The effect of mechanical stimulation on cardiac myocytes: The acute and chronic effects of stress and strain

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Mechanical stimulation has an important regulatory function in the healthy heart, influencing both contractility (The Frank-Starling Law) and rhythm (The Bainbridge effect) on a beat to beat basis. However, chronic increases in stress, via pressure- or volume- overload, are associated with heart disease. Initially the response of myocytes to hypertension is compensatory. These include hypertrophy, a prolongation of the action potential duration (APD) and an increase in the intracellular Ca^{2+} transient with an associated increase in contractility. In rat, these effects seem common to both systemic (*e.g.* the spontaneously hypertensive rat, SHR) and pulmonary (*e.g.* monocrotaline-induced pulmonary hypertension, MCT) models. Possibly as a result of the complex fibre and sheet structure of the left ventricle there are gradients of stress and strain and of gene expression and function of proteins modulated by mechanical stimulation within the normal heart (Kelly *et al.*, 2006; Stones *et al*., 2007). It is therefore interesting, but perhaps not surprising, that the structural and functional response to hypertension is likewise, not uniform across the ventricular wall (*e.g.* as shown in the SHR (McCrossan *et al*., 2004). There is evidence that hypertrophied hearts are more susceptible to arrhythmogenic stimuli, including mechanical stimuli, than normal hearts. Acute increases in left ventricular dilation cause increased arrhythmias in the SHR (Evans *et al.*, 1995). A possible reason for this pre-disposition to arrhythmia is the APD lengthening and alteration in APD dispersion which is combined with increased activity of mechanosensitive channels (Kamkin *et al*., 2000). The generation of arrhythmias can rapidly lead to myocyte death due to the uncontrolled release of intracellular Ca^{2+}. If left unchecked compensatory hypertrophy usually progresses to heart failure where there is depressed contractile function despite the presence of hypertrophy. In addition to changes that affect contractility at a cellular level, there is evidence that increased apoptosis plays a role in the depression of whole heart pump function in both SHR (Bing *et al*., 2002) and MCT (Buermans *et al.*, 2005) hypertensive heart failure, where there is a switch from an anti-apoptotic to pro-apoptotic gene expression profile in the transition from a compensated to failing state.

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