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Short communication

Does stretching velocity affect residual force enhancement?

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ABSTRACT

It is thought that the magnitude of residual force enhancement (RFE) is not affected by stretch velocity. However, the range of stretch velocities studied in previous investigations has been limited to slow and moderate velocities. High velocities of muscle stretching are associated with a loss of force and incomplete cross-bridge attachment to actin, thus creating a unique set of eccentric conditions referred to as slippage. The purpose of this study was to extend the relationship between stretch velocity and RFE to high velocities. We hypothesized that slippage at high velocities might affect RFE. We stretched cat soleus muscles for 4 mm to the plateau of the force-length relationship at speeds of 2, 4, 8, 16, 32, 64 mm/s to induce RFE, and slippage for the fastest condition. For each RFE test, a corresponding isometric reference test was conducted. Residual force enhancement was quantified as the relative increase in isometric steady state force between the experimental stretch and the isometric reference tests. Residual force enhancement was similar for all stretch speeds, as expected, with the exception of the fastest speed (64 mm/s), which was associated with slippage and no significant RFE. These results suggest that if stretch speeds are too fast, and are associated with slippage, RFE is abolished. We conclude from these findings that proper cross-bridge engagement is required during eccentric muscle action to produce RFE.

1. Introduction

The isometric force after active muscle stretching is greater than that attained in a purely isometric contraction at the same muscle length and same activation level. This phenomenon is referred to as residual force enhancement (RFE) (Abbott and Aubert, 1952). Residual force enhancement has been widely examined from the single sarcomere to the human joint level (Lee and Herzog, 2002; Leonard et al., 2010; Morgan et al., 2000). Although a great deal of phenomenological evidence has been accumulated, the precise mechanism(s) underlying RFE is still being debated (Herzog, 2018; Linke, 2018).

One characteristics of RFE is that the magnitude of RFE seems to be independent of the stretch velocity (Lee and Herzog, 2002; Sugi and Tsuchiya, 1988). However, the stretch velocities examined in these studies were all limited to slow or moderate speeds. For fast stretch conditions, muscle force increases steeply at the early phase of stretch, and then, decreases rapidly with further stretching, and force only recovers once the stretching has stopped. This phenomenon has been referred to as "slippage" (Flitney and Hirst, 1978; Griffiths et al., 1980; Katz, 1939; Kuhn, 1978), and has been explained by an inability of cross-bridges to attach properly to actin when stretching speeds exceed a given threshold (Bagni et al., 2005; Malamud et al., 1996; Sugi, 1972). This unique mechanical condition may affect RFE, as the cross-bridge dynamics are altered compared to slow and moderate speed stretches where RFE only depends on the stretch magnitude but not the stretch speed (Lee and Herzog, 2002; Sugi and Tsuchiya, 1988).

Recently, Powers et al., (2014) reported that when cross bridge cycling was completely blocked by 2,3-butanedione monoxime (the isometric active force became virtually zero), RFE was decreased dramatically, suggesting that regular cross bridge cycling may be needed to induce RFE. If indeed proper cross-bridge attachment to actin is required to induce RFE, then fast stretches that cause slippage might not produce RFE.

Therefore, the purpose of this study was to re-examine the influence of stretch velocity on RFE by including high stretch velocities that produce muscle slippage, and thus incomplete cross-bridge cycling in the eccentric phase. We defined "slippage" when force decreased rapidly during a stretch and then recovered following the stretch. We hypothesized that proper cross-bridge cycling is required for RFE, and therefore that RFE is reduced or abolished in fast stretches associated with muscle slippage compared to RFE obtained during stretches of equal magnitude but slow and moderate stretch velocities.

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2. Methods

2.1. Muscle samples and experimental setups

Cat soleus muscles (N = 12) were isolated and prepared for testing from six cats (1-year-old) according to a protocol approved by the University of Calgary's Life and Environmental Sciences Animal Ethics committee. The experimental setup was the same as reported previously (Herzog and Leonard, 1997). Briefly, cats were anaesthetized using a nitrous oxide, halothane, and oxygen mixture. The soleus muscle and its tendon with a piece of the calcaneus bone were isolated from adjacent tissues. The tibial nerve was exposed to implant a nerve cuff electrode for controlled electrical stimulation of the soleus. The remnant piece of bone was attached to a muscle puller (MTS, MTS system corporation, Eden Prairie, USA). The muscle length corresponding to an 80 degree ankle angle (180 degrees = full ankle extension) was defined as 0 mm muscle length, which corresponded to the upper part of the ascending limb of the force-length relationship (Herzog and Leonard, 2000). All trials were performed using supramaximal stimulation to activate all motor units at a frequency of 30 Hz to induce fused tetanic contractions. Force data were recorded with a sampling frequency of 500 Hz (Windaq, DATAQ Instruments, Akron, US). Muscle temperature was kept constant (35 ± 1 °C) using an infrared heat lamp and a temperature controlled saline solution.

2.2. Experimental procedures and measurements

The soleus muscle was stretched using a 4 mm magnitude ending at the plateau of the force-length relationship using speeds of 2, 4, 8, 16, 32, 64 mm/s (Fig. 1). A corresponding isometric reference test at the end length was conducted for each experimental stretch test. The RFE trials started with an isometric contraction at a length 4 mm less than optimal. After 2 s, muscles were actively lengthened using one of the target velocities in ascending order. Once the optimal length was reached, muscles were kept at a constant length until a steady state force was reached (8 s total activation time) (Fig. 1). RFE tests for each stretch speed were repeated three times for each condition. Prior to each stretch condition, an 8 s isometric reference contraction was conducted. RFE was determined as the relative difference in isometric, steady-state force following muscle stretching and the force obtained in the corresponding isometric reference trials. The interval between contractions was at least 1 min. We conducted isometric reference contractions before and after each stretch test to avoid any effect of fatigue on our results, and the magnitude of force loss throughout the entire experiment was 4.4 ± 3.8%.

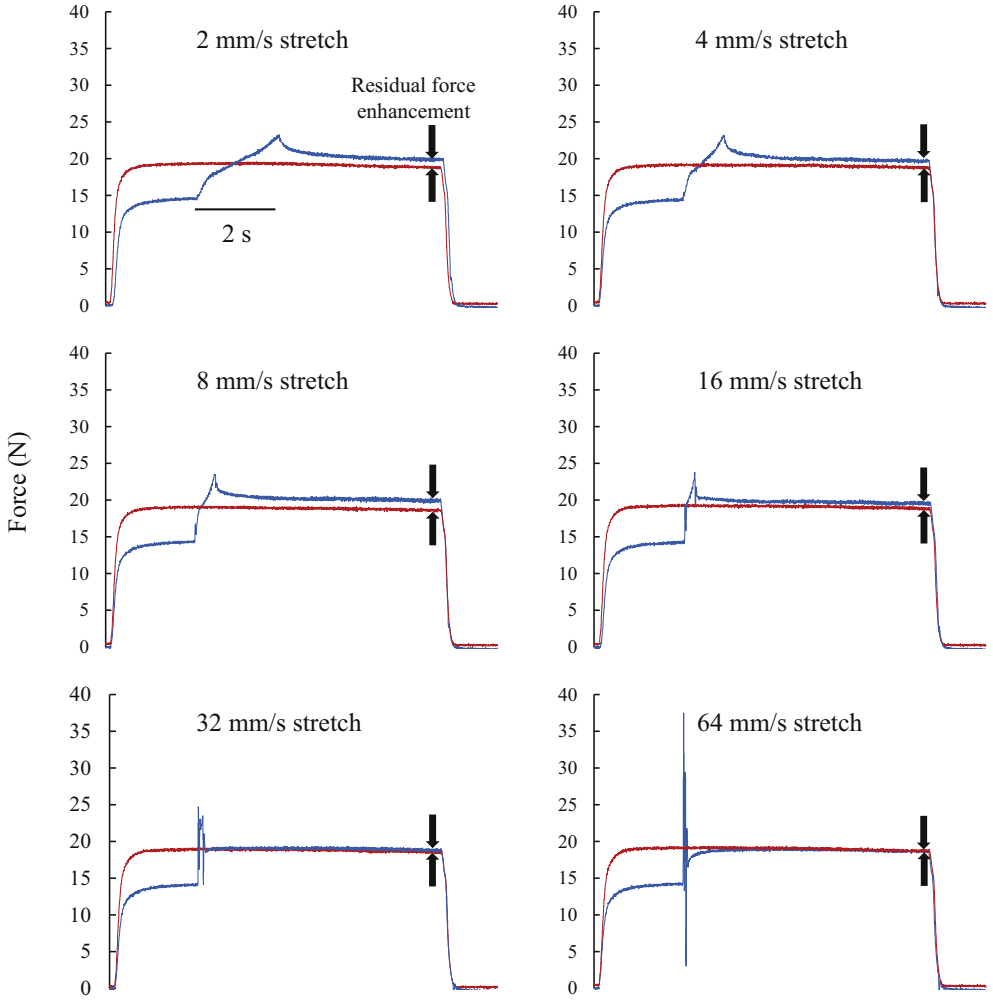

Fig. 1. Force responses for stretch conditions performed at different stretch speeds. Blue lines indicate the RFE trials (isometric-stretch-isometric) and red lines indicate the isometric reference trials (purely isometric contractions at the final stretch length). Black arrows indicate the timing for determination of RFE. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.3. Statistical analysis

Descriptive data are presented as means ± SD. For each stretch condition, a paired *t*-test was used to determine if RFE was present. In addition, a one-way repeated measures ANOVA, with stretch speed as the main factor, was used to test for differences in RFE. If indicated, a Bonferroni's post hoc analysis was conducted. The level of significance was set at $\alpha < 0.05$.

3. Results

All absolute values are shown in Table 1 and relative changes, i.e., the magnitude of RFE are shown in Fig. 2. RFE was observed at speeds of stretching of 2 mm/s ($p < 0.001$), 4 mm/s ($p < 0.001$), 8 mm/s ($p < 0.001$), 16 mm/s ($p < 0.001$), 32 mm/s ($p = 0.009$) but not at 64 mm/s ($p = 0.362$). The magnitude of RFE was similar for stretch speeds of 2 mm/s, 4 mm/s, 8 mm/s, and 16 mm/s ($p = 0.201–0.999$), and for these four conditions, RFE was also significantly greater than that observed following active stretching for the 64 mm/s stretch condition ($p = 0.005–0.043$). In addition, RFE was significantly greater for stretching at 8 mm/s compared to 32 mm/s ($p = 0.038$).

4. Discussion

As hypothesized, the magnitude of RFE was smaller in the fast stretch conditions (32 mm/s and 64 mm/s) compared to the slow and moderate stretch velocity conditions, while there was no difference in the magnitude of RFE among slow to moderate stretch conditions (2 mm/s, 4 mm/s, 8 mm/s, 16 mm/s). These results suggest that stretch velocity affects the magnitude of RFE when the stretch velocity exceeds a given threshold.

Table 1
The actual values for the isometric steady-state force following muscle stretching and the force obtained in the corresponding isometric reference trials.

	Reference trial (N)	RFE trial (N)	*p* value
2 mm/s	20.5 ± 3.8	21.0 ± 3.8	<0.001
4 mm/s	20.4 ± 3.8	20.8 ± 3.8	<0.001
8 mm/s	20.3 ± 3.8	20.8 ± 3.8	<0.001
16 mm/s	20.3 ± 3.7	20.7 ± 3.8	<0.001
32 mm/s	20.3 ± 3.7	20.5 ± 3.8	=0.009
64 mm/s	20.3 ± 3.7	20.4 ± 3.8	=0.362

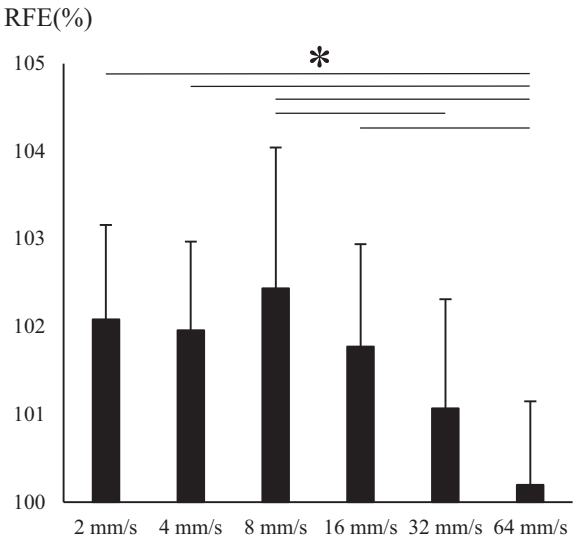

Fig. 2. Magnitude of RFE for the different stretch speed conditions. * indicates significant difference between conditions ($p = 0.05$).

Although previous studies suggested that RFE was not affected by stretch velocity (Lee and Herzog, 2002; Sugi and Tsuchiya, 1988), we found that RFE was decreased (or not observed) in the 32 mm/s and 64 mm/s stretch conditions. This contradiction can be explained by the stretch velocities adopted in these different studies. While previous studies focused on slow and moderate stretch speeds (Lee and Herzog, 2002; Sugi and Tsuchiya, 1988), we used fast stretches that had the hallmark signs of slippage: that is, a rapid decrease of force during the stretch phase, and a recovery of force once stretching was finished and the muscle was kept at a constant length (Fig. 3). Muscle slippage has been described almost a century ago (Flitney and Hirst, 1978; Griffiths et al., 1980; Katz, 1939; Kuhn, 1978), but the detailed mechanisms underlying slippage remain unknown, and eccentric muscle action that produce slippage, has not been studied in the context of RFE. Slippage has been associated with the forcible detachment of cross-bridges from actin (Lombardi and Piazzesi, 1990). However, forcible cross-bridge detachment alone cannot account for the rapid decrease in force during stretching and forcible detachment of cross-bridges has been proposed by Huxley (1957) as an explanation for the decreased metabolic cost of eccentric compared to isometric and concentric muscle contractions. In order to account for the dramatic force loss in slippage, one would have to assume that the increase in force due to increased cross-bridge strain (and thus average cross-bridge force) would be more than offset by the number of forcibly detached cross-bridges. Therefore, a feasible explanation of slippage should contain a decrease in the proportion of attached cross-bridges, probably due to the high relative speed of actin and myosin in fast muscle stretching, and associated decrease in the probability of successful cross-bridge binding to actin. Whatever the detailed mechanism underlying slippage in quickly stretched muscles, it causes a decrease in force during stretch and appears to be associated with a complete loss of RFE. Therefore, it appears that for RFE to develop, proper cross-bridge cycling is required. This finding is insofar of interest as it might provide a hint as to the mechanisms underlying RFE.

Nocella et al., (2014) examined static tension in intact fiber preparations, and they found a significant increase in force for fast stretch speeds. However, they did not mention the magnitude of force enhancement among different stretch velocities, and their stretch speed and stretch magnitude did not produce the typical force profile seen in muscle slippage (i.e., a loss of force during stretch and a recovery of force following stretch). Thus, we would assume that they should see consistent RFE at the fastest speed they tested, as apparently no slippage occurred, and thus we would expect the RFE to be of normal magnitude.

It has been proposed that RFE may be caused by the engagement of titin during active muscle stretching (Joumaa et al., 2008; Leonard et al., 2010; Powers et al., 2014). The idea of titin-actin interactions was born in the treatment of the engagement of a passive elastic element by Edman et al., (1982), with refinements and the explicit mention of titin by Noble (1992). First evidence that indeed a passive structural component was involved in force enhancement was provided by Herzog and Leonard (2002), and Labeit et al., (2003), and Joumaa et al., (2007, 2008) then uniquely identified that this force enhancement must be attributed to titin. Models of titin engagement were developed during (Forcinito et al., 1998) and following these experimental discoveries (Rode et al. 2009), with experimental verification of titin-actin engagement still missing, except for antibody labeling work that provides supporting, but indirect, evidence for an interaction of titin with actin upon stretch of an activated muscle (Duvall et al., 2017). Such engagement does not occur in isometric contractions (e.g., Leonard et al., 2010), and also does not occur with calcium

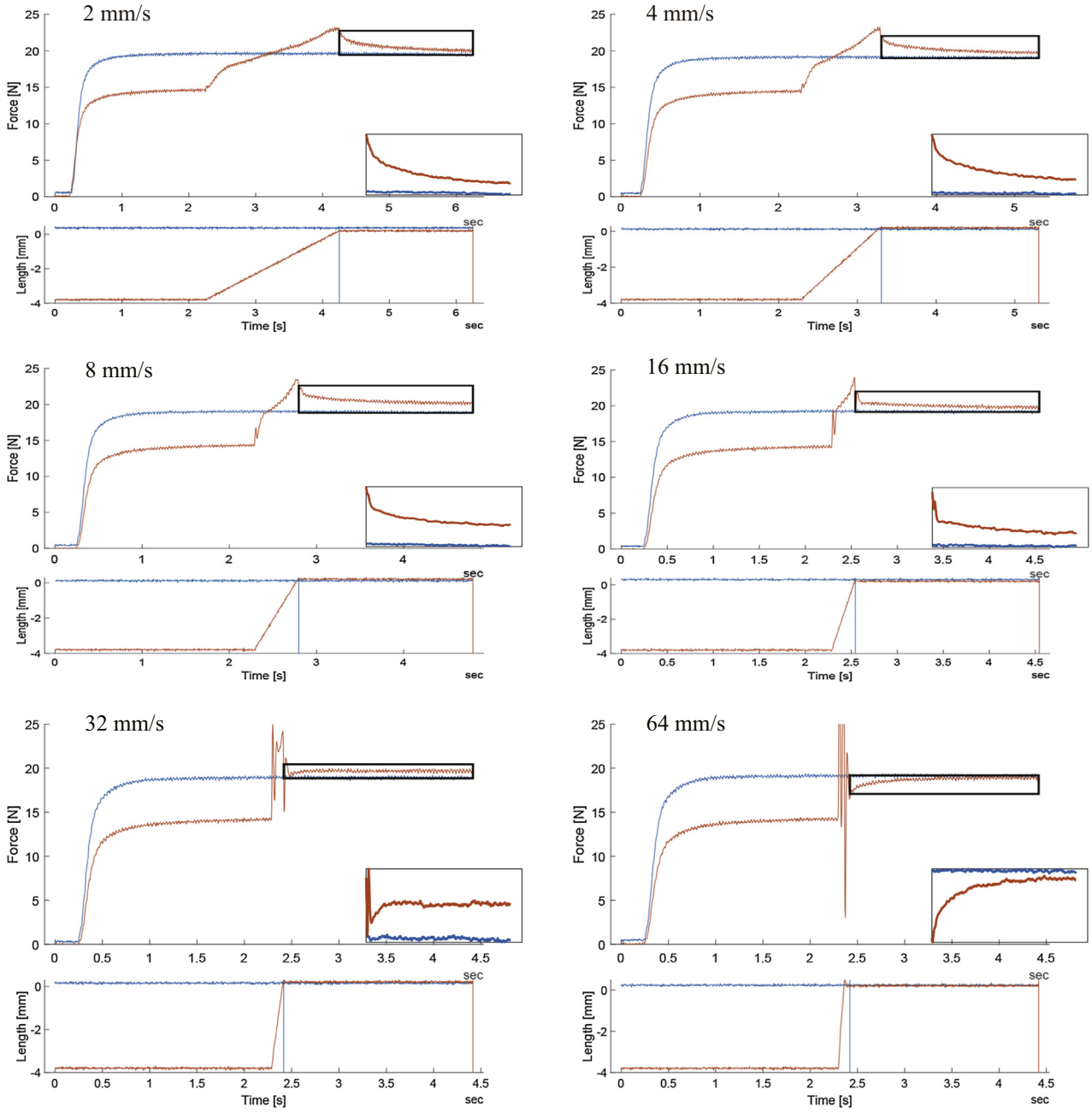

Fig. 3. Fig. 3. Typical force responses after the end of stretch. Note that after the end of stretch (the inset), the force gradually decreased (force-relaxation) in the slow and moderate stretch conditions (2, 4, 8, 16 mm/s conditions), while the force increased (recovered) to the steady-state force in the fast stretch conditions (32, 64 mm/s conditions). The latter indicates that the force decreased during the stretch (slippage).

activation and simultaneous cross-bridge inhibition through 2,3 butanedione monoxime or troponin C deletion (Joumaa et al., 2008, Leonard et al., 2010). However, it does occur when an active muscle (myofibril) is stretched while activated (Duvall et al., 2017). Therefore, a working hypothesis might be that titin engagement only occurs when cross-bridges are fully engaged and go through the full cross-bridge cycle. One might speculate that strong cross-bridge binding is associated with movements of the regulatory proteins tropomyosin and troponin, which in turn might free up binding sites for titin, which then allows titin binding to actin, thereby causing an increase in titin based force and RFE (Herzog, 2018). Needless to say that such a theory needs further experimental verification.

All experiments in this study were performed with the cat soleus muscle, a predominantly slow twitch fibred muscle. Therefore, the question arose if these results would also transfer to fast twitch fibres or fast twitch fibred muscles. In order to address this question, we performed experiments with fast and slow twitch skinned fibres from rabbit soleus and psoas muscles. Our preliminary results indicate that moderate stretch speeds of similar magnitudes and over the same range of the force-length relationship produced the same amount of force enhancement in slow and fast twitch fibres, while very fast stretching of these fibres, in which the typical slippage profile was observed during stretch did not show residual force enhancement in either fibre type. Therefore, we tentatively propose that the observations made here in the slow

twitch fibred soleus muscle also hold in muscles that are predominantly fast twitch fibred; that is, RFE is abolished in stretches occurring at speeds that produce "slippage". This concept will be further strengthened by conducting similar experiments in other species and muscles of different fibre type composition.

Our results were obtained for maximal activation, while human daily activities are executed at submaximal activation. We recently found that the magnitude of RFE was similar between maximal and submaximal activation (Fukutani and Herzog, 2018) in agreement with previous findings (de Ruiter et al., 2000), suggesting that slippage-induced small/negligible RFE might also occur at submaximal levels of activation, and thus during activities of daily living. Although, we would not expect such fast stretch speeds to ever play a role in every day human movements due to the possibilities of damping muscle stretch speeds in the intact body.

In conclusion, RFE does not appear to be affected by stretch velocity when stretch velocities are small or moderate, which is in line with previous findings. However, if the stretch velocity exceeds a certain threshold value, and slippage occurs during stretch, RFE disappears potentially due to inhibited regular cross bridge cycling.

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Conflict of interest statement

The authors declare no conflict of interest associated with this manuscript.

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