Why stretched muscles hurt – is there a role for half-sarcomere dynamics?

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The functional unit of muscle is the half-sarcomere in which crossbridges attach and cycle between interdigitating arrays of thick and thin filaments. Half-sarcomeres shorten during contraction if the force produced by the crossbridges is greater than the external force and are stretched if the force produced by the crossbridges is less than the external force. A typical muscle cell will have many thousands of half-sarcomeres in series so the overall performance of a muscle can be a complex function of the behaviour of individual half-sarcomeres. However, until recently, only whole sarcomere lengths could be measured except in electron micrographs.

Sarcomere uniformity has long been a topic of interest and it is known, for instance, that in isolated single fibres the sarcomere lengths tend to be longer near the end of the fibre than at the middle. For this reason, Gordon *et al.* (1966) in their classic study of the force–length relation of single fibres, developed the length clamp and applied it to a middle region of the fibre where the sarcomere uniformity was greatest. It is also recognized that sarcomere non-uniformity can occur in intact muscles, particularly after they are stretched during contraction, often known as eccentric contractions. Thus, Fridén *et al.* 1981) persuaded men to run down 100 flights of stairs. This resulted in severe pain in the stretched muscle groups in the following 2–3 days and muscle biopsies showed regions of disrupted sarcomeres in which overstretched and understretched sarcomeres could be observed.

Sarcomeres are particularly likely to be unstable at long sarcomere lengths (SLs). In mammalian muscles the plateau of the force–length curve lies between SLs 2.0 and 2.4 μm and force falls at longer SLs reaching zero at 3.9 μm (Edman, 2005). Imagine two sarcomeres in series with SLs > 2.4 μm. If one is slightly weaker, then it will tend to be stretched by its stronger neighbour; but the stretching makes it weaker still. This cycle will tend to lead to increasing variability of SLs on the descending limb but not on the ascending limb or the plateau. This potential instability on the descending limb is minimized by various factors, particularly the passive elasticity provided by titin and the fact that the force–velocity curve has a different slope for stretching rather than shortening. These ideas were greatly expanded by Morgan (1990) who pointed out that the force–velocity relation allows very high velocities once the stretching force exceeds about 1.6 × isometric force. Consequently when muscle are stretched moderately rapidly on the descending limb it is possible for the weakest sarcomeres to stretch very rapidly until stabilized at long (non-overlap, > 3.9 μm) sarcomere lengths by the passive force provided by titin and other cytoskeletal proteins. This 'popping sarcomere' theory has provided many insights in the behaviour of muscles when stretched during contraction (for recent review see Proske & Morgan, 2001).

A new study in this issue of *The Journal of Physiology* by Telley *et al.* (2006) makes an important contribution to this story. In a technical *tour de force* this group has attached fluorescent antibodies to α-actinin in the Z-line and myomesin in the M-band (the centre of the thick filaments). Thus the length of individual half-sarcomeres could be detected rather than the whole sarcomeres. This is potentially important because the two half-sarcomeres of a sarcomere do not necessarily perform in parallel. The preparation used by Telley *et al.* (2006) was a single (skinned) myofibril of rabbit skeletal muscle which can be rapidly activated and relaxed by appropriate solution changes. From images of the preparation, which contained 20–60 half-sarcomeres, the length of each half-sarcomere can be determined during development of force, during stretch and during the subsequent relaxation. The behaviour of half-sarcomeres turns out to be complex. For instance during contraction some half-sarcomeres shorten while others extend. Less easily understood is that half-sarcomeres that stretched during isometric contraction (weak half-sarcomeres) were not necessarily the ones that show the greatest increase in length during the subsequent stretch. In addition, pairs of half-sarcomeres were observed in which one was short and the neighbour was long (asymmetric sarcomeres). A key point, however, is that no overextended sarcomeres (popped sarcomeres; SL > 3.9 μm) were observed despite conditions which might be expected to trigger popping.

Do these observations invalidate the 'popping sarcomere' theory? Not yet. Firstly, the SLs used were only just into the descending limb. Secondly, in a myofibrillar preparation most of the desmin will be lost. The authors argue that this should make the preparation more susceptible to sarcomere popping but in some knock-out studies, muscles lacking desmin appear to be resistant to stretch-induced damage (Sam *et al.* 2000). Thirdly, in the EM study of Brown & Hill (1991) stretched muscles showed over- and under-stretch sarcomeres in myofilaments within a single myofibril, so it is possible that the averaging across a single myofibril disguises some of the heterogeneity of sarcomere lengths.

Nevertheless, the approach used by Telley *et al.* (2006) represents an important step forward for understanding sarcomere properties, and the ability to observe every half-sarcomere in a functioning myofibril will undoubtedly bring new insights into the complexities of muscle contraction.

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