Heart Fi-Re - HEART FIne REgulation through mechanosensing in myosin filaments: merging theory and experiments into a multi-scale heart simulator

It is well established that muscle contraction involves the cyclical interaction of myosin motors with actin filaments that lead to a sliding movement. The recently delineated mechanosensing (MS) mechanism active in the myosin thick filament addresses unresolved mechanistic gaps related to the fine regulation of muscle contraction. The scope of the EU-funded Heart Fi-Re project is to develop a mathematical model capable of quantitatively characterising the MS mechanism at the fibre level. The rationale is to incorporate this mechanosensing model into a powerful whole heart simulator and assess the macroscopic impact of the MS mechanism in various cardiomyopathies.

Multi-scale heart simulators for patient specific treatments are an important challenge for the development of the health system, but require interdisciplinary interaction of several techniques to link experimental observations at the molecular level to the cardiac performance. The mechanosensing (MS) mechanism active in the myosin thick filament, recently discovered, is promising for the understanding of several unresolved questions in muscle field, including the molecular basis of the Frank-Starling law of the heart. MS mechanism finely regulates the number of myosin motors ready to generate force, sensing the tension sustained by the thick filament in any stage of the heart cycle. The mechanism appears to be crucial for the fine regulation of muscle contraction, deserving as a second regulator respect the classical Calcium concentration. However, its theoretical description at present is limited to purely phenomenological models and very few groups in the world are already able to produce clear evidences on it. The present project aims at establishing a collaboration between researchers in this field with complementary theoretical and experimental expertise to quantitatively characterize the MS mechanism at the fibre level through an innovative mathematical model and experimentally validate it with cutting-edge techniques present in the host and partner institutes. The fibre model will be included into a powerful whole heart simulator, to evaluate the macroscopic impact of MS mechanism, and its predicted effects on clinical problems, including its recently discovered relationships with cardiomyopathies. The project will foster an international network of collaborations, where the host institution will be a crucial node. The complimentary knowledges and high excellence of the groups, is a firm foundation on which to build the impact of the project: at my career level, at the institutes level and also at the system level.

UNIPD Team Leader: Nazareno Paolocci

MSCA Fellow: Lorenzo Marcucci

Department: Department of Biomedical Sciences

Coordinator: Università degli Studi di Padova (Italy)

Total EU Contribution: Euro 276.498,24

Call ID: H2020-MSCA-IF-2019

Project Duration in months: 36

Start Date: 01/09/2021

End Date: 31/08/2024

Find out more: **https://cordis.europa.eu/project/id/886232**