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 20 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 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 arrested 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 (MR) 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 images taken 2 days after injury. Transaxial T2-weighted images (T2) were obtained in the second and third minutes of IKE (Fig. 1). Forearm blood flow during the second and third minutes was 19.2 ± 2.1 and 10.2 ± 0.6 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. 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 (trials × exercise interaction, P = 0.39). Heart rate tended to be lower (trials main effect, P < 0.07) after muscle injury, but the responses to exercise were similar (trials × exercise interaction, P = 0.26).

Muscle injury had a significant effect on forearm blood flow (trials × exercise interaction, P = 0.02) and forearm vascular resistance (trials × 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 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−1·min−1 before and 25 ± 4 and 25 ± 4 mmHg·ml−1·min−1 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; trials × exercise interaction, P = 0.38) and forearm vascular resistance (trial main effect, P = 0.27; trials × 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). In the present

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

<table>
<thead>
<tr>
<th>Trial</th>
<th>Isometric Knee Extension, min</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>Before</td>
<td>70±5</td>
<td>85±5</td>
<td>91±4</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>65±3</td>
<td>77±4</td>
<td>82±5</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>Before</td>
<td>97±3</td>
<td>105±3</td>
<td>114±3</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>95±4</td>
<td>104±4</td>
<td>114±3</td>
</tr>
<tr>
<td>Forearm blood flow, ml-100 ml·1·min</td>
<td>Before</td>
<td>5.7±1.1</td>
<td>8.2±1.7</td>
<td>8.0±1.4</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>4.4±0.6</td>
<td>5.9±1.1</td>
<td>6.2±1.0</td>
</tr>
<tr>
<td>Forearm vascular resistance, mmHg·ml·1·100 ml·min</td>
<td>Before</td>
<td>21±3</td>
<td>17±4</td>
<td>17±3</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>25±3</td>
<td>21±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></td>
<td>1</td>
</tr>
<tr>
<td>Control 6</td>
<td>Before</td>
<td>11±1</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>11±1</td>
</tr>
<tr>
<td>Injured 9</td>
<td>Before</td>
<td>12±1</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>13±1</td>
</tr>
</tbody>
</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).
MUSCLE INJURY AND FOREARM BLOOD FLOW
during the first minute of IKE after injury argues that forearm vascular resistance was not changed
forearm vascular resistance. In addition, the finding muscle contraction; however, there was no difference in
discomfort during the 3 min of light knee extensor
knee extensor muscles for 3 min while in the supine
possibility by having two subjects lightly contract their
when the injured leg is exercised. We tested this
appear to be related to a pain or soreness response
in muscle sympathetic nerve activity mediated by the
consistent with the concept of a time-delayed increase
in vascular resistance associated with the inflammatory response to
injury is associated with muscle edema (8, 28). The
swelling of the injured muscle can raise interstitial
pressure (5) and possibly increase the discharge of
mechanically sensitive afferents (12). It would be
expected that if mechanically sensitive afferents did play
a role in regulating forearm vascular resistance, the
increase in forearm vascular resistance found in the
present study would be present during the entire
exercise bout. However, forearm vascular resistance
was not changed by muscle injury during the first
minute of exercise.

It has been demonstrated that altering the chemical
environment of the muscle can facilitate or inhibit
discharge of muscle afferents (15, 20, 21, 25). Muscle
injury is believed to alter the chemical milieu of the
skeletal muscle (1, 26). Increased prostaglandin produc-
tion associated with the inflammatory response to
muscle injury, for example, may augment stimulation of
chemically sensitive afferents and, in turn, increase
sympathetic outflow (27). A preliminary report by War-
ren et al. (32) demonstrates increased release of PGE2
during isometric contraction of the extensor digitorum
longus muscle following eccentric contraction-induced
muscle injury. The increase in PGE2 peaked 48 h after
muscle injury. PGE2 has been shown to stimulate group
IV afferents (14). In addition, it has been proposed that
muscle injury may cause the accumulation of other
metabolites such as histamine, potassium, bradykinin,
and 5-hydroxytryptamine that may stimulate group IV
muscle afferents (1). The increase in vascular resis-
tance during the second and third minutes of IKE is
consistent with the concept of a time-delayed increase
in muscle sympathetic nerve activity mediated by the
muscle metaboreflex during isometric exercise (10, 18).
The increase in forearm vascular resistance does not
appear to be related to a pain or soreness response
when the injured leg is exercised. We tested this
possibility by having two subjects lightly contract their
knee extensor muscles for 3 min while in the supine
position. After muscle injury, the subjects reported
discomfort during the 3 min of light knee extensor
muscle contraction; however, there was no difference in
forearm vascular resistance. In addition, the finding
that forearm vascular resistance was not changed
during the first minute of IKE after injury argues
against a pain response.

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 re-
sponses to IKE at the same absolute force following
injury. Gleson 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 walk-
ing). In our study, despite the greater forearm vascular
response during IKE after muscle injury, mean arte-
rial pressure was unchanged. The lower absolute heart
rate and, possibly, lower cardiac output observed after
injury may have counterbalanced the increase in fore-
arm vascular resistance. In addition, vascular resis-
tance 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 metabo-
lites 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 numer-
ous 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 eccen-
tric exercise and signal intensity of the muscle mea-
sured by MR imaging. Ultrastructural changes of the
muscle were confirmed by electron microscopy of biop-
sied 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 in-
jury protocol was successful in injuring the knee exten-
sor 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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