Downs and ups of calcium in the heart

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It is over 130 years since Sidney Ringer first demonstrated the importance of calcium for contraction of the heart (Ringer, 1883) and almost 40 since the transient rise of intracellular calcium concentration ($[Ca^{2+}]_i$) which activates contraction was first measured (Allen & Blinks, 1978). Subsequent studies have provided much information about the cellular mechanisms which produce this systolic Ca transient (see Eisner *et al.*, (2017) for a recent review). Briefly, the cardiac action potential opens sarcolemmal L-type Ca channels. The resulting Ca influx activates the contractile proteins but its main role is to stimulate calcium-induced calcium release (CICR) from the sarcoplasmic reticulum (SR). This occurs by Ca binding to the SR release channels (ryanodine receptor, RyR) making them open thereby releasing a larger quantity of calcium. Relaxation occurs by Ca being removed from the cytoplasm both back into the SR (by the SR Ca-ATPase, SERCA) or out of the cell, largely on Na-Ca exchange, NCX. Importantly, in the steady state the cell must be in calcium flux balance; the amount of calcium pumped back into the SR must equal that released from it and the amount entering the cell must equal that pumped out. Work from my laboratory has focused on this integrative control of Ca handling and the importance of flux balance.

The force of contraction of the heart is not constant; it increases, for example, in exercise and decreases in heart failure. The Ca content of the SR is a major factor governing the size of the underlying Ca transient. We have found that the SR Ca content is controlled by a negative feedback loop; an increase of SR Ca increases the amplitude of the Ca transient resulting in decreased Ca influx and increased efflux so that the cell and SR Ca decrease (Trafford *et al.*, 1997). This feedback has many other implications for cardiac Ca cycling. For example, it explains why stimulation of the opening of the RyR does not produce a maintained increase in the amplitude of the Ca transient (Greensmith *et al.*, 2014).

For the heart to work as a pump, it must relax during diastole. A major problem in patients with heart failure is impaired diastolic relaxation. Despite this, very little is known about the factors responsible for the control of diastolic $[Ca^{2+}]_i$. In recent work we have studied the effects of changes to SR function that occur in heart failure. A decrease of SERCA or an increased leakiness of the RyR both decrease SR Ca content and thereby systolic $[Ca^{2+}]_i$. We find that these changes are accompanied by an increase of diastolic $[Ca^{2+}]_i$. We suggest that this is a consequence of the need for the cell to be in Ca flux balance. The decrease of systolic $[Ca^{2+}]_i$ decreases Ca efflux during systole thereby requiring an increase of diastolic efflux which is maintained by an increase of diastolic $[Ca^{2+}]_i$ (Sankaranarayanan *et al.*, 2017).

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