

Effects of Muscle Damage Induced by Eccentric Exercise on Muscle Fatigue

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ABSTRACT

ENDO, T., T. NAKAJIMA, M. SAKAMOTO, and T. KOMIYAMA. Effects of Muscle Damage Induced by Eccentric Exercise on Muscle Fatigue. *Med. Sci. Sports Exerc.*, Vol. 37, No. 7, pp. 1151–1156, 2005. **Purpose:** The present study was designed to determine to what extent muscle damage induced by repetitive eccentric exercise with maximal voluntary effort (ECC) affects the time course of central and peripheral fatigue during sustained maximal voluntary contraction (MVC). **Methods:** Ten healthy male volunteers were asked to perform brief (control MVC) and sustained MVC (fatigue test of 60 s in duration) with elbow flexion before and 2 and 4 d after ECC. Transcranial magnetic stimulation (TMS) was applied to the motor cortex to determine changes in voluntary activation (VA), the size of the motor evoked potential (MEP), and length of electromyographic (EMG) silencing. The ratio of the root mean square value for the surface EMG of the biceps brachii and exerted force within 50 ms before TMS was also calculated (RMS/F). **Results:** In two subjects, no significant changes in MVC and muscle soreness were seen after ECC so that their data was excluded from further analysis. Control MVC and muscle soreness was significantly decreased and increased, respectively, 2 and 4 d after ECC compared with that before ECC ($P < 0.001$). During the fatigue test, VA, which was determined by a phasic increase in the twitch force after TMS, significantly decreased 2 and 4 d after ECC compared with that beforehand ($P < 0.01$). In addition, the RMS/F was significantly increased 2 and 4 d after ECC ($P < 0.001$). Although the degree of facilitation of the MEP was significantly increased ($P < 0.05$), the length of EMG silencing was less affected by ECC. **Conclusions:** Muscle damage and/or muscle soreness induced by repetitive eccentric exercise with maximal effort may be a strong modifier of central and peripheral fatigue during sustained MVC. **Key Words:** EXERCISE-INDUCED MUSCLE DAMAGE, MUSCLE SORENESS, CENTRAL FATIGUE, PERIPHERAL FATIGUE, TRANSCRANIAL MAGNETIC STIMULATION, MVC

Acute and unaccustomed eccentric exercise induce muscle damage as can be seen through ultrastructural impairment of the contractile and cytoskeletal components of myofibrils, and the subsequent increase in intramuscular protein expression such as for creatine kinase, lactate dehydrogenase, and myoglobin (12,24). Eccentric exercise-induced muscle damage results in persistent force loss, a reduction in the range of joint motion, swelling, and delayed onset muscle soreness that peaks 24–48 h after exercise (4,19). Although many studies on the peripheral and metabolite contribution to muscle damage induced by eccentric contractions have been carried out (see reviews; 4,8,26), little is known about the effect of damaged muscle

on muscle fatigue and the central nervous system, which interact with one another. Therefore, it is important to determine how central and peripheral fatigue is affected by muscle damage induced by eccentric exercise, since fatigue is one of the predominant limiting factors of sport performance and strength training. We hypothesized that eccentric-induced muscle damage influences central and peripheral fatigue because of changes in afferent discharges arising from damaged muscle.

Central and peripheral fatigue progressively increase during sustained maximal voluntary contraction (MVC; 1,9). Recently, transcranial magnetic stimulation (TMS), which is a noninvasive technique used to investigate the function of the motor cortex, was utilized to examine the properties of central fatigue (9,10). Voluntary activation (VA), which can be estimated by comparing the amplitude of a superimposed twitch evoked by TMS and the voluntary force immediately before the stimulus during MVC, progressively decreases during sustained MVC (9). These findings indicate that a person can not voluntarily access motor output during the progression of central fatigue (9,10). In addition, the electromyographic (EMG) response to TMS, the motor evoked potential (MEP) and the duration of EMG silence (silent

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period, SP) after the MEP can provide crucial information regarding the excitability of the motor cortex and possibly spinal motoneurons as well as the inhibition of motor cortical output, respectively (3,6,14). The size of the MEP and duration of the SP also progressively increase during sustained MVC, indicating that these changes can be used to facilitate the estimation of central fatigue (17,28). These studies provide technical and theoretical bases for investigating possible central mechanisms responsible for the loss of the ability to exert sustained MVC in the presence of muscle damage induced by an eccentric exercise. On the other hand, an increase in the ratio of the EMG and exerted force during sustained MVC is indicative of the impairment of E-C coupling, thus suggesting an increase in peripheral fatigue (1).

The present study was designed to investigate to what extent central fatigue is affected by muscle damage after acute eccentric exercise during sustained MVC using EMG analyses including TMS. In addition, the effect of muscle damage on peripheral fatigue estimated by the ratio of the EMG to the voluntary force was also examined.

METHODS

Subjects. The experiments were performed using 10 healthy male subjects aged 22.3 ± 0.30 yr with a range of 21–24 yr who were free from any musculoskeletal disorders and who had not been involved in any resistance training programs. They were instructed not to take anti-inflammatory drugs during the experimental period, and not to stretch, massage, or do anything to treat their sore muscles. The experiments were performed after obtaining informed consent from each subject according to the Declaration of Helsinki. This study was approved by the local ethics committee.

Experimental setup. Each subject sat in an experimental chair with their trunk vertically fixed and with the left elbow and shoulder flexed at 90° . The forearm was vertically positioned and supinated, and the left wrist was firmly held by an apparatus designed to measure isometric elbow torque as well as isometric and eccentric exercise, which was performed by manipulating the joint locks. All subjects performed the experiments in this posture.

Task. To induce muscle damage, the subjects were asked to perform an eccentric exercise with maximal effort (ECC). One second after starting MVC, an investigator forcibly extended the elbow joint from 90° to full extension (about 180°) for 3 s, and then the subjects were asked to continue exerting MVC for 1 s in the extended position. This mode of eccentric exercise induces a remarkable degree of muscle damage (4). The ECC task was repeated 30 times every 15 s.

Data collection and stimulation. Before, 2 and 4 d after performing the ECC task, the subjects performed brief MVC for 3 s (control MVC) three times with a sufficient resting interval of 60 s and then performed sustained MVC for 60 s (fatigue test). Between control MVC and the fatigue test, an adequate rest period of 3 min was permitted. During control MVC and the fatigue test, TMS was applied to the

contralateral motor cortex to estimate VA, MEP, and SP. For the fatigue test, the first TMS was immediately applied after the subjects reached MVC and was then delivered every 10 s afterward. Each subject received force feedback and constant verbal encouragement while exerting MVC throughout the experiment. Because the SP evoked by TMS during MVC reduces ongoing voluntary force, the subject was instructed to regain maximal force “as fast as possible” after the stimulus was applied. TMS were delivered using a figure-eight coil (100 mm outside diameter, SMN-1100, Nihon Kohden, Japan) positioned over the optimal site in which the MEP was obtainable from the biceps brachii (BB) by a minimal stimulus output of $50 \mu\text{V}$ for three of six trials. A skilled examiner kept the coil in the same position throughout each experiment. Maximal stimulator output (1.5 T) was used to obtain an SP that was longer than 80 ms (28).

VA was estimated during control MVC and the fatigue test by measuring the twitch responses after TMS. The following formula was used to calculate the VA (10);

Voluntary activation (VA, %)

$$= (1 - \text{superimposed twitch/background voluntary force}) \times 100$$

where superimposed twitch is a fraction of the background voluntary force before TMS. The background force was calculated as a mean value for the 50-ms prestimulus interval. It was found in the previous studies that the VA estimated in this way indicates whether voluntary output is sufficient to maximally activate the motoneuron pool or muscle fibers (9,10). The MEP area and the length of the SP after MEP were calculated by off-line analysis. The MEP area was normalized against the maximal size of the direct motor response (Mmax) evoked by supramaximal electrical stimulation (square pulse, 1-ms duration) at Erb's point, and the duration of the SP was taken as the interval between the time at which TMS was delivered and the return of continuous EMG activity. In addition, the ratio of the root mean square value of surface EMG and exerted force within 50 ms before TMS was also calculated (RMS/F). Any increase in RMS/F was thought to indicate an increase in peripheral fatigue (1).

Muscle soreness was estimated by palpation of the left BB. The same skilled experimenter who is one of the authors performed the palpations in all experiments. The subjects were asked to report the level of soreness using a visual analog scale (VAS) that had a 100-mm line with “no pain” marked on one end and “extremely sore” marked on the other. The palpation test was performed before the control MVC.

Signal recordings. The degree of isometric force exerted was recorded using a vertical rod attached to a strain-gauge bridge that transduced the torque change generated by elbow flexion. The force output was amplified using a strain amplifier (Kyowa Dengyo, Co Ltd. Japan) with a band pass of DC–2.5 kHz, and EMG activity was recorded for the left BB using Ag–AgCl surface electrodes (10 mm in diameter) with a bipolar configuration after reducing the skin impedance to below $10 \text{ k}\Omega$ by light abrasion and alcohol cleaning. The EMG signals were then amplified using an EMG amplifier (Model

1206, NEC Sanei, Japan) with a time-constant of 0.01 s and a low-pass filter of 3 kHz. All signals were converted into digital data via an A/D converter system at a sampling rate of 3 kHz for later analysis (CED 1401 interface with Spike2 software, CED, Cambridge, UK).

Statistics. Statistical test for changes in MVC, VA, and VAS obtained before (pre-ECC) and 2 and 4 d after ECC were conducted by repeated measures of ANOVA, and when a significant effect was observed, pair-wise comparisons were carried out using Fisher's *post hoc* test. Changes in the parameters (MVC, VA, RMS/F, the MEP area, and SP) for the fatigue test over time (s) were compared using two-way repeated measures of ANOVA, and Fisher's *post hoc* test was used to detect differences in each parameter at different times. Except for VA, all data were normalized with respect to the value obtained during the control MVC that was performed before the fatigue test. Statistical significance was set for $P < 0.05$. The values are shown as means \pm SEM.

RESULTS

For two subjects tested, the control MVC unexpectedly recovered to more than 80% of pre-ECC, and the VAS test showed negligible muscle soreness 2 d after ECC. To determine in more detail the effect of muscle damage on central and peripheral fatigue, the data obtained for these subjects was omitted from further analyses.

Table 1 shows the changes in MVC and VA that occurred during control MVC and those for VAS obtained pre-ECC as well as 2 and 4 d after ECC. MVC was significantly decreased 2 d ($63.3 \pm 4.40\%$, $P < 0.001$) and 4 d ($69.7 \pm 3.90\%$, $P < 0.001$) after ECC compared with that for pre-ECC. In the same manner, muscle soreness assessed by VAS was significantly higher 2 d (69.4 ± 5.35 mm) and 4 d (53.6 ± 4.78 mm) after ECC compared with that for pre-ECC (4.63 ± 2.53 mm, $P < 0.001$). However, for VA there were no significant differences between the pre-ECC values ($98.7 \pm 0.40\%$) and those for 2 d ($97.9 \pm 0.37\%$) or 4 d ($97.7 \pm 0.57\%$) after ECC. Although VAS significantly recovered 2 to 4 d after ECC ($P < 0.05$), it was significantly higher compared to that for pre-ECC. MVC did not significantly recover 2 to 4 d after ECC.

Figure 1 depicts the changes in MVC, VA and RMS/F that occurred during the fatigue test. MVC progressively decreased for all time periods during the fatigue test (Fig. 1A) and at the end dropped to $57.8 \pm 2.81\%$ for pre-ECC, to $50.1 \pm 4.05\%$ 2 d after ECC, and to $52.6 \pm 5.03\%$ 4 d after ECC. Two-way ANOVA showed that the degree of the decrease in MVC was significantly larger 2 and 4 d after

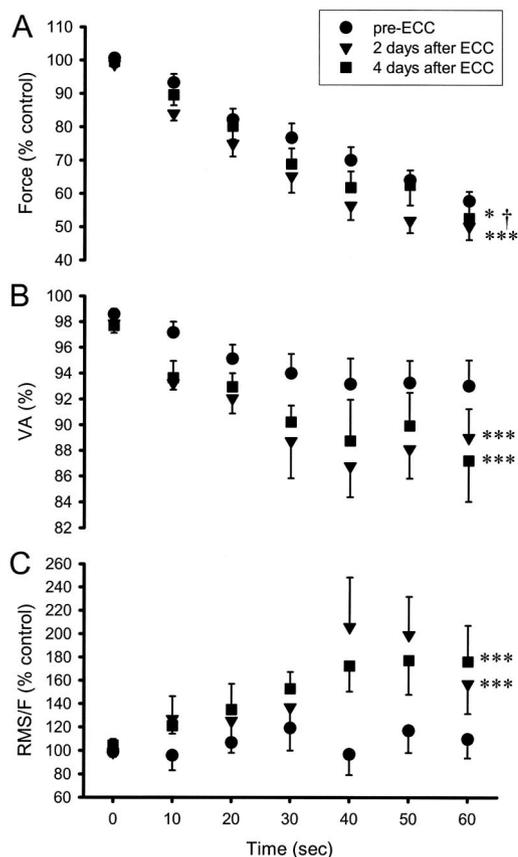


FIGURE 1—Pooled data (mean \pm SEM) for MVC (A), VA (B), and RMS/F (C) during the fatigue test over 60 s. The filled circles, triangles, and squares show the data obtained pre-ECC, and then 2 and 4 d after ECC, respectively. The results for the two-way ANOVA are indicated by * $P < 0.05$ and *** $P < 0.001$ compared with pre-ECC and † $P < 0.05$ compared with 4 d after ECC.

ECC than for pre-ECC (2 d; $P < 0.001$, 4 d; $P < 0.05$). We also found that the degree of the decrease in MVC was significantly larger after 2 d than 4 d after ECC ($P < 0.05$).

Figure 1B depicts changes in VA that took place during the fatigue test, and typical recordings of the twitch evoked after TMS obtained pre-ECC and 2 d after ECC from a single subject are shown in Figure 2. The evoked twitch was consistently larger after than before ECC during the fatigue test, indicating a progressive decrease in VA. On average, during the fatigue test VA decreased to 95.2% for pre-ECC, to 90.6% 2 d after ECC and to 88.9% 4 d after ECC. Although at the beginning of the fatigue test there was no significant difference in VA among all time periods, for the latter half VA was markedly decreased 2 and 4 d after ECC compared to pre-ECC. Two-way ANOVA showed that VA was significantly decreased 2 and 4 d after ECC compared with that for pre-ECC ($P < 0.001$).

Figure 1C illustrates the ratio of the size of EMG and force (RMS/F). Although there was no significant change in RMS/F for pre-ECC, during the latter half of the fatigue test, RMS/F increased 2 and 4 d after ECC, and this increase was significantly larger compared with that for pre-ECC ($P < 0.001$). Although VA and RMS/F were not significantly changed, they tended to recover to their pre-ECC values.

TABLE 1. Summary of the changes in MVC, VA, and VAS obtained pre-ECC as well as 2 and 4 d after ECC (means \pm SEM).

	Pre-ECC	2 d after ECC	4 d after ECC
MVC (% of pre-ECC)	100 \pm 0.00	63.3 \pm 4.40***	69.7 \pm 3.90***
VA (%)	98.7 \pm 0.40	97.9 \pm 0.37	97.7 \pm 0.57
VAS (mm)	4.63 \pm 2.53	69.4 \pm 5.35***	53.6 \pm 4.78***†

*** $P < 0.001$, pre-ECC vs 2 and 4 d after ECC; † $P < 0.05$, 2 d vs 4 d after ECC.

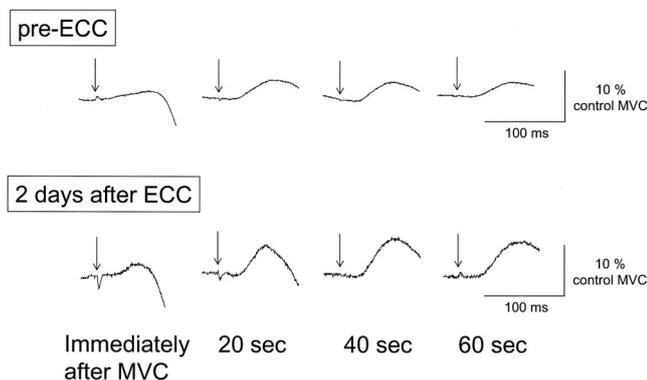


FIGURE 2—Typical recordings of changes in the twitch force (elbow flexion force) after TMS recorded immediately after and 20, 40, and 60 s after starting the fatigue task (from left to right) for one subject. The upper and lower panels show data obtained during pre-ECC and 2 d after ECC, respectively, and the downward-pointing arrows indicate the time at which TMS was applied.

Figure 3 shows the changes that took place in the MEP area and SP induced by TMS during the fatigue test. The MEP area increased up to 174.1% for pre-ECC, 243.8% 2 d after ECC and 196.1% 4 d after ECC. The increase in the area was significantly larger 2 d after ECC than for pre-ECC ($P < 0.01$, Fig. 3A). The duration of the SP after the MEP was also markedly increased to between 150 and 160% in a similar manner for all time periods. However, prolongation of the SP did not significantly differ among all time periods (Fig. 3B).

DISCUSSION

The present study found that the decline in MVC and VA and increase in the RMS/F and MEP areas during the fatigue test tended to progress more quickly 2 or 4 d after ECC than pre-ECC. This suggests that muscle damage and/or soreness induced by ECC modulates central and peripheral fatigue during fatigue tasks. Possible mechanisms underlying these results are discussed below.

Changes in MVC. Warren et al. (30) suggested that a decrease in muscle strength is the most valid and reliable indirect indicator of muscle damage in humans. In the present study, MVC was decreased by more than 65% 2 d after ECC as previously observed (4,26). However, VA during control MVC was not altered by ECC, indicating that the contribution by central drive to performing control MVC was the same for all time periods. These results are in line with those of a previous report (18). Therefore, the substantial decrease in MVC is likely attributable to muscle damage induced by ECC.

In the present study, neither control MVC nor central and peripheral fatigue was significantly altered regardless of intense eccentric exercise for two subjects, suggesting interindividual difference in this type of muscle damage (22). Eccentric exercise-induced muscle damage results in pronounced and prolonged adaptation such as a decrease in loss of force, muscle soreness and creatine kinase activity (repeated bout effect; 18,21,23). Thus, past experience with eccentric exercise could account for these results, although

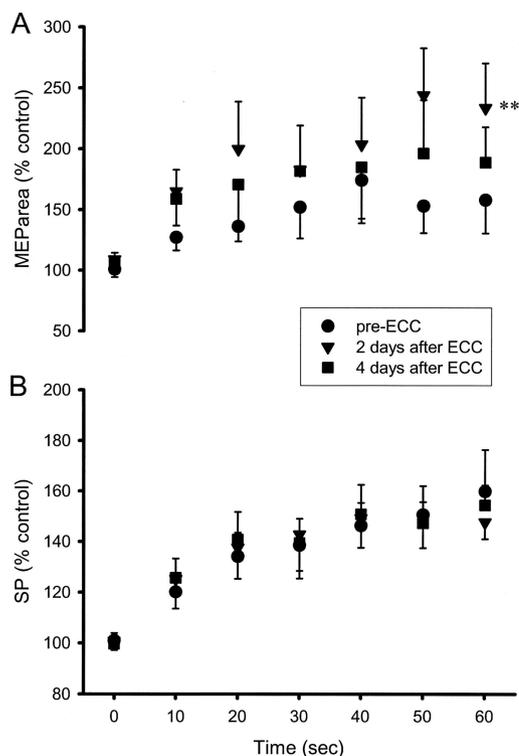


FIGURE 3—Pooled data for the MEP area (A) and SP (B) for the fatigue test. The filled circles, triangles, and squares indicate the data for pre-ECC, 2 and 4 d after ECC, respectively. The results for the two-way ANOVA compared with the pre-ECC data are denoted by ***; $P < 0.01$.

the detailed mechanism responsible for this is not known at present.

Changes in VA, MEP, and SP during the fatigue test. Despite the same level of VA during the control MVC pre- and post-ECC, the decrease in VA during the fatigue test was significantly greater 2 and 4 d after ECC compared with pre-ECC (see Fig. 1). The mechanisms responsible for the duration-dependent modulation of VA in damaged muscle remain to be addressed. A decline in VA may indicate that voluntary output is not sufficient to maximally activate the motoneuron pool or muscle fibers. Thus, some central fatigue occurs during sustained MVC because of the impairment of voluntary drive that is suggested to occur “upstream” of the motor cortical output (10). Our results suggest that faster appearance and enhanced central fatigue during sustained MVC are remarkable features of damaged muscle induced by ECC. The results obtained from the two subjects who showed no sign of muscle damage indicating that there was no significant change in VA during the fatigue test reinforce this notion. Our results also showed that decreased MVC as well as increased muscle soreness occur concurrently after ECC. Thus, it also remains to be determined which mechanism is of preferential importance in the faster appearance of central fatigue, muscle damage, or muscle soreness.

The decrease in VA, increase in the MEP, and prolongation of the SP are manifestations of central fatigue (9,10,28). In the present study, we found that the SP is less affected by ECC irrespective of significant changes in VA and the MEP.

This result supports hypothesis that the MEP, SP, and VA function independently during sustained MVC (9,10). During sustained MVC, an increase in the MEP area and duration of the SP was indicated an increase in the excitability of the motor cortex and intracortical inhibitory pathways, respectively (3,6,14). Therefore, our data further suggest that the excitability of intracortical inhibitory pathways is uniquely controlled during fatiguing contraction in the presence of muscle damage and/or muscle soreness.

It was determined that voluntary drive to elbow flexor muscles during maximal concentric contractions is usually maximal or near maximal, and that this level of drive can be maintained during the development of peripheral fatigue (11). Taking our results and the previous studies into account (11,16), the level of central drive appears to depend on the mode of muscle contraction. Thus, it is of importance to explore to what extent central drive is affected during dynamic (concentric or eccentric) contraction in the presence of muscle damage.

Afferent signals responsible for the modulation of central fatigue. When a muscle is lengthened due to eccentric exercise, muscle fibers are immediately disrupted after and during the exercise, after which noxious chemicals such as histamines, bradykinins, and prostaglandins are released and presumably activate group III and IV muscle afferents (4) and/or nociceptors (27). These afferents modulate the monosynaptic reflex in fatigued muscle via the presynaptic inhibition of group Ia terminals (25). Furthermore, muscle pain induced by the intramuscular injection of hypertonic saline, which stimulates nociceptive afferents, results in a significant reduction in the endurance time for submaximal sustained contraction and reduces the firing rate of motor units (7,13). However, group III and IV muscle afferents do not directly inhibit motoneurons during sustained MVC (2). Therefore, during fatiguing contraction with muscle damage, group III and IV muscle afferents act at supraspinal loci and reduce the descending drive toward motoneurons and presynaptic neurons (9).

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Changes in peripheral fatigue after ECC. The RMS/F increased during the latter half of the fatigue task post-ECC (see Fig. 1C) and this may be explained two factors. The increase in RMS/F may play a role in compensating for a rapid decrease in the failure of E-C coupling and/or sarcolemmal excitability. Alternatively, if the excitability of the sarcolemma remains intact, aberrant mechanical properties of the contractile element may be involved in the increase in the RMS/F due to the depletion of energy substrate, a decrease in pH, and/or the excessive accumulation of metabolites. In either case, an increase in RMS/F indicates an increase in peripheral fatigue (1). Warren et al. (31) found that the membrane resting conductance and the ability of the sarcolemma to conduct action potentials in damaged muscle is not impaired. Therefore, it is likely that an increased RMS/F after ECC accounts for the dysfunction of the excitation process before Ca^{2+} release by the sarcoplasmic reticulum after eccentric exercise (29,31). In addition, the impairment of E-C coupling after eccentric exercise results in persistent low frequency fatigue induced by 20 Hz stimulation (15,20). Because it was not possible to set up the electrodes with similar skin impedance and at the same location over the muscle fiber due to the swelling induced by eccentric exercise, we avoided comparing the absolute RMS values before and after ECC. However, Deschenes et al. (5) reported a significant reduction in the ratio of the exerted torque and integrated EMG after exercise-induced muscle damage. Therefore, any increase in the RMS/F during the fatigue test may have been underestimated in the present study.

In conclusion, the present study showed that while performing sustained MVC, central and peripheral fatigue in damaged muscle progresses faster than that which occurs in intact muscle. These results may reflect physiological properties of damaged muscle induced by acute ECC. Muscle damage due to ECC is therefore a limiting factor in the performance of sustained strength effort. It remains to be explored whether or not the same is true during dynamic (concentric or eccentric) contractions.

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