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Scientific Exchange Grant European Working Group in Cardiac Cellular Electrophysiology

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1) Background and project idea

Family members with cardiomyopathy may remain asymptomatic until the occurrence of life-threatening arrhythmias and sudden cardiac death (SCD). Early detection of subjects at risk for SCD is therefore crucial. Among them, arrhythmogenic cardiomyopathy (ACM) may be caused by mutations in genes, such as plakophilin-2 (PKP2). They may affect the calcium handling in cardiomyocytes, and trigger arrhythmias [1,2], but the responsible pro-arrhythmic mechanisms, as well as the indicators for pro-arrhythmia, remain unclear. Current approaches are based on experimental models or clinical data[3] (deformation imaging, ECG) obtained from mutation carriers. These strategies have suggested novel (patho-)physiological insights, but the translation to humans and scale integration of these findings remains challenging. I aim at developing a humanized computational modeling approach that can integrate both experimental and clinical data to provide insight and allow predicting the effects of ACM mutations on cardiac pump function and arrhythmic risk.

The aims of my work exchange with the Department of Medical Physiology, UMC Utrecht were to 1) get more familiar with experimental data (acquisition/interpretation), 2) predict the effects of experimental findings in the computer model, 3) explore possibilities to link clinical data and experimental findings through computer modeling.

2) Work performed during the exchange and results

We acquired data from various models from collaborators: PKP2 inducible KO mouse model[1,2], PKP2 heterozygous mouse model[4] (collaboration Prof. Delmar, New York University), patient-specific PKP2 mouse model and PKP2 iPSC cardiomyocyte (collaboration Prof. van Rooij, Hubrecht institute). I used the changes in protein expression and functional data from these models to vary molecular parameters in the cellular electromechanical computational model (such as current densities, buffers concentration, pumps activity). Results suggested a reduction in calcium-transient amplitude induced by the calcium handling changes measured in the PKP2 models. This reduction led to a loss of force generation in the cell, suggesting potential loss of contractility in the whole heart, an early phenomenon confirmed in patients through our collaborators at the UMCU[3].

In parallel, I also coupled the cellular model[5] to the CircAdapt model of cardiovascular mechanics and hemodynamics[6] through tension generated by the sarcomeres at the tissue level. Initial results showed the ability to simulate electrophysiological properties all the way to whole-organ/hemodynamic properties.

3) Outcome, feedback, and next steps

This exchange with the Department of Medical Physiology at the UMC Utrecht has been very fruitful for both my research and my personal scientific development. I have enriched my knowledge and expertise with exposure to experimental work, by exchanging with colleagues about how to perform cellular experiments (calcium imaging, transcriptomics and proteomics data), the challenges faced in

data acquisition, and how to interpret these data. The availability of several ACM experimental models has allowed me to feed the computer model with different molecular changes. We are aiming to submit this work for publication later this year. In addition, our work was accepted for presentation at the EWGCCE meeting during EHRA 2021.

This exchange also allowed me to build strong collaborations and connections with the UMC Utrecht. The department of Medical Physiology has been extremely welcoming and has made my stay with them very productive and enjoyable (both personally and scientifically). Dr. van Veen and I have also decided to extend my stay in Utrecht until September 2021 to build on the work that has been performed during this exchange. I have also had the opportunity to interact with clinicians from the Cardiology department and link my research to clinical data and applications. In addition, I will build on these collaborations to apply for personal grants (Dutch Dekker Postdoc and Veni grants).

The pandemic crisis has made the exchange challenging (ban on travel, difficulties to meet face to face or to observe experiments and be present in the lab). However, it has not affected my main objectives due to the portable aspect of my research (computer modeling). I am also confident that with the extension of my stay in Utrecht I will be able to fully benefit from my visit to the lab, with the ease of the corona measures.

This scientific exchange has been very fruitful for both my current project and my future career. I am therefore very grateful to the European Working Group in Cardiac Cellular Electrophysiology and the UMCU for this opportunity.

References

1. Cerrone, M. *et al.* Plakophilin-2 is required for transcription of genes that control calcium cycling and cardiac rhythm. *Nature Communications* **8**, 106 (2017).
2. Kim, J.-C. *et al.* Disruption of Ca2+i Homeostasis and Connexin 43 Hemichannel Function in the Right Ventricle Precedes Overt Arrhythmogenic Cardiomyopathy in Plakophilin-2-Deficient Mice. *Circulation* **140**, 1015–1030 (2019).
3. Mast, T. P. *et al.* Right Ventricular Imaging and Computer Simulation for Electromechanical Substrate Characterization in Arrhythmogenic Right Ventricular Cardiomyopathy. *J. Am. Coll. Cardiol.* **68**, 2185–2197 (2016).
4. van Opbergen, C. J. M. *et al.* Plakophilin-2 Haploinsufficiency Causes Calcium Handling Deficits and Modulates the Cardiac Response Towards Stress. *Int J Mol Sci* **20**, (2019).
5. Lyon, A. *et al.* Differentiating the effects of β-adrenergic stimulation and stretch on calcium and force dynamics using a novel electromechanical cardiomyocyte model. *Am J Physiol Heart Circ Physiol* **319**, H519–H530 (2020).
6. Walmsley, J. *et al.* Fast Simulation of Mechanical Heterogeneity in the Electrically Asynchronous Heart Using the MultiPatch Module. *PLOS Computational Biology* **11**, e1004284 (2015).

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