen when using sub-threshold illumination with linearly graded light intensity. They found that the rotor – which previously had been stable – tended to move towards the part of the tissue where the light intensity was higher (Figure 1B). Moreover, the steeper the gradient, the faster the rotor moved. In another simulation, one region of the tissue was exposed to light of constant, low intensity, while the remaining tissue was not illuminated: here the rotor moved to the illuminated region (Figure 1C). Finally, they predicted that successive partial illuminations of the 2D tissue could be used to steer the rotor to parts of the tissue, where the rotor could not continue to self-sustain.

Hussaini and colleagues propose a novel approach for the termination of cardiac arrhythmias using sub-threshold illumination. In fact, the underlying mechanism may have played a role in previous breakthrough observations in cardiac optogenetics, such as the demonstration of optical defibrillation in animal models mentioned above. Further work is needed to verify effects of interventions proposed based on computational modelling, as hearts are characterized not only by a complex geometry, but also by tissue heterogeneities that rotors might become anchored to. Looking to the future, the obvious question is whether optogenetic modulation of cardiac electrophysiology, as described here, may ultimately be used to terminate
arrhythmias in humans. Answering this question will require further research – it will be necessary, for example, to overcome the challenges associated with the expression of light-gated channels in cardiomyocytes, and with targeted light delivery. The work reported in this paper is undoubtedly an important step in the light direction.

Eike M Wülfers is at the Institute for Experimental Cardiovascular Medicine, University Heart Center Freiburg – Bad Krozingen, and the Faculty of Medicine, University of Freiburg, Germany

Franziska Schneider-Warme is at in the Institute for Experimental Cardiovascular Medicine, University Heart Center Freiburg – Bad Krozingen, and the Faculty of Medicine, University of Freiburg, Germany

Competing interests: The authors declare that no competing interests exist.

References

Arrenberg AB, Stainier DY, Baier H, Huisken J. 2010. Optogenetic control of cardiac function. Science 330:971–974. DOI: https://doi.org/10.1126/science.1195929, PMID: 20881965

Bruegmann T, Malan D, Hesse M, Beiert T, Fuegemann CJ, Fleischmann BK, Sasse P. 2010. Optogenetic control of heart muscle in vitro and in vivo. Nature Methods 7:897–900. DOI: https://doi.org/10.1038/nmeth.1512, PMID: 20881965

Bruegmann T, Boyle PM, Vogt CC, Karathanos TV, Arevalo HJ, Fleischmann BK, Trayanova NA, Sasse P. 2016. Optogenetic defibrillation terminates ventricular arrhythmia in mouse hearts and human simulations. Journal of Clinical Investigation 126:3894–3904. DOI: https://doi.org/10.1172/JCI88950

Bruegmann T, Beiert T, Vogt CC, Schrickel JW, Sasse P. 2018. Optogenetic termination of atrial fibrillation in mice. Cardiovascular Research 114:713–723. DOI: https://doi.org/10.1093/cvr/cvx250, PMID: 29293898

Crocini C, Ferrantini C, Coppini R, Scardigli M, Yan P, Loew LM, Smith G, Cerbai E, Poggesi C, Pavone FS, Sacconi L. 2016. Optogenetic design of mechanistically-based stimulation patterns for cardiac defibrillation. Scientific Reports 6:35628. DOI: https://doi.org/10.1038/srep35628, PMID: 27748433

Hussaini S, Venkatesan V, Biasi V, Romero Sepúlveda J, Quíñonez Uribe R, Sacconi L, Bub G, Richter C, Kriški V, Parlitz U, Majumder R, Luther S. 2021. Drift and termination of spiral waves in optogenetically modified cardiac tissue at sub-threshold illumination. eLife 10:e59954. DOI: https://doi.org/10.7554/eLife.59954

Loewe A, Wülfers EM, Seemann G. 2018. Cardiac ischemia—insights from computational models. Herzschrittmachertherapie + Elektrophysiologie 29:48–56. DOI: https://doi.org/10.1007/s00399-017-0539-6, PMID: 29305703

Nyns ECA, Kip A, Bart CI, Ploom JJ, Zeppenfeld K, Schalij MJ, de Vries AAF, Pijnappels DA. 2017. Optogenetic termination of ventricular arrhythmias in the whole heart: towards biological cardiac rhythm management. European Heart Journal 38:2132–2136. DOI: https://doi.org/10.1093/eurheartj/ehw574, PMID: 28011703

Pandit SV, Jalife J. 2013. Rotors and the dynamics of cardiac fibrillation. Circulation Research 112:849–862. DOI: https://doi.org/10.1161/CIRCRESAHA.111.300158

Petkova-Kirova PS, London B, Salama G, Rasmusson RL, Bondarenko VE. 2012. Mathematical modeling mechanisms of arrhythmias in transgenic mouse heart overexpressing TNF-α. American Journal of Physiology-Heart and Circulatory Physiology 302:H934–H952. DOI: https://doi.org/10.1152/ajpheart.00493.2011

Schneider-Warme F. 2018. The power of optogenetics: potential in cardiac experimental and clinical electrophysiology. Herzschrittmachertherapie + Elektrophysiologie 29:24–29. DOI: https://doi.org/10.1007/s00399-017-0545-8, PMID: 28011703

Williams JC, Xu J, Lu Z, Klimas A, Chen X, Ambrosi CM, Cohen IS, Entcheva E. 2013. Computational optogenetics: empirically-derived voltage- and light-sensitive channelrhodopsin-2 model. PLOS Computational Biology 9:e1003220. DOI: https://doi.org/10.1371/journal.pcbi.1003220, PMID: 24068903

Zgierski-Johnston CM, Schneider-Warme F. 2021. Observing and manipulating cell-specific cardiac function with light. Advances in Experimental Medicine and Biology 1293:377–388. DOI: https://doi.org/10.1007/978-981-15-8763-4_24, PMID: 3398827