The Effect of Manipulating Titin Length and Conformation on Residual Force Enhancement in Single-Skinned Muscle Fibres

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Summary

The mechanism of residual force enhancement (rFE) is not fully understood. The passive element titin has been suggested to play a key role in rFE by mechanisms including regulation of titin free spring length through titin-calcium and/or titin-actin interactions. This study was aimed at investigating the role of titin in rFE in skinned muscle fibres by manipulating titin length/conformation before active stretch using active shortening alone and active shortening followed by a 1s pause. We found that rFE was reduced in the active shortening trials and partially recovered when a pause was introduced following the shortening, indicating that a passive element whose length and conformation have been manipulated during the shortening phase is likely contributing to rFE.

Introduction

rFE is defined as the increase in steady-state muscle force after active stretching compared to the corresponding isometric force produced at the same muscle length and activation [1]. The mechanisms responsible for rFE remain unknown. One frequently proposed mechanisms of rFE is related to the structural sarcomeric protein titin [2]. It has been proposed that titin stiffness increases in the presence of Ca^{2+} and/or that titin binds to actin during activation resulting in a decrease in its free spring length and thus an increase in its force when actively stretched compared to the isometric contraction at the same final length.

If rFE is indeed caused by titin, manoeuvres that manipulate titin-based force, titin conformation, and potential titin-actin interactions, for example by active shortening and active shortening followed by a pause performed before the stretch, would be expected to affect the magnitude of rFE.

The aim of this study was to further investigate titin's role in rFE by examining the effects of active shortening alone and active shortening followed by a pause performed before the active stretch on rFE. We hypothesized that titin changes its conformation or detaches from actin during shortening and that it recovers and re-attaches if there is sufficient time between the shortening and the stretch. Therefore, shortening was expected to result in a decrease in rFE, and a pause before stretching results in recovery of rFE.

Methods

Single skinned fibres (n=10) from rabbit psoas muscle were mounted between two hooks connected to a length controller and a force transducer (Aurora Scientific Inc.). An isometric reference contraction (Ref) was performed at a sarcomere length (SL) of 3.6μm. Active stretch tests consisted of 3 trials: i) rFE-Regular: an activation at a SL of 2.4μm followed by an active stretch to a SL of 3.6μm, ii) rFE-NoPause: activation at a SL of 3.6μm followed by active shortening to a SL of 2.4μm, immediately followed by an active stretch to a SL of 3.6μm, and iii) rFE-Pause: similar to rFE-NoPause, except that active shortening was followed by a 1s pause before active stretch.

rFE in rFE-Regular, rFE-NoPause and rFE-Pause trials was determined as the difference between the steady-state forces reached at the end of the trials at a SL of 3.6 μm and the Ref force, normalized relative to the Ref force.

Results and Discussion

rFE in rFE-Regular was significantly greater than rFE-NoPause and rFE-Pause (21.5±3.1 vs. 3.3±1.4 and 6.4±1.3%, respectively, Fig 1). rFE-Pause showed a partial recovery of rFE compared to rFE-NoPause.

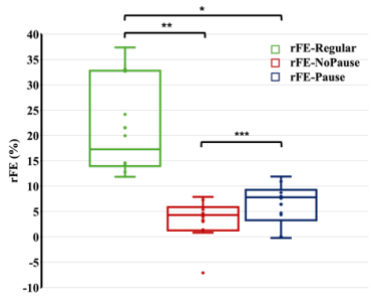

Figure 1: rFE-Regular (green), rFE-NoPause (red) and rFE-Pause (blue). *p<0.05.

Shortening before active stretch likely caused a perturbation in the passive element, resulting in a decrease in rFE. A pause of 1s after shortening results in a partial recovery of titin's conformation and rFE. A longer pause between shortening and stretch is expected to restore the full magnitude of rFE.

Conclusions

Based on these results, we conclude that titin is a strong candidate to partly explain rFE, as manipulation of titin length and conformation resulted in predictable changes in rFE.

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References

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