Original Article

Slow torque recovery after eccentric exercise and the repeated bout effect; the role of primary and secondary muscle damage

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Abstract

Objectives: To determine the role of primary and secondary damage in the variation between people of maximum voluntary contraction (MVC) torque recovery following eccentric exercise and the faster recovery following a repeated bout of exercise. **Methods:** Twenty-one healthy, active but untrained young female subjects undertook eccentric exercise of the elbow flexors and 11 repeated the exercise 28 days later. Changes of MVC torque and creatine kinase (CK) were followed for 7 days after each bout of exercise. **Results:** Following the first bout, 45% of subjects showed a continuing decline in MVC torque, suggesting secondary damage, which was correlated with a large delayed CK release (R^2=0.54, p<0.001). After the second bout of exercise, the initial MVC torque loss was similar to that after the first bout while torque recovery was faster, but only for the previously slow recovering subjects. Comparing the time course of MVC torque recovery of first and second bouts suggests secondary damage develops over 4 days. **Conclusions:** The data are consistent with primary damage being similar between subjects and unaffected by the repeated bout while it is secondary damage which accounts for differences in MVC torque recovery and is suppressed following a repeated bout of exercise.

Keywords: Eccentric Exercise, Muscle Damage, Elbow Flexor Muscles, Strength, Creatine Kinase

Introduction

Although muscle damage as a consequence of eccentric exercise, where the active muscle is stretched, has been extensively studied there remain a number of unresolved questions. The two main indicators of damage, the loss of force, and the release of creatine kinase (CK) have different time courses. The loss of force is usually maximal immediately after the end of the eccentric exercise and is thought be due to damage of sarcomere structure[1] or to the process of excitation-contraction coupling[2] and this might be considered to be the primary form of damage. In contrast, the major release of CK is characteristically delayed for several days and indicates a loss of integrity of the sarcolemma[3] which would also reduce the force generated by the muscle. One explanation for the delayed of CK release could be that the enzyme is slow to diffuse out of the damaged muscle but this is unlikely since CK is released rapidly with, at most, a 24 hr delay from muscle following orthopaedic surgery[4] or muscle reperfusion injury[5]. This suggests that where there is a delayed CK release there is also delayed damage to the sarcolemma and raises the possibility of a secondary delayed form of damage which may modify the time course of recovery from the initial damage evident immediately after the exercise.

Another unexplained feature of muscle damage caused by eccentric exercise is the large variation between subjects in their responses, most obviously with the delayed appearance of CK, but also the rate force, or torque, recovery. It is notable, in this respect, that slow recovery of force is often associated with high CK responses[6-8]. The association between the rate of force recovery and CK response is emphasised by the fact that recovery of force is faster following a second bout of eccentric exercise (the repeated bout effect) and this is

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associated with a much reduced CK release[9-11]. The extent of the secondary damage clearly varies between people, and between first and repeated bouts of exercise. Thus it is possible that it is variations in the extent of the secondary damage that accounts for the differences in the rate of torque recovery between people and the faster recovery after the repeated bout.

The first objective was to test the hypothesis that variations in the rate of torque recovery will be associated with CK release, as an indicator of secondary damage, rather than differences in the extent of the initial damage, as evidenced by loss of torque. The second objective was to test the hypothesis that faster torque recovery following a repeated bout of exercise is due to suppression of the secondary damage while the extent of the initial damage is unaffected.

Materials and methods

Participants

Twenty-one, healthy and physically active female subjects were recruited. Exclusion criteria were an involvement in resistance exercise during the last 6 months, neuromuscular or skeletal problems or regular use of analgesic or anti-inflammatory drugs. All procedures were approved by the Regional Ethics Committee for Biomedical Research and were conducted according to the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all subjects.

There were two studies. For the first study, 10 subjects (22.5±3.4 years old; 61.2±11.9 kg; 170.3±8.2 cm) exercised the forearm flexors and their recovery was monitored over the following 7 days. For the second study, 11 subjects (21.4±0.5 years old; 68.6±12.9 kg; 168.0±4.6 cm) likewise exercised, with recovery followed over 7 days, but then, 4 weeks later, repeated the exercise with the same arm, and again, recovery was followed for the next 7 days. For each exercise bout a note was made of whether the dominant or non-dominant arm was used and subjects were asked about the phase of their menstrual cycle; none were using oral contraception. The repeated bouts were undertaken 28 days after the first bout to ensure the subjects were in the same phase of the menstrual cycle. For both studies subjects first attended a laboratory session in which they were familiarized with the apparatus and procedures and baseline data were collected. All exercise and testing was carried out by the same team of investigators.

Eccentric exercise of the elbow flexors and isometric strength testing

The subjects were seated on a Biodex System 3 isokinetic dynamometer (Biodex Medical Systems, Inc., Shirley, New York, USA) with the back rest fixed at 90° and with the trunk, pelvis and upper arm stabilized with Velcro straps. The axis of rotation was fixed at the elbow joint and the lever arm pad attached at the wrist. Subjects were instructed to perform 6 sets of ten maximal voluntary eccentric contractions of the elbow flexors starting from 60° elbow flexion until full extension (180°) with 1 min rest between sets. Verbal encouragement and visual feedback were used to maintain a maximal effort throughout each stretch. Peak torque and work done on the muscle during each eccentric action were recorded. For the first 10 subjects the angular velocity was 90°.s^{-1}, while for the 11 subjects in the repeated bout part of the study the angular velocity was reduced to 60°.s^{-1}.

Measurements of isometric muscle strength were made with the subjects stabilized in the Biodex chair, as for the eccentric exercise, but with the elbow fixed at 90°. Subjects were encouraged to make maximum voluntary contractions (MVC) for 2-3 sec, with visual torque feedback, and 60 sec rest between contractions. Provided the two values differed by no more that 5%, the highest torque was recorded, otherwise the test was repeated and the highest value accepted for further analysis.

Creatine kinase

Approximately 0.25 mL of capillary blood was drawn from the finger. Samples were immediately centrifuged and plasma analysed for CK activity using the biochemical analyser Spotchem™ EZ SP-4430 (Menarini Diagnostics, UK) with soft reagent strips (ARKRAY Factory, Inc., Shiga, Japan) and plasma enzyme activity reported as micro-Katal per Litre (µkat.L^{-1}). One µkat.L^{-1}, the SI unit of CK activity, is equivalent to 60 of the more commonly used International Units. The coefficient of variation for the CK assay was less than 8% calculated from the ratio of standard deviation to the mean in repeated measurements (n=8) of the same sample.

Data and statistical analysis

Sample size was based on published human studies of eccentric exercise where the numbers of participants ranged from 7 to 18[9,10,12-15]. In general, torque data are expressed as a percentage of the MVC torque measured immediately prior to the first bout of eccentric exercise. The rate of torque recovery was assessed as the difference between the torque immediately after the exercise and the torque after 7 days' recovery (all expressed as a percentage of pre-exercise values). A Shapiro-Wilk test for normality was used and, where normally distributed, descriptive data are presented as mean±SD. Data for creatine kinase were not normally distributed and these are reported as median and interquartile range (IQR). Data which were not normally distributed were investigated with a non-parametric Kruskal-Wallis test to assess differences over time. Relationships between plasma CK and torque recovery at Day 7 were examined by linear regression. Statistical significance was assumed at p≤0.05.

Results

At the end of the first study there was some concern that the variation in response to the exercise might be due to subjects finding it difficult to maintain full activation of the

Table 1. Factors that may influence the response to eccentric exercise. MVC torque immediately after the exercise (Post) or 7 days later. Data are expressed as percentage of the pre-exercise MVC torque (Mean±SD). Exercise was at either 60 or 90°.s⁻¹, in the follicular or luteal phases or of dominant or non-dominant arm.

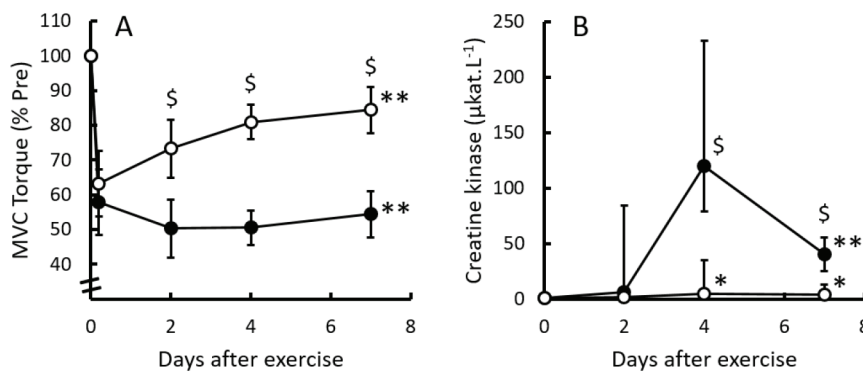|	N	MVC Post (%)	MVC Day 7 (%)
90°.s⁻¹	10	60.0±10.4	76.2±18.8
60°.s⁻¹	11	59.8±8.2	62.9±14.3
p		0.94	0.09
Follicular	13	60.4±8.1	65.7±19.2
Luteal	8	59.1±11.3	74.9±13.7
p		0.77	0.25
Dominant	14	61.0±9.1	68.6±20.2
Non-dominant	7	57.8±9.5	70.5±11.8
p		0.46	0.82

Figure 1. Recovery following eccentric exercise. A, MVC torque. B, Creatine kinase. Open symbols, the 10 subjects showing greatest recovery at 7 days, filled symbols the 10 subjects showing the least recovery. Data for MVC torque are mean±SD, for creatine kinase median and IQR. * Significant difference from pre-exercise. ** Significant difference from pre-exercise at all time points. $ Significant difference between groups (p<0.05).

muscle when being stretched at 90°·s⁻¹; consequently, in the second study the angular velocity was reduced to 60°·s⁻¹ for both the first and the second, repeated, bout of exercise. In the event, no differences were seen in the loss of torque immediately following the eccentric exercise and while the torque ay Day 7 had recovered more after exercise at 90°·s⁻¹ it did not differ significantly from that at the slower angular velocity (p=0.09) (Table 1). Two other factors which might influence the response to eccentric exercise, phase of the menstrual cycle and arm dominance were also examined and found to have no significant effect (Table 1). Consequently, data from the 10 subjects of study 1 have been combined with those for the first bout of exercise of the 11 subjects of study 2 giving 21 subjects in total.

As a result of the first unaccustomed bout of exercise of the elbow flexors (N=21), isometric torque decreased to 60±9% of the pre-exercise value with very slow recovery over the next 7 days and with considerable variation between subjects. Subjects were ordered according to the recovery
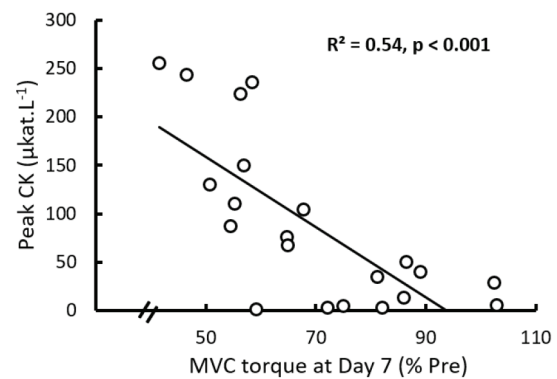

Figure 2. Relationship between creatine kinase response and MVC torque recovery. Data are for peak CK as a function of MVC torque at Day 7 (N=21).
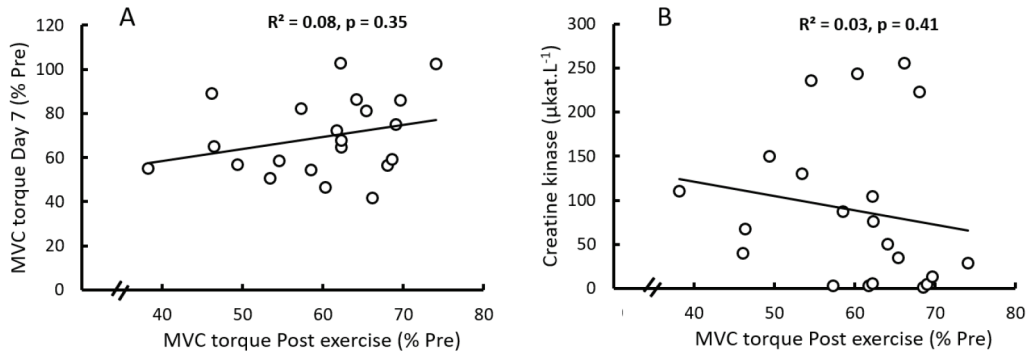
Figure 3. Torque recovery and creatine kinase in relation to initial torque loss. A, MVC torque at Day 7 as a function of torque immediately after eccentric exercise (Post). B, peak creatine kinase activity as a function of post exercise torque (N=21).
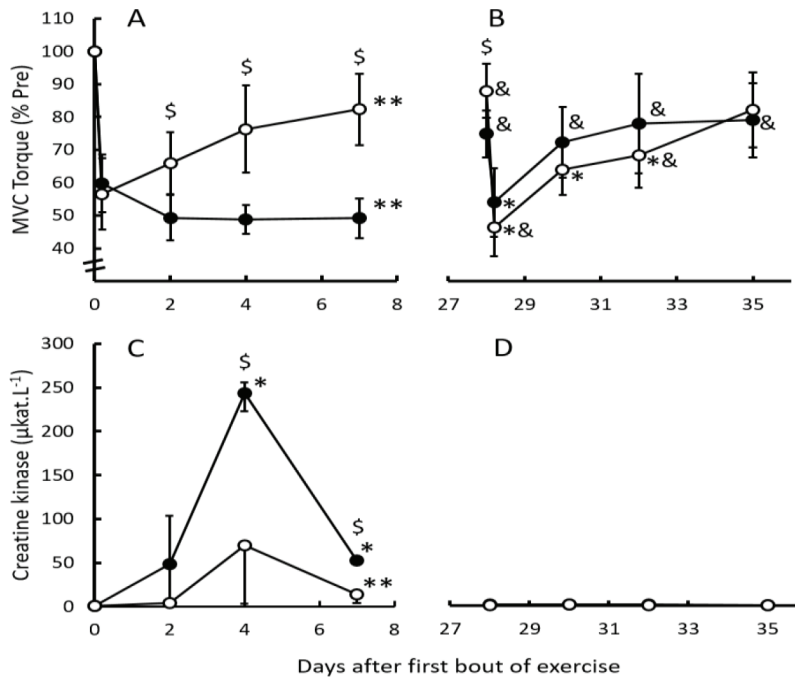
Figure 4. Repeated bouts of eccentric exercise. A, MVC torque following the first bout of exercise. B, MVC torque following the second bout of exercise. Data are mean±SD, N=5. C, creatine kinase response to the first bout of exercise. D, response to the second bout. Data are median and IQR. Open symbols are for the 5 subjects with the greatest recovery at day 7; filled symbols are for the 5 subjects with the least recovery. *Significant difference from pre-exercise. ** Significant difference from pre-exercise at all time points. $Significant difference between groups. & Significant difference between exercise bouts (p<0.05).

of MVC torque at Day 7 after the exercise and the data for the 10 with the greatest (faster) recovery, together with the 10 with the least (slower) recovery are shown in Figure 1. MVC torque immediately after the eccentric exercise was the same for the two groups (p=0.19) but thereafter the values diverge significantly (Figure 1A). For the slow recovering group, the torque at day 7 did not differ significantly from the value immediately after the eccentric exercise (p=0.37)

and, notably, the MVC torque at day 2 was significantly lower than the immediate post exercise value (p=0.026). For the fast recovering group there was a steady increase in torque reaching, on average, 85% of the pre-exercise value by day 7.

The creatine kinase responses to the eccentric exercise differed markedly between the two groups (Figure 1B), while both showed a peak of activity at 4 days, the median value for the slow recovering group was 27-fold higher than for

the fast recovering group, indicating considerable disruption of the sarcolemma. The relationship between Peak CK and recovery of MVC torque at Day 7 is shown in Figure 2. There was, however, no relationship between the extent of torque loss immediately following the eccentric exercise and either the recovery at Day 7 (Figure 3A) or the peak creatine kinase response (Figure 3B).

Repeated bout

The eleven subjects in study 2 repeated the eccentric exercise with the same arm 4 weeks after the first exercise bout. Subjects were ordered according to MVC torque recovery by day 7 following the first bout of exercise and divided into the 5 fastest and 5 slowest recoveries. Data for these two groups for both the first and the repeated bouts are shown in Figure 4.

For the fast recovering group, torque at 28 days, just before the second bout of exercise, was 86±10.0% of the value immediately before the first bout, while for the slow recovering group it was 75.9±6.4% of the initial value (Figure 4A). Work done on the elbow flexors during the second bout of exercise was lower than during the first bout but, for both groups this was in proportion to the reduction in isometric torque. Isometric torque measured immediately after the second bout of exercise (Figure 4B), declined to values that were slightly, although not significantly, lower than following the first bout, but the subsequent recovery was rapid with both groups recovering, by Day 7, to values close to those measured immediately before the second bout, with no significant difference between groups. For the previously slow recovering group the recovery of torque was significantly greater 2, 4 and 7 days after the second bout compared to the first (p<0.02). For the fast recovering group torque recovery, was a slightly, but not significantly, greater, 2 days after the second bout compared to the first but, overall, there was no significant difference in the rate of recovery between the first and second bouts.

Creatine kinase responses for the two groups are shown in Figures 4C & D. Following the second bout, median CK did not differ from baseline at any time for either group (Figure 4D).

Discussion

The objective of the study was to examine the proposition that slow recovery following a bout of eccentric damage is due to some form of secondary damage that slows torque recovery and, furthermore, that the faster recovery of MVC torque following a repeated bout of eccentric exercise is due to the suppression of the secondary damage. The results presented here are largely consistent with these ideas.

The responses to the first bout of eccentric exercise of the elbow flexors in terms of torque loss immediately after the exercise, the subsequent recovery and the extent of the delayed CK release into the circulation, were very similar to those reported in similar studies[3,10,16-18]. What has not previously been examined in any detail is the extent of variation between

subjects nor the relationship between the rate of recovery and either the initial loss of torque or the CK response.

It is notable that the mean decrement of MVC torque immediately following the eccentric exercise was very similar for the fast and slow recovering groups (Figure 1) and Chen[6] also reported very similar initial decrements of elbow flexor isometric force between the medium, high and highest responding subjects. The initial decrement was also very similar between the first and repeated bouts of exercise (Figure 4) and a number of other studies of elbow flexors also report the immediate force, or torque, loss after a repeated bout to be very similar to that seen after the first bout[10,19,20].

The initial decrement was not associated with either the rate of MVC torque recovery (Figure 3A), or the CK response (Figure 3B). Nosaka et al.[21] also found that the extent of force loss immediately after eccentric exercise of the elbow flexors to be largely unrelated to subsequent measures of muscle damage. This lack of association rules out causation indicating that the extent of the initial loss of torque, the primary damage, was not the determinant of the rate of torque recovery. In contrast, there were clear associations between the magnitude of the delayed CK response and the rate of torque recovery, evident in Figures 1 and 4 and Figure 2, indicating that the delayed secondary damage process can result in serious disruption of muscle fibre structure and integrity of the surface membrane which would lead to further loss of torque. These results support the first hypothesis set out in the introduction, that variation in the rate of torque recovery, especially slow recovery, is due to secondary, delayed, muscle damage and not to differences in the initial torque loss.

Faster recovery of torque following the repeated bout of exercise was only seen in the subjects who recovered slowly from the first bout of exercise and who had relatively large CK responses on that occasion (Figure 4). Following the repeated bout, torque recovery was at the same rate for all subjects and very similar to that of the faster subjects following the first bout of exercise (Figure 4). These results support the second hypothesis that faster recovery of torque following the repeated bout is due to a suppression of the secondary delayed form of damage while the initial loss of torque is unaffected.

If the initial decrement of MVC torque and subsequent recovery following the repeated bout of exercise represents only the primary damage, then it is possible to estimate the extent and time course of the secondary damage by subtracting the MVC torque values from the corresponding time points following the first bout of exercise (Figure 5). Fitting an exponential curve to the data for the slow recovering group shows the secondary damage to develop with a half time of 23 hrs so that by Day 7 the MVC torque deficit was approximately 30% of the pre-exercise MVC torque. For the faster recovering group there was no significant difference in time course following the first and second bouts of exercise and consequently no indication of secondary damage in the data shown in Figure 5.

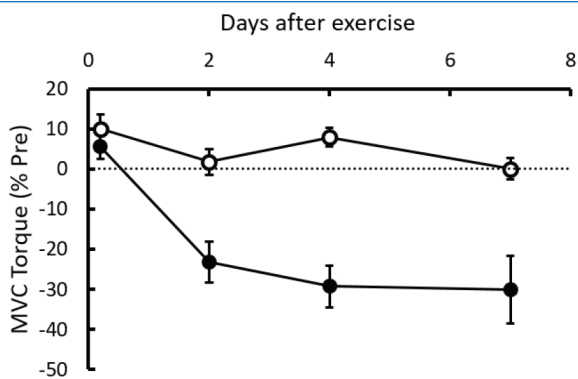The data for the faster MVC torque recovery following

Figure 5. Time course of secondary damage. MVC torque data for individual subjects following the repeated bout of exercise (Figure 4B) subtracted from data for the first bout (Figure 4A) to demonstrate the extent and time course of secondary damage. Filled symbols, the 5 subjects with the least torque recovery 7 days after the first bout of exercise; open symbols, the 5 subjects with the greatest recovery of torque 7 days after the first bout of exercise. Data are mean±SD.
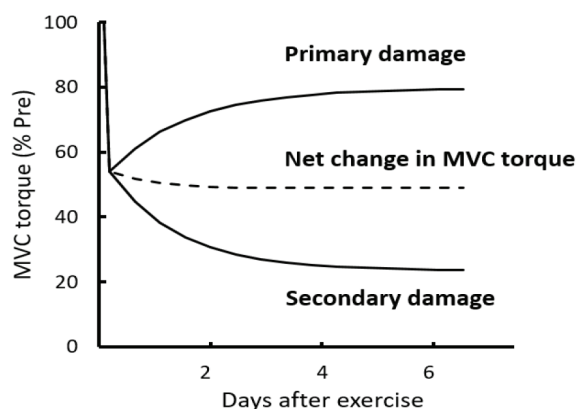

Figure 6. The contributions of primary and secondary damage to MVC torque following eccentric exercise. Data for primary damage are for the slow recovering subjects from Figure 4B and for secondary damage from Figure 5.

the repeated bout show in Figure 4B can also be fitted with a single exponential curve with a half time of 28 hrs and combining this with the fitted curve from Figure 5, shows the time course and relative contributions of the putative primary and secondary damage processes to the observed change in MVC torque (Figure 6). The analysis in Figure 6 suggests that the recovery of primary damage is offset by the development of secondary damage so that by Day 7, while there was a 30% recovery of primary damage, this was nearly balanced by the development of 30% secondary damage. The slightly shorter half time for the development of secondary damage accounts for the slight decrease in the observed MVC torque

(dashed line in Figure 6, see also Figures 1A & 4A). The data presented here and the inferences drawn in Figures 5 & 6 indicate that the extent of primary damage and, most likely, the time course of its recovery were similar in the slow and fast recovering groups. Consequently, the differences in recovery of MVC torque between the two groups can be ascribed to differences in the extent of the secondary damage process. This is consistent with the relationship between MVC torque recovery and CK response (Figure 2).

It is only possible to speculate about the nature of the primary and secondary damaging processes, but there are probably several reasons for the immediate loss of force following unaccustomed eccentric exercise which may be broadly divided, on the one hand, into impaired excitation-contraction coupling (EC coupling) and, on the other, to sarcomere damage and loss of the contractile elements, actin and myosin[1].

The first assessments of EC coupling changes following eccentric exercise were made by Warren et al[2] and Ingalls et al[22], showing with isolated preparations that while tetanic force was reduced, caffeine contracture force was largely unaffected following eccentric exercise. Kamandulis et al.[23] examined the function of myofibrils isolated from muscle biopsies taken from subjects showing considerable loss of torque 24 hrs after a series of drop jumps but could find no major changes in the force developed in response to Ca^{2+} nor any substantial structural damage. These results are consistent with changes in muscle function being due to problems of EC coupling rather than damage to the contractile elements. There is other evidence of EC coupling deficit in human muscle following eccentric exercise. A feature of damaged muscle is that when stimulated at a range of frequencies there is a disproportionate loss at the lower frequencies, often expressed as the ratio of forces generate at 20 and 100Hz stimulation[10,23-25], and this has been linked with reductions in calcium released per action potential[26,27]. The reduction in 20/100 ratio is maximal immediately following the eccentric exercise and recovers with a time course that is similar to that of the putative primary damage in the present study, and faster than MVC force[10]. It seems reasonable therefore to identify the primary damage with a deficit in EC coupling.

The secondary damage clearly involves substantial structural changes to the muscle fibre and there have been a number of studies examining the possibility that it may be due to white cell infiltration of the muscle or increased intracellular Ca^{2+} activating phospholipase or proteases enzymes[28-30]. What initiates the secondary damage, and why it should be suppressed following a repeated bout of eccentric exercise, is not known but may be associated with the expression of heat shock proteins[30,31]. The time course of the development of secondary damage suggested in Figure 6 is compatible with the evolution of an inflammatory reaction reaching a maximum at around 4 days when there is the peak of CK release. The subsequent recovery of the structural damage is clearly very slow, taking several weeks to return to pre-exercise levels.

The major limitation of the study is the uncertainty

surrounding the influence that factors such as limb dominance, menstrual status, and the speed of eccentric stretching may have on the responses studied here. The data presented in Table 1 suggest little influence, but because of the limited subject numbers, cannot be taken as definite proof there is no effect. Nevertheless, the influence of these potential confounding factors appears to be relatively small compared to the effects described here and are unlikely to invalidate the conclusions drawn. The analysis in Figures 5 & 6 makes the assumption that the extent and time course of recovery of the primary damage is not affected by the repeated bout effect. Certainly the initial torque loss was very similar between first and repeated bouts and the fact that the time course of recovery for the fast recovering subjects was the same on the two occasions, and similar to that of the slow recovering subjects after the repeated bout, argues that it was not subjected to the repeated bout effect.

In summary, the present study has examined the possibility that variation in the rate of recovery of MVC torque between subjects and between first and repeated bouts of exercise, can be attributed to difference in the extent of primary and secondary damaging processes. In slightly under half the subjects MVC torque continued to decline in the days after the initial loss and this, together with the fact that slow recovery was associated with CK release, is taken as an indication of secondary damage. Comparing the time courses of MVC torque recovery for the first and repeated bouts of exercise suggests that, for the slow recovering subjects, a secondary form of damage develops over about 4 days and this offsets the recovery of the primary damage thereby slowing the overall recovery of MVC torque. The data are also consistent with suppression of the secondary damage being the reason for the faster recovery of MVC torque following a repeated bout of eccentric exercise.

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