A Model Based Analysis of Steady-State versus Dynamic Aspects of the Relationship between Calcium and Force

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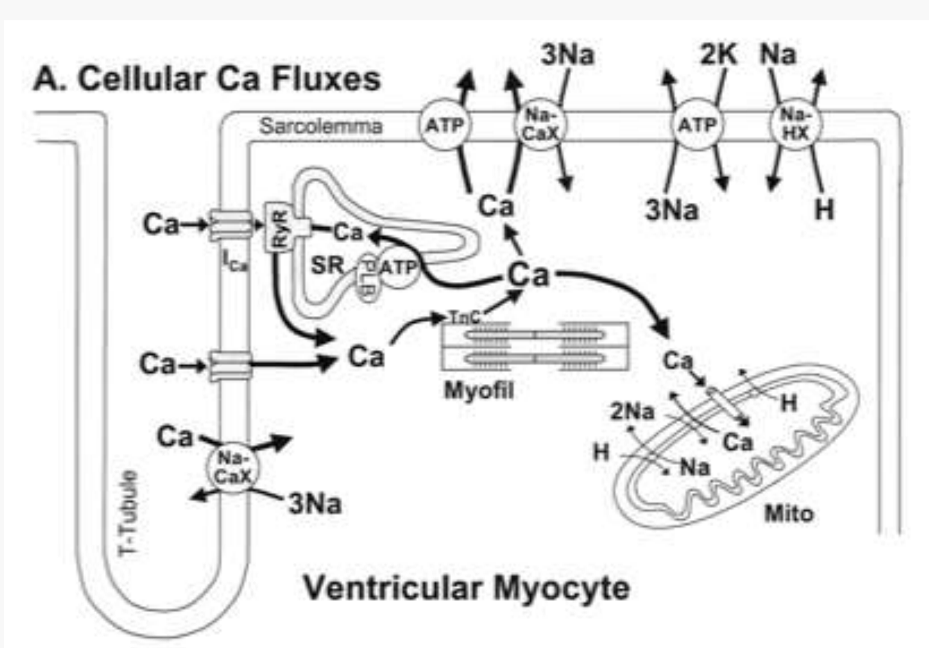
INTRODUCTION

- The calcium-force relationship is dynamic (i.e. calcium-induced force generation is not instantaneous) during physiological contraction of cardiac muscle.
- Often, the calcium-force relationship is studied *only* under steady-state conditions.
- A mathematical model allows us to simultaneously study both dynamic and steady-state aspects of the calcium-force relationship.

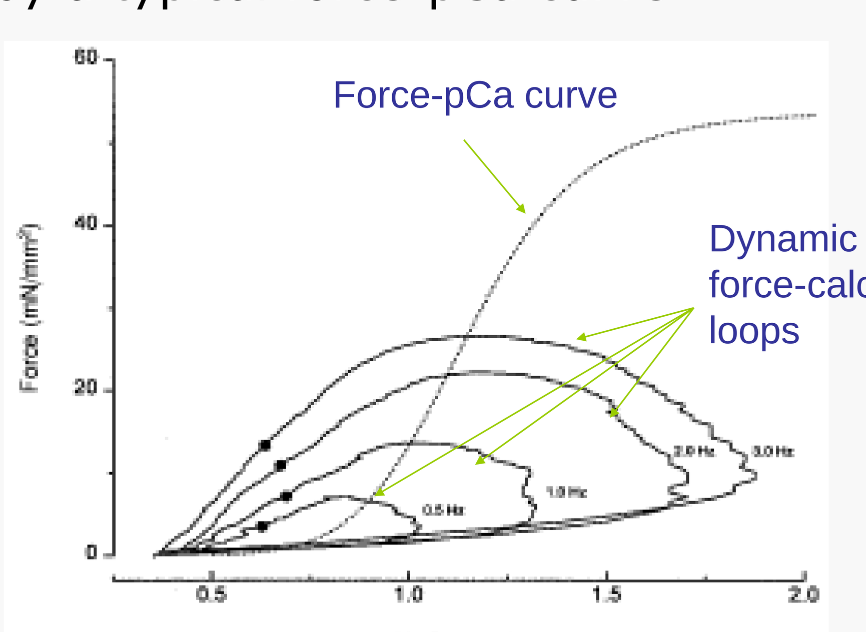
BACKGROUND

Calcium is required for cardiac contractile activation and relaxation



Static vs. Dynamic calcium force relationship

- Myofilament response to calcium is often studied in skinned fibers
- Data produced using this technique is presented as force-pCa curves
- Exist characteristics of the calcium-force relationship that may not be described well by a typical force-pCa curve



METHODS

Model-based Techniques

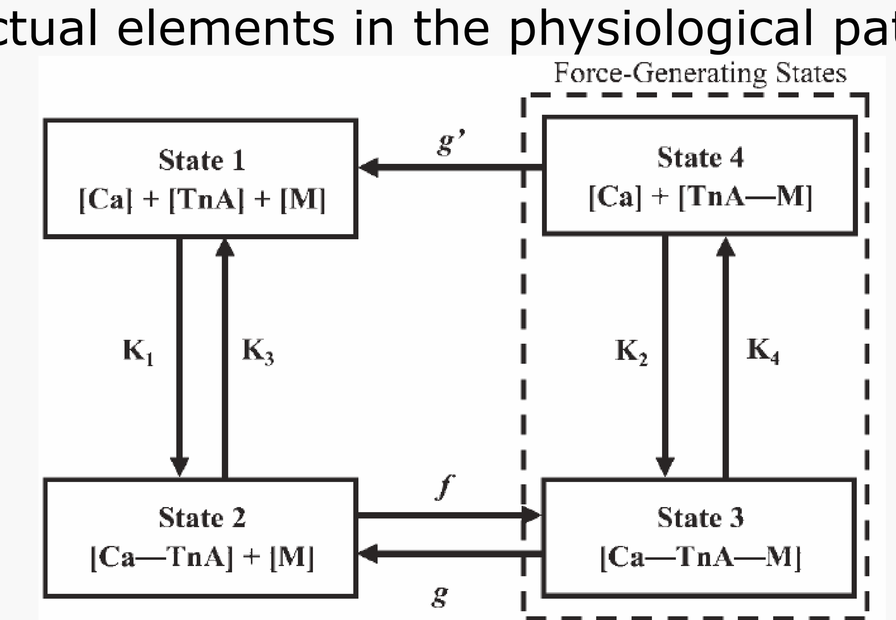
- A mathematical model was used to predict calcium force pairs for a given calcium input.

$[Ca]_i(t)$ → **Model Parameters** → **F(t)**

- Applied time-varying calcium and constant calcium inputs in order to observe dynamic and steady state responses.

Four State Model

- The Four State Model was used to represent actual elements in the physiological pathway



Determination of Parameter Sets

- Determined subsets of parameters in the four-state model associated with our 3 cellular processes of interest

Process	Parameter Set
Calcium-Troponin interaction	Set 1: K_1, K_2, K_3, K_4
Crossbridge cycling	Set 2: f, g, g'
Cooperativity feedback mechanism	Set 3: α_1, α_f, β_1, β_f

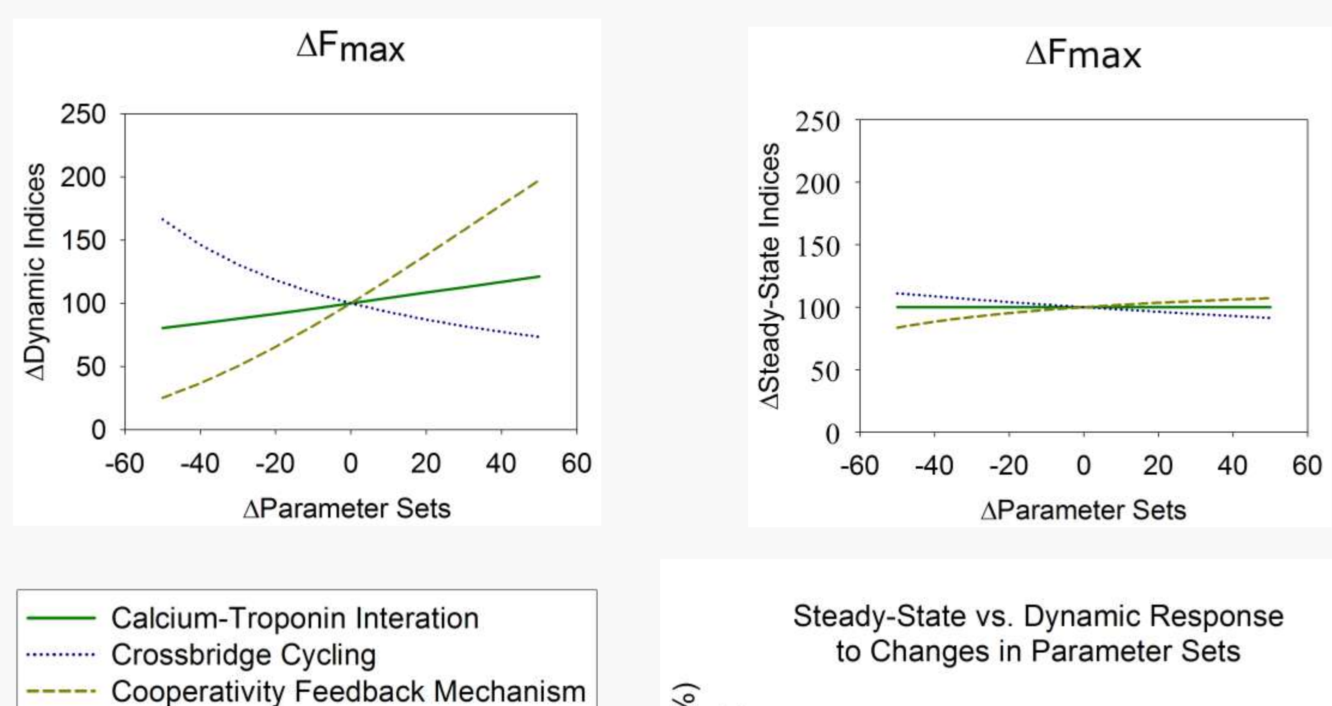
Determination of Baseline Parameters

- Attained basis parameter set by adjusting values until fit experimental data in the literature

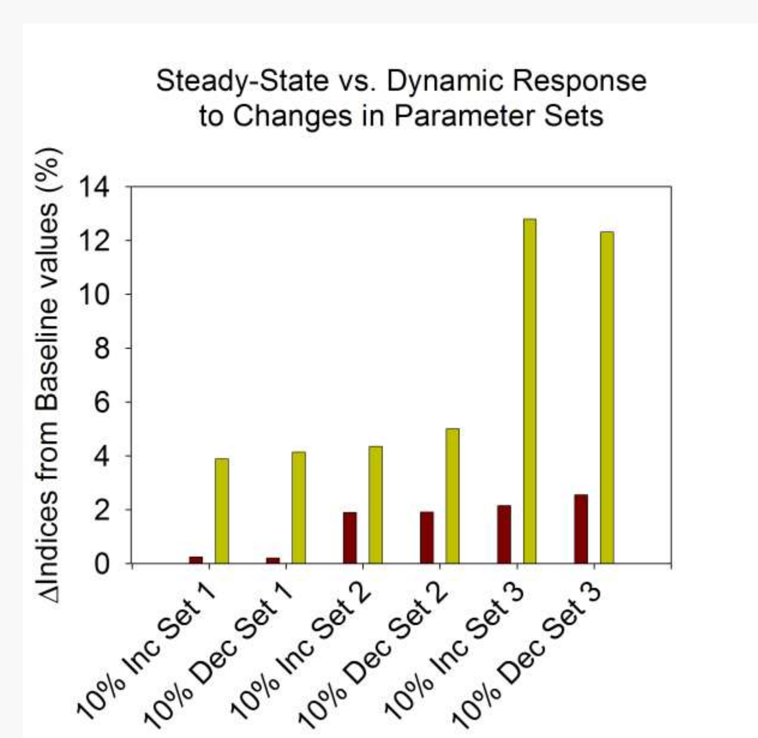
RESULTS

Systematic Varying of Parameters

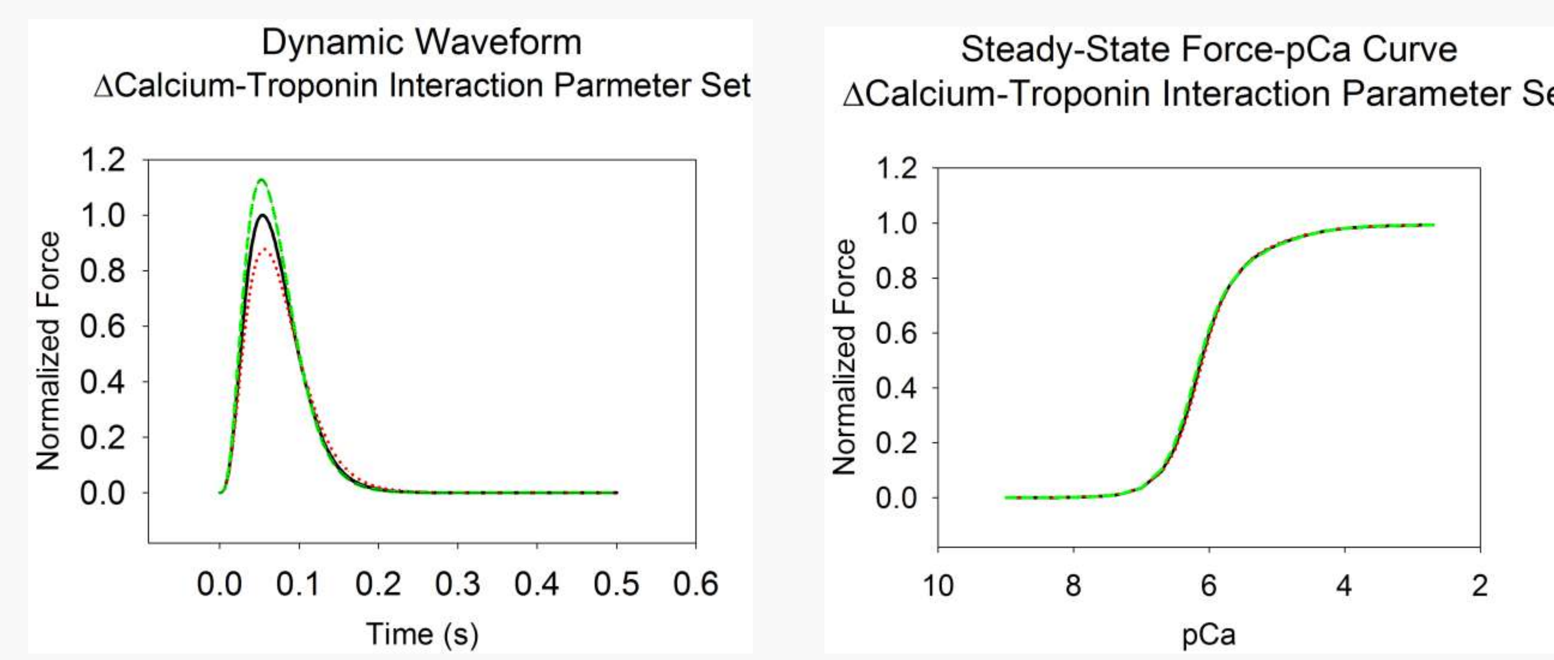
- Made simultaneous adjustments of baseline parameters from -50% to 50% and analyzed indices describing steady-state and dynamic waveform characteristics



- Recorded the average change in Steady-State vs. Dynamic Indices



Effect on Steady-State Force-pCa curve vs. Dynamic Force Waveform



Conclusions

- Changes in all three processes (calcium binding kinetics, crossbridge kinetics, and cooperativity) affected both steady-state and dynamic aspects
- Relative sensitivity of changes in dynamic aspects were significantly greater (2.3-21.4 fold increase, P = 0.011)
- Dynamic aspects of calcium-force relationship is physiologically important in cardiac contraction
- Model-based analysis may help guide future experimental work

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