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Can the Human Heart be Reset by Light?

An optogenetic alternative to traditional electrical cardioversion

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Traditionally, patients suffering with sustained arrhythmia, i.e. atrial and ventricular fibrillation, haemodynamically unstable supraventricular tachyarrhythmia etc, undergo cardioversion to restore sinus (normal) rhythm. This generally involves defibrillation of a sedated patient with a high-energy electrical shock (Nusair *et al*., 2010). Despite this, it is well documented that electrical cardioversion has low spatiotemporal resolution (i.e., cardioverts the entire heart, rather than the specific arrhythmic area), reducing its therapeutic success. It is also associated with some damaging effects, such as electroporation of cell plasma membranes (Al-Khadra *et al*., 2000).

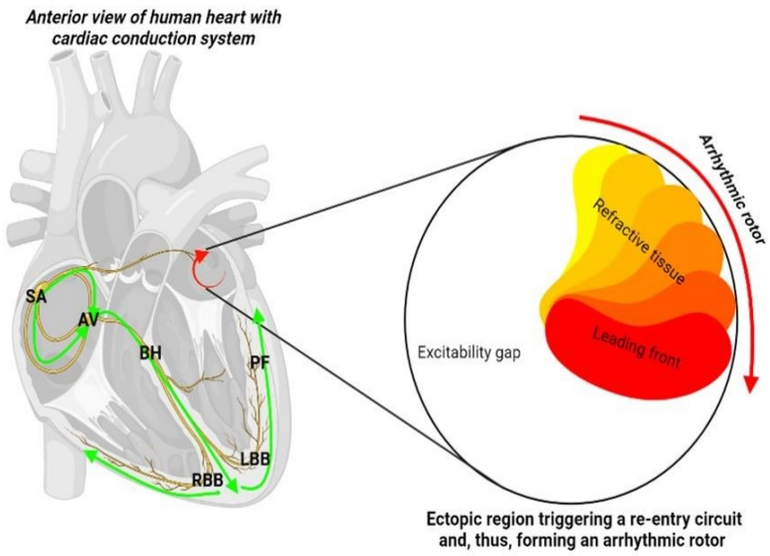

Figure 1. Arrhythmic contractions form when ectopic foci generate re-entrant circuits. These re-entrant circuits develop into arrhythmic rotors, which then move through the excitability gap and generate regions of uncoordinated myocardial contraction. The excitability gap is the primary target of photo-defibrillators as, in essence, preventing conduction of the pro-arrhythmic wave through would terminate the uncoordinated contraction. Normal cardiac conduction system pathway (green) and pathological arrhythmic re-entrant circuits (red). SA; Sinoatrial node, AV; Atrioventricular node, BH; Bundle of His, LBB; Left Bundle Branch, RBB; Right Bundle Branch, PF; Purkinji Fibres. *Original figure, generated via BioRender.com*

As such, multiple research groups have suggested an alternative form of cardioversion that does not require an electrical shock: optogenetics. This aims to overcome the canonical issues of electrical cardioversion by improving spatial accuracy. Optogenetics is so powerful that it won the 'Nature 2010 Method of the Year' award (Nature, 2010). In essence, optogenetics involves exposing photo-sensitive proteins to light in order to propagate signalling and elicit a response. For example, Campos & Herbison (2014) demonstrated how they could artificially control gonadotropin-releasing hormone (GnRH) neuron firing rates to determine their gonadotropin release patterns using photosensitive Cre-dependent channelrhodopsin (ChRS) opsin proteins. Such proteins were delivered to the aforementioned GnRH neurones via adenoviral transduction. Specifically, the neurones were exposed to blue light, this activates the ChRS proteins to stimulate action potentials and neuronal firing. Ultimately, it has been demonstrated that excitable cell behaviour can be directly modulated by light exposure.

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This theory can be applied to cardioversion as excitable cardiomyocytes in the myocardium can be artificially depolarised if they contain photo-sensitive cardiac ion channels (Knollman, 2010). This has led to the proposal of so-called 'photo-defibrillators'. By exposing a newly photo-sensitive myocardium to a specific frequency of light, cardioversion can effectively be achieved to eliminate arrhythmia.

Pathophysiology of arrhythmia

The most common mechanism by which an arrhythmia is generated is through the presence of ectopic triggers in the myocardium (see Figure 1). In atrial fibrillation, the base of the pulmonary vein is the most common location of such ectopic foci (Gong *et al*., 2007). Put simply, these are random regions within the heart that initiate contraction in areas other than the sino-atrial (SA) node. As such, small waves of contraction (called re-entry circuits) form which can combine and form pro-arrhythmogenic rotors. These rotors circulate in slow conducting, relaxed tissue; the excitable gap. Such rotors are responsible for the seemingly uncoordinated contraction seen in atrial fibrillation, for example. In effect, different regions of the

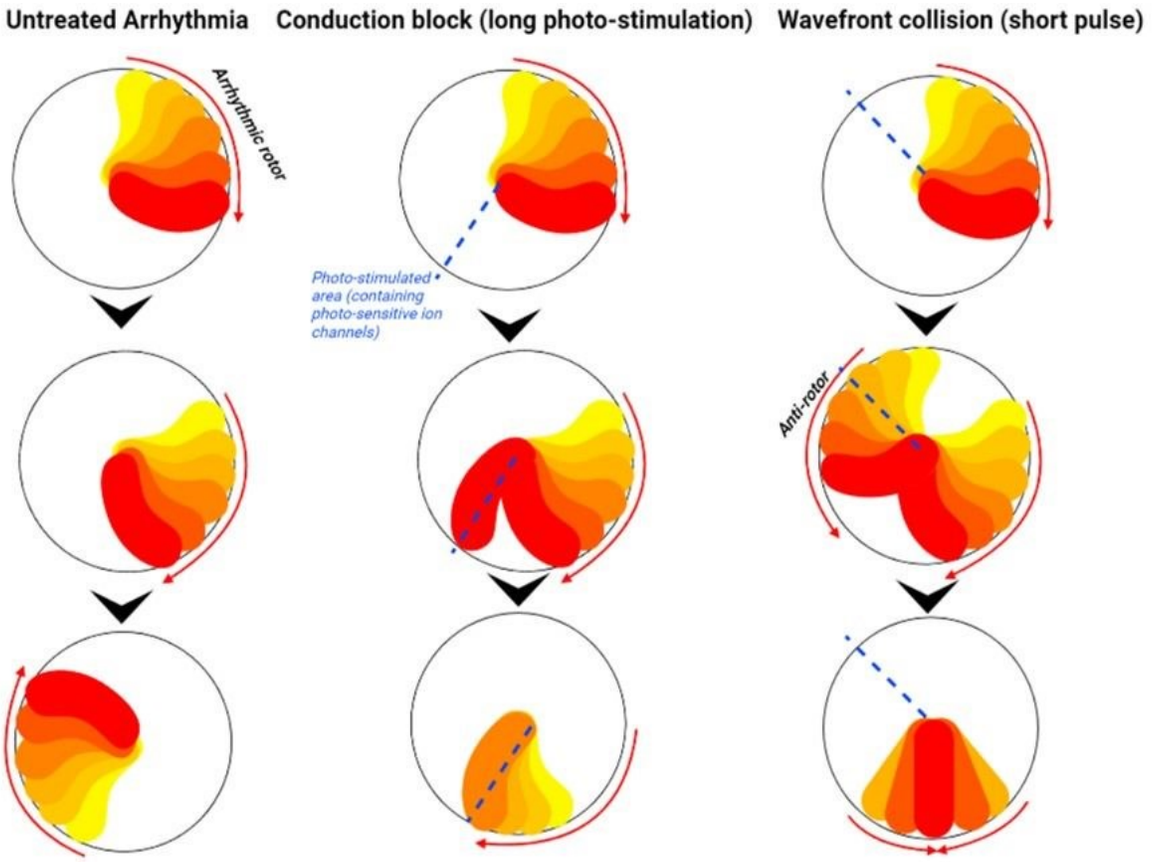

Figure 2. There are 2 proposed mechanisms for optogenetic-based cardioversion. In an untreated arrhythmia (left panel), the arrhythmic rotor continues to circulate through the myocardial tissue, generating prolonged uncoordinated contraction. When long photo-stimulation is applied to the excitatory gap (middle panel), the area becomes refractory. As such, the arrhythmic rotor cannot propagate through it and, thus, terminates. In short-pulse photo-stimulation (right panel), the excitatory gap is depolarised in such a way that a discrete anti-rotor is generated. When the two wavefronts collide, they mutually destroy one another and the arrhythmic rotor is eliminated. *Original figure, generated via BioRender.com.*

myocardium have differing action potential durations; this phenomenon is known as spatially discordant alternans (Sato *et al*., 2013). The spatiotemporal heterogeneity of tissue refractoriness is responsible for subsequent fatality.

In fact, further rotors can develop from a primary arrhythmic rotor as they form wave breaks (Pandit & Jalife, 2014). As such, it is clear that complex three-dimensional arrythmias can form, with an extremely challenging spatiotemporal profile. Thus, it is not surprising that the low-specificity electrical cardioversion demonstrates an unimpressive efficacy. In this way, optogenetic engineering of photo-defibrillators that take into account these three-dimensional arrhythmic profiles may provide improved therapeutic application (Figure 2).

Current research into photo-defibrillators

Optogenetic cardioversion essentially works to depolarise this excitable gap before these rotors can form. This is the so-called 'conduction block' mechanism (Watanabe *et al*., 2017). In this way, the re-entry circuit cannot continue as its path through the excitability gap becomes blocked. On a cellular level, this occurs as sodium channels essentially enter a refractory period, ensuring the arrhythmia cannot activate these channels (Bruegmann *et al*., 2016). Conduction blocks depend on a longer exposure to light to ensure the excitability gap has remained depolarised and, thus, refractive. Alternatively, researchers have aimed to generate counter-rotors that collide with the pathological rotors to essentially cancel one another out via destructive interference (Sasse *et al*., 2019). By using a short pulse of light, discreet waves of contraction, directly opposing the arrhythmia-induced contraction, can be formed. In effect, both mechanisms can eliminate the arrhythmia by terminating the pathological rotors.

Recently, Uribe *et al*., (2018) demonstrated how global illumination of the murine epicardium of arrhythmia-induced Langendorff-perfused hearts containing light-sensitive cardiac ion channels could successfully restore sinus rhythm. Specifically, at a light intensity <1.10 mW mm^{-2}, and a pulse time of 10-10,000 ms^{-1} successful cardioversion occurred. In this way, at least in an *ex vivo* capacity, there is sound evidence for the potential efficacy of novel photo-defibrillators.

Technical challenges

Optogenetics/photo-defibrillation for cardioversion and cardiac pacing is still in its advent. As such, multiple translational hurdles remain to be overcome before sufficient clinical application can be achieved.

Genetic modification of the arrhythmic cardiomyocytes is

required prior to photo-stimulation. As such, the safety of these delivery mechanisms must be scrutinised. For example, viral transduction has been used prior to transform the murine myocardium. In particular, adeno-associated viruses (AAVs) have been suggested due to their reduced mutagenicity and, hence, pleiotropy when compared to traditional lentivirus or adenovirus (Williams *et al*., 2010). Alas, 72% of the global population posses anti-AAV antibodies- making the need for personalised "designer" viral transduction increasingly important to improve therapeutic scope (Ambrosi & Entcheva, 2014). Likewise, donor cells that carry photosensitive proteins have been suggested.

Light delivery *in-situ* is also being considered. For this, the recently bioengineered 'ReaChR', a red-shifted photo-sensitive protein, may prove useful (Jiang *et al*., 2018). In this, ReaChR is sensitive to shorter wavelength light than normal opsins (such as ChRS) and, so, can be activated from a light source outside of the body. Obviously, this comes with the benefit of being less invasive than endoscopic fibre optic tools. In fact, ReaChR's efficacy has already been demonstrated in transcranial excitation of the Vibrissa motor cortex of intact mice skulls (Lin *et al*., 2013).

Future prospects

Despite the novelty of photo-defibrillators, given the promising strides being made by multiple research groups globally, their prospective therapeutic application in the future seems promising. The potential for breakthrough optogenetic cardioversion to be utilized has been demonstrated in murine myocardium models. Preclinical *in vivo* analysis of efficacy and, more importantly, safety is the next step in understanding the true potential photo-defibrillators may possess in modern cardiovascular medicine.

The use of long-term implantable photo-defibrillators to replace traditional implantable pacemakers and cardioverter–defibrillators (ICDs) has been suggested (Boyle *et al*., 2013; Nussinovitch & Gepstein, 2015). Such photo-pacemakers would show a high degree of tissue specificity when cardiac pacing is considered, i.e. distinguishing between His bundle and Purkyne tissue, relying on tissue-specific photoprotein expression.

It will be interesting to see how photo-defibrillators, and even photo-pacemakers, are applied to general cardiovascular medicine in the future.

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