Dose effect on intramuscular metabolic stress during low-intensity resistance exercise with blood flow restriction

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Skeletal muscle mass and strength relate to prognosis as well as exercise capacity, metabolic disorders, and quality of life in elderly people (12, 18) and patients with various other disorders (14, 27, 32). Therefore, skeletal muscle is now becoming an important therapeutic target in rehabilitation.

Although usual resistance training can achieve muscle hypertrophy and strength increase, it generates intensive stress in skeletal muscle and requires hard work. The common resistance training theory proposes that significant muscle hypertrophy and strength increase require a high intensity, over the 65% 1 RM threshold (16, 22). Thus resistance training cannot generally be applied for weak individuals, such as elderly and diseased patients, because of the large stress to their musculo-

skeletal and cardiovascular systems. Recommended resistance training for these groups is limited to relatively low exercise intensity (2, 39). Although resistance training with a low-intensity load can increase muscle strength and mass, those increases are significantly lower than those achieved by high-intensity resistance training (4, 13, 36)

Resistance training with blood flow restriction (BFR) is a new training method that can accommodate lower exercise intensity. Growing evidence suggests that this training method can lead to dramatic muscle hypertrophy and strength development (1, 20, 29, 35–37) and that such training can achieve effects similar to those of high-intensity resistance training (36). It was speculated that low-intensity resistance exercise with BFR might result in enhanced metabolic stress in skeletal muscle (8, 26, 34–37). To test this hypothesis, our previous study (31) investigated intramuscular metabolic stress during BFR exercise using 31P-magnetic resonance spectroscopy. The results showed that metabolic stress, as indicated by intramuscular metabolites and pH, was significantly increased by combining moderate BFR pressure with low-intensity resistance exercise at 20% 1 RM, but that the effects could not reach the level of those during high-intensity resistance exercise. Given this result, we attempted to optimize the BFR protocol to get effects equal to those of the standard high-intensity resistance training. In the present study, we investigated the dose effect of exercise intensity and pressure in BFR exercise. Our results should provide useful information for clinical rehabilitation.

METHODS

Subjects. Twelve subjects (men/women 6/6, age 20 ± 1 yr, height 168 ± 7 cm, weight 59 ± 9 kg, means ± SD) participated in the present study. All subjects were healthy and without orthopedic or cardiovascular diseases, and all provided informed consent. This study was approved by the Ethics Committee of Hokusho University (HOKUSHO-SPOR: 200704).

Exercise procedures. Subjects performed a unilateral plantar flexion exercise under six conditions: two resistance exercises without BFR and four BFR protocols. The two resistance exercises without BFR were low-intensity (L) and high-intensity (H) exercises, at 20% and 65% 1 RM, respectively. The four BFR protocols were as follows: 20% 1 RM with moderate pressure (MP), 30% 1 RM with MP, 40% 1 RM with MP, and 20% 1 RM with high pressure (HP). The exercise intensities used in the present study have been assigned to the level of low-intensity resistance training (2, 16, 39). The experimental exercises were set for 2 min with 30 repetitions per min, lifting the weight 5 cm above ground. The 1 RM was determined as a successful concentric-only contraction on the same plantar flexion apparatus equipped with a magnetic resonance device. Subjects were instructed to lift the load through the range of motion to prevent assistance from any other body part (e.g., the thigh). The 1 RM trials were designed...
using increments of 10 kg until 60–80% of the perceived maximum. Then the load was gradually increased by 1- to 5-kg weights until lift fail, in which the subject was not able to maintain proper form, or to completely lift the weight. The last acceptable lift with the highest possible load was determined as 1 RM. Means ± SD of resistance exercise loads, in kilograms, were 8 ± 3 at 20% 1 RM, 12 ± 4 at 30% 1 RM, 15 ± 7 at 40% 1 RM, and 25 ± 9 at 65% 1 RM, respectively. MP for BFR was set as 130% of resting systolic blood pressure (SBP) (6, 31, 33); HP was set at 200 mmHg (7, 8, 34, 35, 37). The mean ± SD of MP was at 147 ± 17 mmHg. HP for 200 mmHg was equivalent to 179 ± 21% of resting SBP. Subjects performed exercises under all six conditions in random order, on 2 days separated by at least 1 wk. Before each protocol, we confirmed the recovery in altered intramuscular metabolites and pH to baseline levels. BFR was carried out using a pneumatic rapid inflator (E-20 rapid cuff inflator, Hokanson) with an 18.5-cm-wide pressure cuff placed around the right thigh. The cuff was inflated for 10 s before the exercise protocol and promptly released after the exercise was completed. The real-time cuff pressure was monitored digitally and precisely maintained during exercise.

**31P-magnetic resonance spectroscopy.** Subjects lay in the supine position on an original apparatus equipped with a magnetic resonance device, and the right foot was attached to the pedal by a Velcro strap. 31P-magnetic resonance spectroscopy (MRS) was performed using a 55-cm bore, 1.5-T superconducting magnet (Magnetom Vision VB33G, Siemens Erlangen). A 80-mm surface coil was placed under the muscle belly of the right gastrocnemius. Shimming was adjusted to minimize the chemical shift. Spectra were acquired at a pulse width of 500 μs, a transmitter voltage of 20 V, and a repetition time of 2,000 ms. The spectra were acquired at rest and every 30 s during exercise. Each spectrum consisted of an average of 8 scans during 16 s before each time point. Peaks corresponding to high-energy phosphates were determined based on the chemical shifts. Peak areas were automatically calculated by peak fitting and integration after baseline correction using MR software (LUISE, Siemens Erlangen). The intramuscular phosphocreatine (PCr) millimolar concentration ([PCr]) assumed that [PCr] + creatine (Cr) concentration ([Cr]) = 42.5 mM (11) and supposed that the inorganic phosphate (Pi) concentration ([Pi]) is equal to [Cr] (15). Diprotonated phosphate (H2PO4) was calculated using the obtained [Pi] (17). Intramuscular pH was calculated from the chemical shift of P, relative to P<sub>c</sub>. When distinct P<sub>c</sub> splitting was shown, the pH was calculated by standardizing the obtained individual pH on the basis of peaks corresponding to each P<sub>i</sub> (17).

**Statistical analyses.** Repeated measures of ANOVA (time × condition) were used for comparisons among conditions. Post hoc comparisons were made by Bonferroni’s test. The comparisons of split-peak P<sub>c</sub> appearance among exercise conditions were performed by a χ² test. The level of significance was set at P < 0.05. All statistical tests were performed using SPSS 13.0 for Windows software.

### RESULTS

All 12 subjects could carry out unilateral plantar flexion with all protocols. There were no significant differences in resting intramuscular metabolites and pH among all six exercise conditions (Table 1). The PCr depletion and H2PO4 increase at the end of exercise showed significant changes compared with resting values in all six exercise conditions (P < 0.001). Intramuscular pH was significantly decreased in all four BFR protocols and HP (P < 0.05) but not in L.

![Fig. 1. Time course of phosphocreatine (PCr) depletion during exercise. Symbols indicate means, and error bars indicate SE. Significant difference in PCr depletion was observed for the exercise intensities (white, gray, and black squares), but not in the blood flow restriction (BFR) pressures (white and black triangle) (P < 0.05, by ANOVA). L, low-intensity resistance exercise at 20% of one repetition maximum (1RM); H, high-intensity exercise at 65% 1RM; MP, moderate pressure at 130% of resting systolic blood pressure; HP, high pressure at 200 mmHg.](http://jap.physiology.org/content/fig/bfr)[Fig. 1. Time course of phosphocreatine (PCr) depletion during exercise. Symbols indicate means, and error bars indicate SE. Significant difference in PCr depletion was observed for the exercise intensities (white, gray, and black squares), but not in the blood flow restriction (BFR) pressures (white and black triangle) (P < 0.05, by ANOVA). L, low-intensity resistance exercise at 20% of one repetition maximum (1RM); H, high-intensity exercise at 65% 1RM; MP, moderate pressure at 130% of resting systolic blood pressure; HP, high pressure at 200 mmHg.](http://jap.physiology.org/content/fig/bfr)
intramuscular pH showed similar trends (Table 1 and Fig. 1). In contrast, the changes in intramuscular metabolites and pH during 30% 1 RM with MP were similar to those during H (Table 1 and Fig. 1). The H2PO4− increase and intramuscular pH decrease during 40% 1 RM + MP were significantly greater than those during H (P < 0.05, Table 1). In the BFR protocols, dose effects were significant in the exercise intensity range from 20% 1 RM to 40% 1 RM (P < 0.001), but none were observed between the two BFR pressures, MP and HP.

The splitting of Pi peaks, which represents the recruitment of fast-twitch (FT) fiber (25, 38), was observed in the four BFR protocols and H, but not in L. The highest percent of subjects, 83%, showing split-peak Pi was obtained at the condition of protocols and H, but not in L. The highest percent of subjects, fast-twitch (FT) fiber (25, 38), was observed in the four BFR protocols. The findings agree with the result of Cook et al. (6), who reported that total tasks completed during three sets of exercise. The purpose of the present study was to investigate the dose effect of exercise intensity and pressure and to optimize the BFR protocol. The results of the present study have shown that an increase of exercise intensity in BFR protocols produced a significant dose effect. Moreover, the application of greater exercise intensity, 30% 1 RM compared with 20% 1 RM (the typical load in this training), resulted in intramuscular metabolic stress equivalent to that of high-intensity resistance exercise. In contrast, no dose effect for applied BFR pressure in the BFR protocol was observed, and the high BFR pressure protocol showed significantly lower metabolic stress than that during high-intensity resistance exercise. The findings agree with the result of Cook et al. (6), who reported that total tasks completed during three sets of BFR exercise showed a significant dose effect for increased exercise intensity between 20% 1 RM and 40% 1 RM, but no difference in effect between moderate (130% of resting SBP) and very high (300 mmHg) pressures. Thus the result of the present study confirms that the added stress in skeletal muscle during BFR exercise could be more strongly stimulated by increasing exercise intensity than by increasing BFR pressure. It is possible that the BFR protocol combining 30% 1 RM with MP could replace high-intensity resistance exercise for various purposes including rehabilitation in weak individuals.

**Application of exercise intensity for BFR exercise.** The progressive increase of exercise intensity in usual resistance training can effectively lead to muscle hypertrophy and strength enhancement (16). In contrast, before the present study it was not fully understood whether an increase of exercise intensity in long-term BFR training is required for such effects. Although many previous studies (1, 7, 8, 26, 33, 34, 37) have reported that application of 20% 1 RM in the BFR protocol could lead to dramatic training effects, the result of the present study showed that an increase of exercise intensity could greatly enhance intramuscular metabolic stress during BFR exercise. Moreover, the BFR protocol combining 40% 1 RM with MP showed greater intramuscular metabolic stress than that during high-intensity resistance exercise without BFR. This result suggests that the application of a higher-intensity load in the BFR protocol could more strongly stimulate the skeletal muscle than the usual high-intensity resistance exercise. A progressive increase of exercise intensity would be needed for long-term BFR training, such as 20% 1 RM at the novice stage, and 30% 1 RM and >40% 1 RM at the intermediate and advanced stages, respectively. This progression might be effective at obtaining a higher training effect than simple high-intensity resistance training. Further studies are needed to confirm the optimal long-term BFR protocol.

**Application of pressure for BFR exercise.** In the reports of Burgomaster et al. (3) and Moore et al. (23), no significant difference in increased maximal strength was observed between arms trained at 50% 1 RM with or without BFR. They used a low BFR pressure, 100 mmHg. MacDougall et al. (19) reported that SBP during moderate resistance exercise at 50% 1 RM was elevated to 200 mmHg. If moderate intensity such as 50% 1 RM is used, the application of low BFR pressure in the BFR protocol might not achieve a training effect. Thus BFR pressure higher than 100 mmHg might be needed in conjunction with moderate-intensity training. In the result of the present study, no dose effect was observed between moderate and high BFR pressures. However, our previous study (31) showed that the combination of low BFR pressure, 100 mmHg, at a load of 20% 1 RM in the BFR protocol created significantly lower metabolic stress than that during the moderate BFR pressure protocol at 150 mmHg. The low-pressure BFR, 100 mmHg, was lower than the elevated SBP during low-intensity exercise without BFR in our previous study (31). Therefore, the applied BFR pressure would need to be higher than the SBP level during exercise.

**Implications in 31P-MRS measurements during BFR exercise.** Previous studies (1, 8, 20, 26, 33–37) have determined that BFR exercise has a dramatic effect on both growth hormone (GH) secretion and muscle hypertrophy. It has been known that the metabolic stress parameters, such as lactate and H+ in blood level, are correlated to the elevated post exercise GH concentration (9, 10). Thus the large GH response induced by BFR could be explained by the increased metabolic stress during exercise. In addition, the metabolic stress might stimulate some other hormonal release and cytokine production, including insulin-like growth factor 1 and IL-6 as well as GH (1, 33, 34). Those growth factors and cytokines have been
suggested to regulate muscle growth/hypertrophy (24, 28, 30). Therefore, the evaluation of metabolic stress using $^{31}$P-MRS is an important tool for examining both acute and chronic effects in BFR exercise.

Our previous study (31) showed that FT fiber is recruited by applying BFR during low-intensity resistance exercise at 20% 1RM; however, the subjects who showed split Pi peaks (representing FT fiber recruitment) during the BFR exercise were few in number compared with those during high-intensity resistance exercise. In the present study, the increase of the exercise load in the BFR protocol was effective for inducing FT fiber recruitment, and the application of 30% 1RM showed results similar to those of high-intensity resistance exercise. To achieve successful muscle hypertrophy and strength gain by resistance training, a greater volume of FT fibers needs to be recruited, and can be recruited by employing a higher workload (16). It is known that resistance training-induced muscle hypertrophy occurs more extensively in FT fibers than in slow-twitch fibers (5, 21), suggesting that FT fiber recruitment during exercise is required to obtain a significant training effect. Therefore, the P$_i$ splitting detected by $^{31}$P-MRS might also be useful tool for evaluating the training effect of BFR exercises.

In conclusion, the result of the present study confirms that intramuscular metabolic stress during BFR exercise could be effectively enhanced by increasing the exercise intensity. To replace high-intensity resistance exercise, a BFR protocol combining at least 30% 1RM with moderate BFR pressure is needed. Such low exercise intensity could be safely performed by elderly and diseased patients (2, 39).

Although we demonstrated success at increasing exercise intensity with BFR, exercise volume could be also enhanced by increasing exercise repetition. The relationship between exercise repetition and intensity during BFR exercise should be clarified in future study.

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DISCLOSURES

No conflicts of interest (financial or otherwise) are declared by the authors.

REFERENCES


