Cardiac electro-mechanical coupling in relation to ventricular arrhythmias in the intact human heart: from cardiac mapping and speckle tracking echocardiography to biomarkers

Reporting

Project Information

CARDIO MEF
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Final Report Summary - CARDIO MEF (Cardiac electro-mechanical coupling in relation to ventricular arrhythmias in the intact human heart: from cardiac mapping and speckle tracking echocardiography to biomarkers)
BACKGROUND: The electrical activity and mechanical function of the human heart are highly intertwined. In normal conditions, electrical activation and repolarization ensure cardiac relaxation and contraction and adequate cardiac function. This interaction from electrical to mechanical activity is not the only pathway of interaction as mechanical deformation of the heart induces changes in the cardiac electrophysiology. This mechanism is called electro-mechanical feedback (MEF) and is poorly characterised in the in-vivo human heart. My project aimed to investigate MEF in patients undergoing open heart cardiac surgery by assessing electrical and mechanical activity simultaneously by means of a multi-electrode heart sock and trans-esophageal echocardiography. Specific interest was placed on assessing the spatio-temporal organization of ventricular repolarization, including beat-to-beat dynamics and spatial dispersion.

RESULTS ON MECHANO-ELECTRIC FEEDBACK: The experimental set-up for simultaneous assessment of cardiac strain and electrical activity was developed within the first months of the project. Few months after the beginning of the data collection in the cardiac theatre, the Heart Hospital moved to the new Barts Heart Centre. This resulted in a delay in the data collection, which could be resumed only 17 months later. Analysis of data collected at the Barts Heart Centre has shown a change in repolarization and premature contractions during changes in ventricular loading due to transient aortic occlusion and establishment and disconnection of cardio-pulmonary bypass. This has been discussed in a review article currently in revision (Orini et al., Progress in Biophysics & Molecular Biology). With collaborators, I have studied MEF at the cellular level using computational modelling supported by human experimental data (1). The computational model showed that mechanical strain and adrenergic activation can induce cardiac repolarization dynamics that parallel those observed in-vivo. Furthermore, their effect is synergistic and in case of cardiac conditions such as reduced repolarization reserve and/or calcium overload they can lead to dangerous arrhythmia (1).

RESULTS ON REPOLARIZATION DYNAMICS: I have assessed the interactions between electrical activation and repolarization dynamics during heart rate changes in a study in which epicardial human data were analysed and explained by a mathematical model (2,3). I have compared two methodologies to assess repolarization dynamics during heart rate changes and identified the most accurate one (4). I have described the activation and repolarization spatial heterogeneity along anatomical cardiac axes in the intact human heart both in sinus rhythm and during ventricular activation from the right and left ventricle and from the epicardium (5). This information is relevant for a better understanding of arrhythmia mechanisms. Furthermore, I have assessed the sequence of events from normal sinus rhythm to ventricular arrhythmia during acute ischemia using both unique in-vivo human data and a simple analytical model (6,7).

Finally, in collaboration with researchers from the University of Manchester and Oxford, I have contributed to clarify the molecular determinants of repolarization alternans, an electro-mechanical phenomenon that is associated with an increased cardiac risk. We first carried out a combined in-vivo in-silico analysis to study its possible underlying mechanisms (8). Then we conducted a study involving the analysis of electrophysiological recordings, human cardiac tissue and computational modelling which showed that upregulation of Calcequestrin and Ryanodine, proteins involved in the Ca2+ handling, is a primary factor in the development of repolarization alternans. This study began before my fellowship, but it has been recently finalised and is relevant to my project. The paper describing this study is in revision at the moment (Orini et al, European Heart Journal).
METHODOLOGIES: I have supervised a study where we have proposed a novel methodology to measure changes in the spatio-temporal distribution of ventricular repolarization based on morphological changes in the T-wave of the surface ECG (9). Furthermore, I have validated a recently proposed ECG marker of dispersion of ventricular repolarization (10).

REFERENCES
7. Orini M, Taggart P, Hayward M, Lambiase PD. Spatio-temporal characterization of the transition from sinus rhythm to ventricular fibrillation during an acute ischemic event in the intact human heart by whole-heart sock-mapping. Hear Case Reports. 2017 Feb; Available from: http://linkinghub.elsevier.com/retrieve/pii/S2214027117300106