Exercise-induced muscle injury augments forearm vascular resistance during leg exercise

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Ray, Chester A., Edward T. Mahoney, and Keith M. Hume. Exercise-induced muscle injury augments forearm vascular resistance during leg exercise. Am. J. Physiol. 275 (Heart Circ. Physiol. 44): H443–H447, 1998.—The purpose of the present investigation was to examine the effect of exercise-induced muscle injury on hemodynamic responses during exercise. Ten subjects performed unilateral isometric knee extensions (IKE) at 30% of preinjury maximum voluntary contraction to fatigue and for 3 min before and after muscle injury. Muscle injury was elicited by performing 8 sets of 10 repetitions of eccentric muscle actions of the knee extensor muscles (i.e., quadriceps muscles) by lowering a weight equivalent to 75% of eccentric maximum load. Exercise time to fatigue for IKE at 30% of maximum voluntary contraction was significantly decreased from preinjury to postinjury IKE (257 ± 21 to 203 ± 23 s; n = 10), but was unchanged in the control leg (244 ± 16 to 254 ± 20 s; n = 7). With the use of a 10-cm visual analog scale, ratings of muscle soreness in the injured leg increased from 0 to 5.1 ± 0.7 cm (P < 0.001) but were not changed in the control leg (0 both times). Both heart rate and mean arterial pressure responses to exercise were unchanged following muscle injury. Forearm blood flow and forearm vascular resistance were not different at rest and during the first minute of exercise before and after muscle injury. However, after muscle injury, forearm blood flow was significantly lower and forearm vascular resistance was significantly higher (P < 0.03) during the second and third minutes of exercise. There were no significant changes in any variables with the contralateral control leg. In four subjects, resting magnetic resonance images demonstrated a 23% greater relative cross-sectional area of the knee extensor muscles with an elevated transverse relaxation time in the injured versus control leg. The results indicate that forearm vascular resistance is augmented during isometric knee extension following muscle injury of the knee extensor muscles. The data suggest that muscle injury alters vascular control to non-exercising skeletal muscle during exercise.

EXERCISE-INDUCED delayed-onset muscle soreness is a common physiological phenomenon. There has been considerable effort to identify the mechanisms responsible for delayed-onset muscle soreness and/or muscle injury. Despite the commonality of exercise-induced muscle injury, there is little information regarding the hemodynamic consequences that muscle injury may have on exercise responses in humans.

Cardiovascular responses to exercise are believed to be primarily regulated by activation of higher brain centers (i.e., central command) associated with volitional effort and by feedback from muscle afferents originating within the exercising muscle. Muscle injury may provide a unique opportunity to examine the contribution of both of these mechanisms. Exercise following muscle injury has been associated with higher ratings of perceived exertion during exercise (7, 16), and muscle injury is believed to change the chemical milieu of the injured muscle (1, 26). Thus these changes may provide insight into cardiovascular control mechanisms during exercise.

The purpose of the present investigation was to determine the effect of muscle injury on hemodynamic responses during isometric exercise. To test this question, we measured forearm blood flow and determined forearm vascular resistance during isometric knee extension before and after muscle injury of the knee extensor muscles. Muscle injury was elicited by eccentric exercise of the knee extensor muscles from one leg with the contralateral leg serving as a control. We hypothesized that muscle injury would alter hemodynamic responses to nonexercising muscles.

METHODS

Subjects. Ten male volunteers (20–33 yr old) with no known health problems were studied. Written informed consent was obtained from all subjects, and the study was approved by the Institutional Review Board of the University of Georgia.

Experimental design. The following protocol was conducted on all subjects before and after 48 h after the knee extensor muscles (i.e., quadriceps muscles) of the dominant leg were injured. The laboratory temperature was maintained between 21 and 23°C.

Subjects were tested in the supine position with the dominant leg hanging freely over the edge of the table. The ankle was encapsulated by a strap that was attached to a force transducer. After maximum voluntary contraction (MVC) of the knee extensor muscles was determined in both the right and left leg, isometric knee extension (IKE) at 30% MVC was performed to fatigue with each leg. Subjects were given verbal encouragement to facilitate maximal effort. The force output produced by the subject was displayed on a digital recording device for visual feedback. Fatigue was defined as the point at which subjects were no longer able to maintain the predetermined force (30% MVC) during IKE.

Forty minutes after the time to fatigue was determined in each leg, preexercise (baseline) measurements of heart rate, arterial blood pressure, and forearm blood flow were collected for 3 min. After the baseline period, IKE at 30% MVC was performed by the dominant leg for 3 min. Subjects were asked to rate their perceived exertion each minute of the exercise bout with the use of the Borg scale, with 6 being “very, very light” to 19 being “very, very hard” (2). In seven subjects, the protocol was repeated 45 min later in the nondominant (control) leg. The leg order was randomized. After completion of testing on both legs, exercise-induced muscle injury (see Muscle injury protocol) on the knee extensor muscles of the dominant leg was induced either immediately following test-
ing (n = 8) or 2 days posttesting (n = 2). During the experimental protocol, the same absolute force was used during IKE before and after muscle injury.

Before the start of testing, subjects were asked to give a subjective rating of muscle soreness of both of their knee extensor muscles while standing. A 10-cm visual analog scale was used to assess soreness in the knee extensor muscles. The scale ranged from "no soreness at all" to "the most soreness ever felt." Subjects were asked to draw a straight line through the scale at a point that reflected the magnitude of soreness.

Muscle injury protocol. Eccentric actions of the knee extensor muscles were performed with the dominant leg by lowering a weight from the extended knee to the flexed knee position. Eight sets of ten repetitions at seventy-five percent of the subject's eccentric maximum load were performed. The weight was lowered in a controlled manner over a period of 3–5 s. A 2-min rest period was given between sets. If subjects were unable to maintain control of the weight in the latter sets, the load was reduced in subsequent sets to ensure the completion of the protocol. The eccentric maximum load of the subject was defined as the maximum weight the subject could lower in a controlled manner.

Measurements. Continuous measurements of arterial blood pressure and heart rate were made using a Finapres blood pressure monitoring unit (Ohmeda, Englewood, CO). Forearm blood flow was measured by venous occlusion plethysmography (Hokanson EC 4 plethysmograph, D. E. Hokanson, Bellevue, WA) using a mercury-in-Silastic strain gauge. The strain gauge was placed around the largest area of the forearm. Circulation to the hand was assured by inflating a cuff around the wrist to 200 mmHg during measurements of forearm blood flow. The pressure of the venous-congesting cuff around the arm was 40 mmHg. Forearm blood flow was measured at 15-s intervals. Forearm vascular resistance was calculated by dividing mean arterial pressure by forearm blood flow. All data were collected on-line (MacLab 8e, ADInstruments, Milford, MA) with a Macintosh computer (Quadra 840AV).

Magnetic resonance imaging. In four subjects, magnetic resonance imaging (MRI) images were taken of the control and injured knee extensor muscles after the muscle injury protocol. Three subjects had the MR images taken 4 days after injury, and one subject had the MR images taken 2 days after injury. Transaxial, transverse relaxation time (T2)-weighted images of the thigh 1 cm thick and spaced 1 cm apart (repetition time 2,000 ms per echo times 30 and 60 ms, 256 × 256 matrix, 1 pulse sequence repeated per acquisition, 40-cm field of view) were collected from the knee joint to the head of the femur using a 1.5-tesla superconducting magnet (General Electric, Milwauke, WI). MR images were transferred to a computer for analysis with the use of a modified version of the public domain NIH Image program (written by W. Rasband at the National Institutes of Health and available from the Internet by anonymous FTP from http://zippy.nimh.nih.gov or on floppy disk from the National Technical Information Service, 5285 Port Royal Rd., Springfield, VA 22161). Briefly, after spatial calibration, the outline of each knee extensor muscle was traced in serial images to determine cross-sectional area (CSA). Subsequently, T2 was determined per pixel using the native images. Resting muscle was defined by pixels with a T2 between 20 and 35 ms. The CSA of muscle with a T2 greater than the T2 (mean + SD) of the defined resting muscle was determined. CSA of muscle with an elevated T2, in both the control and treated knee extensor muscles, was expressed relative to the CSA of the entire muscle with a T2 between 20 and 35 ms.

Data analysis. A two-within repeated-measures ANOVA (pre-/postinjury, trial, exercise time) was used to determine the significance of muscle injury on the dependent variables. A significance level of P < 0.05 was used for all tests. All values are means ± SE. Because of technical problems, heart rates for only nine subjects are presented for the injured leg.

RESULTS

Muscle injury resulted in a significant decrease in IKE time to fatigue. Time to fatigue was decreased from 257 ± 21 to 203 ± 23 s (P < 0.03) in the injured leg but was not decreased in the control leg (244 ± 16 to 254 ± 20 s). Ratings of muscle soreness in the injured leg increased from 0 to 5.1 ± 0.7 cm (P < 0.001) but were not changed in the control leg (0 both times).

IKE elicited significant increases in heart rate and mean arterial pressure (Fig. 1). Mean arterial pressure was not significantly different between trials (trial × exercise interaction, P = 0.39). Heart rate tended to be lower (trial main effect, P < 0.07) after muscle injury, but the responses to exercise were similar (trial × exercise interaction, P = 0.26).

Muscle injury had a significant effect on forearm blood flow (trial × exercise interaction, P = 0.02) and forearm vascular resistance (trial × exercise interaction, P = 0.04). Resting forearm blood flow and its response during the first minute of IKE was not different before and after muscle injury (Fig. 1). However, after muscle injury, forearm blood flow was significantly lower (P < 0.02) during the second and third minutes of IKE (Fig. 1). Forearm blood flow during the second and third minutes was 7.6 ± 1.2 and 7.1 ± 1.0 ml·100 ml·min before and 6.0 ± 1.1 and 5.8 ± 0.7 ml·100 ml·min after muscle injury, respectively. Forearm vascular resistance at rest and during the first minute of IKE was not affected by muscle injury (Fig. 1). However, during the second and third minutes of IKE, forearm vascular resistance was significantly higher (P < 0.04). Forearm vascular resistance during the second and third minutes was 19 ± 3 and 21 ± 3 mmHg·ml·100 ml·min before and 25 ± 4 and 25 ± 4 mmHg·ml·100 ml·min after muscle injury, respectively. Ratings of perceived exertion were 1–2 units greater (P < 0.03) during IKE after muscle injury (Table 2).

Results for the control leg are presented in Table 1. There were no differences in mean arterial pressure and heart rate responses at rest and during exercise compared with the injured leg. Heart rate during the second trial was lower at rest and during IKE. Forearm blood flow (trial main effect, P = 0.26; trial × exercise interaction, P = 0.38) and forearm vascular resistance (trial main effect, P = 0.27; trial × exercise interaction, P = 0.95) responses were unchanged between trials. Ratings of perceived exertion were not different between trials (Table 2).

The relative CSA of the knee extensor muscles that had an elevated T2 was 23% (16%, 22%, 24%, and 28% for the four subjects, respectively) greater in the injured versus control knee extensor muscles. The increased CSA of the injured muscle with an elevated T2 provides strong evidence that the muscle injury protocol was successful in eliciting muscle injury.
DISCUSSION

The major finding of this study was that forearm vascular resistance was augmented during IKE 2 days after muscle injury of the knee extensors. This result suggests that vascular control of nonworking skeletal muscle during exercise is altered by muscle injury to the exercising muscle. The discussion will focus on the possible mechanisms responsible for the change in exercising forearm vascular resistance that occurred during IKE after muscle injury of the knee extensors.

Because vascular resistance was increased to noninjured, nonworking muscle, it is unlikely that a local mechanism (i.e., change in vascular reactivity) caused the change in vascular resistance. However, it might be speculated that the forearm was affected during the muscle injury protocol by its role in helping to stabilize the body (i.e., gripping to hold the body in place) during the repeated eccentric knee extensor exercise. Thus subsequent forearm hemodynamics may be altered by the previous exercise bouts. However, forearm hemodynamics were the same during IKE with the control leg before and after muscle injury, indicating that this was not a factor.

An increase in sympathetic outflow could be a mechanism for the increase in forearm vascular resistance. Sympathetic outflow to skeletal muscle during isometric exercise is regulated by 1) central command (30), 2) neural feedback from the exercising muscle (10, 18), and 3) baroreflexes (22, 23). It is unlikely that baroreflexes would mediate any change in sympathetic outflow because arterial pressure was the same during both trials, and engagement of cardiopulmonary baroreflexes would not be expected to be different during the trials. An increase in central command has been shown to augment sympathetic outflow to nonactive skeletal muscle during intense effort (19, 31).

Table 1. Responses of control leg to isometric knee extension before and after muscle injury

<table>
<thead>
<tr>
<th>Trial</th>
<th>Baseline</th>
<th>Isometric Knee Extension, min</th>
</tr>
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<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>Before 70±5</td>
<td>85±5</td>
</tr>
<tr>
<td></td>
<td>After 65±3</td>
<td>77±4</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>Before 97±3</td>
<td>105±3</td>
</tr>
<tr>
<td></td>
<td>After 95±4</td>
<td>104±4</td>
</tr>
<tr>
<td>Forearm blood flow, ml·100 ml·min⁻¹</td>
<td>Before 5.7±1.1</td>
<td>8.2±1.7</td>
</tr>
<tr>
<td></td>
<td>After 4.4±0.6</td>
<td>5.9±1.1</td>
</tr>
<tr>
<td>Forearm vascular resistance, mmHg·ml⁻¹·100 ml·min⁻¹</td>
<td>Before 21±3</td>
<td>17±4</td>
</tr>
<tr>
<td></td>
<td>After 25±3</td>
<td>21±3</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 7 subjects. *Trial main effect (P < 0.05).

Table 2. Ratings of perceived exertion during isometric knee extension before and after muscle injury

<table>
<thead>
<tr>
<th>n</th>
<th>Trial</th>
<th>Isometric Knee Extension, min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Before</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
</tr>
<tr>
<td>Injured</td>
<td>9</td>
<td>Before</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>13±1</td>
</tr>
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</table>

Values are means ± SE of perceived exertion on the Borg scale (see METHODS); n = no. of subjects. *Significantly different between trials at all time points (P < 0.03).
Despite the large amount of data from examination of muscle responses to muscle injury, little information exists regarding cardiovascular responses to exercise following muscle injury. Miles et al. (16) reported that heart rate and mean arterial pressure responses to isometric contractions were greater in the arm that performed high-force eccentric exercise of the elbow flexors 1–5 days before testing than in the control arm. The absolute force of the contractions was the same in both arms; however, the force used was lower than that used before eccentric exercise. Despite the lower force, the eccentric exercise arm had similar absolute values for heart rate and mean arterial pressure during isometric elbow flexion. In our study, we did not observe any differences in heart rate or arterial pressure responses to IKE at the same absolute force following injury. Gleeson et al. (7) reported slightly higher heart rates during submaximal cycling 2 days after eccentric exercise (bench stepping) that elicited higher muscle soreness ratings than concentric exercise (uphill walking). In our study, despite the greater forearm vascular resistance during IKE after muscle injury, mean arterial pressure was unchanged. The lower absolute heart rate and, possibly, lower cardiac output observed after injury may have counterbalanced the increase in forearm vascular resistance. In addition, vascular resistance may have been decreased to the injured thigh during exercise. Gaffney et al. (6) showed an increase in vascular resistance of the exercising leg during the second and third minutes of IKE at 25% MVC. It is possible that there was an increased release of metabolites from the injured muscle that may have mediated greater local metabolic vasodilatation and attenuated the increase in local vascular resistance. In addition, vascular resistance may have been reduced to other vascular beds such as the viscera. However, the current study does not permit us to determine whether this occurred.

We used MR imaging to assess the efficacy of our exercise-induced muscle injury protocol in eliciting muscle injury to the knee extensor muscles. Contrast shift due to muscle injury, assessed in this study by a CSA with an elevated T2, has been reported in numerous studies (3, 4, 9, 17, 24, 28). Nurenberg et al. (17) found a good correlation between ultrastructural changes of muscle subjected to muscle injury by eccentric exercise and signal intensity of the muscle measured by MR imaging. Ultrastructural changes of the muscle were confirmed by electron microscopy of biopsied muscle. Similar findings between ultrastructural changes and signal intensity were found in rat muscle by Mattila and co-workers (11). In our study, relative CSA of the muscle that had an elevated T2 was 23% greater in the injured thigh than in the control leg. This finding indicates that our exercise-induced muscle injury protocol was successful in injuring the knee extensor muscles. Furthermore, Dudley et al. (3) used a similar eccentric exercise program to elicit muscle injury to the knee extensor muscles and also showed an increase in the CSA of muscle with an elevated T2. Additional support for muscle injury is that time to fatigue was significantly decreased during IKE after...
muscle injury but did not change in the control leg. Finally, soreness ratings of the injured leg were significantly increased. Comparable results, based on a similar soreness scale, were found by Teague and Schwane (29), who elicited muscle injury to the elbow flexors. Although we did not have direct evidence of muscle injury (i.e., muscle biopsy), the described changes provide compelling evidence that the knee extensor muscles were injured.

In conclusion, our results indicate that injury to the exercising muscle can alter vascular responses to non-active muscle during exercise. The exact mechanism for this response is not known, but altered feedback from muscle afferents of the injured muscle appears to be a likely mediator of this response.

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