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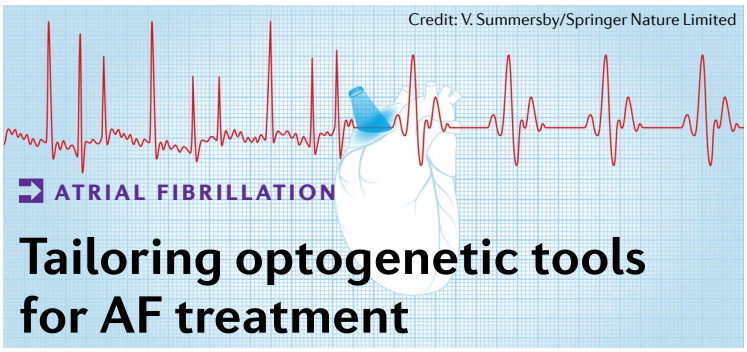

Tailoring optogenetic tools for AF treatment

> This is the first demonstration of the utility of cardiac optogenetics in automatically triggered arrhythmia therapy in a closed-chest experimental model

A new approach that combines an implantable light source and automated arrhythmia detector with optogenetic engineering to terminate the arrhythmia shows promise in an experimental animal model for the autogenous restoration of sinus rhythm in atrial fibrillation (AF) without the need for electrical shocks. "We created a bioelectronic defibrillator by combining electronic arrhythmia detection with biological arrhythmia termination," says lead investigator Daniël Pijnappels (Leiden University Medical Center, Netherlands). "This bioelectronic defibrillator is able to stop AF without an electrical shock. In this way, the heart can be reset in a fully automated manner and at any time."

Previously, Pijnappels and colleagues had shown in vitro using optogenetic engineering that fibrillation in atrial cardiomyocyte monolayers could be terminated by a light-induced depolarizing current produced by the arrhythmogenic substrate itself. "This was a crucial finding for us," explains Pijnappels, "because now we knew that the electrical current produced by the fibrillating atrial cardiomyocytes themselves could potentially be used for therapeutic purposes, in other words, to terminate the arrhythmia from within." Studies by other groups had also shown that optogenetic engineering of whole hearts and arrhythmia termination were possible in vivo in rodent models. However, Pijnappels points out that in these studies, the viral vectors encoding the light-inducible ion channel were delivered systemically, and the thorax was kept open for human-controlled illumination outside the animal body. "We have now shown that it is possible to apply these viral vectors only where they are needed (atrium in this case) and that a light-emitting diode (LED) device can be built small but effective enough to be implanted near the heart, allowing complete closure of the chest." In addition, to avoid human intervention, the research team created a system in which the LED device is automatically activated upon detection of AF. "The collaboration with Technical University Delft was absolutely crucial because the engineers were able to create this customized LED device fully optimized for our research purposes," notes Pijnappels, who highlights the importance of the multidisciplinary team required for this type of research.

To induce light sensitivity exclusively in the right atrium in rats, the researchers used atrial gene painting to deliver adeno-associated viral vectors encoding a light-gated depolarizing ion channel. After testing the feasibility of optogenetic pacing and arrhythmia termination ex vivo and in vivo with an external LED source, the researchers assessed the hybrid bioelectronic system — consisting of an implantable LED device and a machine-based cardiac rhythm monitor — in adult rats in vivo under closed-chest conditions. The LED device was implanted into the thoracic wall, facing the anterior side of the right atrium and without physical contact with the heart. After artificial induction of AF, the cardiac rhythm monitor detected the arrhythmia automatically and generated an output signal that switched on the implanted LED device, triggering the delivery of a light pulse to part of the atria that resulted in the depolarization of the light-sensitive right atrium and restoration of normal heart rhythm.

"This is the first demonstration of the utility of cardiac optogenetics in automatically triggered arrhythmia therapy in a closed-chest experimental model," highlights Natalia Trayanova (Johns Hopkins University, USA), who was not involved in this study. "Should such a system be translated into the clinic, it would allow rapid restoration of sinus rhythm in symptomatic AF, without the need for in-hospital delivery of high-voltage electric shocks," she adds.

Commenting on the clinical translation of the findings, Pijnappels explains that more research in rats as well as in larger animal models is needed. Trayanova points out that demonstrating the feasibility and safety is crucial. "First, new advances in cardiac optogenetics, and particularly in developing light-activated ion channels that are sufficiently sensitive to the low level of light penetration in the thick human heart wall, will be needed to achieve optogenetic actuation in the human heart. Additionally, developing safe and minimally invasive or non-invasive approaches for local transgene delivery to a part of the atrium and light delivery to the heart by an implanted light source are the two major steps to be undertaken to advance the potential of clinical translation," she explains.

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