MOLECULAR LEVEL INVESTIGATIONS ON THE SARCOMER DYNAMICS (FRANK-STARLING RELATIONSHIP) IN DIFFERENT MAMMALS UNDER PHYSIOLOGICAL AND PATHOLOGICAL CONDITIONS

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Sarcomere length (SL) regulates the Ca^{2+}-sensitivity of force production in the heart and thereby explains the Frank-Starling mechanism at the level of the cardiomyocytes. Nevertheless, the molecular determinants of this SL-dependence are unknown. Our new important observation with the Frank-Starling regulation is the independence of the actin-myosin cross-bridge cycling rate (k_{tr}) from the SL. This observation has been found to be true in three examined species (human, porcine and murine myocardia). On one hand, the k_{tr} has been found to be dependent on the inorganic phosphate and Ca^{2+} concentrations ($[P_i]$ and $[Ca^{2+}]$), temperature and the myofibrillar protein composition (MHC isoforms). On the other hand, k_{tr} has been found to be completely unaffected by SL under all experimental conditions. Based on these data, we propose that kinetic alterations of the actin-myosin cross-bridge cycle (k_{tr}) are not prerequisites for the Frank-Starling regulation (SL-dependent Ca^{2+} sensitization). Therefore, the Frank-Starling mechanism is best explained by models that include a three-stage model of thin filament activation and increased cross-bridge recruitment at longer SLs.

We have shown that in a transgenic DCM mice model (Tgαq*44) a decreased protein kinase A (PKA) activity is one of the most important underlying mechanisms responsible for the pathological alterations of the myofibrillar function (i.e. increased Ca^{2+}-sensitivity of force production). The Frank-Starling regulation (SL-dependent Ca^{2+} sensitization), was found to be fully operational during the development of DCM in Tgαq*44 mice. Additionally, SL failed to modulate k_{tr} not only in the control (healthy), but also in Tgαq*44 mice. Hence, these data confirm and extend our proposal from the healthy to the failing myocardium (DCM) on the independence of the Frank-Starling mechanism from k_{tr}.

The observed biochemical alterations in the Tgαq*44 mice (reduced ß-adrenergic activation) correlate with the human findings on congestive heart failure, despite the species-dependent differences in the myofibrillar protein compositions.

Keywords: Frank-Starling, myofibril, Ca^{2+}-sensitivity, DCM