

The history dependence of force production in mammalian skeletal muscle following stretch-shortening and shortening-stretch cycles

W. Herzog*, T.R. Leonard

Faculty of Kinesiology, University of Calgary, Calgary, AB, Canada T2N 1N4

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Abstract

The purpose of this study was to determine the history dependence of force production during and following stretch-shortening and shortening-stretch cycles in mammalian skeletal muscle. Thirty-three different isometric, stretch, shortening, stretch-shortening and shortening-stretch experiments were performed in cat soleus ($n = 8$) using previously established methods. Stretch-shortening and shortening-stretch cycles are not commutative with respect to the isometric forces following the length changes. Whereas force depression following shortening is virtually unaffected by previous stretching of the muscle, force enhancement following stretch depends in a dose-dependent manner on the amount of muscle shortening preceding the stretch. The history dependence of isometric force following shortening-stretch cycles can conveniently be modelled using an elastic (compressive and tensile) element that engages at the length of muscle activation. Such an “elastic” mechanism has been proposed by Edman and Tsuchiya (1996) (Edman, K.A.P., Tsuchiya, T., 1996. Strain of passive elements during force enhancement by stretch in frog muscle fibres. *Journal of Physiology* 490.1, 191–205) based on experimental observations, and has been implemented theoretically in a rheological model of muscle (Forcinito et al., 1997) (Forcinito, M., Epstein, M., Herzog, W., 1997. Theoretical considerations on myofibril stiffness. *Biophysics Journal* 72, 1278–1286). The history dependence of isometric force following stretch-shortening cycles appears independent of the stretch preceding the shortening, except perhaps, if stretching occurs at very high speeds (i.e. 6–10 times fibre length per second). The results of this study are hard to reconcile with the two major mechanisms associated with history dependence of force production: sarcomere length non-uniformity (Edman et al., 1993) and stress-induced cross-bridge inhibition (Maréchal and Plaghki, 1979) (Maréchal, G., Plaghki, L., 1979. The deficit of the isometric tetanic tension redeveloped after a release of frog muscle at a constant velocity. *Journal of General Physiology* 73, 453–467). It appears that studying the history dependence of force production under more functionally relevant conditions than has been done to date may provide new information that contributes to our understanding of possible mechanisms associated with force depression and force enhancement following muscular length changes. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Muscle properties; Force depression; Force enhancement; Mechanisms of contraction

1. Introduction

It has been well documented and well accepted that the isometric forces following active muscle shortening are depressed and following active muscle lengthening are enhanced compared to purely isometric forces obtained at the corresponding muscle lengths (Herzog and Leonard, 1997; Abbott and Aubert, 1952; Sugi and Tsuchiya, 1988; Maréchal and Plaghki, 1979; Edman et al., 1993; Meijer et al., 1997). However, the mechanism(s) underly-

ing force depression and force enhancement following muscle shortening and lengthening, respectively, are not well understood (Maréchal and Plaghki, 1979; Granzier and Pollack, 1989; Edman et al., 1993; Herzog, 1998).

Force depression following shortening is increased for increasing amounts of shortening (Abbott and Aubert, 1952; Maréchal and Plaghki, 1979) and increasing forces during the shortening phase (Herzog and Leonard, 1997; De Ruiter et al., 1998). There is some controversy over the idea whether or not the speed of shortening affects the magnitude of force depression. Although many studies found an inverse relationship between the speed of shortening and the magnitude of force depression (Abbott and Aubert, 1952; Maréchal and Plaghki, 1979), there is evidence that force depression is unaffected by the

* Corresponding author. Tel.: +1-403-220-8525; fax: +1-403-284-3553.

E-mail address: walter@kin.ucalgary.ca (W. Herzog)

speed of shortening provided that the force during shortening remains constant (Herzog et al., 2000). It is also not clear if sarcomere length non-uniformities that occur during shortening in single fibre preparations may account for the observed force depression following shortening. Although there is direct evidence in favour of the idea that sarcomere length non-uniformities in single fibres are responsible for most, if not all, of the observed force depression (Edman et al., 1993), others have found that eliminating sarcomere length non-uniformities in single fibre preparations does not alleviate force depression, therefore force depression does occur even in the absence of sarcomere length non-uniformities (Granzier and Pollack, 1989). Finally, single fibre stiffness was found to be lower during isometric contractions following shortening than during purely isometric contractions at the corresponding lengths (Sugi and Tsuchiya, 1988). This result suggests that force depression is associated with a decrease in the proportion of attached cross-bridges (Ford et al., 1981; Forcinito et al., 1997). Corresponding stiffness data for whole muscle are not available.

Force enhancement following muscle lengthening is directly related to the amount of stretch (Abbott and Aubert, 1952; Sugi and Tsuchiya, 1988), appears to be independent of stretch speeds in single fibres (Sugi and Tsuchiya, 1988), but depends on stretch speeds for whole muscles (Abbott and Aubert, 1952). Force enhancement following muscle stretch (like force depression following muscle shortening) is long lasting (Herzog et al., 1998), and single fibre stiffness is similar following stretch compared to the purely isometric contraction at the corresponding lengths (Sugi and Tsuchiya, 1988). This last result leads to the suggestion that force enhancement is associated with an increase in the average cross-bridge force, rather than an increase in the proportion of attached cross-bridges (Ford et al., 1981). Corresponding stiffness measurements in whole muscle have not been made.

During functional use, muscles continuously undergo stretch-shortening or shortening-stretch cycles while activated. However, there are no systematic data on the history dependence of muscle force production following stretch-shortening and shortening-stretch cycles. Investigating the history dependence of muscle force production for stretch-shortening and shortening-stretch cycles is significant for three reasons: first, these data are required for the increasing number of theoretical models of skeletal muscle that are aimed at accounting for history-dependent effects; second, it is not intuitively apparent whether the effects of force enhancement and force depression cancel each other, nor is it obvious whether stretch-shortening and shortening-stretch cycles are commutative with respect to force production following the dynamic phase; and third, data on the history dependence of muscle force following

stretch-shortening and shortening-stretch cycles may provide new insight into the mechanism(s) underlying these phenomena.

The purpose of this study was to determine the history dependence of force production during and following stretch-shortening and shortening-stretch cycles in mammalian skeletal muscle. Also, muscle stiffness was assessed during force enhancement and force depression and compared to the corresponding stiffness obtained during purely isometric contractions. All experiments were performed on cat soleus at physiological temperature.

2. Methods

Force depression following stretch-shortening and shortening-stretch cycles were determined in cat soleus ($n = 8$) using a setup that has been described earlier (Herzog and Leonard, 1997). Briefly, cats were anaesthetized using a nitrous oxide, halothane, oxygen mixture. The soleus, soleus tendon and calcaneus were exposed using a single cut on the posterior, lateral shank. The soleus tendon was isolated from the rest of the Achilles tendon and was cut from the calcaneus with a remnant piece of bone after a reference length (corresponding to an 80° included ankle angle) had been determined. A second cut was made on the posterior, lateral thigh and the tibial nerve was exposed and implemented with a bipolar cuff-type electrode (Herzog et al., 1995) for soleus stimulation. The cat was secured in a prone position in a hammock and the pelvis, thigh, and shank of the experimental hindlimb were fixed with bilateral bone pins to a stereotaxic frame. The bone piece at the distal end of the soleus tendon was attached with sutures to a muscle puller (MTS, Eden Prairie, MN, natural frequency > 10 kHz). The soleus forces ($100 \text{ N} = 10 \text{ V}$) and excursions ($20 \text{ mm} = 10 \text{ V}$) were measured continuously by the muscle puller and were collected at a frequency of 500 Hz. The muscle length corresponding to the 80° included ankle angle was taken as zero length. This length is on the upper part of the ascending limb of the force-length relationship and is associated with a passive force of about 1 N. All tests were performed within a range corresponding to the ascending limb and the beginning of the plateau region of the force-length relationship. Shortening from the zero length was taken as negative, lengthening as positive. For example, a muscle length of -4 mm corresponds to a length 4 mm shorter than the reference length.

Five conceptual test protocols were performed. The aim of the first protocol was to assess muscle stiffness during isometric reference contractions and during isometric contractions following muscle shortening, i.e. at a time when muscle force was depressed. All isometric reference contractions were performed for 7 s at a muscle

length of -4 mm (i.e. 4 mm shorter than the 0 mm reference length). The experimental contractions consisted of a 1 s isometric contraction at a length of $+4$, $+2$, 0 , and -2 mm, followed by a shortening at a speed of 4 mm/s to the -4 mm reference length, followed by a 3–4.5 s isometric contraction at a length of -4 mm for the contractions starting at $+4$ and at -2 mm, respectively (Fig. 1a). Therefore, all contractions lasted for 7 s and the distance of shortening was 2, 4, 6, and 8 mm. Stiffness for the isometric reference contraction and all experimental contractions was assessed 6 s following the onset of stimulation, therefore giving ≥ 3 s of recovery following the shortening contractions (Fig. 1a). This time was sufficient to ensure that forces following shortening had recovered to near steady-state values. Stiffness was assessed by stretching muscles for 1 mm at a speed of 32 mm/s. The resulting force-displacement data were nu-

merically differentiated, and the peak value of the derivative was taken as the stiffness.

The aim of the second protocol was to assess muscle stiffness during isometric reference contractions and during isometric contractions following muscle stretch, i.e. at a time when muscle force was enhanced. All isometric reference contractions were performed at the 0 mm reference length. The stretching tests were performed as a mirror image of the shortening tests described above. Therefore an isometric contraction at a short length (1 s) was followed by a muscle stretch of 2, 4, 6, or 8 mm to the 0 mm reference length, followed by an isometric contraction (≥ 3 s) at the reference length (Fig. 1b). Stiffness was assessed exactly in the same manner as described above.

The aim of the third protocol was to assess force depression following muscle shortening in one or two steps at the same or different speeds of shortening.

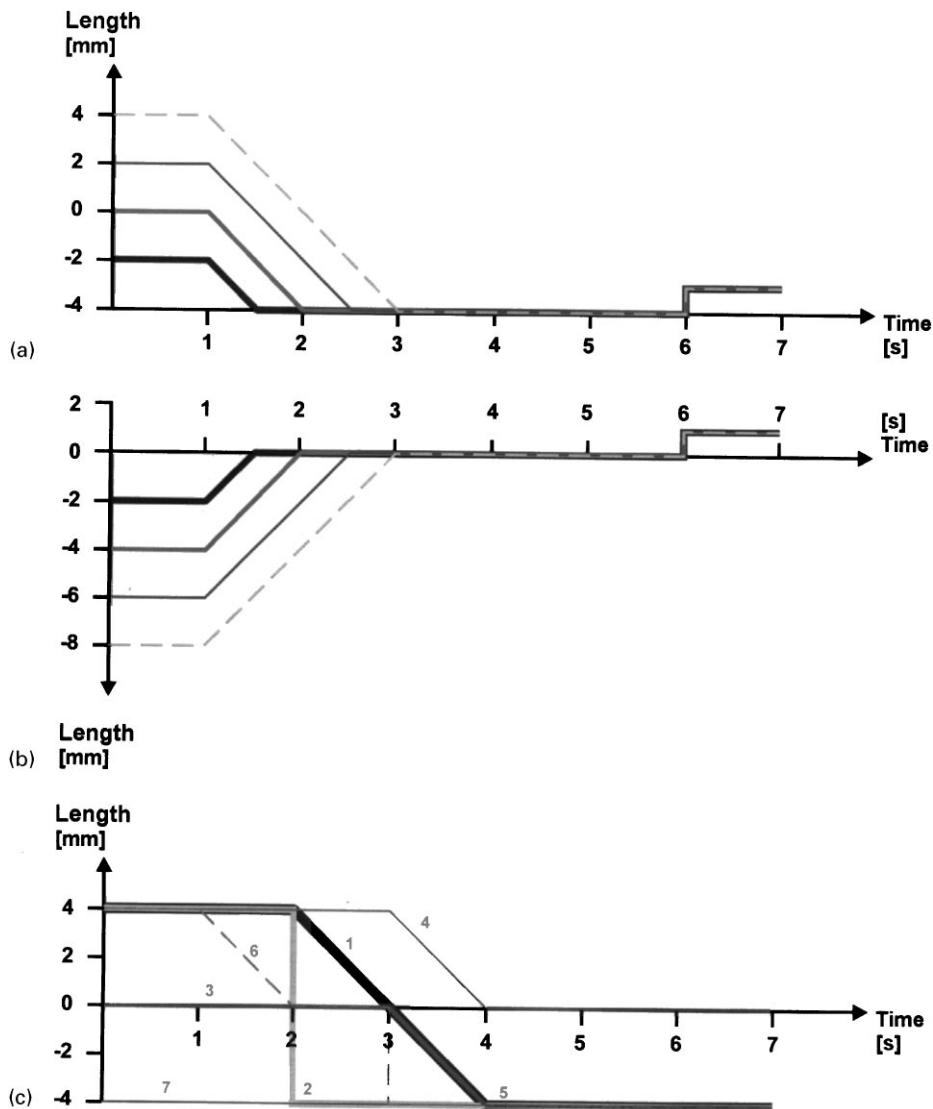


Fig. 1. Muscle length-time histories of all tests performed in the five separate protocols (a–e).

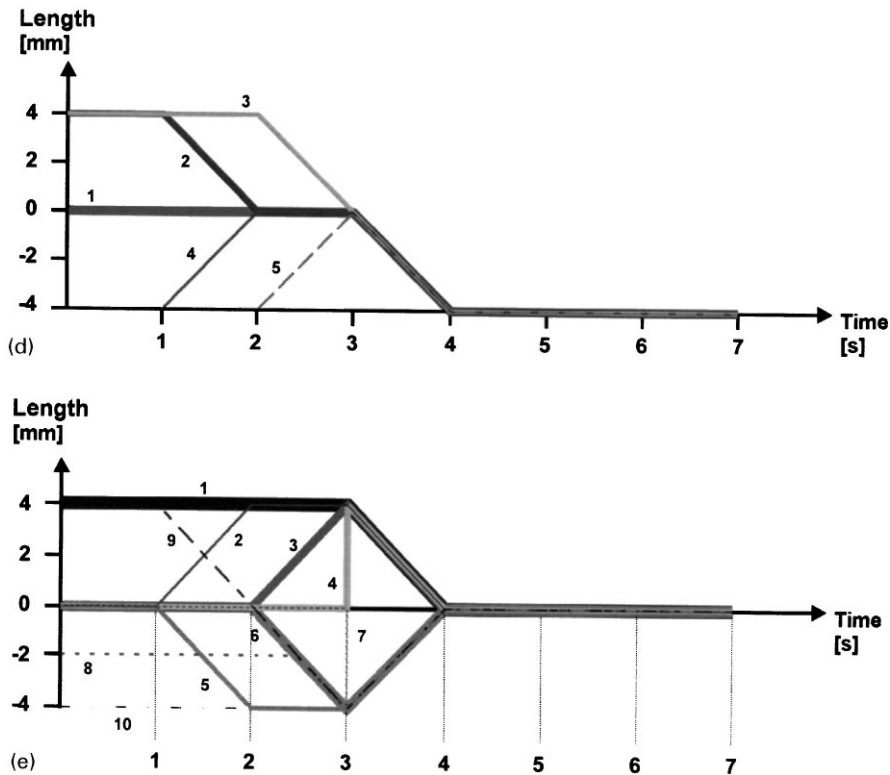


Fig. 1 (Continued).

Conceptually, shortening contractions were performed over 8 mm in one or two steps at speeds of 4 or 256 mm/s (Fig. 1c). In detail, the following experiments were made: isometric reference contractions were performed at either 0 or -4 mm depending on the final length of the muscle following shortening. Six different shortening tests were performed. In the first and second, the muscle was shortened from a length of +4 to a length of -4 mm at a speed of 4 and 256 mm/s, respectively. In the third, the muscle was shortened from a length of 0 mm to a length of -4 mm at a speed of 4 mm/s. In the fourth, the muscle was shortened from a length of +4 mm to a length of 0 mm at a speed of 4 mm/s. In the fifth and sixth tests, the muscle was shortened from a length of +4 mm to a length of 0 mm at a speed of 4 mm/s, was held isometrically for 1s at the 0 mm length, and then was shortened to a length of -4 mm at 4 mm/s and at 256 mm/s respectively.

The aim of the fourth protocol was to investigate the effects of prior stretch or shortening on the force depression of a given (4 mm shortening at a speed of 4 mm/s) shortening contraction. Conceptually, a given shortening contraction was preceded by muscle stretch, muscle shortening or an isometric contraction. In detail, five tests were performed. All isometric reference contractions were done at a muscle length of -4 mm (Fig. 1d). The five experimental contractions were: first, an isometric contraction of 3s preceded a shortening contraction from

a length of 0 mm to a length of -4 mm at 4 mm/s, which was followed by an isometric contraction at a length of -4 mm for a further 3 s. Second, an isometric contraction at a length of +4 mm (1 s) was followed by a shortening contraction to a length of 0 mm at a speed of 4 mm/s. The muscle was held isometrically at 0 mm (1s) and then released to a length of -4 mm at a speed of 4 mm/s and held at this length for 3 s. Third, an isometric contraction at a length of +4 mm (2s) was followed by muscle shortening to -4 mm at a speed of 4 mm/s. The muscle was held at this length for 3 s. Fourth, an isometric contraction at a length of -4 mm (1s) preceded a muscle stretch of 4 mm (at a speed of 4 mm/s). Following the stretch, the muscle was held isometrically (0 mm length for 1s) and released again to a length of -4 mm at a speed of 4 mm/s. The muscle was held at the final length for 3 s. The fifth contraction was the same as the fourth, except that there was no isometric hold between the stretch and the shortening phase.

The aim of the fifth and final protocol was to determine whether stretch-shortening and shortening-stretch cycles were commutative with respect to the isometric forces following the length changes, and to assess whether the amount of shortening preceding a given stretch influenced the following isometric force in a dose-dependent manner. Ten different tests were performed. All isometric reference contractions were performed at the 0 mm muscle length (Fig. 1e).

Test 1: isometric contraction at +4 mm for 3 s, shortening to 0 mm at a speed of 4 mm/s, isometric contraction at 0 mm for 3 s.

Test 2: isometric contraction at 0 mm for 1 s, stretch to +4 mm at 4 mm/s, isometric contraction at +4 mm for 1 s, shortening to 0 mm at 4 mm/s, isometric contraction at 0 mm for 3 s.

Test 3: isometric contraction at 0 mm for 2 s, stretch to +4 mm at 4 mm/s, shortening to 0 mm at 4 mm/s, isometric contraction at 0 mm for 3 s.

Test 4: isometric contraction at 0 mm for almost 3 s, stretch to +4 mm at 256 mm/s, shortening to 0 mm at 4 mm/s, isometric contraction at 0 mm for 3 s.

Test 5: isometric contraction at 0 mm for 1 s, shortening to -4 mm at 4 mm/s, isometric contraction at -4 mm for 1 s, lengthening to 0 mm at 4 mm/s, isometric contraction at 0 mm for 3 s.

Test 6: isometric contraction at 0 mm for 2 s, shortening to -4 mm at 4 mm/s, stretch to 0 mm at 4 mm/s, isometric contraction at 0 mm for 3 s.

Test 7: isometric contraction at 0 mm for almost 3 s, shortening to -4 mm at 256 mm/s, stretch to 0 mm at 4 mm/s, isometric contraction at 0 mm for 3 s.

Test 8: isometric contraction at -2 mm for 2.5 s, shortening to -4 mm at 4 mm/s, stretch to 0 mm at 4 mm/s, isometric contraction at 0 mm for 3 s.

Test 9: isometric contraction at +4 mm for 1 s, shortening to -4 mm at 4 mm/s, stretch to 0 mm at 4 mm/s, isometric contraction at 0 mm for 3 s.

Test 10: isometric contraction at -4 mm for 3 s, stretch to 0 mm at 4 mm/s, isometric contraction at 0 mm for 3 s.

In each of the five protocols, one isometric reference contraction always preceded two identical experimental contractions which in turn, were followed by another isometric reference contraction, thus giving two repeat measurements for each contraction.

All tests were performed using supramaximal stimulation (i.e. a current of 3 times the α -motoneuron threshold, a pulse duration of 0.1 ms, a frequency of 30 Hz, and a stimulation duration of 7 s). Muscle temperature was kept constant at $35^{\circ}\text{C} \pm 1^{\circ}\text{C}$ using an infrared heat lamp and a temperature controlled saline solution. Rest intervals between contractions were two minutes which proved sufficient for complete recovery of the muscle. All procedures were approved by the Animal Ethics Committee of the University of Calgary.

3. Results

Stiffness following muscle stretching, when force was enhanced, was significantly increased compared to the corresponding values obtained during purely isometric contractions (Table 1). Following muscle shortening, when force was depressed, stiffness was the same as that

Table 1

Mean \pm 1SD stiffness values for the cat soleus at a length of -4 mm for purely isometric contractions ($n = 16$), for isometric contractions preceded by 2–8 mm of muscle shortening ($n = 32$), and for isometric contractions preceded by 2–8 mm of muscle stretch ($n = 32$)

Contraction type	Stiffness
Isometric reference contractions	320 ± 34 (N/mm)
Shortening contractions of 2–8 mm	324 ± 35 (N/mm)
Lengthening contractions of 2–8 mm	$339^* \pm 22$ (N/mm)

*Significant $p < 0.01$, non-parametric sign rank test. Isometric stiffness following muscle stretch was significantly larger than the corresponding stiffness during the isometric reference contractions.

obtained during the purely isometric reference contractions.

Stretch-shortening and shortening-stretch cycles produced different isometric forces following the dynamic muscle length changes indicating that stretching and shortening of skeletal muscle are non-commutative processes. The isometric forces following shortening-stretch cycles of equal magnitude (± 4 mm) were the same as those obtained for purely isometric contractions (Fig. 2). The isometric forces following stretch-shortening cycles of equal magnitude (± 4 mm) were always ($n = 8$) below the corresponding purely isometric forces.

From the results shown in Fig. 2, it appears that the effects of force depression following muscle shortening are offset when followed by a stretch of equal magnitude as the shortening. However, a stretch preceding a muscle shortening does not prevent force depression. In fact, we found that a stretch at a speed of 4 mm/s preceding muscle shortening produced the same amount of force depression as an isometric contraction preceding shortening (Fig. 3). When the stretching speed preceding shortening was very large (i.e. 256 mm/s), force depression was increased in all muscles compared to the situation in which shortening was preceded by an isometric contraction, although the increase was very small in absolute terms.

As shown in Fig. 2, a shortening-stretch cycle of equal magnitude (e.g. 4 mm shortening followed by 4 mm stretch) gave the same isometric force following the length changes as a purely isometric contraction at the corresponding length. However, if the shortening preceding the stretch was larger than the stretch (e.g. 8 mm shortening and 4 mm stretch, Fig. 4), the net result was a force depression in all cases compared to the purely isometric case at the corresponding length. Similarly, if the amount of shortening was smaller than the amount of stretch (e.g. 2 mm shortening and 4 mm stretch) the net result was a force enhancement compared to the corresponding purely isometric case (Fig. 4).

Combined, the results from Figs. 2–4 suggest that muscle lengthening alone gives a force enhancement.

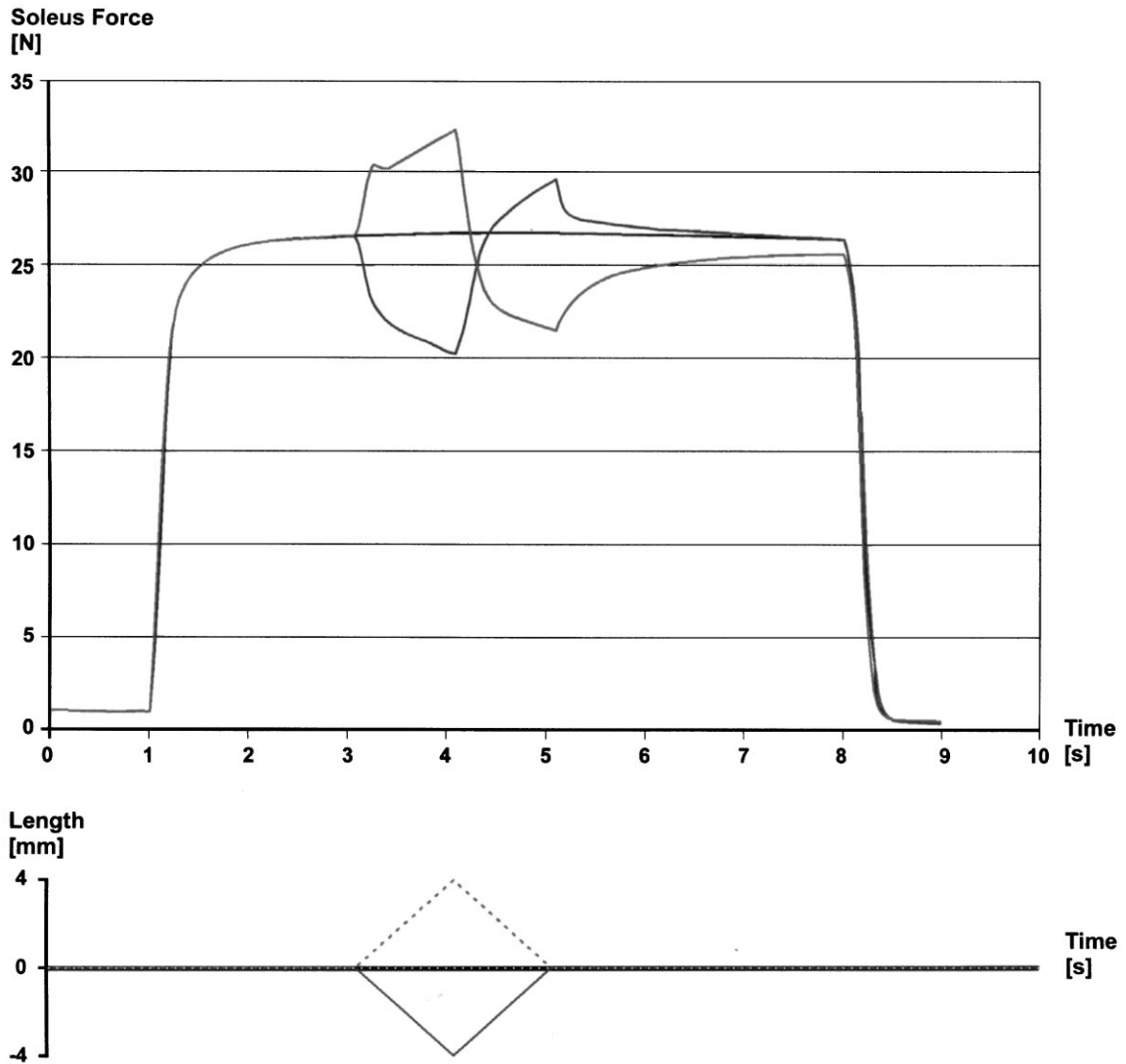


Fig. 2. Representative, raw data of force-time histories for an isometric reference contraction (0 mm) and a stretch-shortening (± 4 mm) and a shortening-stretch cycle (± 4 mm). The isometric forces following shortening-stretch cycles of equal magnitude were always ($n = 8$) very similar as those obtained for purely isometric contractions. The isometric forces following stretch-shortening cycles of equal magnitude were always ($n = 8$) below the corresponding purely isometric forces.

Muscle shortening preceding muscle lengthening affects the force enhancement in a dose-dependent manner. Muscle shortening alone gives force depression, and a stretch preceding muscle shortening does not affect the amount of force depression compared to a shortening-induced force depression. These combined results are illustrated in Fig. 5 for an isometric reference contraction, a stretch of 4 mm, a shortening of 4 mm, a shortening-stretch cycle (± 4 mm), and a stretch-shortening cycle (± 4 mm).

Finally, shortening over a distance of 8 mm at a speed of 4 mm/s produced the same amount of force depression independent whether the shortening was done in one or two steps (Fig. 6).

4. Discussion

4.1. Stiffness

The only previous study in which stiffness was determined during isometric reference contractions, during force depression, and during force enhancement, was performed on isolated frog fibres. In that study, it was shown that stiffness was the same during force enhancement and the corresponding isometric reference contractions (Sugi and Tsuchiya, 1988), suggesting that the force enhancement was accomplished by an increased average cross-bridge force rather than an increase in the proportion of attached cross-bridges. To our knowledge, this is

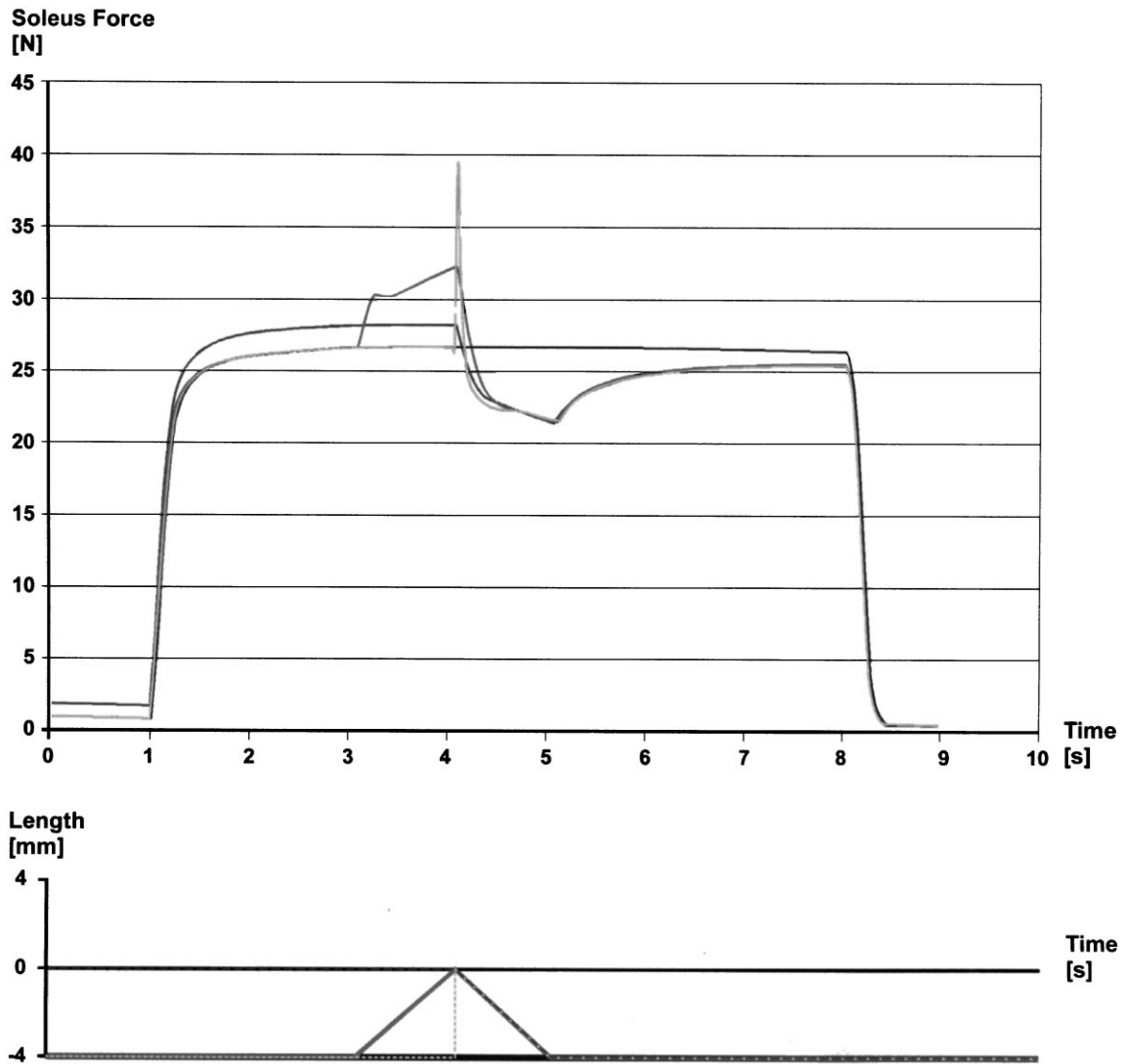


Fig. 3. Representative, raw data of force-time histories for an isometric reference contraction (-4 mm), an isometric (0 mm)-shortening (4 mm/s)-isometric (-4 mm) contraction, and two stretch-shortening contractions with speeds of stretching of 4 mm/s and 256 mm/s, respectively. The isometric forces following stretch-shortening cycles of equal magnitude were always ($n = 8$) below the corresponding isometric forces, independent of the speed of stretch preceding the shortening phase.

the first study in which corresponding stiffness measurements were performed in whole muscle. We found that stiffness was significantly ($p < 0.01$) higher during force enhancement compared to the stiffness during isometric control contractions (Table 1). At a first glance, one might be tempted to assume that this result indicates that force enhancement in whole muscle is caused by an increased proportion of attached cross-bridges. However, as pointed out elsewhere (Forcinito et al., 1997), one cannot calculate the proportion of attached cross-bridges without knowing the attachment distribution. Therefore, the present result should be considered with caution, but it does suggest that force enhancement following stretch in whole muscle might be caused in part by an increase in the proportion of attached cross-bridges.

Sugi and Tsuchiya (1988) found that the stiffness in single frog fibres was decreased during force depression compared to the stiffness measured during isometric control contractions. In their preparation, the decrease in stiffness was directly proportional to the amount of force depression, suggesting that the loss of force in the depressed force state was directly related to the loss of attached cross-bridges. The stiffness in cat soleus was found to be the same during force depression and the corresponding isometric control contractions, suggesting that force depression in entire muscle may be associated in part with a loss of average cross-bridge force rather than a decrease in the proportion of attached cross-bridges. The same cautionary note, as expressed in the previous paragraph, applies

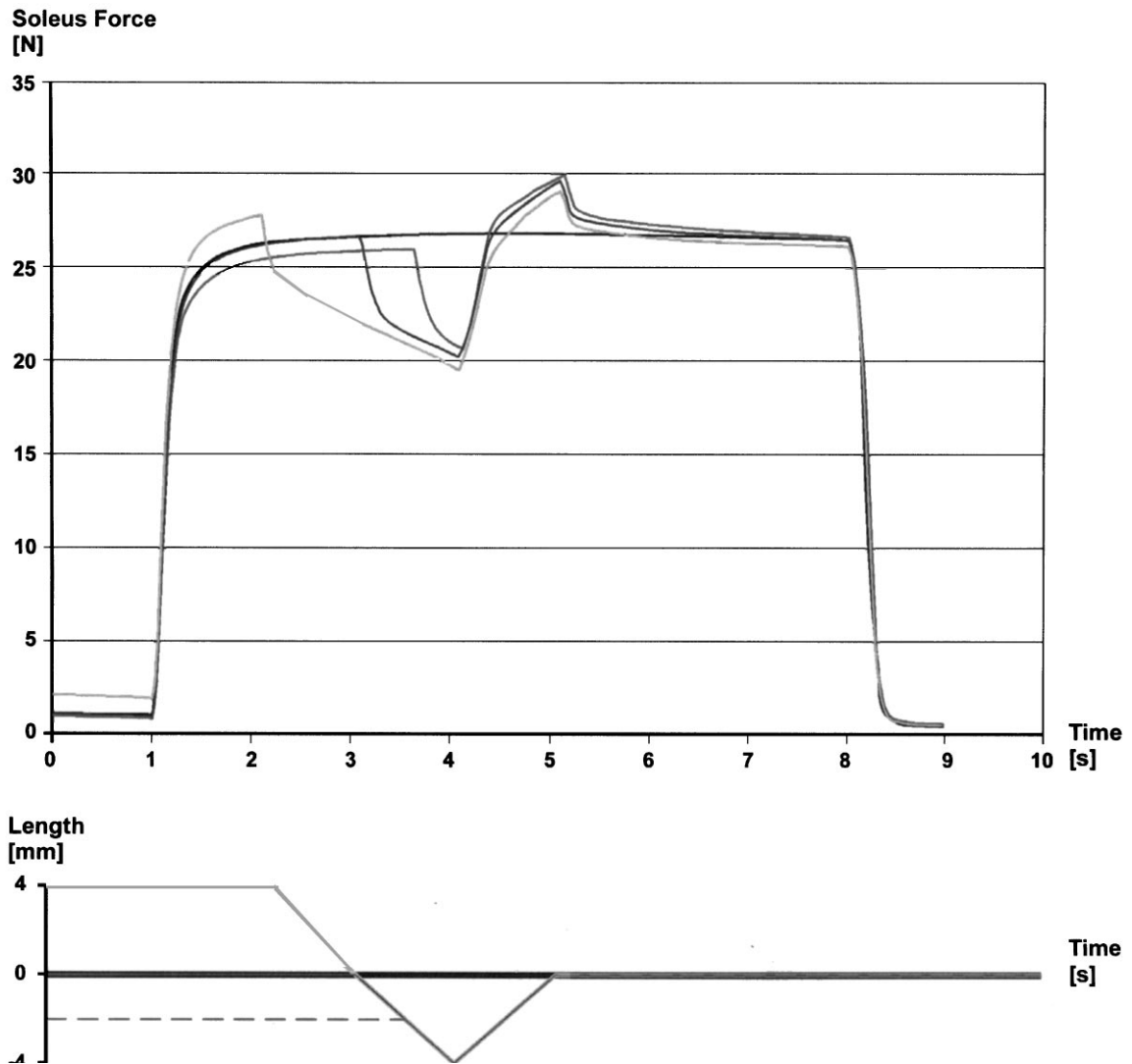


Fig. 4. Representative, raw data of force-time histories for an isometric reference contraction (0 mm) and three shortening-stretch cycles. The shortening-stretch cycles differed in the amount of shortening (i.e. 2, 4, and 8 mm shortening) but were the same in the amount of stretch (4 mm). The speeds of shortening and stretching were 4 mm/s in all cases. If the amount of shortening was equal to the amount of stretch, the isometric forces following the dynamic contractions were always ($n = 8$) about the same as the corresponding purely isometric contractions. If the shortening was larger (smaller) than the stretch, the isometric forces following shortening-stretch were always ($n = 8$) smaller (larger) than the corresponding isometric forces.

to this situation. Nevertheless, based on the differences in the stiffness results obtained for whole muscle and isolated fibre, the idea that force depression/enhancement might be associated with different phenomena in these two preparations should be considered a possibility.

4.2. History dependence of force production

The results of this study strongly support the idea that muscle shortening and lengthening are not commutative with respect to the isometric force produced following the length changes (Fig. 2). Furthermore, shortening preceding a stretch decreases the force enhancement of the

stretch in a dose-dependent manner, i.e. when the amount of shortening and stretch are equal, the net result is no force enhancement; when the amount of shortening is larger than the amount of stretch, the net result is an overall force depression, and when the amount of shortening preceding the stretch is smaller than the amount of stretch, the net result is a force enhancement (Fig. 4). Finally, muscle lengthening preceding shortening does not appear to influence the magnitude of force depression if the lengthening occurs at a slow speed (4 mm/s) but increases the magnitude of force depression slightly (but consistently, i.e. in all eight muscle preparations) if the lengthening speed is high (256 mm/s) (Fig. 3).

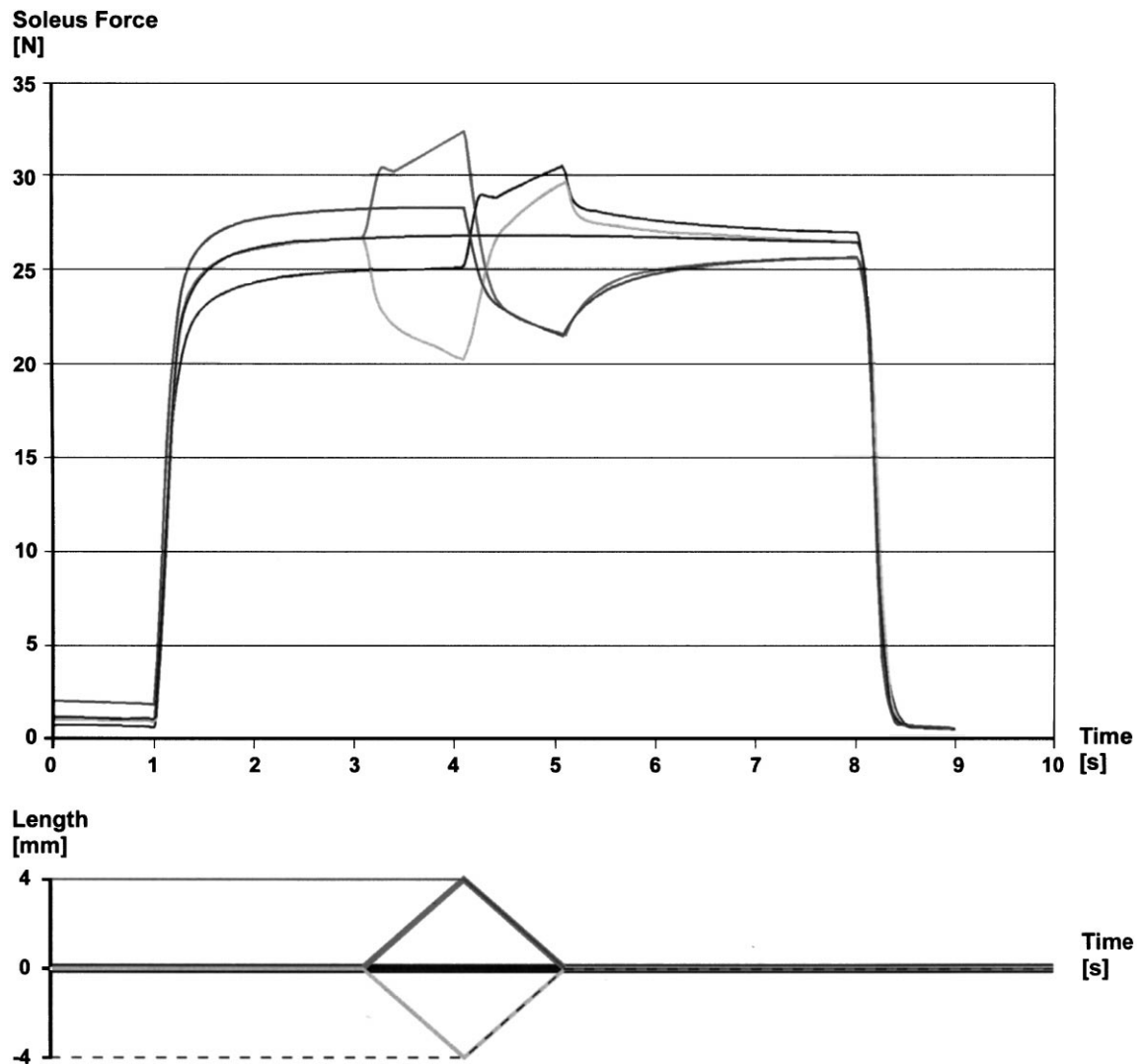


Fig. 5. Representative, raw data of force-time histories for an isometric reference contraction (0 mm), a pure shortening (4 mm) and stretch (4 mm) contraction, and a stretch-shortening (± 4 mm) and shortening-stretch contraction (± 4 mm). A pure stretch always ($n = 8$) resulted in force enhancement, a pure shortening always in force depression compared to the corresponding isometric forces. A shortening preceding stretch always ($n = 8$) offset the force enhancement of the stretch in a dose-dependent manner, whereas a stretch preceding shortening never ($n = 0$) offset the force depression of the shortening phase.

To our knowledge, there are no corresponding experimental data to which the above results can be compared to. However, there are selected theoretical studies in which history-dependent effects were incorporated into muscle models. For example, Forcinito et al. (1998) proposed a rheological model of skeletal muscle in which history-dependent effects were accounted for using an elastic rack that was engaged at the time of activation. Shortening of the muscle following activation caused force depression, and elongation caused force enhancement. Producing stretch-shortening or shortening-stretch cycles with this particular model gives the same steady-state force following the length changes; a result that is not correct according to the experimental results

presented here. However, the model by Forcinito et al. (1998) is additive in terms of the force enhancement and force depression effects, and the additive effect is directly proportional to the amount of lengthening and shortening. Therefore, this particular model predicts conceptually the results observed for the shortening-stretch cycles (Fig. 4). However, it does not predict the force depression observed after stretch-shortening cycles (Fig. 3). Similarly, models that use memory functions to account for force enhancement following stretch and force depression following shortening (Meijer et al., 1997; Wu and Herzog, 1999) would account conceptually for the history-dependent effects observed following shortening-stretch cycles but would predict a conceptually

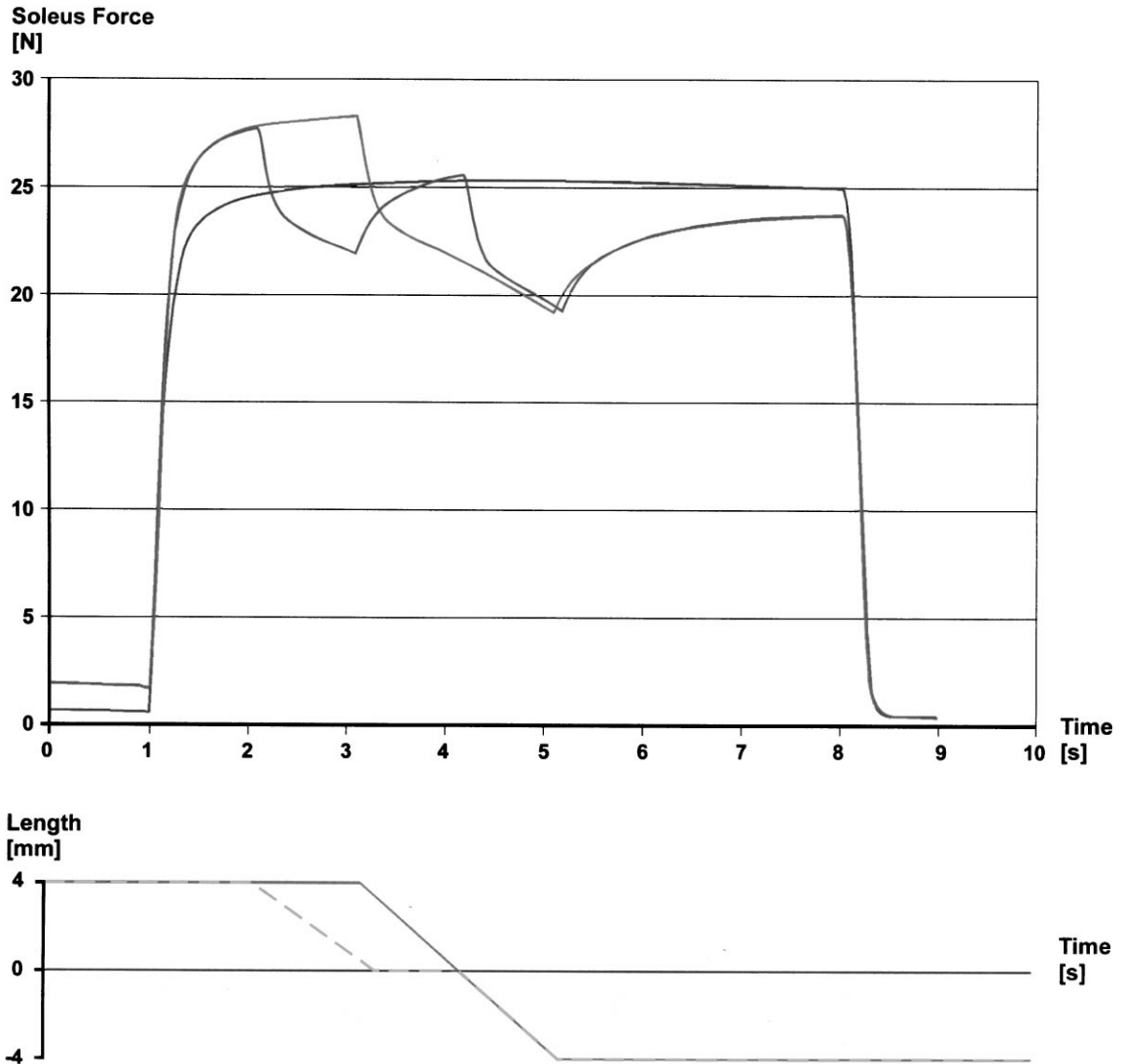


Fig. 6. Representative, raw data of force-time histories for an isometric reference contraction (0 mm), and two shortening contractions over a distance of 8 mm executed in one and two steps, respectively. The speed of shortening was 4 mm/s in all cases. For this experiment, the amount of shortening was always ($n = 8$) similar independent whether the shortening was performed in one or two steps.

incorrect result following stretch-shortening cycles (i.e. these models would predict that the force enhancement following the stretch tends to offset the force depression following shortening, rather than the experimentally observed result that the force enhancement following the stretch does not affect the amount of force depression to a large degree when shortening follows the stretch (Fig. 3)).

4.3. Mechanisms

Maréchal and Plaghki (1979) were the first to suggest that force depression following shortening may be caused by a stress-induced inhibition of cross-bridge attachment in the overlap zone between actin and myosin filaments

formed during shortening. In accordance with this mechanism of force depression, Herzog et al. (1998) showed that the amount of force depression for isometric-shortening-isometric contractions could be explained to a large extent (i.e. $0.87 \leq r^2 \leq 0.96$, $n = 6$) with the mechanical work performed by the muscle during the shortening phase. Therefore, our first attempt at explaining the results of this study for all protocols that end with a shortening contraction involved the “mechanical work theory”. According to the work theory, two specific results should have come out of this study: first, force depression following a stretch-shortening cycle should have been larger than force depression following an isometric-shortening contraction (Fig. 3); second, force depression following a two step shortening contraction

should have been larger than that following a one step shortening contraction (Fig. 6). However, these two results were not observed, as force depression was about the same for all these scenarios.

The most common mechanism associated with force depression following shortening is sarcomere length non-uniformity (Edman et al., 1993). According to this mechanism, sarcomere length non-uniformities develop during muscle shortening, and the amount of non-uniformity is directly proportional to the amount of force depression. If sarcomere length non-uniformity was the primary mechanism for force depression following shortening, then sarcomere length non-uniformities should have evolved as follows during our experiments:

- Sarcomere length non-uniformities that develop during muscle shortening should all be reversed during the stretch that follows the shortening phase in a dose-dependent manner.
- Sarcomere length non-uniformities should be increased for a given shortening protocol when the shortening is preceded by a fast stretch.
- Sarcomere length non-uniformities should not be affected when a given amount of shortening (at a given speed) is accomplished in one or two steps.

Although the present study cannot exclude the sarcomere length non-uniformity theory for lack of direct sarcomere length measurements, it appears unlikely that the above conditions are all satisfied. Specifically, the idea that sarcomere length non-uniformities that developed during muscle shortening should be offset by a muscle stretch of equal magnitude has no support in the literature and is hard to reconcile intuitively. However, an experiment aimed at demonstrating the effects of stretch and shortening on sarcomere length non-uniformities must be made in whole muscle before this mechanism may be excluded from causing force depression following muscle shortening.

4.4. Implications

To our knowledge, this is the first study to address systematically the history dependence of isometric force production following stretch-shortening and shortening-stretch cycles, and to determine whole muscle stiffness in normal, depressed and enhanced force states. Therefore, no final conclusions should be made based on the present results, as they require independent verification. Nevertheless, some suggestions for possible implications of the present results are given below.

According to the results of this study, we might expect that force enhancement following whole muscle stretch is, at least in part, caused by an increase in the number of attached cross-bridges. If so, mechanisms of force enhancement should focus on how the proportion of attached cross-bridges might be (permanently) increased

following stretch. Using classic cross-bridge mechanics, the only way that the steady-state proportion of attached cross-bridges can be increased in an isometric contraction following stretch is by an increase in the rate function of attachment, a decrease in the rate function of detachment, or a combination of the two (Huxley, 1957; Huxley and Simmons, 1971).

The results of this study further suggest that force depression following muscle shortening is caused by a decrease in the average force per cross-bridge. A decrease in average cross-bridge force can result from two sources according to the cross-bridge theory: a decreased “x”-distance (Huxley, 1957), or a systematic change in the attachment configuration of the cross-bridge head (Huxley and Simmons, 1971).

The results found here relating to all shortening-stretch results (Fig. 4) can be adequately represented in a theoretical model of muscle by using an elastic (tensile and compressive) element that engages upon activation. The existence of such an element has been suggested in the past based on experimental observations (Edman and Tsuchiya, 1996), and has been implemented theoretically in a rheological model of muscle (Forcinito et al., 1997). The dose-dependent nature of force production following shortening-stretch cycles should not be interpreted to mean that history dependence of force production following shortening-stretch cycles is necessarily caused by an elastic element in skeletal muscle that engages upon activation. However, the simplicity of this result is appealing from a theoretical modelling point of view. Furthermore, the idea that cross-bridges engage upon activation and act as “elastic” elements whose average isometric force depends on the history of length changes during shortening-stretch cycles is an attractive and a possible mechanism that should be studied further.

An intriguing result of this study is associated with the isometric forces following stretch-shortening cycles. Stretching a muscle before shortening does not appear to influence the force depression caused by shortening to a significant amount. This result is hard to reconcile with the “mechanical work theory” (Herzog and Leonard, 1997) or the sarcomere length non-uniformity theory (Edman et al., 1993). Furthermore, the stretch-shortening experiments do not mirror the results of the shortening-stretch experiments. Whatever the mechanisms of force depression following muscle shortening and force enhancement following muscle stretch, the force enhancement mechanism is influenced and offset by shortening. In contrast, the force depression mechanism is not influenced (possibly slightly enhanced) by stretching. This result, that manifests itself in the non-commutativity of the stretch-shortening and shortening-stretch cycles, may hold an important clue for the mechanisms associated with force depression and force enhancement, and should be considered carefully in future studies.

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