

STRUCTURAL MAPPING OF ACTION POTENTIAL PROPAGATION PATHWAYS THROUGH HEALTHY AND DISEASED HEART

Erica Lazzeri and Leonardo Sacconi

European Laboratory for Non-Linear Spectroscopy (LENS) and National Institute of Optics–National Research Council (INO-CNR), Florence, Italy

Email: sacconi@lens.unifi.it

KEY WORDS: Tissue clearing, Light Sheet Microscopy, Voltage Imaging, Heart, Correlative imaging

Remodelling processes, associated with genetic and non-genetic cardiac diseases, can cause alterations of the electrical conduction and mechanical dysfunction. Current models employed to predict functional alterations caused by structural remodeling commonly do not draw upon comprehensive function and structural data and furthermore are often based on low-resolution and not integrated information. Here, we present a multi-modal optical approach to correlate electrophysiological dysfunction found in a Hypertrophic Cardiomyopathy mouse model with its structural alterations.

In detail, we first employed an optical mapping system to characterize action potential propagation in diseased and control whole-heart preparations. To gain the structural data on the same intact hearts, we combined advances in tissue clearing, staining and high-resolution light-sheet microscopy to reconstruct the three-dimensional organization of the cardiac conduction system on a cellular level. In particular, we optimized a passive Clarity protocol for clearing the whole heart and for achieving homogeneously fluorescent probe penetration into the entire tissue. Moreover, we developed a cytoarchitectonic analysis software to identify cells and to map myofilaments alignment in three-dimensions.

The structural reconstruction was exploited to simulate the conduction pathway of action potential propagation across the whole organ with the aim to elucidate the role of myofilaments disorganization in the electrical dysfunctions mapped previously with the optical system.

We believe that this innovative experimental approach will pave the way for a unifying model which integrates functional and structural data and enable a comprehensive investigation of the morphological causes that lead to electrical alterations after structural remodelling.