REAL-TIME OPTICAL MANIPULATION OF CARDIAC CONDUCTION IN INTACT HEARTS

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Optogenetics, a combination of targeted light and gene delivery originating in the neurosciences, has provided novel insights also in cardiovascular research [1,2]. Interventions like cardiac pacing, resynchronization therapy and cardioversion have clearly demonstrated the feasibility of cardiac manipulation using light. A want of current methodologies, however, was the possibility to react to cardiac wave dynamics in real time. Here, we present a platform for optical mapping and optogenetic stimulation of intact mouse hearts which has been complemented with integrated software to monitor and control electrical activity in a closed-loop approach [3]. The system comprises a wide-field mescoscope with a digital projector for customizable optogenetic activation. Cardiac function can be manipulated either with sub-millisecond temporal resolution in free-run mode or else in a closed-loop fashion where the platforms allows for real-time intervention capable of reacting within 1ms [4].

We demonstrate the capabilities of the methodology by restoring normal electrical activity after atrioventricular block and real-time intra-ventricular manipulation of electrical wavefront propagation, the latter opening prospects for real-time resynchronization therapy and cardiac defibrillation. Finally, we applied the closed-loop approach to simulate a re-entrant circuit across the ventricle which demonstrates the high versatility of our system to manipulate healthy heart conduction towards arrhythmogenic conditions. This platform promises an exciting new approach to investigate the (patho)physiology of the heart.

[1] Arrenberg AB, Stainier DY, Baier H & Huisken J (2010). Optogenetic control of cardiac function. Science 330, 971–974.
[2] 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. Nat methods 7, 897–900.
[3] Scardigli M*, Müllenbroich C*, Margoni E*, Cannazzaro S, Crocini C, Ferrantini C, ... & Sacconi, L. (2018). Real-time optical manipulation of cardiac conduction in intact hearts. The Journal of physiology, 596(17), 3841-3858.
[4] F. Giardini, V. Biasci, M. Scardigli, F. S. Pavone, G. Bub and L. Sacconi (2019). A Software Architecture to Mimic a Ventricular Tachycardia in Intact Murine Hearts by Means of an All-Optical Platform. Methods Protoc., 2, 7.