Prevention of Disuse Muscular Weakness by Restriction of Blood Flow

ATSUSHI KUBOTA1, KEISHOKU SAKURABA1,2, KEISUKE SAWAKI1,2, TAKAHIRO SUMIDE3, and YOSHIFUMI TAMURA4

1Department of Sports Medicine, Graduate School of Medicine, Juntendo University, Tokyo, JAPAN; 2School of Health and Sports Science, Juntendo University, Chiba, JAPAN; 3Juntendo Sports Clinic, Juntendo University Hospital, Tokyo, JAPAN; 4Department of Medicine, Metabolism and Endocrinology, School of Medicine, Juntendo University, Tokyo, JAPAN

ABSTRACT

KUBOTA, A., K. SAKURABA, K. SAWAKI, T. SUMIDE, and Y. TAMURA. Prevention of Disuse Muscular Weakness by Restriction of Blood Flow. Med. Sci. Sports Exerc., Vol. 40, No. 3, pp. 529–534, 2008. Purpose: The aim of the present study was to compare the effects of periodic restriction of blood flow to lower extremities with those of isometric exercise on disuse muscular atrophy and weakness induced by immobilization and unloading. Methods: The left ankle of each of 15 healthy males was immobilized for 2 wk using cast, and subjects were instructed to walk using crutches with non-weight bearing during this period. Subjects were divided into three groups: a restriction of blood flow (RBF) group (application of external compressive force of 200 mm Hg for 5 min followed by 3 min of rest, repeated five times in a single session, two sessions per day for 14 d); an isometric training (IMT) group (20 “exercises” of 5-s isometric contraction of the knee extensor, flexor, and ankle plantar flexor muscles followed by rest, twice a day, daily for 2 wk); and a control (CON) group (no intervention). We measured changes in muscle strength, thigh/leg circumferences, and serum growth hormone levels. Results: Immobilization/unloading resulted in significant decreases in muscle strength of knee extensor and flexor muscles (P < 0.01 and < 0.05, respectively) and thigh and leg circumferences (P < 0.05, each) in the CON group, and significant decreases in muscle strength of the knee flexor muscles, ankle plantar flexor muscles, and leg circumference (P < 0.05) in the IMT group. RBF protected against these changes in muscle strength and thigh/leg circumference (P < 0.01 and < 0.05, respectively). No changes in serum growth hormone levels were noted. Conclusion: Our results indicate that repetitive restriction of blood flow to the lower extremity prevents disuse muscular weakness. Key Words: DISUSE ATROPHY, MUSCLE STRENGTH, IMMOBILIZATION, NON–WEIGHT BEARING, GROWTH HORMONE

Muscle training increases muscle volume and strength. Concerning these training effects, it has been reported that muscle training under low load with blood flow restriction results in muscular hypertrophy and increased muscle strength, changes that are comparable with muscle training under high load (1,16,18,19). While the exact mechanism of the effects of muscle training program under restricted blood flow is not fully understood, it has been suggested that increased growth hormone (GH) levels might have a positive effect on muscular hypertrophy, because GH secretion was greatly enhanced when muscle training was combined with blood flow restriction compared with normal blood flow groups (1,20).

Chronic unloading such as space flight (2,3,7,11) and cast immobilization (15) induces muscular atrophy and reduces muscle strength. Recent data have reported that restriction of blood flow without any muscle training prevented muscle atrophy after knee surgery (17). In that study, patients who underwent reconstruction of the anterior cruciate ligament were divided into two groups: the control and vascular occlusion group. In both groups, the standard program for recovery of patients with knee injury was applied (light exercise). In addition, patients of the vascular occlusive group underwent two sessions of occlusive stimulation, each consisting of five, 5-min vascular occlusion episodes (application of external pressure) followed by 3-min release of occlusion, applied daily to the proximal end of the thigh from the 3rd to the 14th postoperative days. Although muscle atrophy was observed in both groups after the 2-wk intervention, the cross-sectional area of thigh muscles determined by magnetic resonance imaging was significantly larger in the vascular occlusion group compared with the control group (17). These results suggest that blood flow restriction may augment the effect of muscle training on muscle atrophy, and that blood flow restriction may prevent the detrimental effects of chronic unloading on skeletal muscle. However, it is still not clear whether blood flow restriction without any muscular activity prevents...
muscular atrophy after chronic unloading. In addition, a previous report has shown the effects of blood flow restriction on muscular atrophy, but muscle strength and GH levels were not examined.

The purpose of the present study was to investigate the effects of repeated muscle blood flow restriction without any muscle training on muscular atrophy or muscular weakness induced by immobilization and non-weight bearing. During this period, we measured muscle strength of the knee extensor–flexor muscles, the ankle plantar flexor muscle, and the circumference of the lower extremities, as well as changes in serum GH level.

METHODS

Subjects

The subjects were 15 healthy males with negative histories of injuries to the lower extremities and serious medical history. Table 1 shows the characteristics of participating subjects. The present study was approved by the human ethics committee of Juntendo University. Prior to the experiment, the purpose of the study, contents, experimental protocol, possible risk involved, and management or security offered if an accident were to occur were fully explained to these subjects, and their consent in writing was obtained.

Experiment Procedure

Protocol 1. In this protocol, we compared the effects of blood flow restriction and muscle training on muscular atrophy or weakness. In each subject, we measured muscle strength (see below) and circumference of the lower extremities at baseline (before intervention). To determine changes in the volume of thigh and leg muscles, we measured the circumference of the thigh region at 10 and 15 cm above the upper border of the patella and the maximum circumference of the leg using a tape while the subject was standing. Three measurements were made, and the average of these measurements was used. Subjects were then divided at random into the following three groups: subjects who received repetitive blood flow restriction (RBF group, \( N = 5 \)), subjects who underwent isometric training (IMT group, \( N = 4 \)), and subjects who did not receive any of the above two interventions (control group (CON), \( N = 6 \)). To induce muscular atrophy/weakness, the left ankle joint was fixated at neutral position by using a cast, and the subject was instructed to walk using crutches for non-weight bearing for 2 wk. During the 2-wk period, blood flow to the lower extremity was restricted in subjects of the RBF group using the tourniquet (77 mm wide, 770 mm long) and the protocol described by Takarada et al. (17). Briefly, this involved application of external compressive force of 200 mm Hg for 5 min followed by 3 min of rest (release of compression). Our preliminary data demonstrated that compared with the control (before compression), the pulse wave velocity (PWV) measured with a sphygmometer during the application of external compression of 100, 200, 250, and 300 mm Hg was reduced to 78.6 ± 26.0, 61.8 ± 23.1, 17.3 ± 19.5, and 2.6 ± 7.3%, respectively (\( N = 8 \), mean ± SD). In addition, 200 mm Hg of cuff pressure induced blood flow restriction but did not induce complete vascular occlusion. However, PWV disappeared in three subjects at 250 mm Hg of cuff pressure and in seven subjects at 300 mm Hg of cuff pressure, respectively. The compression/decompression was repeated five times in the single session, and each subject underwent two sessions per day (morning and afternoon) for 14 d. None of the subjects complained of muscle bruising, muscle soreness, or nerve “tingling” during or after the application of compression. Subjects of the IMT group performed 20 repetitions of 5-s isometric contraction and 5-s rest of the knee extensor (flexion of the hip joint in supine position with the knee kept at full extension), flexor (extension of the hip joint and flexion of the knee joint in prone position), and ankle plantar flexor (plantar flexion of the ankle joint in supine position with the knee kept at full extension) muscles, twice a day, daily, for 2 wk. At the end of the 2-wk period, muscle strength and circumference were measured again.

Protocol 2. We investigated changes in serum concentrations of GH in five subjects of the RBF, IMT, and CON groups at 1 month after protocol 1. After resting for at least 30 min, blood samples were collected from the antecubital vein. After that, subjects underwent blood flow restriction to the lower extremities using the protocol described above for the RBF group. At 0 (immediately), 15, and 30 min after the fifth compression, blood samples were collected. At the same time of the day, 1 wk later, blood samples were collected at rest, and at 0, 15, and 30 min after isometric training as described above for the IMT group. Blood samples were used to determine the concentration of GH.

Measurement of muscle strength. The knee extensor–flexor torque under isokinetic and isometric contractions and the ankle plantar flexor torques under isokinetic contraction were measured quantitatively using an apparatus that determines isokinetic muscle strength (System 3 Dynamometer, Biodex Medical Systems, Inc., Shirley, NY). The peak torque (PT) of all determinations was used as an index of muscle strength.

To determine the knee extensor–flexor torque, subjects were seated, and the measured femoral region and upper part of the subject were fastened by one to three belts. The

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TABLE 1. Physical characteristics of subjects.

<table>
<thead>
<tr>
<th></th>
<th>Control Group (( N = 6 ))</th>
<th>Isometric Training (( N = 4 ))</th>
<th>Restriction of Blood Flow (( N = 5 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>23.2 ± 1.5</td>
<td>22.3 ± 0.5</td>
<td>23.2 ± 1.3</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174.3 ± 4.0</td>
<td>172.0 ± 4.1</td>
<td>175.8 ± 5.8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71.8 ± 5.8</td>
<td>64.3 ± 6.8</td>
<td>70.0 ± 8.9</td>
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</table>

Data are means ± SD.
subject extended and flexed the knee joints three or five times at angular speeds of 60, 180, and 300°·s⁻¹ under concentric contraction (CC60, 180, and 300) and angular speeds of 60 and 180°·s⁻¹ under eccentric contraction (EC60 and 180). Isometric contraction was determined with the knee joint flexed at an angle of 60° (IM). The subject continued extending or flexing the knee joints for 5 s with a 10-s break between knee extension and flexion. Following determination of the ankle plantar flexor torque, the subject rested in supine position and the measurement limbs were fastened with a belt. The subject then extended and flexed the ankle joints three times at CC60, CC120, EC60, and EC120.

**Measurement of serum concentration of GH.** The collected blood sample was left at room temperature for 1 h, and then serum was extracted by centrifugation. The sample was stored at −80°C until measurement. It was defrosted on ice, and GH concentration was measured by radioimmunoassay (RIA) (Health Sciences Research Institute, Yokohama). The area under the curve (AUC) for GH concentration was calculated under blood flow restriction and isometric training conditions. Because the GH concentration values did not show normal distribution, they were log transformed before analysis.

**Statistical analysis.** All values were expressed as means ± SD. Differences in muscle strength and circumference before and after the intervention in RBF, IMT, and CON groups were examined for statistical significance, using the Student’s t-test. Differences in percent changes in muscle strength and circumference among the three groups were tested by one-way ANOVA followed by Scheffe’s post hoc analysis. ANOVA was also used for comparison of GH levels at different time points after blood flow restriction or isometric training. Changes in AUC after blood flow restriction and isometric training were examined by Student’s paired t-test. The reported P values for the post hoc tests were corrected for multiple comparisons, and all P values less than 0.05 denote the presence of a statistically significant difference.

**RESULTS**

**Knee extensor–flexor muscle strength.** Table 2 shows the knee extensor–flexor muscle strength before and after 2 wk of immobilization and non–weight bearing. The muscle strength decreased significantly in the CON group and tended to decrease in the IMT group after the protocol, while RBF significantly protected against such changes in muscle strength of both the knee extensor and flexor muscles. ANOVA analysis showed significant differences in the levels of percent changes of knee extensor torques in EC180, 60, IM, and CC60, and knee flexor torques in EC60 and CC60. Figures 1 and 2 show the results of Scheffe’s post hoc test. As shown in Figure 1, the percent changes in knee extensor torques after EC180 in the RBF group were significantly smaller than those in the CON group (−0.6 ±
10.6% and −23.5 ± 5.4%, \( P = 0.015 \), EC60 (−4.7 ± 10.1% and −26.9 ± 7.1%, \( P = 0.019 \)), IM (−4.4 ± 8.6% and −22.7 ± 6.5%, \( P = 0.027 \)), and CC60 (−2.9 ± 6.3% and −22.1 ± 7.7%, \( P = 0.007 \)). In addition, a significantly smaller decrease was found after EC180 in the RBF group compared with the IMT group (−22.6 ± 14.2%, \( P = 0.038 \)).

As shown in Figure 2, the percent changes in knee flexor torques after EC60 in the RBF group were significantly smaller than those of the CON group (−2.4 ± 5.4% and −20.2 ± 10.5%, \( P = 0.011 \)) and CC60 (1.2 ± 10.1% and −20.9 ± 12.0%, \( P = 0.02 \)).

**Ankle plantar flexor muscle strength.** Table 3 shows the muscle strength of ankle plantar flexor muscles before and after 2 wk of immobilization and non–weight bearing. The muscle strength decreased significantly in both the CON and IMT groups after the protocol, while RBF protected against such changes in muscle strength. In particular, the percent changes in ankle plantar flexor torques after EC120 were significant (ANOVA). Scheffe’s post hoc test showed a significantly smaller decrease after EC120 in the RBF group (−5.2 ± 10.5%) compared with IMT group (−26.4 ± 8.8%, \( P = 0.044 \)).

**Changes in thigh and leg circumferences.** Table 4 shows the circumferences of thigh and leg regions before and after 2 wk of immobilization and non–weight bearing. The latter resulted in significant decreases in the thigh circumference (10 cm: −2.3%, 15 cm: −2.7%) and leg circumference (−2.8%) in the CON group. Immobilization and non–weight bearing resulted in a significant decrease in leg circumference (−2.2%) but no changes in the thigh.
TABLE 3. Ankle plantar flexor torques at baseline and after a 2-wk immobilization and non–weight-bearing period combined with blood flow restriction (RBF), isometric training (IMT), and no intervention (CON).

<table>
<thead>
<tr>
<th></th>
<th>EC120</th>
<th></th>
<th>P Value</th>
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<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CON (N·m)</td>
<td>116.0</td>
<td>24.6</td>
<td>100.8</td>
<td>30.9</td>
<td>0.081</td>
<td>131.1</td>
<td>29.7</td>
<td>110.2</td>
<td>30.6</td>
<td>0.016</td>
<td>76.3</td>
<td>17.9</td>
</tr>
<tr>
<td>IMT (N·m)</td>
<td>137.8</td>
<td>53.9</td>
<td>100.8</td>
<td>26.7</td>
<td>0.033*</td>
<td>131.8</td>
<td>53.9</td>
<td>113.2</td>
<td>30.1</td>
<td>0.248</td>
<td>76.1</td>
<td>15.2</td>
</tr>
<tr>
<td>RBF (N·m)</td>
<td>124.2</td>
<td>57.1</td>
<td>114.1</td>
<td>41.3</td>
<td>0.366</td>
<td>130.5</td>
<td>56.8</td>
<td>121.2</td>
<td>42.0</td>
<td>0.353</td>
<td>78.5</td>
<td>17.9</td>
</tr>
</tbody>
</table>

Data are means ± SD. * P < 0.05. EC120, 120%·s⁻¹ under eccentric contraction; EC60, 60%·s⁻¹ under eccentric contraction; CC60, 60%·s⁻¹ under concentric contraction; CC120, 120%·s⁻¹ under concentric contraction.

circumference in the IMT group. In contrast, no changes in the circumference of the thigh and leg regions were noted in the RBF group following immobilization and non–weight bearing.

Changes in serum GH concentrations. There were no significant changes in GH during each intervention. The AUC was 80.17 ± 26.09 and 78.73 ± 26.03 min·pg⁻¹·mL⁻¹ in the RBF and IMT groups, respectively, and the difference was not significant.

DISCUSSION

The main finding of the present study was that repetitive blood flow restriction during a 2-wk immobilization and non–weight-bearing period prevented muscle weakness and any decrease in thigh and leg circumferences. These effects of blood flow restriction to the lower extremities were better than those achieved by isometric training. Our results also show that changes in muscle strength and thigh/leg circumference after immobilization and non–weight bearing were not associated with changes in serum GH concentration, suggesting that restriction of blood flow per se, rather than changes in GH, prevented muscle weakness and atrophy.

Blood flow restriction, combined with muscle strength training under low-load conditions, significantly increases muscle strength and muscle volume compared with the same training without blood flow restriction (1,16,19). On the other hand, it has been shown that blood flow restriction and light exercise prevented muscle atrophy after reconstruction of the anterior cruciate ligament (17). Thus, we presume that blood flow restriction does not only increase muscle volume and strength relative to baseline, but also prevents muscular atrophy induced by unloading. Accordingly, in the present study, we carefully examined whether blood flow restriction per se (without any exercise) prevents muscle atrophy and weakness induced by immobilization and non–weight bearing, and the results demonstrate that blood flow restriction prevents muscular dysfunction induced by unloading. Considered together with the results of others (17), our data suggest that blood flow restriction alone protects against muscle atrophy and weakness induced by unloading.

It is still not clear how blood flow restriction prevents muscle dysfunction induced by chronic unloading. Our preliminary data suggest that 200 mm Hg of cuff pressure induced blood flow restriction but did not induce complete vascular occlusion. However, the level of blood flow restriction induced by 200 mm Hg of cuff pressure should depend, at least partly, on leg size. Thus, restricted blood flow level might vary among the subjects. In addition, we cannot completely exclude the possibility that blood flow was occluded in some subjects, because we did not evaluate blood flow in the present study. In any case, we presume that the 200 mm Hg of cuff pressure used in our study at least restricted blood flow and possibly changed intramuscular metabolism. In this regard, Schott et al. (14) have shown that prolonged continuous muscle contraction induced more muscular hypertrophy and strength compared with intermittent contraction training. This effect was accompanied by greater changes in intramuscular phosphate metabolite and pH in a continuous contraction group compared with an intermittent contraction group (14). Thus, it is hypothesized that intramuscular metabolic changes may prevent muscle atrophy induced by chronic unloading. On the other hand, recent studies have reported that the effect of blood flow restriction on muscle hypertrophy depends on muscle fiber composition (9) and that muscle atrophy is dependent on muscle fiber composition (5). In addition, based on the results of studies involving measurement of changes in muscle strength and mass following a non–weight-bearing period (4,6,10,13), muscle weakness could occur independently of muscle atrophy. Thus, the relationship between muscle strength and neuromuscular function cannot be ignored (5) when considering the mechanism of

TABLE 4. Changes in thigh circumference at 10 and 15 cm above the upper border of the patella and changes in maximum leg circumference before and after a 2-wk immobilization and non–weight-bearing period combined with blood flow restriction (RBF), isometric training (IMT), and no intervention (CON).

<table>
<thead>
<tr>
<th></th>
<th>Thigh Circumference at 10 cm above the Upper Border of the Patella</th>
<th>Thigh Circumference at 15 cm above the Upper Border of the Patella</th>
<th>Maximum Leg Circumference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>P Value</td>
</tr>
<tr>
<td>CON (cm)</td>
<td>48.8</td>
<td>3.1</td>
<td>47.6</td>
</tr>
<tr>
<td>IMT (cm)</td>
<td>45.5</td>
<td>5.0</td>
<td>44.6</td>
</tr>
<tr>
<td>RBF (cm)</td>
<td>46.8</td>
<td>4.8</td>
<td>46.1</td>
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</table>

Data are means ± SD. * P < 0.05.
the beneficial effects of blood flow restriction on muscle weakness. Further studies are required to clarify the underlying mechanisms of the antiatrophic effects of blood flow restriction.

Akima and colleagues (3) have shown that muscle strength and volume of the knee extensors decreased by 16% and 8%, respectively, after 20 d of bed rest, and that isometric training prevented such changes. In the present study, 2 wk of unloading also induced muscle atrophy and weakness in the control group. Interestingly, blood flow restriction prevented muscle weakness and atrophy induced by chronic unloading. However, in contrast to the previous studies (3,14), isometric training did not completely prevent these muscle dysfunctions. This discrepancy might be explained by differences in isometric training protocols, because our isometric training protocol seemed milder than those used in previous studies (3,14).

The importance of GH and insulin-like growth factor-I (IGF-I) on muscle hypertrophy and prevention of muscle atrophy are well established. For example, GH is involved in augmented secretion of IGF-I, which plays an important role in activation of satellite cells and is considered to exert direct and indirect effects on muscle hypertrophy (8,12). Takarada and coworkers (20) have shown that low-load muscle strength training with blood flow restriction markedly increased serum GH concentration compared with the same strength training without blood flow restriction. Thus, it is hypothesized that increased GH secretion may mediate the effect of blood flow restriction on muscle hypertrophy. However, in the present study, no significant changes in serum GH levels were observed during each intervention. These results suggest that other mechanisms (e.g., intramuscular metabolic changes) could be involved in the antiatrophic effect of blood flow restriction independently of serum GH concentration.

In summary, we have demonstrated that repetitive restriction of blood flow to the lower extremity prevents muscular weakness induced by chronic unloading. Further studies are required to clarify the underlying mechanisms of antiatrophic effects of blood flow restriction.

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