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 (Tg\(\alpha q^{*44}\)) 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 Tg\(\alpha q^{*44}\) mice. Additionally, SL
failed to modulate \(k_{tr}\) not only in the control (healthy), but also in Tg\(\alpha q^{*44}\) 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 Tg\(\alpha q^{*44}\) mice (reduced \(\beta\)-adrenergic
activation) correlate with the human findings on congestive heart failure, despite the species-
derpendent differences in the myofibrillar protein compositions.
Keywords: Frank-Starling, myofibril, Ca\(^{2+}\)-sensitivity, DCM