Pressure-calcium relationships in perfused mouse hearts

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May 31, 2007
BBSI Journal Club Presentation

Outline

- Purpose
- Questions
- Anatomy and Physiology of the Heart
- Protocol 1: Frank-Starling
- Protocol 2: Mechanical Restitution
- Model-based Analysis
- Questions Answered
- Conclusion

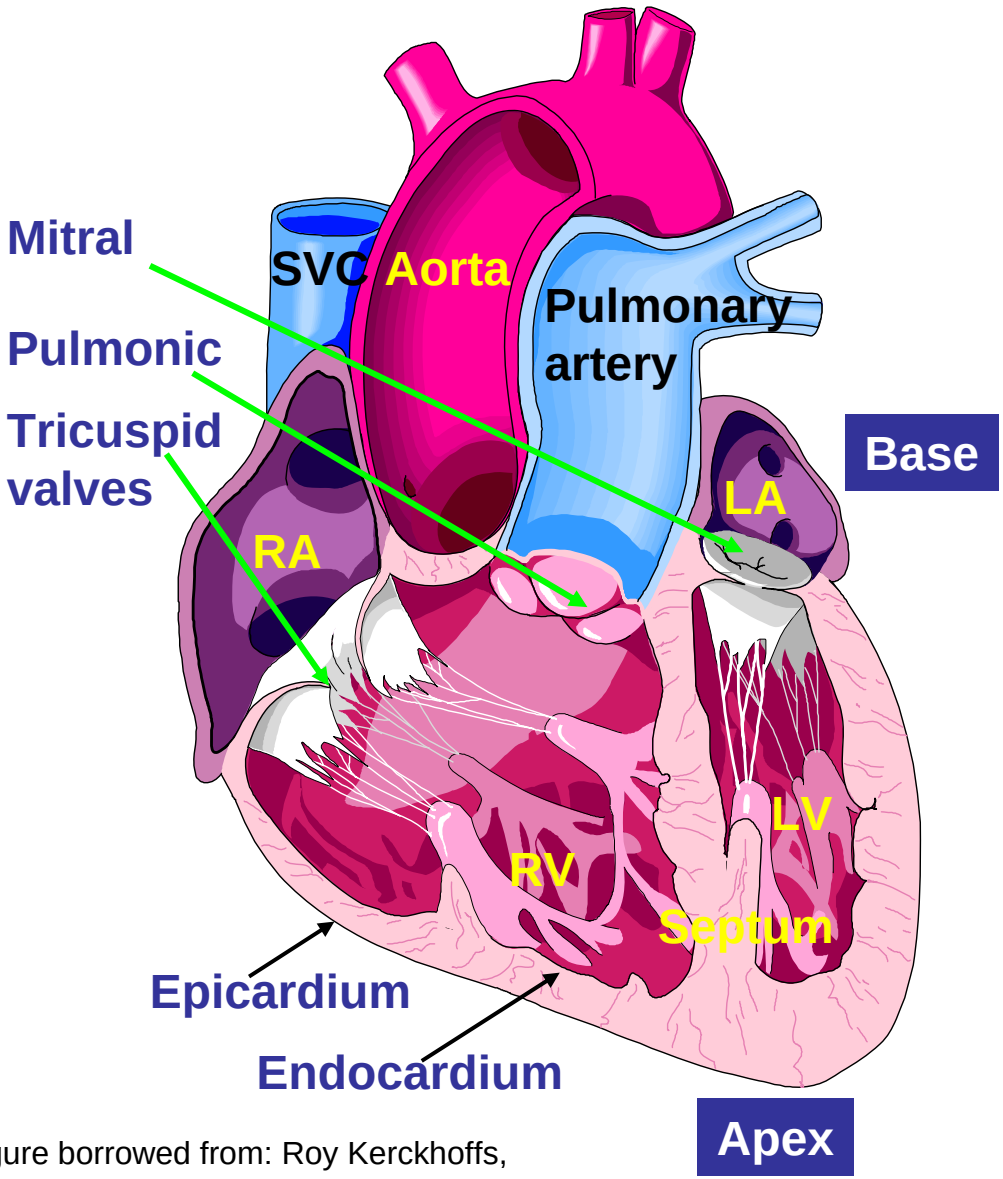
Purpose

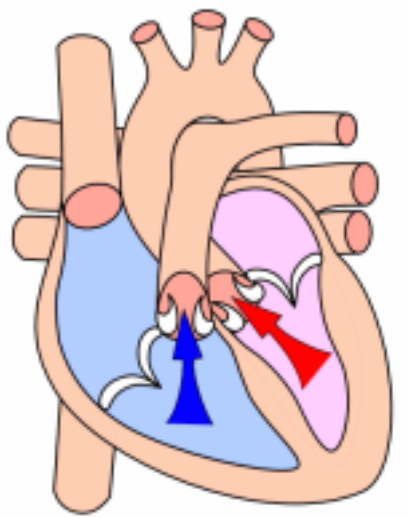
- Characterize the relationship between pressure and intracellular free calcium in the perfused mouse hearts

Questions

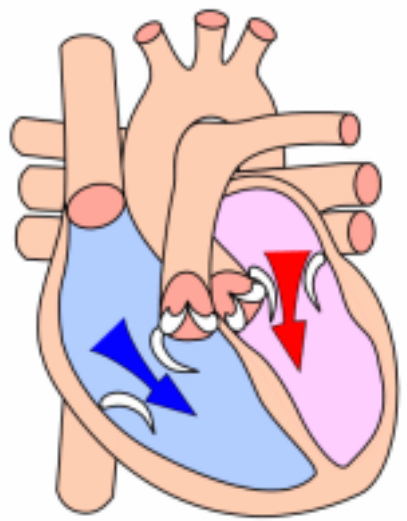
- Q1: Can peak developed pressure change significantly without change in the peak systolic intracellular free calcium?
- Q2: Is the late component of length-dependent activation absent?
- Q3: What are the determinants of pressure relaxation?

Cardiac Anatomy and Cardiac Cycle





Systole



Diastole

Figure borrowed from: Roy Kerckhoffs, Tutorial on heart and lungs, Ohio State University (2006)

Figures borrowed from Wikipedia.com

Cardiac Cycle

Systole:

1. Isovolumic contraction
2. Ejection

Diastole:

3. Relaxation
   - Early
   - Isovolumic
4. Filling
   - a) Early, rapid
   - b) Late, diastasis

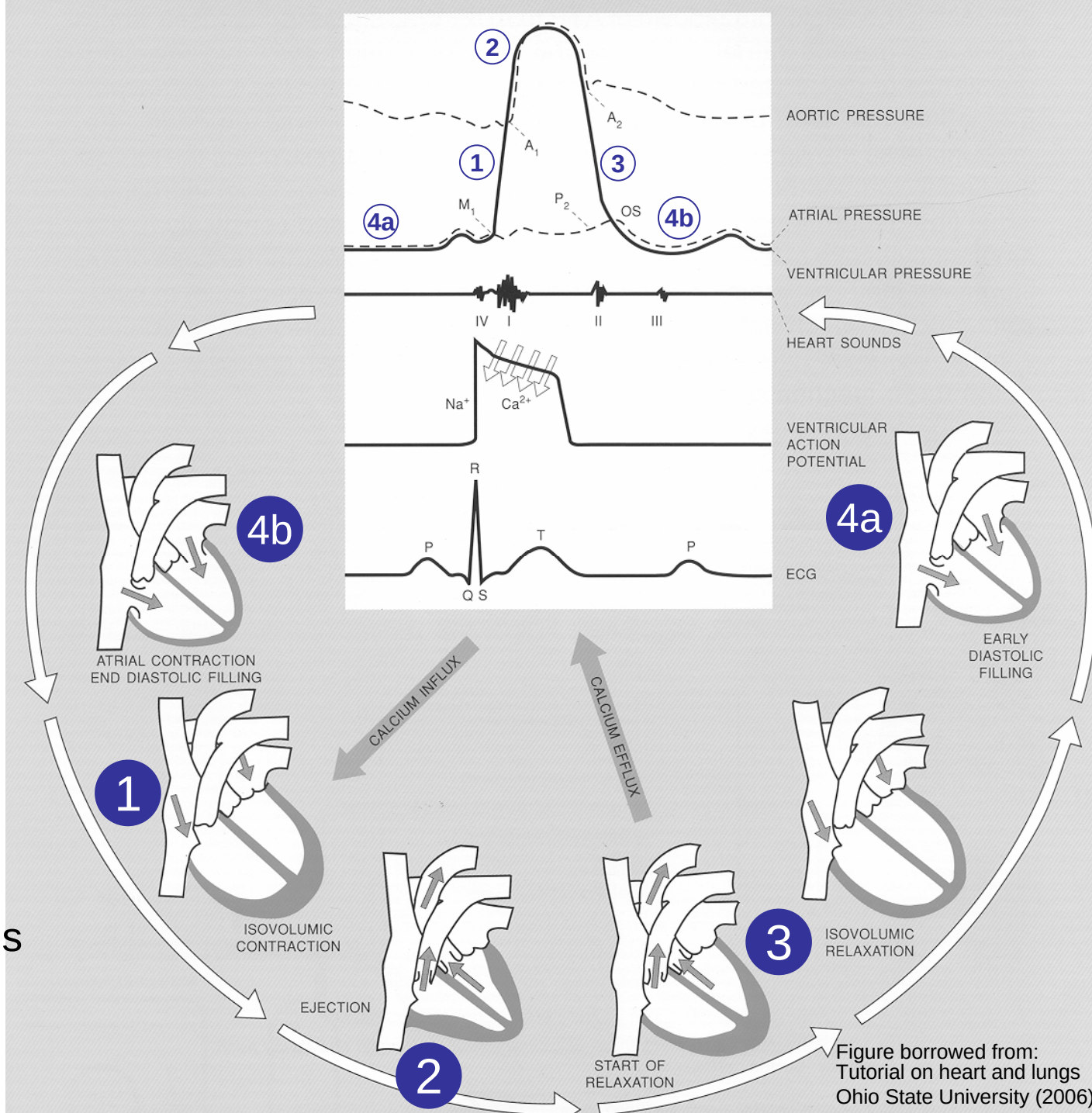
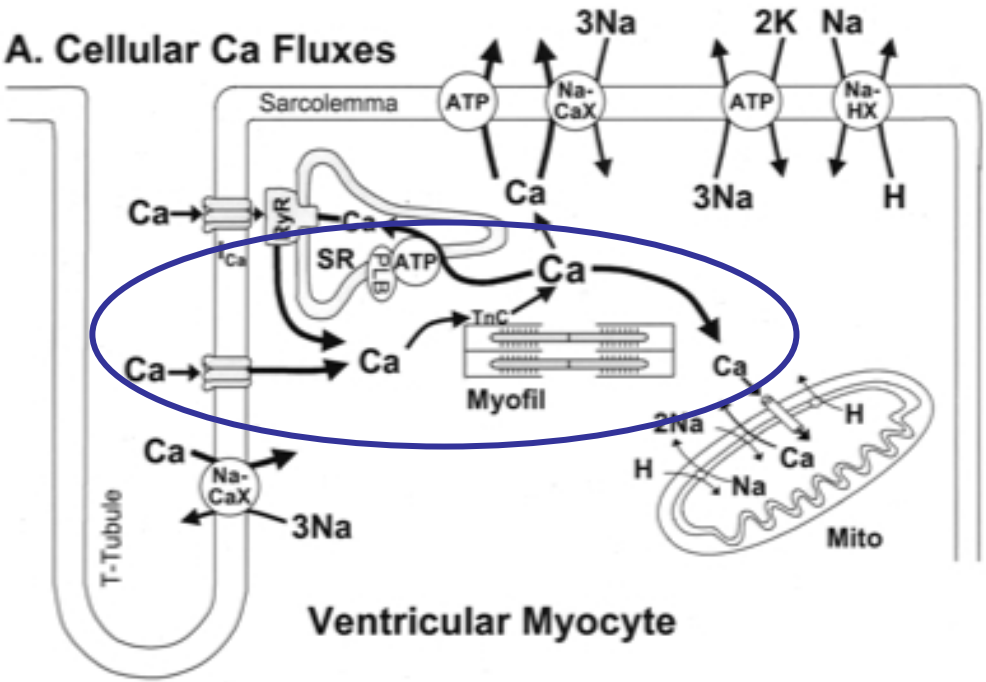


Figure borrowed from:
Tutorial on heart and lungs
Ohio State University (2006)

Role of Calcium

- Calcium is required for contractile activation



Bers, C^{2+} Transport in Cardiac Myocytes
(Circ Res. 2000;87:275-281.)

Video

Methods Used

- Isolated perfused heart system (Langendorf)
  - In vitro preparation of hearts

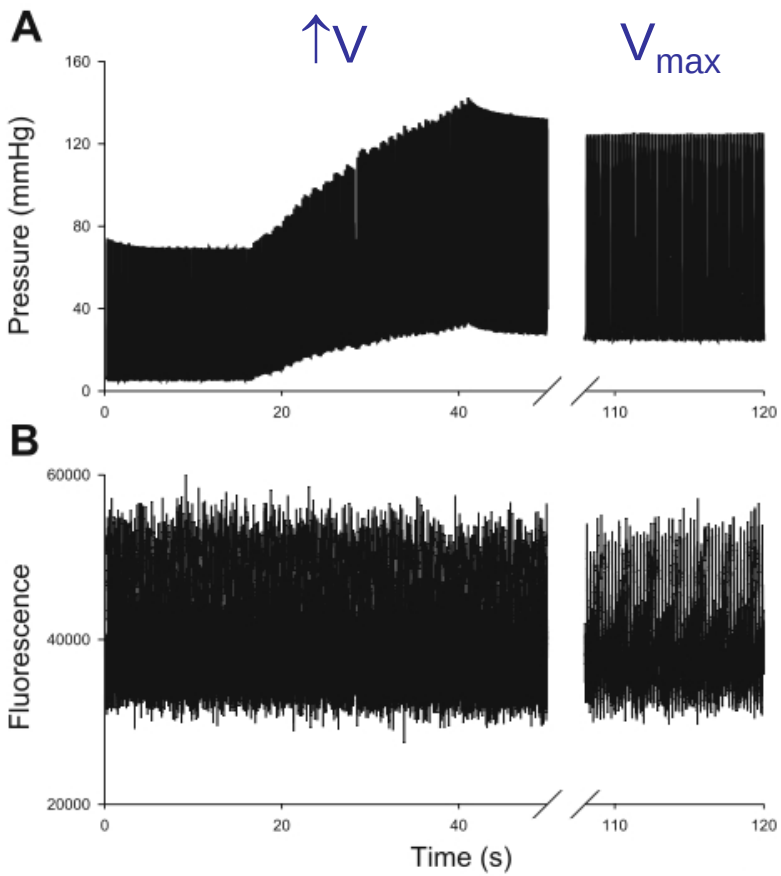
- Flourescence measurements
  - Calcium sensitive fluorescent dye rhod-2 was used to record pairs of LV pressure and $[Ca]_i$

Protocol 1: Frank Starling

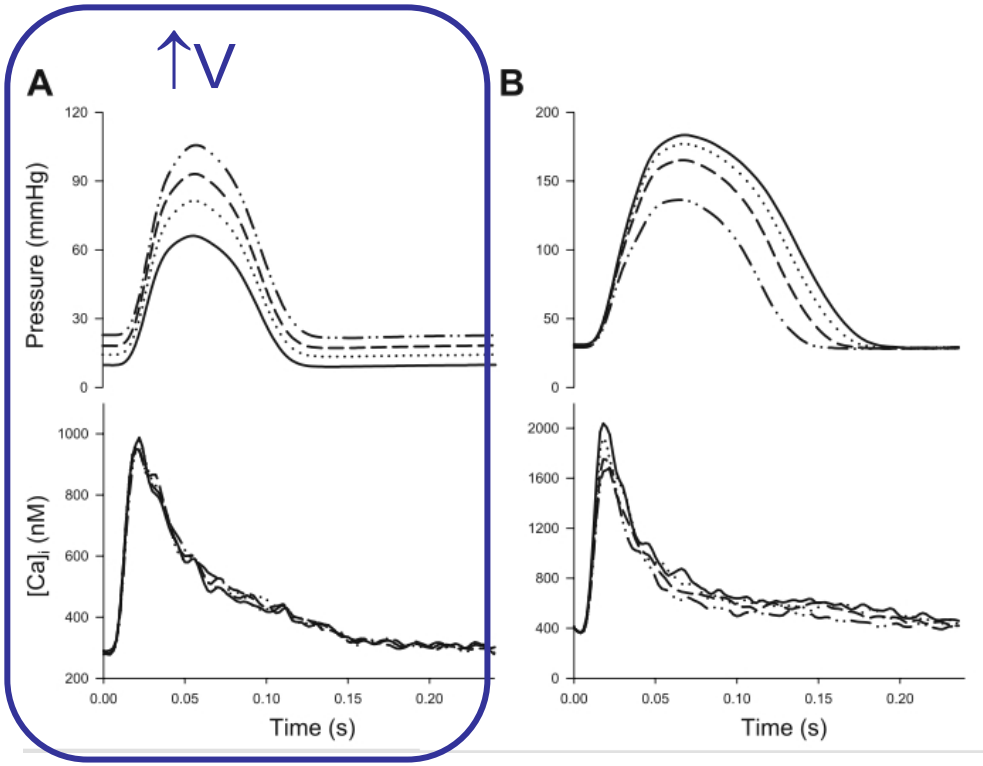
- Frank-Starling mechanism: The more the ventricle is filled with blood during diastol, the greater the volume of ejected blood during systolic contraction

- Excitation-Contraction Coupling: A mechanism to explain how preload influences contractile force
  - Length dependent activation:
    - ↑ sarcomere length =>
    - ↑ TnC calcium sensitivity =>
    - ↑ the rate of cross-bridge attachment and detachment

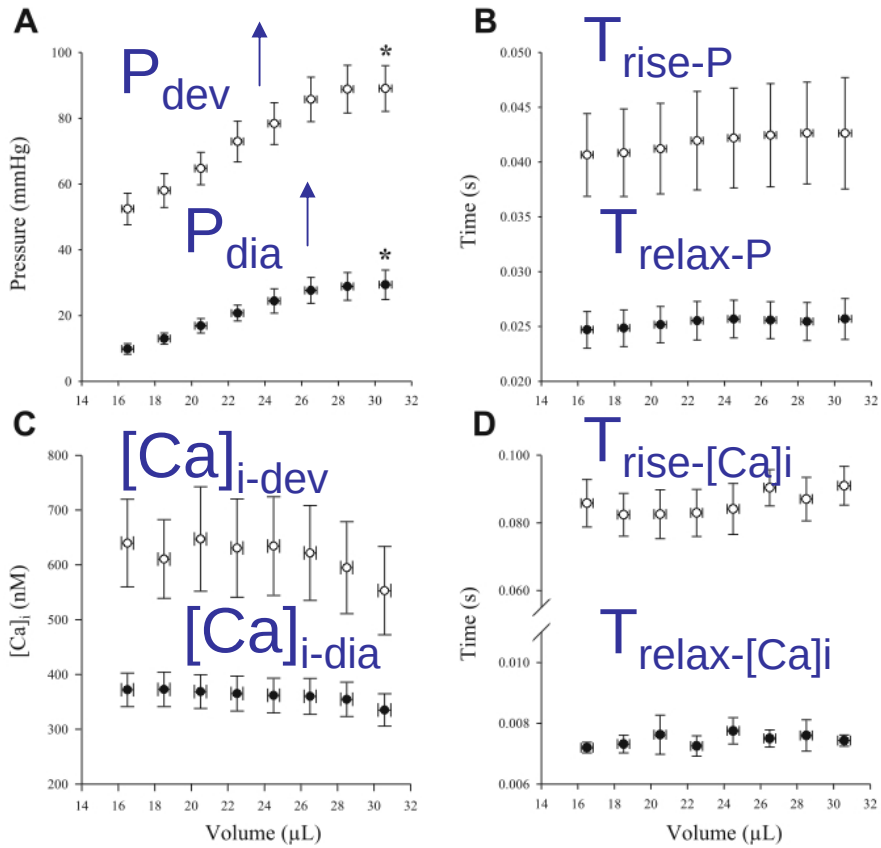
Examined result of changes in ventricle volume at a fixed stimulation interval



Protocol 1: Results



Determine if changes in morphology and/or magnitude occur with changes in LV volume

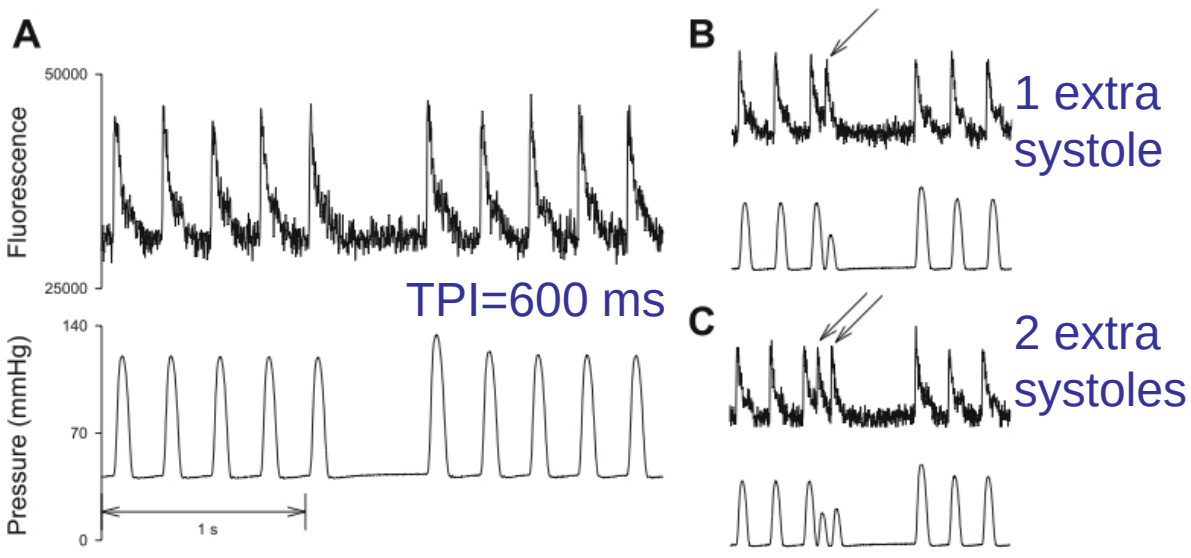


Protocol 2: Mechanical Restitution

- Examine single-beat changes in stimulation interval at a fixed ventricle volume
  - Fixed LV volume (V_{max})
  - Pressure and flouresence data recorded for..
    - Steady-state contractions at the control period interval (CPI) of 240 ms
    - Single-beat perturbation of the test period interval (TPI) at 200, 400, 600 and 800 ms

3 Modes
of deployment

No extra systole



Protocol 2 Results

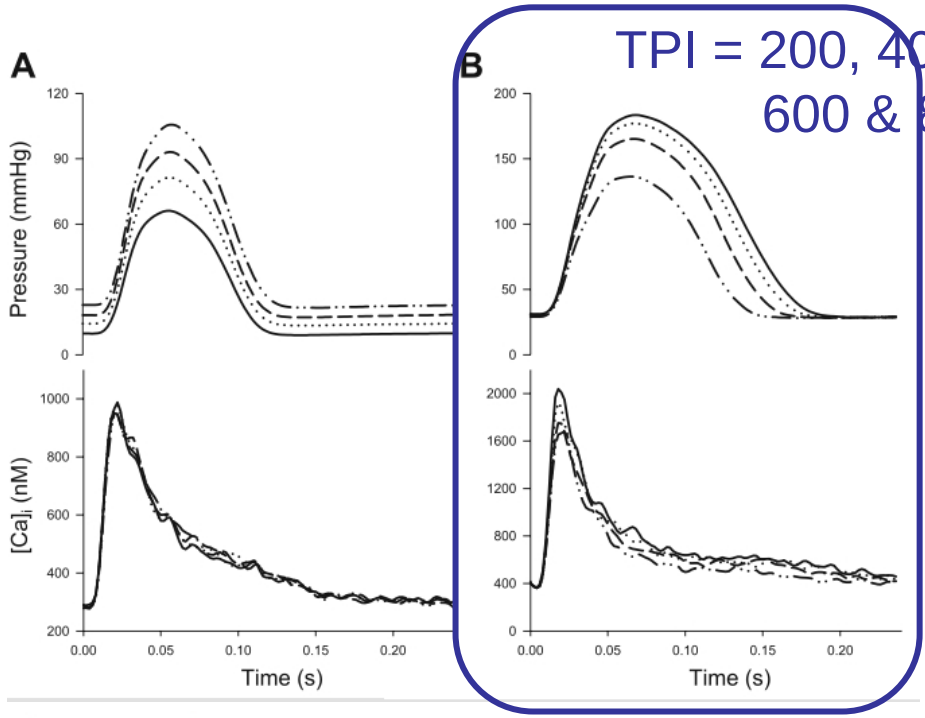
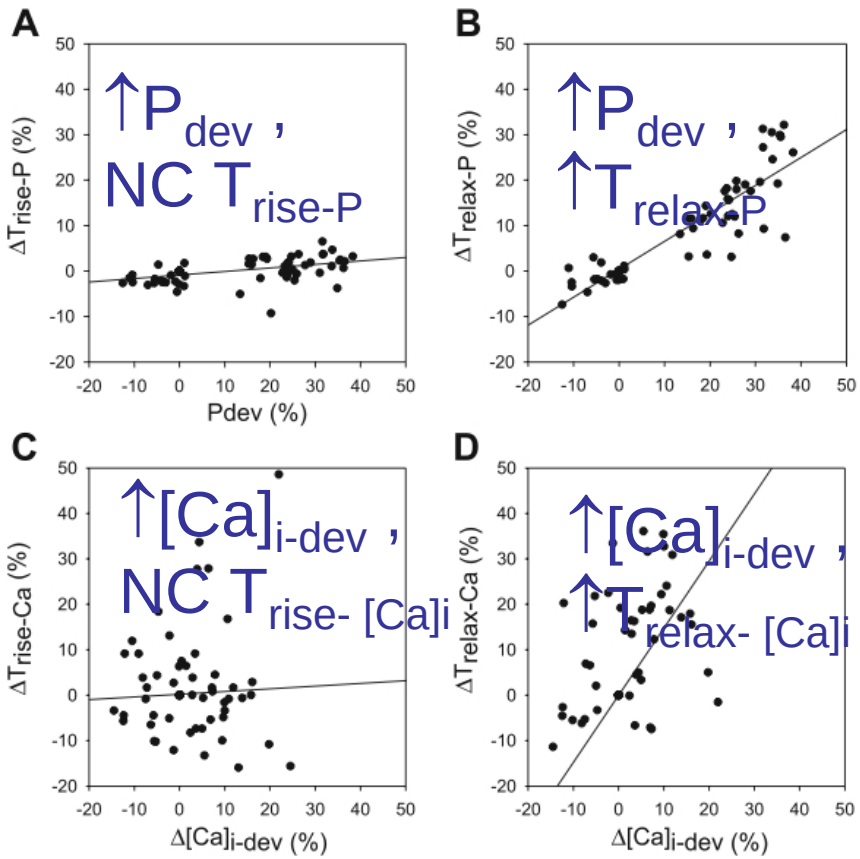


Table 1. *Summary of data from the mechanical restitution protocol*

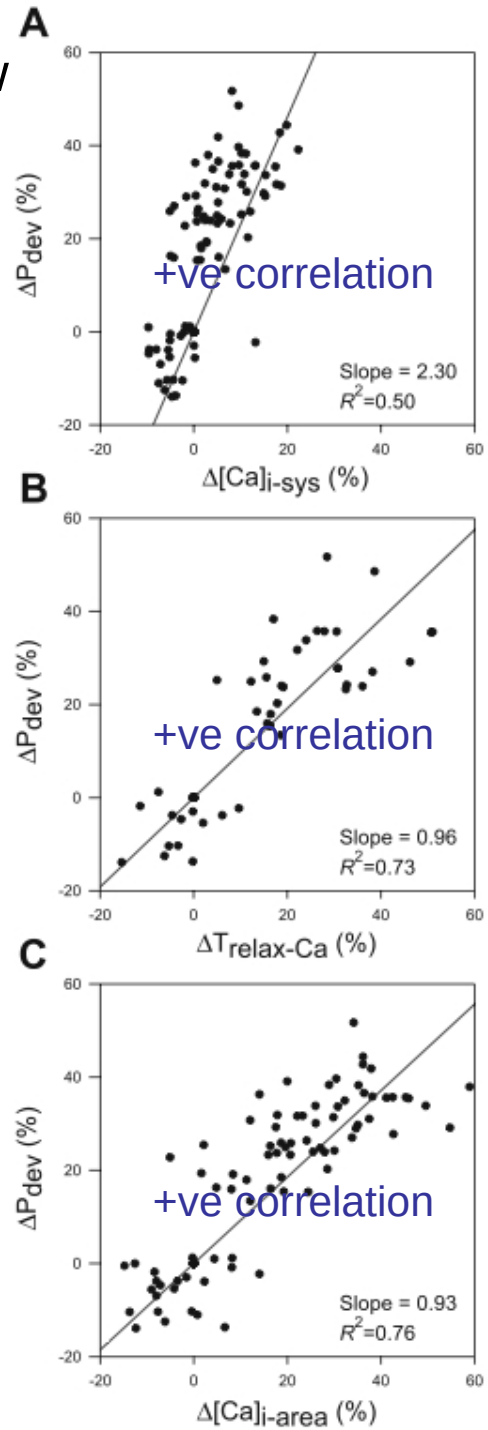
	Interval, ms			
	200	240 (control)	400	600
Pressure data				
P_{sys}, mmHg	102.9±4.3	106.5±4.0	123.9±4.7†	133.3±5.1†
P_{dia}, mmHg	28.5±1.7	28.4±1.7	29.2±1.7†	29.6±1.9†
P_{dev}, mmHg	74.4±4.2	78.1±4.0	94.7±4.9†	103.8±5.5†
dP/dt_{max}, mmHg/s	3,028±138	3,108±123	3,657±148†	3,960±155†
dP/dt_{min}, mmHg/s	−1,916±107	−1,982±102	−2,148±105†	−2,159±105†
$T_{rise\text{-}P}$, ms	26.2±1.0†	26.7±1.0	27.1±1.1	27.2±1.2
$T_{relax\text{-}P}$, ms	43.1±2.9	43.8±3.0	49.0±3.6†	53.6±4.4†
Calcium data				
$[Ca]_{i\text{-}sys}$, nM	948±59*	990±63	1,009±63	1,094±72†
$[Ca]_{i\text{-}dia}$, nM	365±14*	381±15	375±15	394±15
$[Ca]_{i\text{-}dev}$, nM	582±54	610±57	633±58	700±66†
$[Ca]_{i\text{-}area}$, nM·s	24.8±2.3	25.3±2.1	29.8±2.7†	34.0±2.9†
$T_{rise\text{-}Ca}$, ms	8.3±0.3	8.4±0.4	8.2±0.4	8.3±0.4
$T_{relax\text{-}Ca}$, ms	79.9±4.2	82.5±3.6	91.6±5.2	105.9±5.1†

Protocol 2 Results Cont.

Examine morphological changes in LV pressure and $[Ca]_i$ signals individually

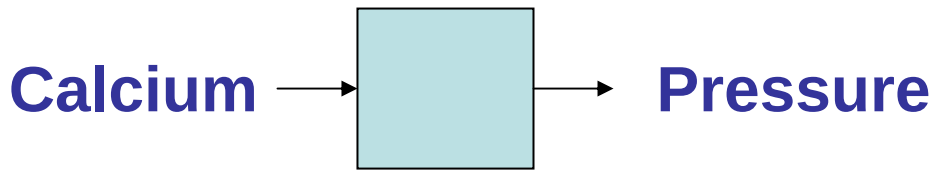


Examine how ΔP_{dev} (%) are related to changes in verious indexes of $[Ca]_i$



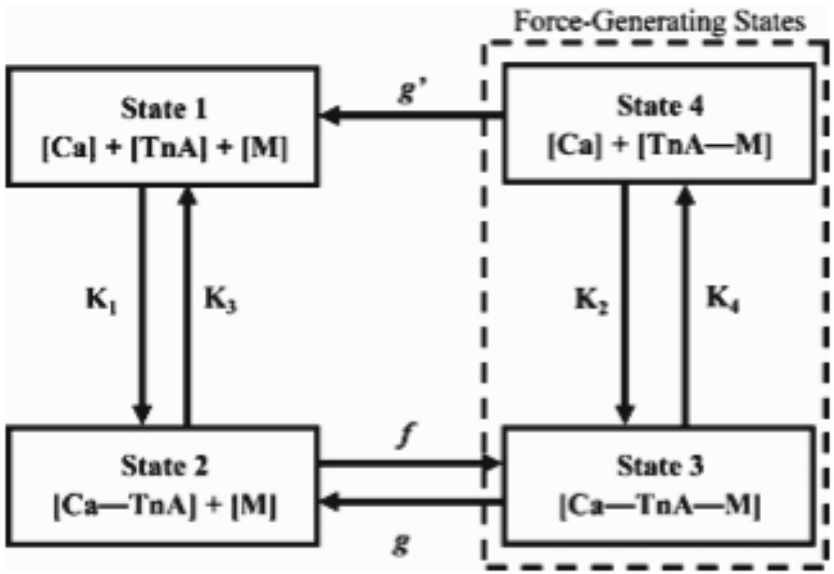
Model-Based Analysis

- Used to obtain additional insights into dynamics of pressure-calcium relationships

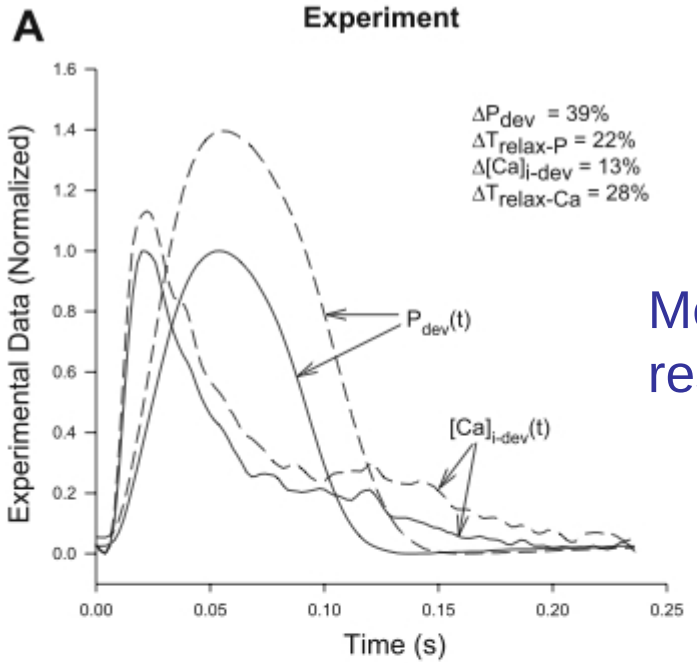


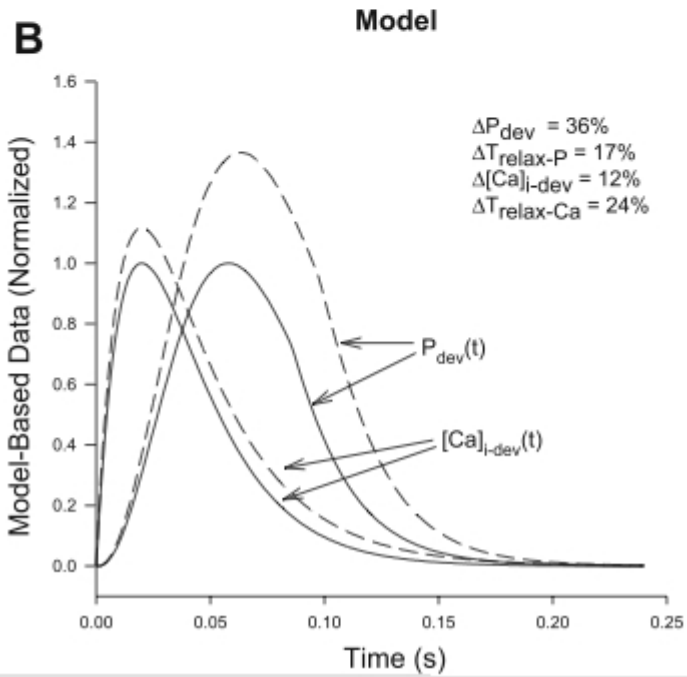
Methods Used

- 4 state model
  - Used to predict pressure wave form for a given calcium transient



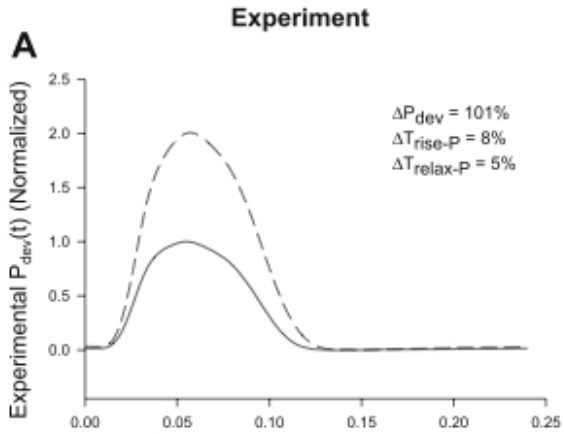
Results

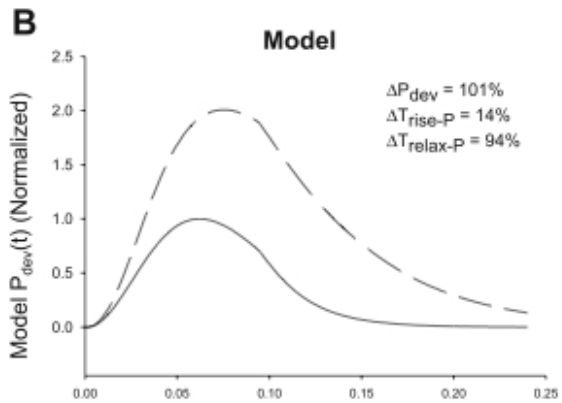


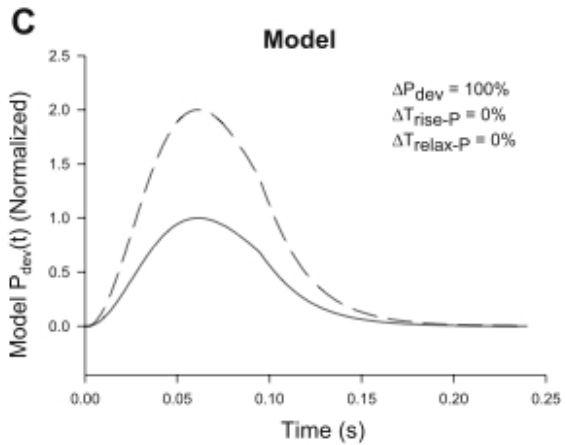


Mechanical restitution protocol

Frank-Starling protocol







Questions Answered

- Q1: Can peak developed pressure change significantly with a minimal (or no) change in the peak systolic intracellular free calcium?

  Yes, (Results of Protocol 1)

- Q2: Is the late component of length-dependent activation absent?

  Yes, Load independent (Results of Protocol 1)

- Q3: What are the determinants of pressure relaxation?

  Slower pressure relaxation can be explained in terms of slower calcium relaxation. (Results of Protocol 2)

Conclusions

- Mouse myocardium appears to be unique in that significant changes in peak developed pressure can occur with little or no change in the peak of the calcium transient
- Unlike other mammalian species, pressure relaxation is load independent and primarily governed by calcium removal
- Exercise caution while extrapolating findings from mouse models to the human setting