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Editorial

Optogenetic Pacing for Resynchronization Therapy of Heart Failure

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Heart Failure (HF) is a disease of wide prevalence in the United States (5.7 million) and the incidence increases steady (>550,000 new cases per year) as the general population ages [1]. Despite recent advances in drug treatment, heart failure mortality approaches 60% within 5 years of diagnosis. Furthermore, in patients with advanced heart failure, the disease process not only depresses cardiac contractility but also affects the conduction pathways by causing a delay in the onset of right or left ventricular systole [1,2]. This intra ventricular conduction delay may further impair the contractile ability of the failing heart and enhance the severity of mitral regurgitation. These patients are usually not responsive to drug treatment and the only medical interventions currently available are heart transplantation and Cardiac Resynchronization Therapy (CRT), which utilizes implantable leads to optimize atrioventricular delay and synchronize the beating of the two ventricles [3-10]. Although CRT has been shown to improve cardiac function, symptoms and quality of life in some HF patients [11], malfunctions related to abnormal sensing of electrical activity or failure to capture may occur, with the most desire complications being embolic events, lead displacement and replacement, pneumothorax and battery depletion. In addition, CRT usually requires the implantation of multiple leads into the atrium and ventricles [12], which may cause additional problems such as unsuccessful implantation, coronary sinus dissection or perforation, and infection. Indeed, device-related infections have been rising steadily in the past decades not only because of the increases in the number of device implantations but also because of a higher incidence of bacterial infections in the US and worldwide [13]. Finally, CRT is not effective for all heart failure patients. Therefore, development of alternative therapy that overcomes these shortcomings is critical.

Recent advances in the innovative field of optogenetics have led to a variety of strategies to produce an optical pacing device that may complement or replace the multi-wire electrical pacing units in the context of CRT. Optogenetics utilizes genetically targeted, light-activated proteins, such as Channel Rhodopsin 2 (ChR2), to remotely and dynamically mediate activities of excitable cells in live animals (for review see references [14-17]). Once activated by blue light (475 nm), ChR2 allows the influx of cationic ions, mainly Na^+, consequentially depolarizing the membrane potential and evoking action potentials. Since its first description, ChR2 has been widely used in the field of neuroscience to manipulate the electrical activities of various types of neuron cells both *in vitro* and *in vivo* [18-21]. Meanwhile, ChR2 has been successfully expressed in other type of cells such as skeletal muscle, stem cell, and HEK cell [22-24]. Recent studies using transgenetic mice [25] and zebrafish [22] have demonstrated that ChR2-mediated optical pacing of the heart can be performed *in vivo*, opening up new vistas of application in the therapy of cardiac arrhythmias and heart failure. Compared with CRT, optical pacing has the advantages of being a relatively easier implant procedure (and therefore safer), having remote control access, and having lower energy consumption (and therefore a longer life time). Most importantly, optical pacing can be easily expanded to multiple sites, making it particularly suitable for CRT in advanced heart failure. Optogenetic pacing also has evident advantages over the biological pacemaker, another potential alternative to the electric pacing device, such as precise and active control. However, some major issues must be addressed before this promising technique can be utilized in a clinical setting.

First of all, it is critically important to examine if ChR2 can be stably expressed in adult (healthy and failing) hearts and if long-term *in vivo* ChR2 expression has deleterious effects on cellular and cardiac functions. In this context, Brugemann et al. [25] have created the transgenic mice that express cardiac specific ChR2 and investigated the electrophysiology of cardiomyocytes expressing ChR2. They showed that ChR2 expression did not significantly alter cardiac action potentials and calcium transients. In addition, they showed that illuminating as few as 50 cardiomyocytes is sufficient for functional cardiac pacing, suggesting that only a small volume of the heart tissue need to express ChR2. This increases the feasibility of *in vivo* application of optogenetic cardiac pacing. Having that said, there is still lack of report of ChR2 expression in heart failure.

Another important issue needs be addressed is whether and how long-term, continuous optical pacing affects cardiomyocyte electrophysiology and function. While it is difficult to examine it *in vivo*, isolated cardiomyocytes such as H9C2 or neonatal rat ventricular myocytes expressing ChR2 can be paced with blue light *in vitro* (e.g. in incubator) [26]. Mitochondrial energetic state, ions (e.g., Ca^{2+} & Na^+) homeostasis and action potentials can be measured using confocal microscopy and/or patch clamp setup before and after the long-term pacing to determine its effect.

One of the technical challenges to overcome is to efficiently transfer ChR2 gene to cardiac tissue. One of the commonly used methods is viral gene delivery. The adenovirus or Adeno-Associated Virus (AAV) methods are used to induce transient gene expression that ranges from days to years [27, 28]. The more stable and long-lasting gene transfer can be achieved using lentivirus. The disadvantages of

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viral gene delivery include innumogenesis and tumogenesis [29]. Another way to transfer gene *in vivo* is *via* stem cells such as human Induced Pluripotent stem (iPS) cells and Mesenchymal Stem Cells (MSC). iPS can be easily obtained from patient skin biopsy specimens and differentiated to fully immune-compatible cardiomyocytes. Thus, transplantation of iPS cells expressing ChR2 is an appealing strategy to induce stable ChR2 expression in heart tissue.

Finally, it is essential to develop and optimize method for safe and efficient light delivery in order to achieve *in vivo* optical pacing for heart failure treatment. The visible light used to activate ChR2 or its red-shift mutants such as C1V1 or MChR1 does not penetrate deep into tissue. Thus, it is infeasible to illuminate the tissue expressing rhodopsin channels through the chest wall. Alternatively, epicardial illumination has been used to stimulate mouse hearts expressing ChR2, suggesting that it could be used for future clinical application. Epicardial illumination can be achieved by using flexible strips of Light-emission Diodes (LED) arrays [30]. Other possibilities include electroluminescent foils and wires.

In summary, although the application of optogenetics in cardiac pacing is still in the infancy, this innovative approach has great potentials in CRT of heart failure due to its capability of precise, multi-sites and remote control of cardiac tissue. Future experiments are needed to characterize the effects of long-term ChR2 expression and illumination on cardiac physiology and function and to develop and optimize strategies for efficient ChR2 gene transfer and light delivery.

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