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Force depression decays during shortening in the medial gastrocnemius of the rat

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ABSTRACT

Force depression due to shortening of activated skeletal muscles has previously been described to be long lasting during isometric contractions following the shortening. In the present study, using the medial gastrocnemius of the rat, effects of force depression have been made apparent during shortening by computationally partially compensating for the direct effect of shortening velocity due to the tension–velocity relation. Evidence was found for the decay and complete disappearance of force depression already during continuation of the shortening contraction to short muscle lengths.

1. Introduction

Force depression refers to a diminished ability of a skeletal muscle to produce active tension due to a preceding shortening contraction (Herzog, 1998). While the phenomenon has been known for a long time (Abbott and Aubert, 1952), its mechanism is still under dispute. Most experimental characterizations revealed that force depression increases with the extent of shortening, is correlated with the initial length of the muscle, and is more pronounced for shortening at slower velocities (Maréchal and Plaghki, 1979; Meijer et al., 1997, 1998; Van Noten and Van Leemputte, 2011). The latter dependence is usually attributed to a positive correlation of force depression to tension during shortening (Maréchal and Plaghki, 1979; Herzog, 1998; Leonard and Herzog, 2005), since tension in turn is negatively correlated to shortening velocity (Hill, 1938).

Based, among others, on the above experimental observations, one hypothetical mechanism of force depression is that binding sites for cross-bridges at the part of the thin filament not overlapping the thick filament are partially inactivated by tension, and remain inactivated as long as tension continues, even after this part of the thin filament becomes overlapping with the thick filament due to muscle shortening. This could explain the positive correlation of force depression to tension during shortening (Maréchal and Plaghki, 1979; Herzog, 1998).

An alternative hypothesis, based on experimental and modeling results, is that inhomogeneities of sarcomere lengths lead to diminution of tension during shortening (Edman et al., 1993). Further alternative hypotheses include accumulation of metabolic products (Granzier and Pollack, 1989) and reduced calcium affinity of troponin (Edman, 1996).

Force depression in muscle preparations is usually experimentally quantified by continuing a shortening contraction into an isometric phase (i.e. a phase with constant muscle length) and comparing tension in the latter phase with that of a purely isometric contraction at the target muscle length. The quantity of force depression is then defined as the difference between the tensions of the purely isometric and the shortening-preceded isometric contractions (Maréchal and Plaghki, 1979). However, each of the currently considered hypothetical mechanisms obviously implies that force depression not only develops during shortening, but also already affects tension while shortening is still in progress. For the first mentioned hypothetical mechanism, this is acknowledged e.g. in Herzog et al. (2000). Also, Meijer et al. (1998) incorporated this effect into a numerical model, Siebert et al. (2008) explained deviations of their model predictions with this effect, and McDaniel et al. (2010) identified effects of force depression during shortening in cat soleus muscle. In the current study, which focuses on force depression *during* active shortening, force depression *during* and *after* shortening is regarded to be, though observed at different times, caused by the same mechanism; so they are only explicitly distinguished if adequate. Observation of force depression *during* shortening is somewhat hindered by the fact that tension in this phase is also directly influenced by the *current* shortening velocity due to the tension–velocity relation (Hill, 1938). However, in the current study on the medial gastrocnemius of the rat, tracing muscle tension, partially corrected for effects of current velocity, during shortening contractions of different velocities allowed observation of development and decay of force depression. It could be shown that at short muscle lengths force depression decays again and disappears completely before the end of the shortening contraction.

2. Methods

Experiments were approved according to Section 8 German animal protection law (Tierschutzgesetz, BGBl I 1972, 1277). The experimental setup was essentially

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as described in Till et al. (2008). Briefly, young male Wistar rats (body mass 300–340 g) were deeply anesthetized with sodium pentobarbital to the point where the foot withdrawal reflex was abolished. The medial gastrocnemius was dissected free of surrounding tissues, leaving its blood and nerve supply intact. Femur and tibia of the animal were fixed with steel pins. A piece of bone with the distal insertion of the muscle was cut off and connected to a muscle lever system (Aurora Scientific Inc., 305B-LR), to control either muscle length or muscle tension, and to measure length and tension at 1000 Hz. Stimulation was performed with a bipolar electrode at the sciatic nerve, with square pulses of 100 μs and a frequency of 80 Hz, yielding maximal muscle tension and an almost smoothly fused tetanus. Stimulation current was set to be thrice the twitch threshold. Body temperature was maintained at 34.5–35.5 °C. The muscle was regularly moistened with saline. The time between two contractions was at least 2 min.

The tension–length relation of the muscle was determined by isometric contractions of 0.3–0.7 s duration, at typically 20 different muscle lengths. Passive tension was not subtracted, but, as indicated later, did not exceed 3.5% of muscle tension even at the longest muscle lengths considered. The tension–velocity relation was determined at optimal muscle length by isotonic contractions of typically 7 different tensions, and suitable parameters of Hill's (1938) model were fitted.

Isovelocity shortening contractions were started from initial muscle lengths of either 5 mm or 1 mm longer than optimal muscle length, and shortening was continued down to a muscle length where the tension became zero. Shortening velocities were 5 mm/s, 10 mm/s, 20 mm/s, and 40 mm/s. In each contraction, stimulation started 0.5 s before shortening, which was sufficient to develop full isometric tension. To make effects of force depression during shortening better apparent, the direct effects on tension of *current* non-zero shortening velocity were partially compensated for by the following calculation: (1) calculating the ratio of tension at the imposed shortening velocity to isometric tension using the previously fitted tension–velocity relation, (2) dividing measured tensions in isovelocity shortening contractions by this ratio. The adequacy of this calculation will be discussed.

Within each series of four shortening contractions from the same initial muscle length, the following additional calculation was performed to compensate for variations of overall muscle force between different contractions. The isometric tension at optimal muscle length at the start of all experiments (f_s) was noted. Immediately before the series of shortening contractions, the isometric tension at optimal muscle length was checked again (f_c). Furthermore, the tensions of the initial isometric parts (not at optimal muscle length) of each shortening contraction were noted ($f_{i1}, \ldots, f_{i4}$). The overall muscle force at the time of the first shortening contraction of the series (reflected by f_{i1}) was assumed to be unchanged with respect to the overall muscle force reflected by f_c. For the following shortening contractions of the series, variations in $f_{i\ldots}$ were assumed to be proportional to variations in overall muscle force. Accordingly, the ratios of overall muscle force at the time of each shortening contraction to overall muscle force at the start of all experiments were calculated as $(f_c f_{i\ldots})/(f_s f_{i1})$. Tensions of shortening contraction were corrected by dividing them by the so-calculated ratio. This was intended to compensate, separately for each contraction, for the change in overall muscle force with respect to the start of all experiments. The calculated ratios are noted as percentages in the results; their variations within each series were small ($\leq 2\%$ of f_s for all series at the longer initial muscle length, $\leq 7\%$ of f_s for all series at the shorter initial muscle length).

3. Results

In four different rats, isovelocity shortening contractions of different velocities were performed from a starting muscle length at the descending limb of the tension–length relation down to a length with zero muscle tension (Fig. 1). Corrected tension was consistently lower for smaller velocities in the middle part of the traces. The difference of tensions of the contractions with the fastest and the slowest shortening velocity increases until a muscle length in the upper part of the descending limb of the tension–length

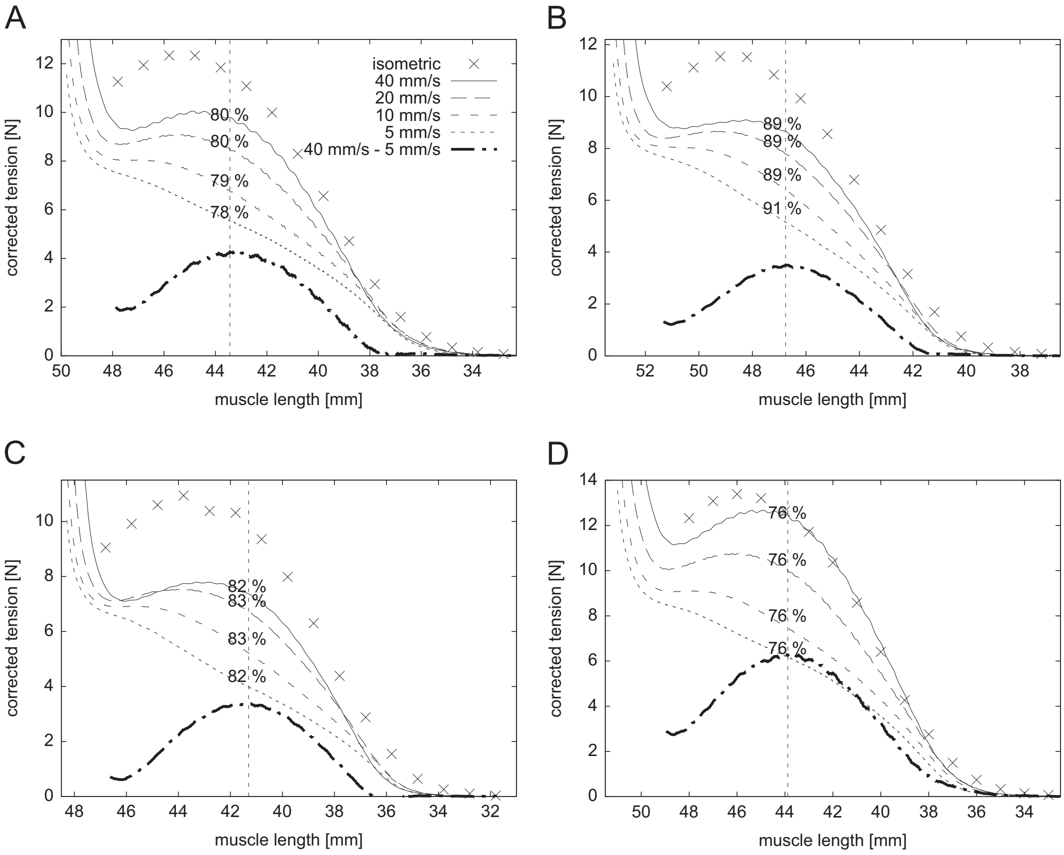

Fig. 1. Isovelocity shortening contractions from a starting length 5 mm above optimal muscle length in the medial gastrocnemius of four different rats (A–D). Four different velocities are shown, together with the experimentally determined isometric tensions over the considered range of shortening. Passive tension was at most 3.5% of the shown isometric tensions. Shortening was preceded by an isometric pre-contraction of 0.5 s duration, which is not shown. The initial rapid drop in tension, which is only partially shown, corresponds to the initial velocity change from zero to the imposed value and is not further discussed here. Tensions have been corrected by a factor partially compensating for the direct effect of velocity as described, so that effects of shortening history are better apparent. An additional correction was performed to compensate for variations in overall muscle force as described; the percentages of overall muscle force with respect to the start of all experiments are indicated. The lowest trace shows the difference of the tensions of the fastest and the slowest shortening contraction. The vertical dashed line indicates the muscle length corresponding to the maximum of this difference. This muscle length is in the upper part of the ascending limb of the tension–length relation. In the lower part of the ascending limb, the difference vanishes.