Calcium and the control of cardiac contraction

From physiology to heart failure

David Eisner

(eisner@man.ac.uk)
From excitation to contraction

\[ \left[ \text{Ca}^{2+} \right]_i \text{ (nM)} \]

-90
800
45

\[ E_m \text{ (mV)} \]

\[ I_m \text{ (1 nA)} \]

\[ 1 \text{ second} \]

voltage clamp control

Ca current

vary to alter force of heartbeat

contraction
Ca cycling in the heart

- **L-Ca channel**
- **SR**
- **RyR**
- **SERCA**
- **NCX**

**Ca$^{2+}$**

In steady state, influx = efflux

- **3Na$^+$**
- **phospholamban**

↑cytoplasmic Ca ↑ $p_o$

in steady state
influx = efflux
Ryanodine Receptors

Evidence for CICR in intact cardiac cells


Membrane potential (mV)

Ca

I_{Ca}
Why isn’t CICR “All or None”? 

Common-pool models inherently unstable*

Local control theory: 
  independent release sites  
  “all or none” release at each site 
  Ca transient graded by altering number of sites releasing 

*Stern, 1992; Biophys J 63, 497-517
Release Units

SR

mito
Loss of t-tubules in ventricle in heart failure

Control

What controls the size of the Ca transient?
Positive inotropic effects of catecholamines

30 nM isoprenaline

[Graph showing the effects of 30 nM isoprenaline on calcium transient]
Ca transient $\alpha (SR \text{ Ca})^3$

Ca transient amplitude (µM)

SR Ca content (µmol/L)

Consequences of steep relationship

➢ small changes of SR content inotropically significant
decreased systolic Ca in heart failure

Consequences of steep relationship

- small changes of SR content inotropically significant
- Must control SR Ca content precisely

![Graph showing Ca transient amplitude vs. SR Ca content](image)
control of Ca entry and efflux by the systolic Ca transient controls SR Ca content: a simple feedback mechanism

Relevance of feedback mechanism to HF

L-Ca channel

RyR

NCX

SERCA

Ca^{2+}

3Na^+

↑ NCX

↓ SERCA

↓ SR Ca
Does systolic modulation of the RyR affect systolic Ca?

- phosphorylation $\uparrow$ RyR $p_o$
- $\beta$-adrenergic stimulation $\uparrow$ systolic Ca partly by phosphorylating RyR (Shan et al)
- $\uparrow$ rate $\uparrow$ systolic Ca via CAMKII phosphorylation of RyR (Kushnir et al)
- but cf MacDonnell et al

Shan et al (2010). JCI 120, 4388-98
Eschenhagen (2010) JCI 120, 4197-203
Increasing RyR opening does not increase Ca transient in the steady state.

The RyR and Heart Failure

- **Diastole**
  - **Normal**
  - **Decreased systolic opening**
  - **Diastolic leak**

- **Systole**
  - **Normal**
  - **Decreased systolic opening**
  - **Diastolic leak**
Ca cycling in the heart

L-Ca channel

SR
**Measurement of Ca efflux and influx**

- **L-type Ca current** (Ca entry)
- **Na-Ca exchange** (Ca efflux)

**Graphical Representation**

- **[Ca^{2+}]_i (µM)**
- **I_m (600 pA)**
- **Sarcolemmal Ca flux (µmol/L)**

- **Sarcolemmal Ca entry = exit**

**Key Points**

- L-type Ca current (Ca entry)
- Na-Ca exchange (Ca efflux)

**Values**

- Initial [Ca^{2+}]_i (µM) = 0.0
- Final [Ca^{2+}]_i (µM) = 0.8
- I_m (600 pA)
- Sarcolemmal Ca flux (µmol/L)

**Timeline**

- 0.5 sec
- 100 ms