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Preserved contractile function of unloaded cardiomyocytes despite diminished sarcomere size is associated with troponin I activation

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Objective: Myocardial unloading with ventricular assist devices in patients with severe heart failure (HF) can lead to reversal of certain aspects of pathological remodeling. However, these effects do not translate into recovery of myocardial function in the human heart, possibly due to detrimental atrophic processes also elicited through unloading. We have studied the effects of long-term unloading on sarcomeric morphology and function in a small animal model of ventricular unloading, heterotopic heart transplantation (HTX) in rats.

Methods: Native rat hearts were unloaded via HTX for 30 days, CMs from control and unloaded hearts were isolated (n=8 hearts/>250 individual cells/group). CM overall size was determined, sarcomere length/contractility assessed and Calcium transients as well as E-C coupling gain analyzed in patch-clamped CMs. Additionally, phosphorylation of Troponin I, indicative of sarcomere activation, was measured with western blotting.

Results: CM cross-sectional area was diminished in unloaded cells by about one third (2787 $\pm$ 345 vs 1993 $\pm$ 230 μm2) as was cell capacitance in patched cells. Accordingly, baseline sarcomere length was significantly reduced by ~0.2μm (Figure). However, this reduction did not diminish contractile function: fractional shortening was significantly higher in unloaded CMs (8.0 $\pm$ 3 % vs 6.6 $\pm$ 2.5 % in CTR, p = 0.01). Departure velocity of the transients was similar (-135.2 $\pm$ 48 vs -119.4 $\pm$ 40 dL/dt), and return velocity was slightly increased in unloaded cells (120.7 $\pm$ 54 vs 94.0 $\pm$ 46 dL/dt, $p < 0.05$), indicating preserved relaxation. Calcium transient amplitudes and current-voltage relationship under basal condition and isoproterenol stimulation was not changed. Troponin I phosphorylation was elevated and may contribute to the maintenance of sarcomeric function in long-term unloaded CMs.

Conclusion: Although there are limitations regarding assessment of contractility in isolated cells, we may conclude that the considerable size reduction in CMs induced by unloading does not translate into diminished contractile function or E-C coupling.