Mechanisms underlying the stretch-dependent slow inotropic response in isolated mouse myocardium

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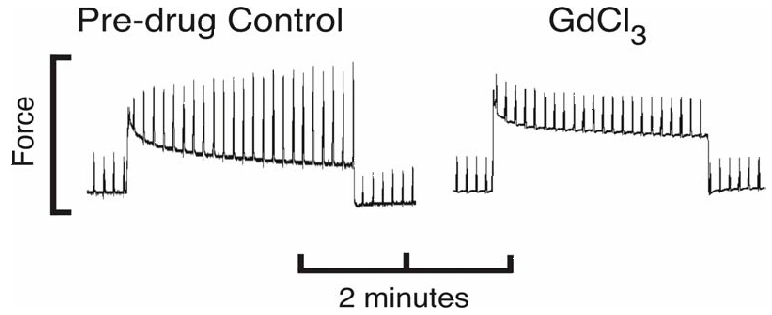
When cardiac muscle is subjected to stretch the force of contraction increases, allowing the intact heart to adjust its output to the body's demand (Allen & Kentish, 1985). This increase in contractility has been shown *in vivo* to occur in two distinct phases. Initially there is an abrupt increase in force that coincides with the stretch, and secondly there is a slower response that develops over a period of a few minutes (the ''slow force response''). The first of these responses is largely due to a change in the sensitivity of the contractile proteins to Ca^{2+}, whereas the slow force response is accompanied by a concomitant increase in the magnitude of the intracellular Ca^{2+} transient (the event that initiates contraction). It has been proposed that stretch-activated channels contribute to Ca^{2+} entry after stretch (Calaghan & White, 2004). The aim of the present study was to reinvestigate the mechanisms underlying the slow force response of cardiac muscle.

Mice were euthanased and cardiac trabeculae or papillary muscles (< 1 mm in length, and 0.1 - 0.3 mm in diameter), dissected from the right ventricle of mouse hearts, were mounted in a muscle chamber between a hook attached to a force transducer and a lever connected to a motor capable of making precise changes in muscle length. Each preparation was then subjected to a step increase in length for 2 minutes whilst isometric force was recorded.



Response of a representative mouse papillary muscle subjected to step increases in length before, and during application of $GdCl_3$.

One minute after the initial length change, active force increased by 77 ± 17% of the force immediately following the stretch (n = 16). Subsequent application of either 400 µM streptomycin, or 20 µM $GdCl_3$ (blockers of stretch-activated channels) reduced the slow force response ($p \leq 0.01$) for identical step increases in length (streptomycin: from 86 ± 25% to 38 ± 14% (n=9), or $GdCl_3$: from 65 ± 21% to 12 ± 7%, n=7), suggesting a possible role for stretch-activated channels in the slow force response.

Allen, D.G. & Kentish, J.C. (1985) *Journal of Molecular and Cellular Cardiology* **17**, 821-840.
Calaghan, S. & White, E. (2004) *Journal of Physiology* **559**, 205-214.