Cardiomyopathies: When is Ca^{2+} the culprit?

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The coordinated contraction and relaxation of the heart that allows it to function as a pump arises from transient changes in the concentration of Ca^{2+} within the myocytes. Influx of Ca^{2+} during the cardiac action potential triggers release from the intracellular Ca^{2+} store (the sarcoplasmic reticulum, or SR), rapidly increasing the cytosolic [Ca^{2+}] ~10-fold. Ca^{2+} then activates cross-bridge cycling, and force production, by binding to the regulatory sites on troponin C. Relaxation takes place when the [Ca^{2+}] returns again to resting levels as it is removed from the cytosol by two principle transport mechanisms: re-uptake into the SR by the Ca^{2+}-ATPase (SERCA2a); and transport across the sarcolemma (SL) by the Na^{+}/Ca^{2+} exchanger (NCX). Given the key role of Ca^{2+} in the mechanical activity of the heart, it is not surprising that Ca^{2+} mis-handling is often implicated in cardiomyopathies where force production is compromised. However, many other changes also occur in hearts *en route* to failure, such as extracellular matrix remodelling and increased ß-adrenergic stimulation. The impact of these changes on a beat-to-beat basis remains unclear, particularly since most studies only examine force and Ca^{2+} during steady-state, or single beat responses. In this study, we utilised an animal model of hypertensive failure to gain insights into Ca^{2+} homeostasis in the recovery from non-steady-state interventions in isolated left ventricular preparations.

Measurements of isometric force and $[Ca^{2+}]_i$ were made at 37°C in left ventricular trabeculae from failing spontaneously hypertensive rat (SHR) hearts, and their normotensive Wistar-Kyoto (WKY) controls. At 1Hz, peak stress was reduced in SHR (14.5 ± 2.4 mN mm^{-2} *versus* 22.5 ± 6.7 mN mm^{-2} for WKY), although the Ca^{2+} transients were bigger (peak $[Ca^{2+}]_i$ 0.60 ± 0.08 μM *versus* 0.38 ± 0.03 μM for WKY) with a slower decay of fluorescence (time constant 0.105 ± 0.005 s *versus* 0.093 ± 0.002 s for WKY). Two experimental protocols were used to potentiate force as a probe of dynamic Ca^{2+} cycling: (i) an interval of 30s rest, and (ii) a 30s train of paired-pulses, and the recirculation fraction (RF) calculated for recovery to steady-state. No difference was found between rat strains for RF calculated from either peak force or Ca^{2+}, although the RF was dependent on potentiation protocol. Since SR uptake is slower in SHR, the lack of change in RF must be due to a parallel decrease in trans-sarcolemmal Ca^{2+} extrusion. This view was supported by a slower decay of caffeine-induced Ca^{2+} transients in SHR trabeculae. Confocal analysis of LV free wall showed t-tubules were distorted in SHR myocytes, with reduced intensity of SERCA2a and NCX labelling in comparison to WKY.