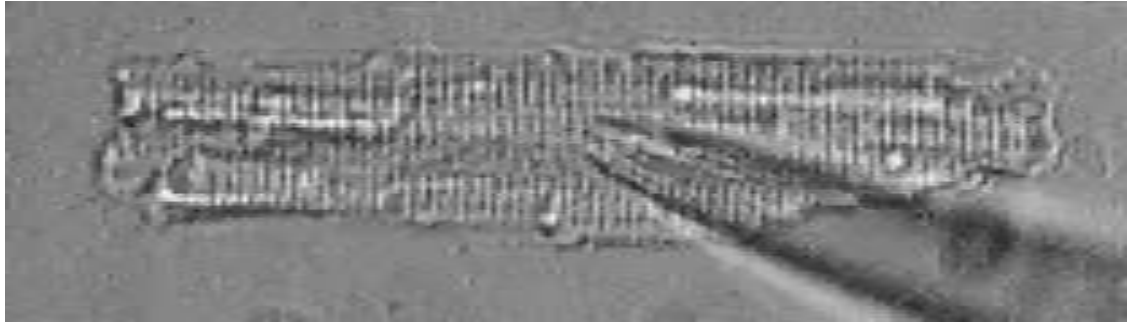


Calcium and the control of cardiac contraction

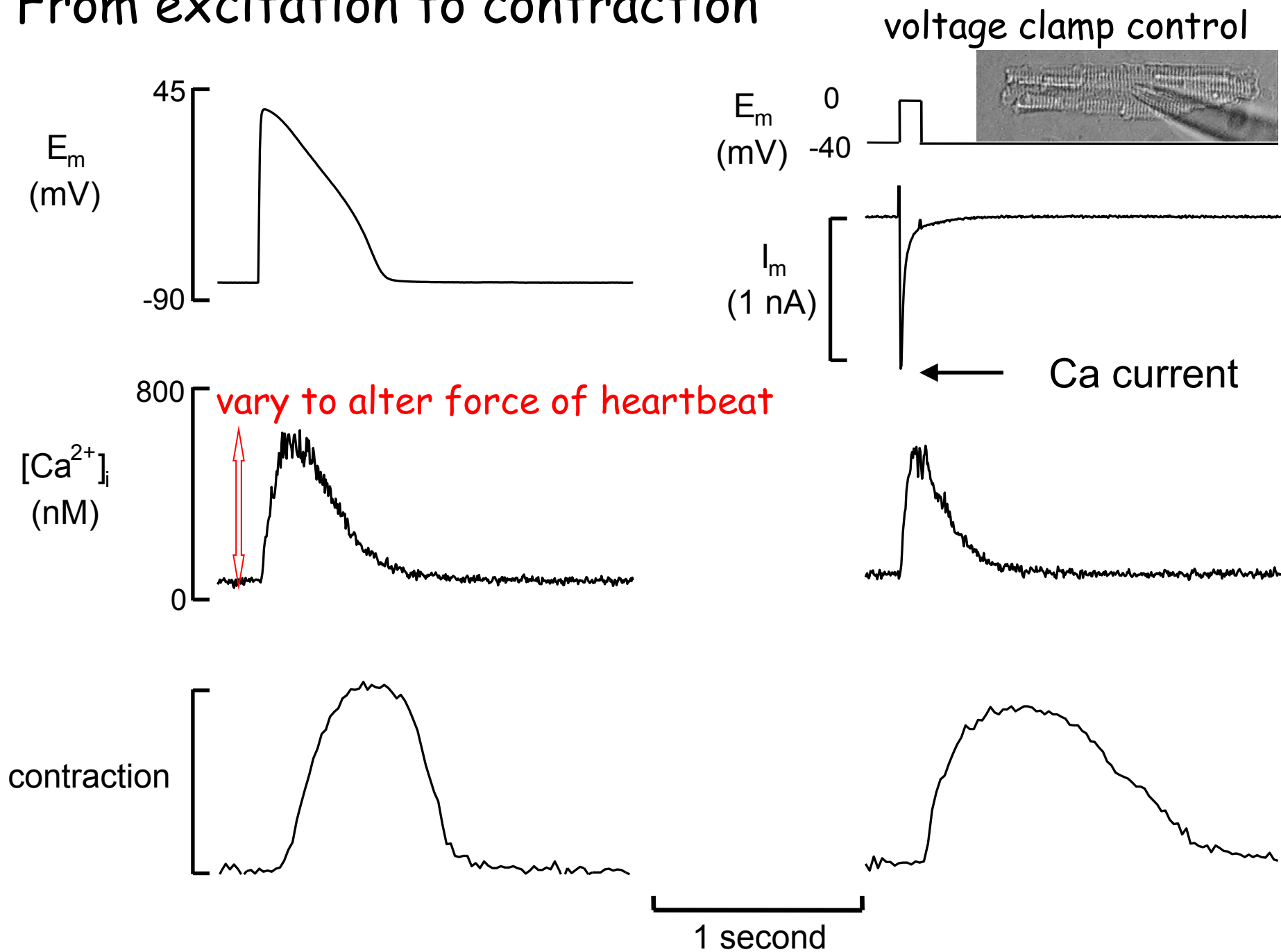
From physiology to heart failure

David Eisner

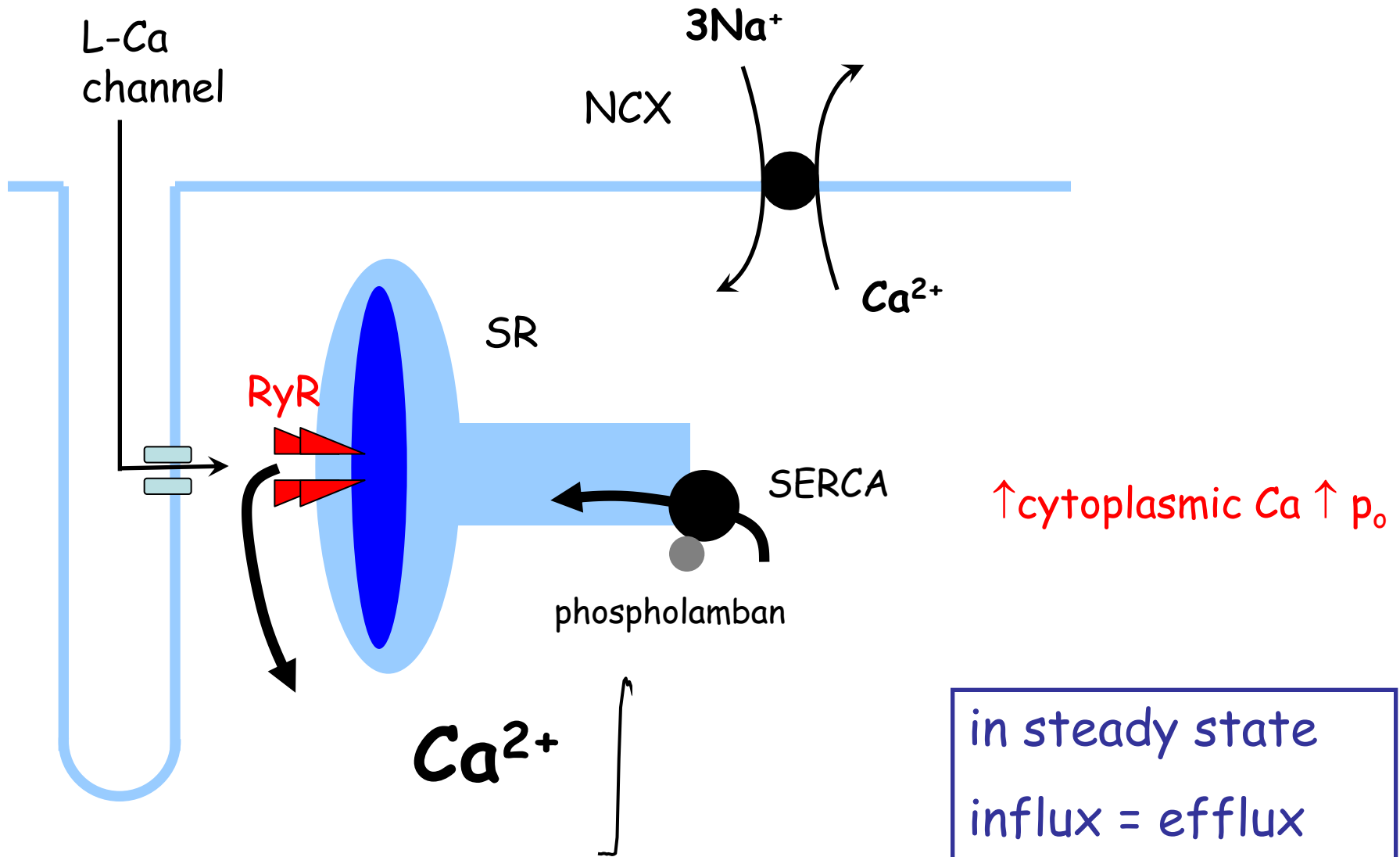
(eisner@man.ac.uk)



From excitation to contraction

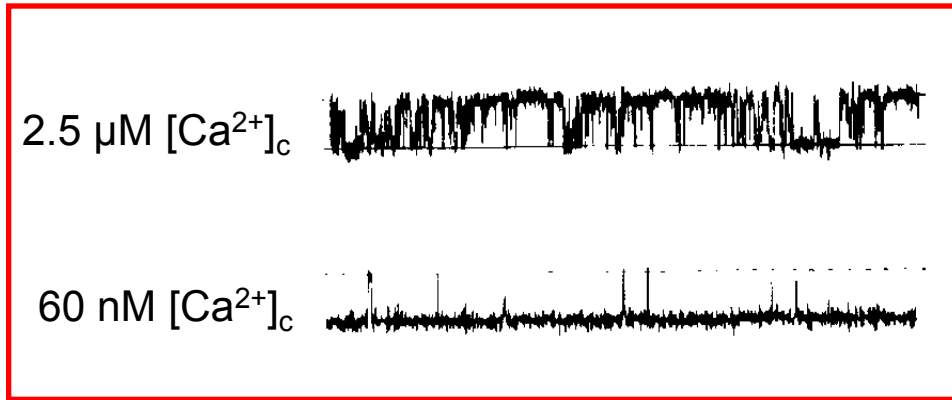


Ca cycling in the heart

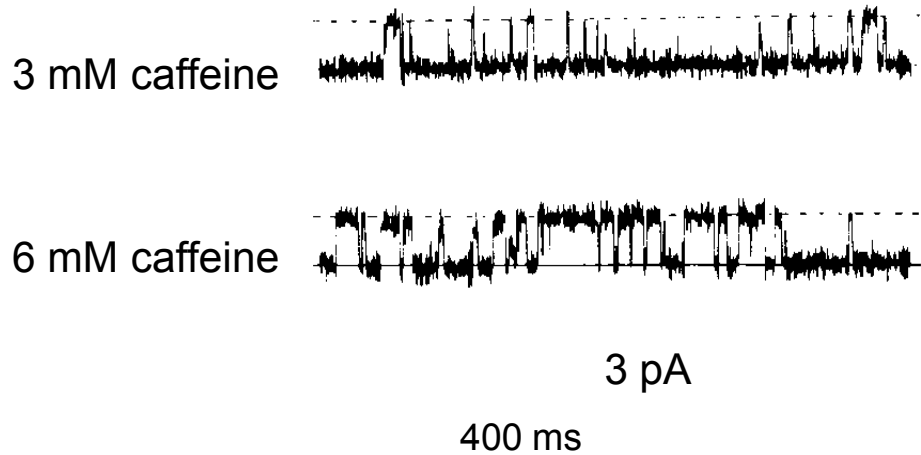
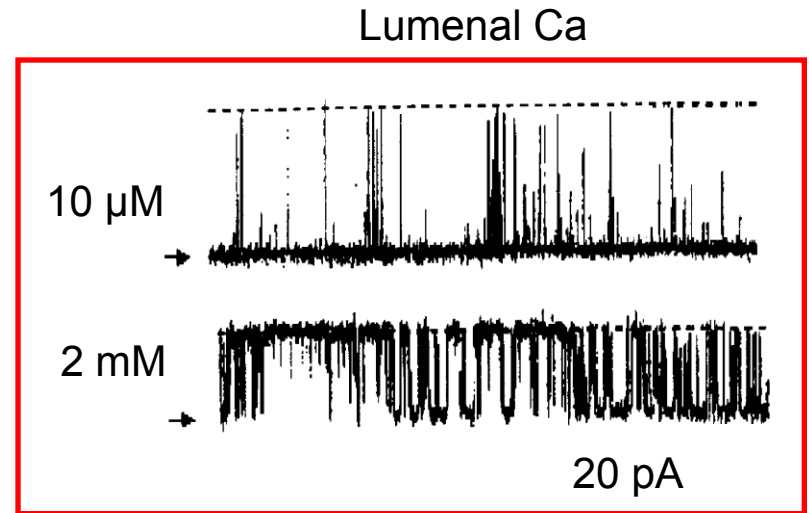


Ryanodine Receptors

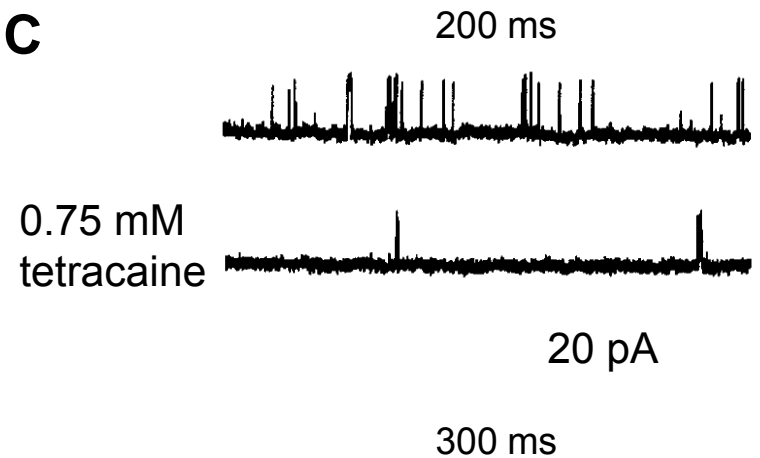
A



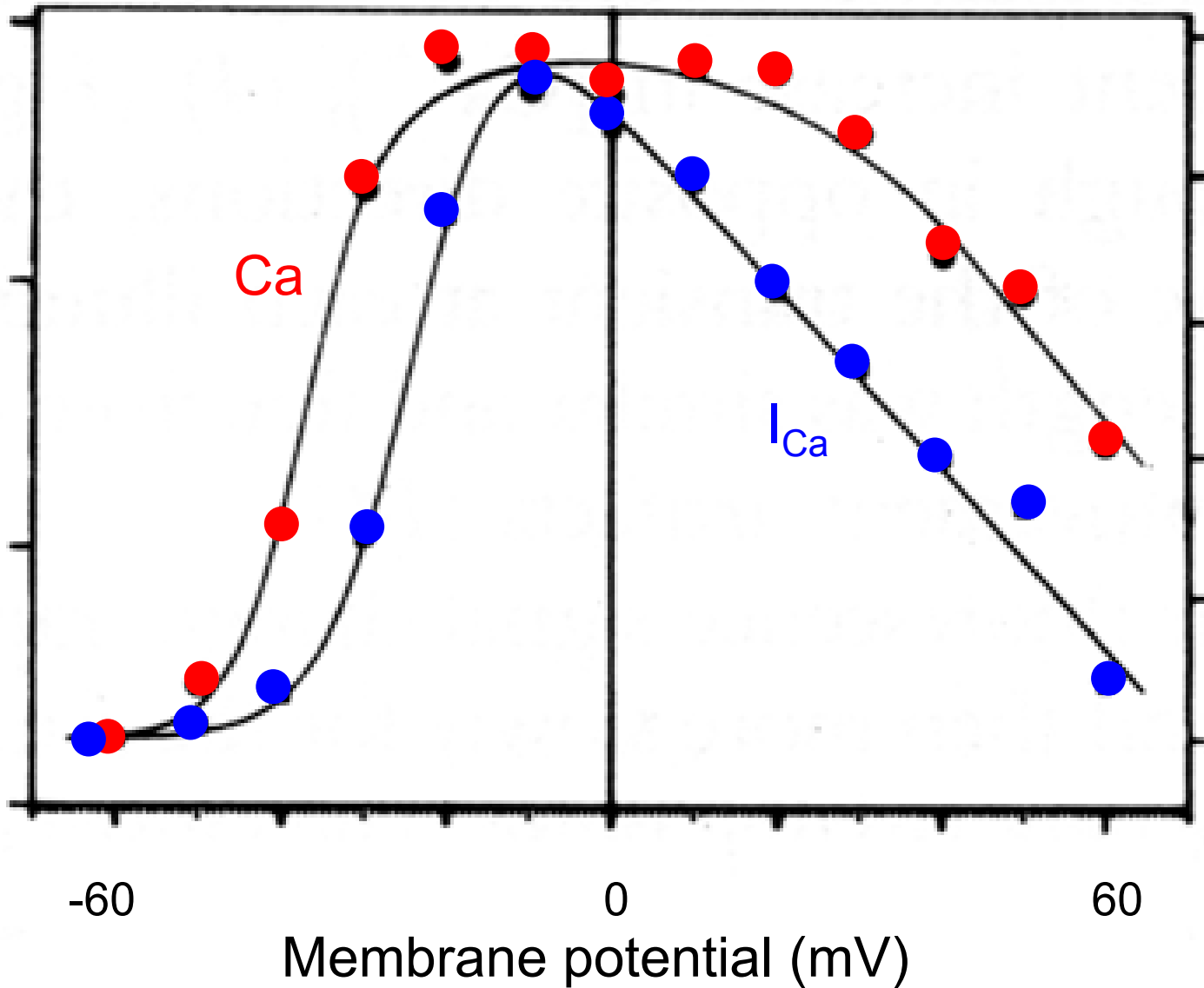
B



C



Evidence for CICR in intact cardiac cells



Why isn't CICR "All or None" ?

Common-pool models inherently unstable*

Local control theory:

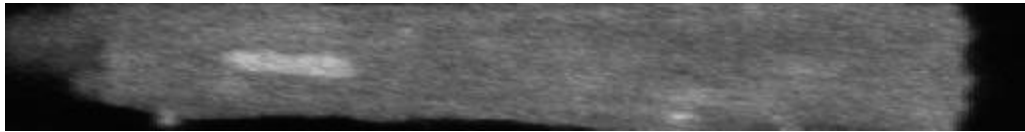
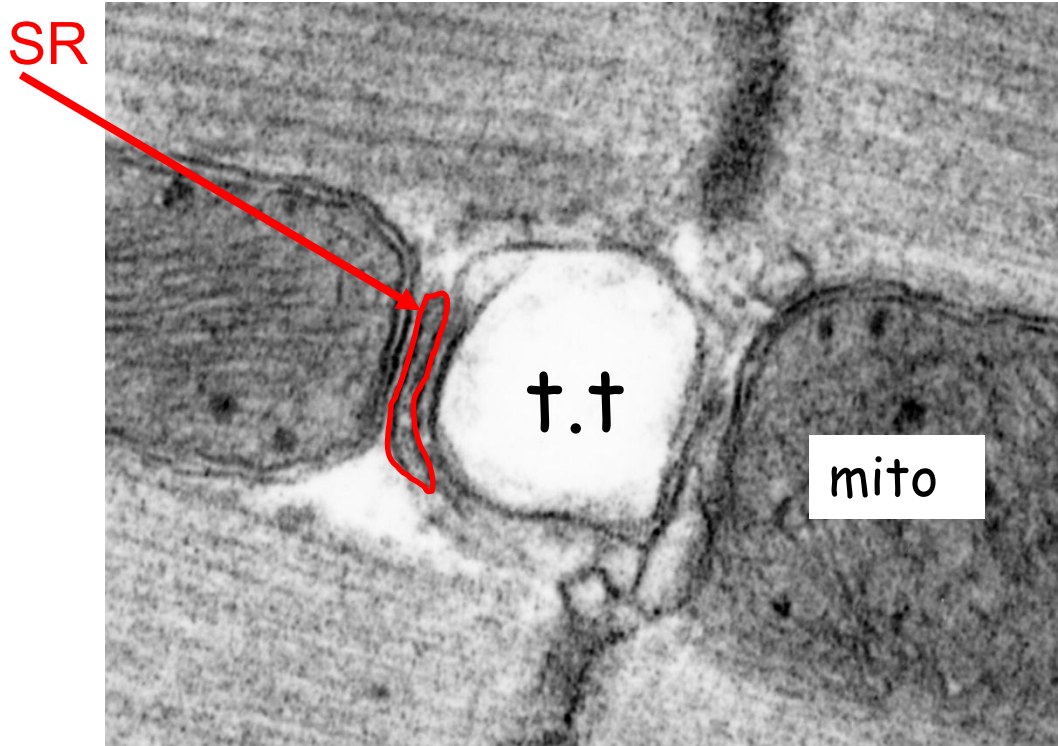
- independent release sites

- "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



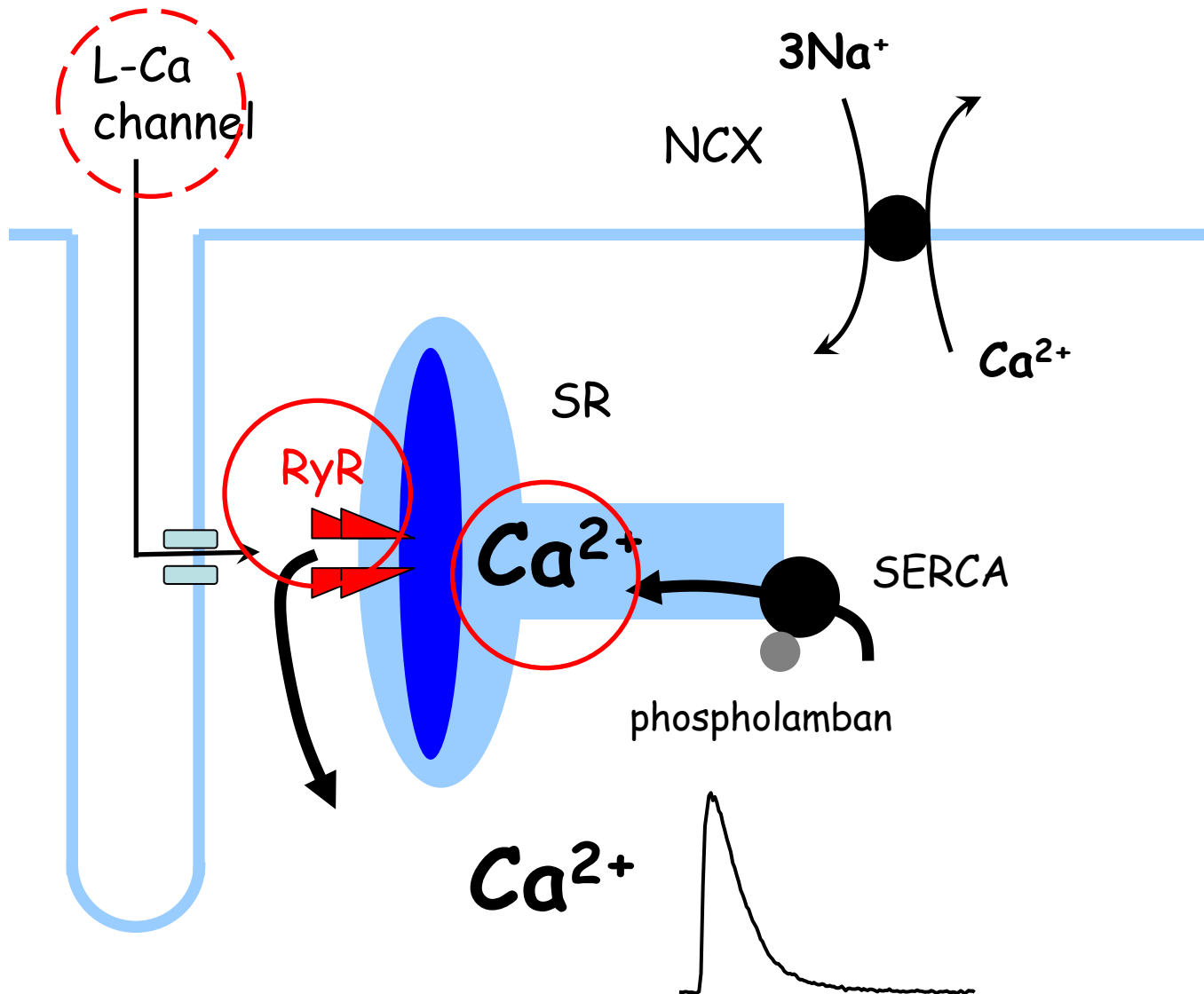
Loss of t-tubules in ventricle in heart failure

Control



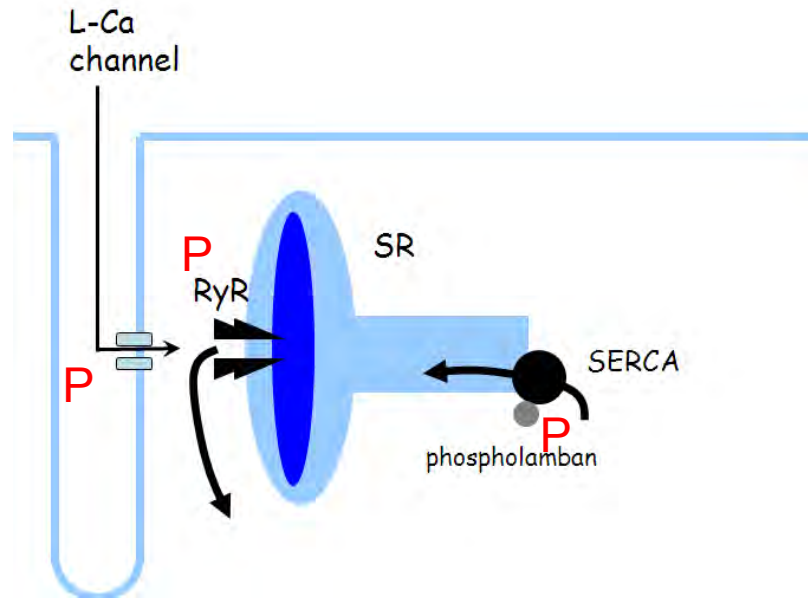
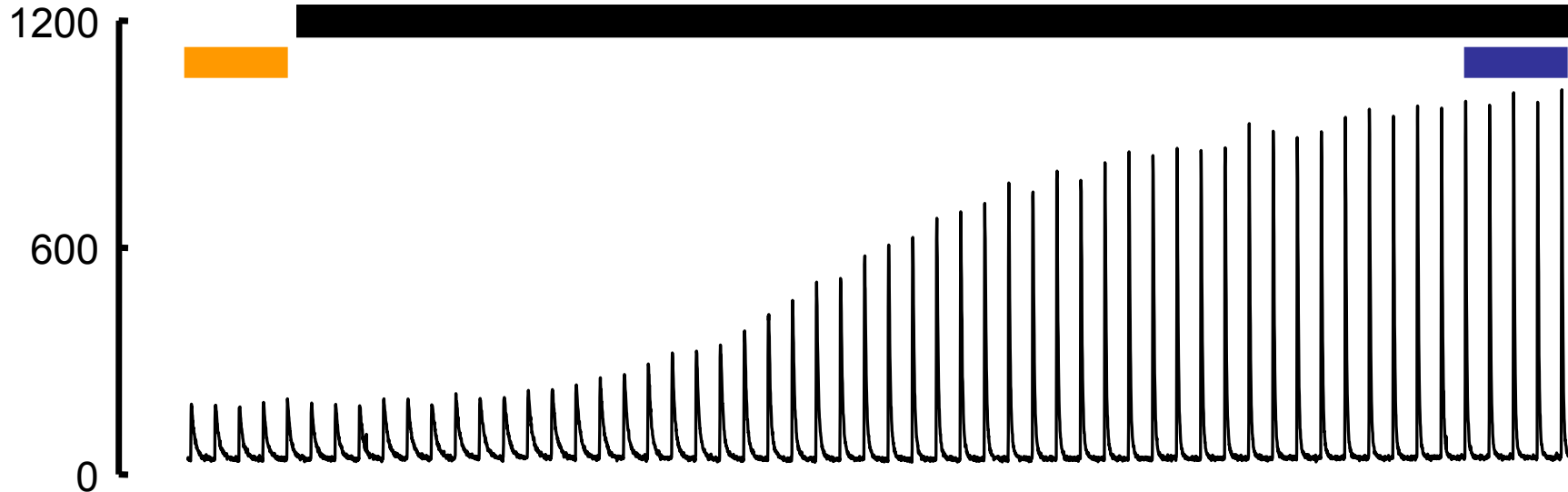
He, J.-Q. et al. (2001) *Cardiovasc Res* 49, 298-307

What controls the size of the Ca transient?

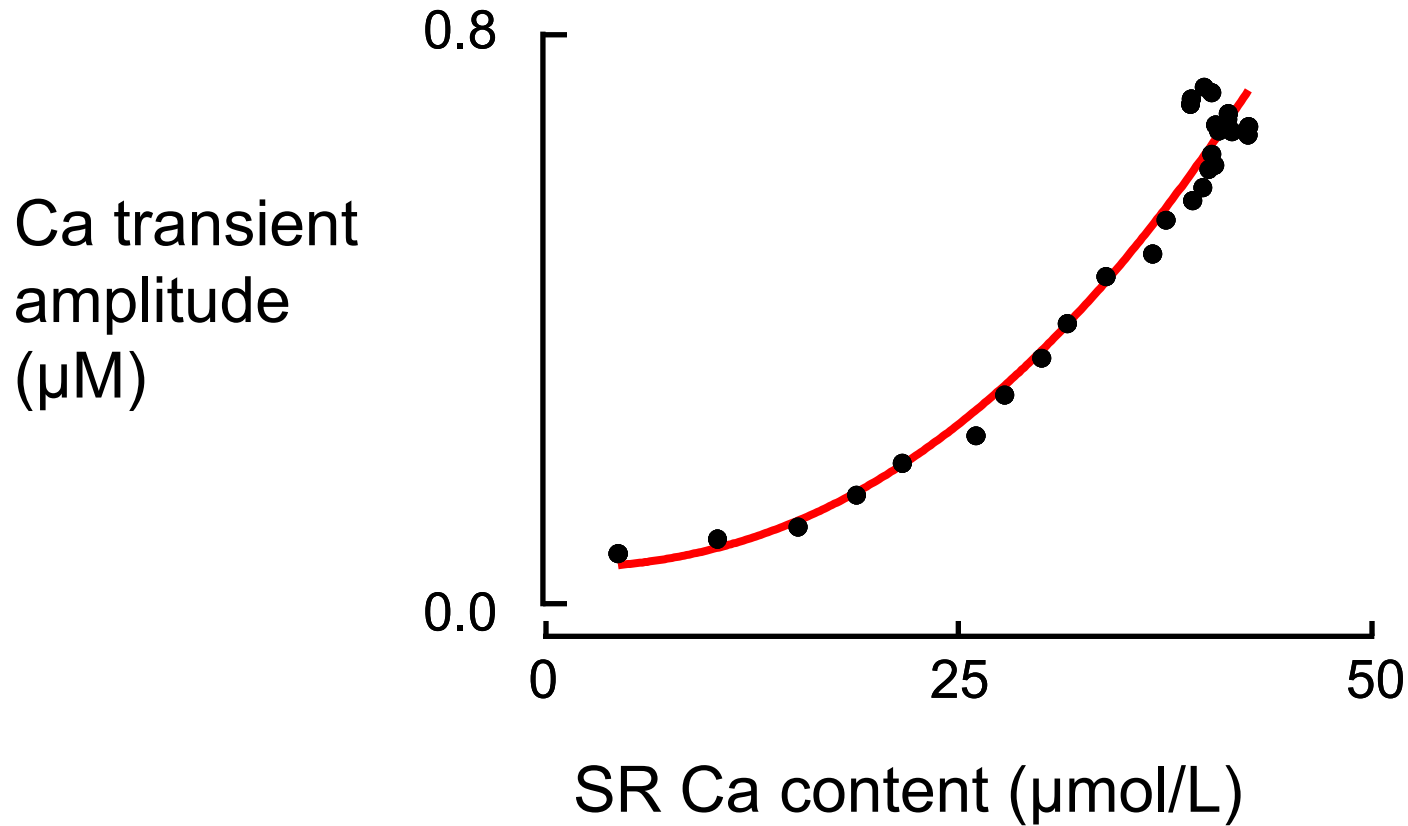


Positive inotropic effects of catecholamines

30 nM isoprenaline

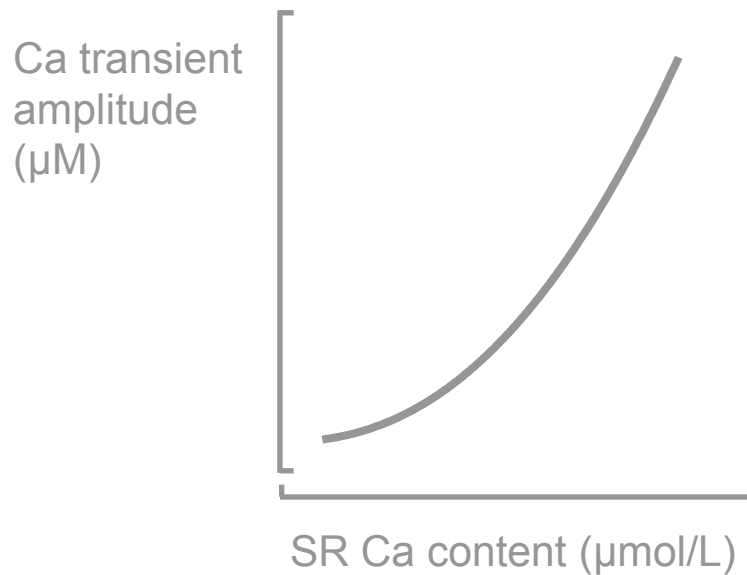


Ca transient \propto (SR Ca)³

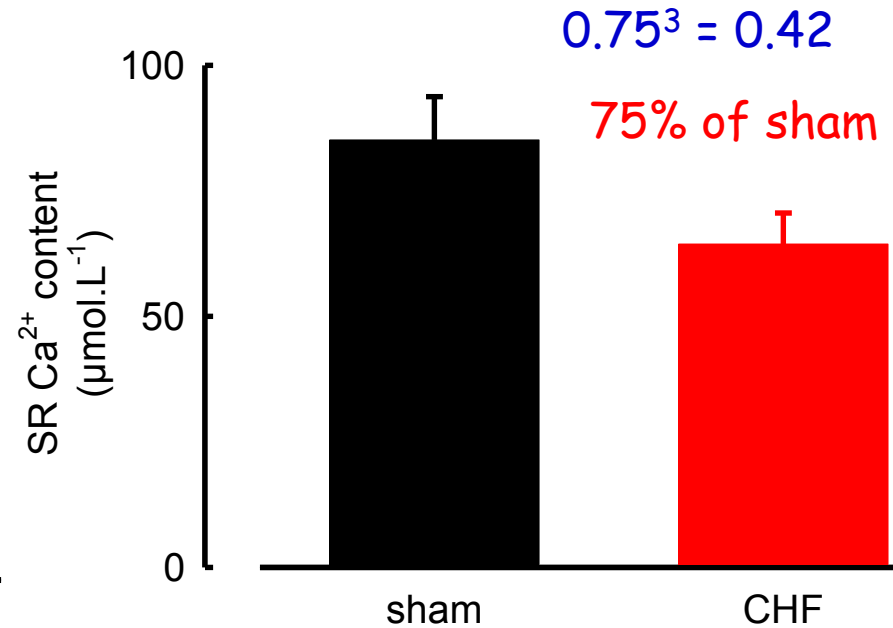
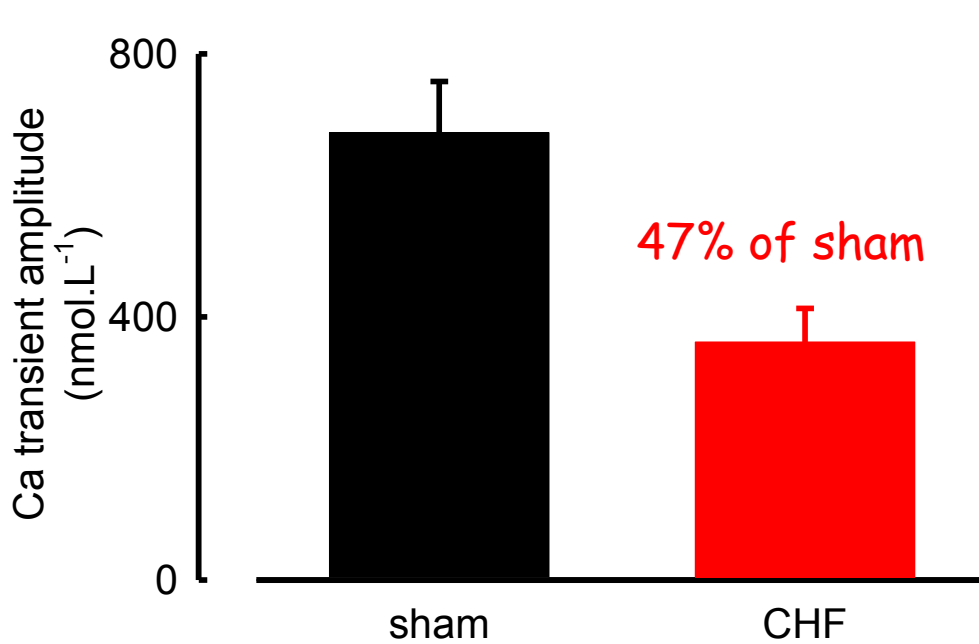
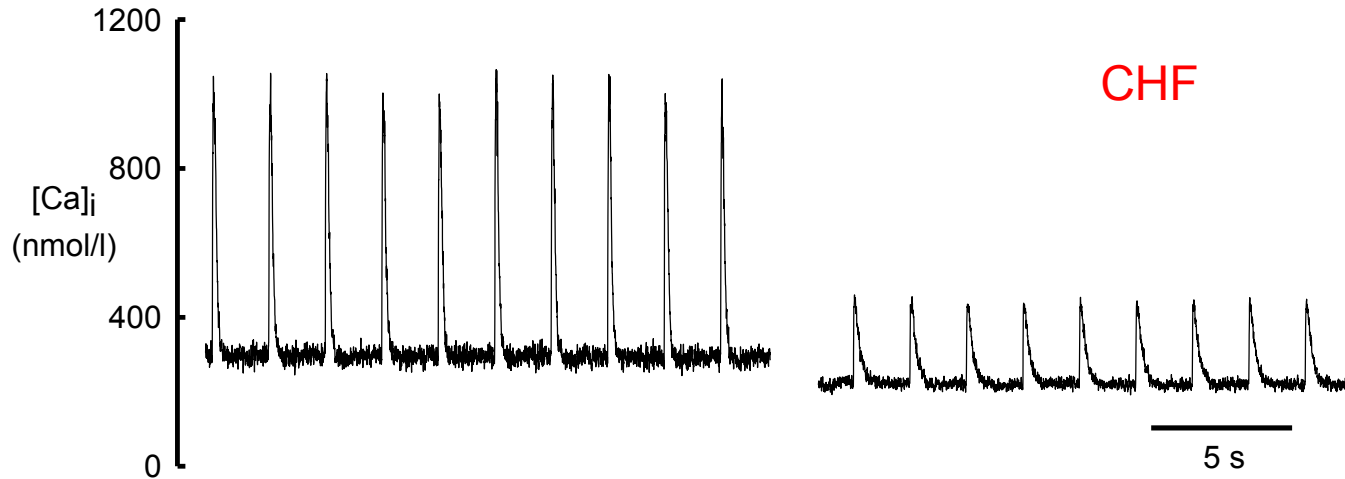


Consequences of steep relationship

- small changes of SR content inotropically significant

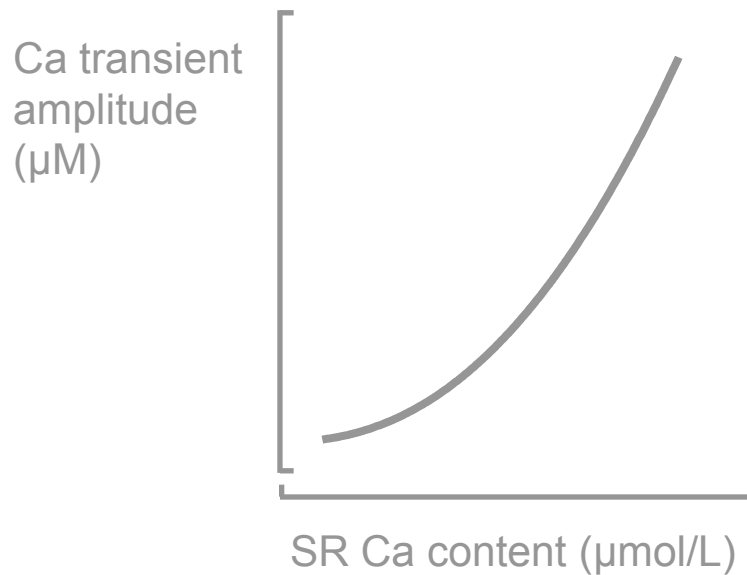


decreased systolic Ca in heart failure



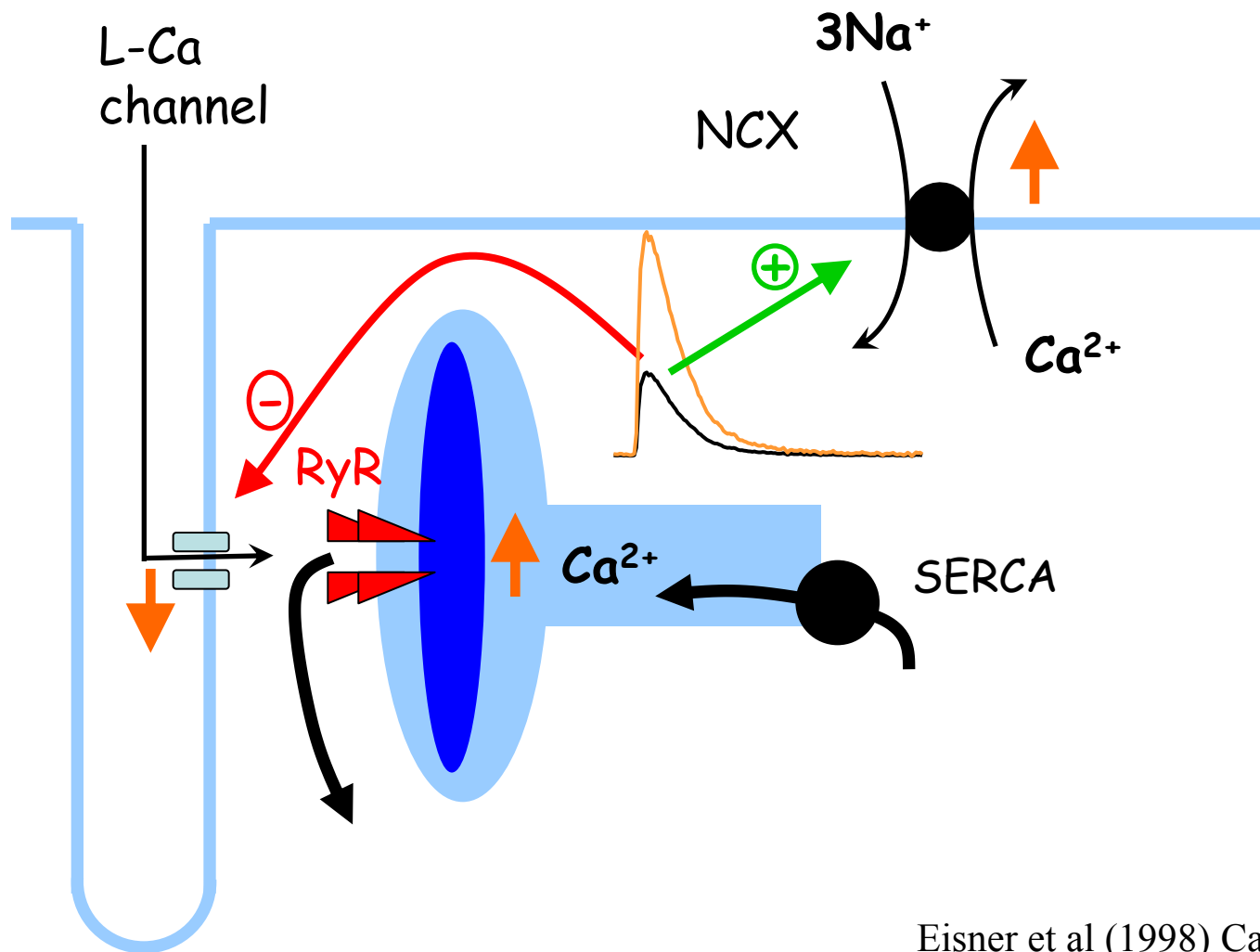
Consequences of steep relationship

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



control of Ca entry and efflux by the systolic Ca transient

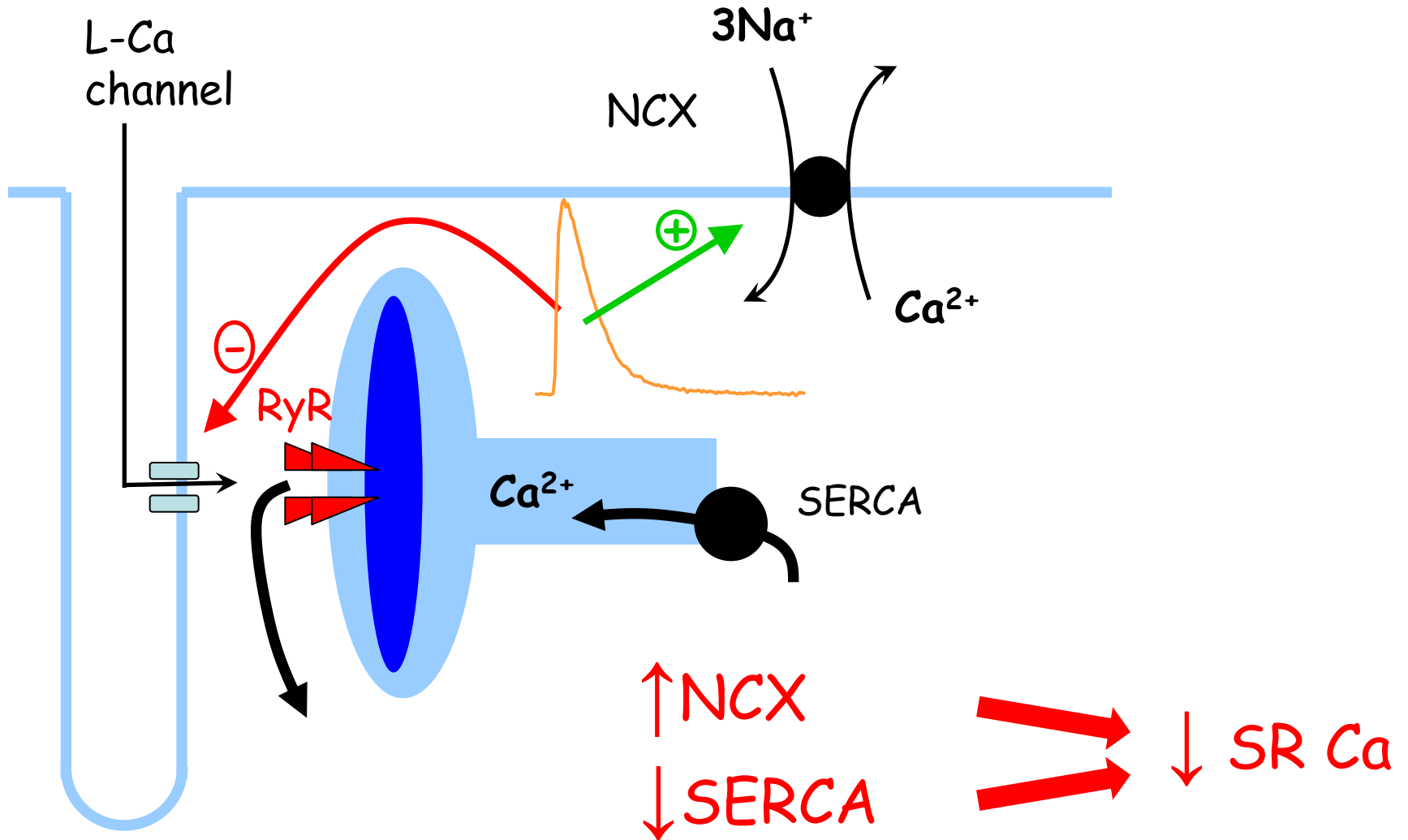
controls SR Ca content: **a simple feedback mechanism**



Eisner et al (1998) Cardiovasc Res 38, 589-604

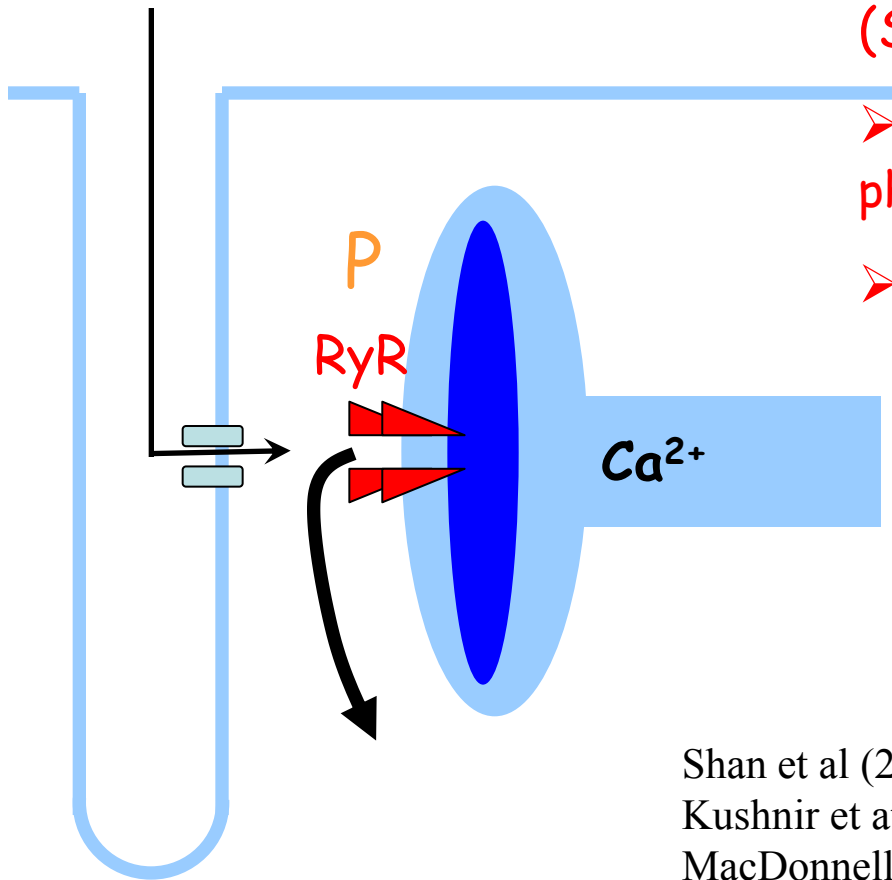
Eisner et al (2000) Circ Res 87, 1087-1094

Relevance of feedback mechanism to HF



Does systolic modulation of the RyR affect systolic Ca?

- phosphorylation \uparrow RyR p_o
- β -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



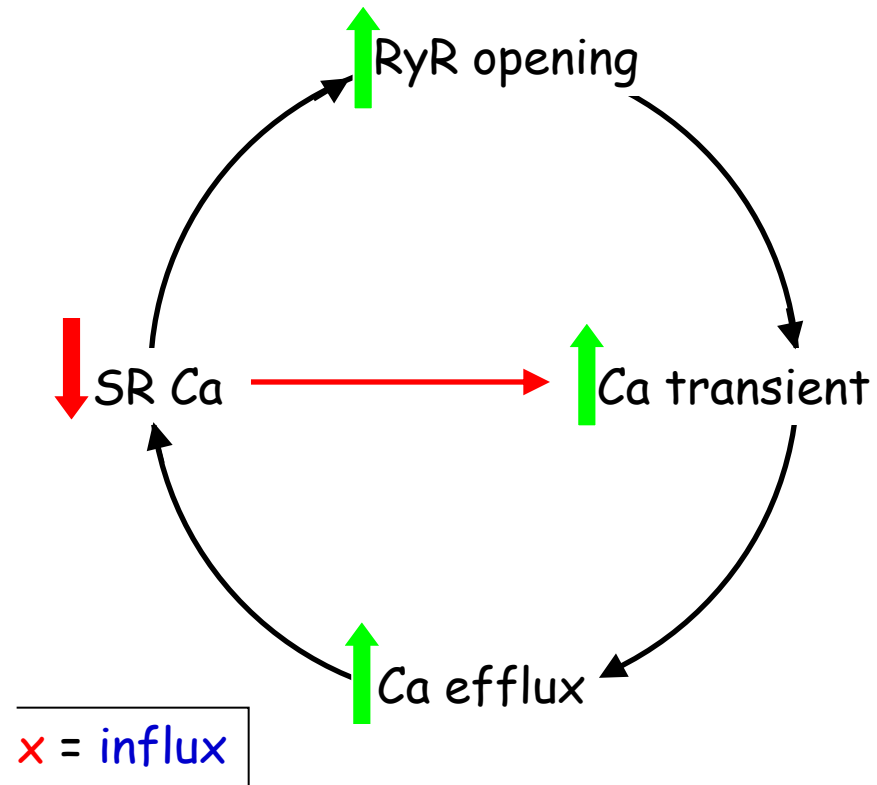
Shan et al (2010). JCI 120, 4388-98

Kushnir et al (2010) PNAS 107, 10274-9

MacDonnell et al (2008). Circ Res. 102:e65-72

Eschenhagen (2010) JCI 120, 4197-203

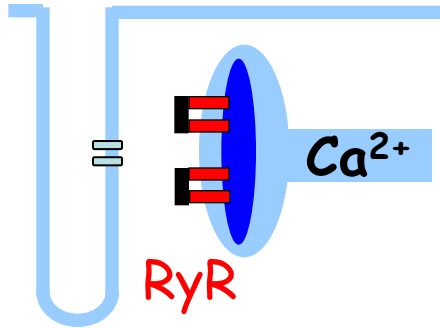
Increasing RyR opening does not increase Ca transient in the steady state



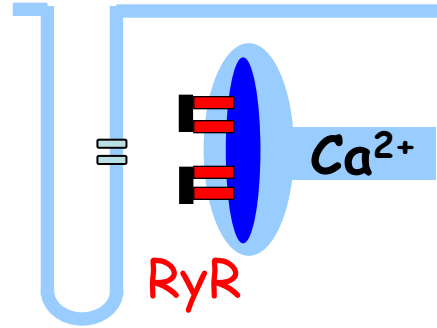
The RyR and Heart Failure

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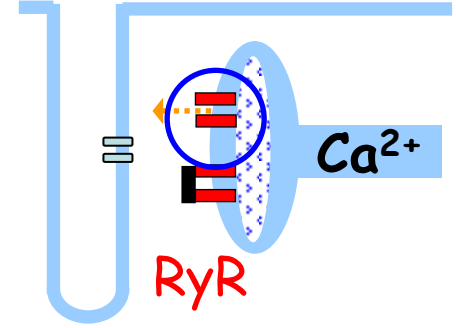
normal



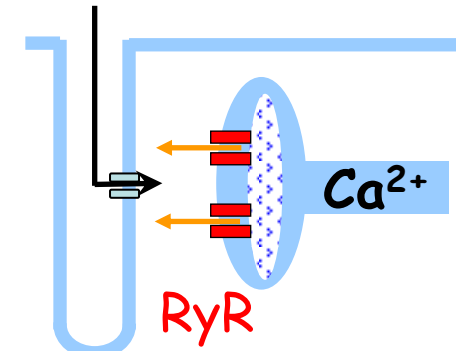
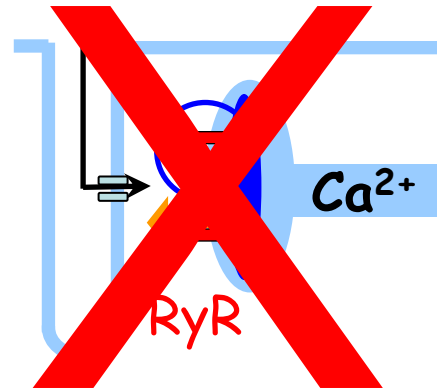
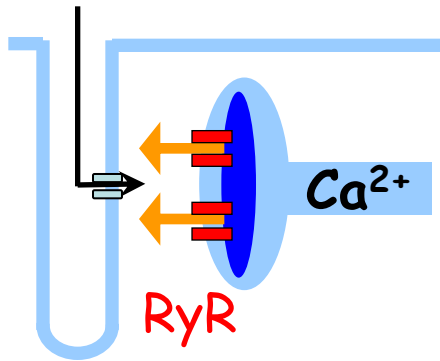
decreased systolic opening



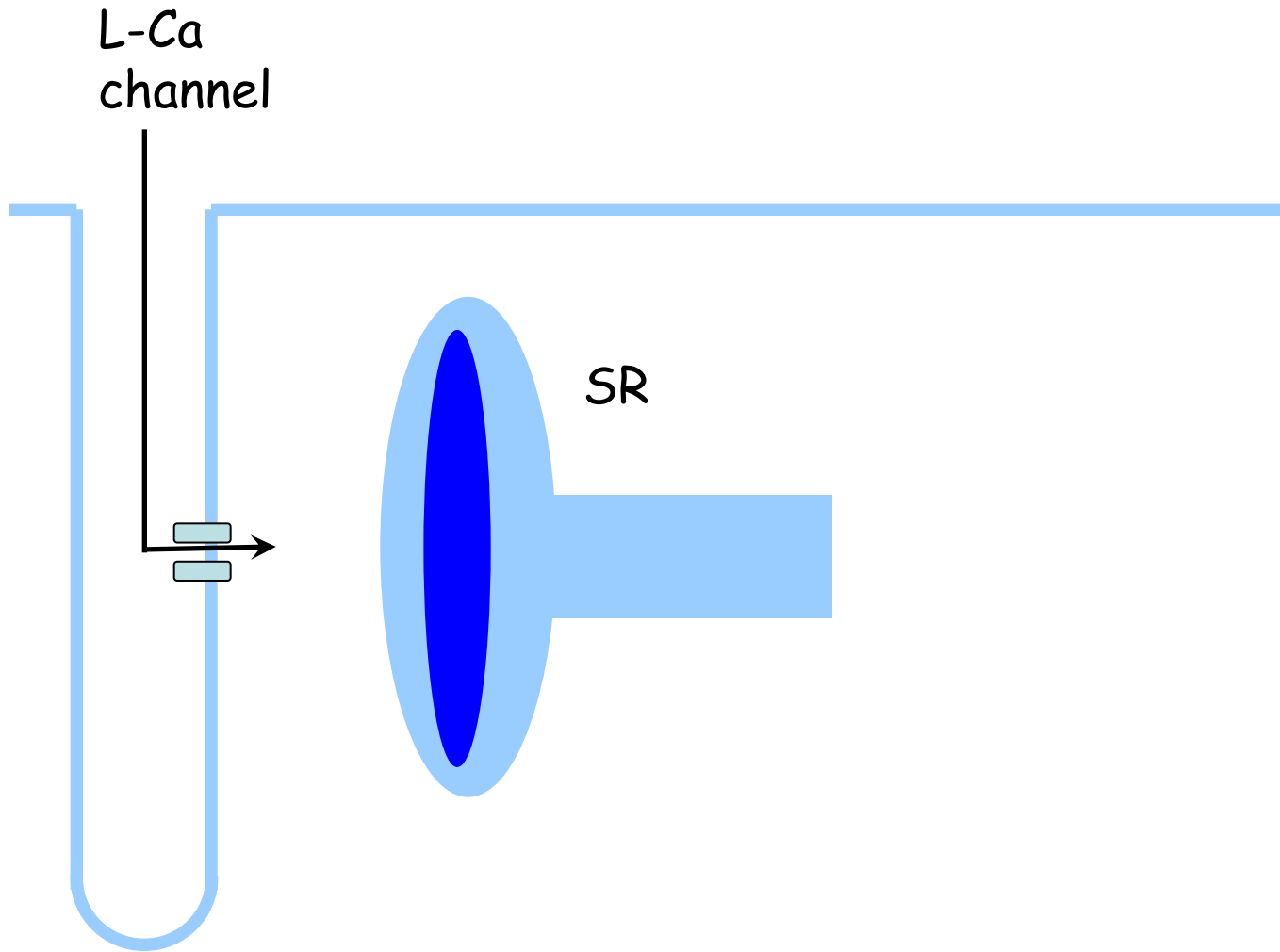
diastolic leak



S
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Ca cycling in the heart



Measurement of Ca efflux and influx

