Omecamtiv Mecarbil Improves Contraction Behaviour in a 3D Electromechanical Tissue Model of Heart Failure

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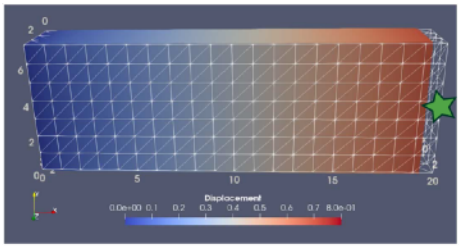
Inotropic drugs are a promising treatment option for patients with heart failure with reduced ejection fraction. An example of this type of drug is Omecamtiv Mecarbil (OM), which selectively recovers contractility to counteract heart failure symptoms, while minimising unwanted side-effects. Even though simulation and modelling are becoming increasingly prevalent in the drug development process for cardiovascular disease, there are limited computational models available of OM. We present a 3D electromechanical model to simulate inotropic drug effects, aiming to assess pharmacological mechanisms and effects on human cardiac tissue.

An electromechanical model of ventricular tissue was developed by coupling the cellular O'Hara-Rudy and Land models, which was embedded in a continuum mechanics model representing the tissue. This FEniCS based electromechanics solver (SimCardEMs) was used to simulate healthy and heart failure 3D tissue blocks with dimension 20x7x3 mm. A model of OM behaviour was created by fitting to experimental data at the cell level to replicate stabilisation of the pre-powerstroke state of myosin.

Traces of resulting tension and motion were extracted at the freely contracting side of the tissue for further analysis. The OM model replicates experimentally observed concentration dependent drug effects such as delayed peak contraction, reduced tissue resting length, increased active tension and minimal effect on calcium transient. Therapeutic concentration of OM (0.2 µM) increased active tension by 28% in heart failure tissue. Fractional shortening remains unchanged, but duration of contraction increased which may translate to increased ejection fraction. However, the model does not reflect the magnitude of change as was observed in primary human cardiomyocytes (>10% increase in sarcomere shortening). These simulations enable detailed assessment of drug mechanisms and indicate that the model of OM in tissue electromechanics requires further development to better represent the pharmacological effect.



	Peak active tension *(% of healthy tissue)*	Fractional shortening *(% of healthy tissue)*	Time-to-peak contraction *(% of healthy tissue)*	Contraction duration *(% of healthy tissue)*
Heart failure	46.8%	32.8%	135.9%	135.4%
Heart failure + 0.2 µM OM	75.2%	32.6%	146.9%	148.3%