Effects of low-load resistance exercise with blood flow restriction on high-energy phosphate metabolism and oxygenation level in skeletal muscle

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Abstract: We aimed to evaluate the effects of low-load resistance exercise with blood flow restriction (BFR) on high-energy phosphate metabolism, intracellular pH, and oxygenation level in the skeletal muscle. Seven males performed low-load ankle plantar flexion exercise (120 repetitions, 30% of one-repetition maximum) with and without BFR (130% of systolic blood pressure) inside a magnetic resonance device. Inorganic phosphate (Pi)-to-phosphocreatine (PCr) ratio, intracellular pH, and tissue oxygenation index (TOI) in the medial gastrocnemius were determined using 31P-magnetic resonance spectroscopy and near-infrared spectroscopy before and during exercise. The Pi-to-PCr ratio significantly increased during exercise in both conditions, with the BFR-condition values significantly exceeding the control-condition values. The BFR and control conditions showed significantly decreased intracellular pH during exercise, with the BFR-condition values being significantly lower than the control-condition values. The TOI significantly decreased during both exercises, but the decreases in the BFR condition were significantly greater than those observed in the control condition. Low-load BFR exercise places greater metabolic stress (greater PCr depletion, lower intracellular pH, and lower oxygenation level) on an exercising muscle than low-load non-restricted exercise.

Keywords: near-infrared spectroscopy, 31P-magnetic resonance spectroscopy, phosphocreatine, intracellular pH, tissue oxygenation index

Introduction

High-load resistance training with a mechanical load greater than 70% of one-repetition maximum (1RM) are generally required to increase muscle size and strength [1]. Similarly, low-load resistance training (20%–30% of 1RM) combined with blood flow restriction (BFR) has also been reported as an effective training method for increasing muscle size and strength [2, 3]. Some previous studies reported that low-load BFR exercise stimulates protein synthesis and suppresses proteolysis [4–6]. However, the exact mechanism has not yet been clarified. It is possible that greater metabolic stress induced by BFR is associated with muscle hypertrophy and strength gain after low-load resistance training with BFR.

Intramuscular energy metabolism is an important indicator of local metabolic stress on an exercising muscle. 31P-magnetic resonance spectroscopy (31P-MRS) can non-invasively assess changes in the relative concentrations of intramuscular metabolites involved in high-energy phosphate metabolism, such as adenosine tri-phosphate (ATP), phosphocreatine (PCr), inorganic phosphate (Pi), as well as changes in intracellular pH during exercise. Suga et al. [7–9] reported using 31P-MRS that intramuscular PCr depletion and decrease in pH during low-load BFR exercise were significantly greater than those observed during low-load non-restricted exercise. They also suggested that additional recruitment of fast-twitch fibers during low-load resistance exercise occurs with the application of BFR [7–9]. Although these responses...

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can be associated with a greater hypoxic environment during BFR exercise, the relationship has not been fully clarified.

Muscle oxygenation level has also been used as an indicator of intramuscular metabolic stress during exercise [10–13]. Near-infrared spectroscopy (NIRS) allows for non-invasive evaluation of the oxygenation level (a dynamic balance between oxygen supply and utilization) within the localized region of a specific muscle by continuously monitoring the \( \text{O}_2 \)-dependent absorption of hemoglobin (Hb) in the muscle microcirculation (i.e., arterioles, capillaries, and venules) and myoglobin (Mb) in the muscle cytoplasm. Larkin et al. [13] reported using NIRS that the dynamic knee extension exercise (120 repetitions, 40% of 1RM) with BFR resulted in significantly higher deoxygenated Hb concentration in the vastus lateralis than the exercise with normal blood flow. However, little attention has been given to the difference in muscle oxygenation level between low-load resistance exercise with and without BFR. Therefore, the relationship between intramuscular energy metabolism and oxygenation level has not been fully investigated in low-load BFR and non-restricted exercises.

This study aimed at comparing low-load BFR and non-restricted exercises for changes in high-energy phosphate metabolism, intracellular pH, and oxygenation level within a specific muscle during exercise using \(^{31}\text{P-MRS}\) and NIRS simultaneously. We hypothesized that low-load BFR exercise would place greater metabolic stress (greater Pcr depletion, lower intracellular pH, and lower oxygenation level) on an exercising muscle than low-load non-restricted exercise. These findings might enable a better understanding of the mechanism in which low-load BFR training results in muscle hypertrophy and strength gain comparable to those observed in traditional high-load resistance training.

**Materials and Methods**

**Participants**

In this study, we evaluated seven healthy male participants [mean and standard deviation (SD); age: 21.7 ± 1.7 years; height: 171.9 ± 6.0 cm; body weight: 66.9 ± 7.5 kg] who did not suffer from orthopedic and cardiovascular diseases. None of the participants regularly performed any lower extremity exercises. We instructed them to avoid any physical exercises for 1 week before the day of experiment. This study was approved by the Ethics Committee of Waseda University. Prior to the measurement, all participants were explained the purpose, potential risks, and examination procedures of this study. A written informed consent was obtained from each participant, and the participants’ rights were fully protected.

**Dynamic ankle plantar flexion exercise inside an MR device**

A non-magnetic custom-made exercise device (Senju, Tokyo, Japan) was used to perform dynamic ankle plantar flexion exercise inside a 1.5-T MR device (Signa Excite XIV, GE Healthcare, Milwaukee, WI, USA) (Fig. 1). After the measurement of systolic blood pressure with an electronic upper arm-type sphygmomanometer (HEM-7420, OMRON, Kyoto, Japan), each participant performed self-stretching of the calf muscles. The participants were then instructed to assume the supine position on the exercise device placed on the examination table of the MR device. The right foot, which was dominant in all participants (defined as the preferred kicking leg), was firmly secured to the foot holder of the exercise device using a Velcro strap with the knee fully extended.

First, the position of a weight cage (without weight) when each subject maximally flexed the ankle joint was marked on the exercise device. Next, 1RM of ankle plantar flexion was determined with a successful lift to the marked position without any assistance from the other body parts. The exercise load was set to 30% of 1RM (kg) because a BFR protocol with a load of at least 30% of 1RM is needed to replace high-load resistance exercise (65% of 1RM) [7]. After the participants performed ankle plantar flexions several times to obtain accustomed to the exercise load, they rested for approximately 10 min to neutralize any effects of the warm-up on pre-exercise data from \(^{31}\text{P-MRS}\) and NIRS. Then, the surface coil of the \(^{31}\text{P-MRS}\) device and the probes of the NIRS device were attached to the muscle belly of the medial gastrocnemius (MG) (proximally 70% of the distance between the medial point of the knee joint space and the central point of the medial malleolus) [14]. In addition, a non-magnetic occlusion cuff (width: 80 mm; MIZUHO, Tokyo, Japan) was firmly worn around the distal end of the right thigh.

\(^{31}\text{P-MRS}\) and NIRS measurements were concurrently performed. After obtaining pre-exercise \(^{31}\text{P-MRS}\) spectra, each participant performed dynamic ankle plantar flexion exercise for 4 min (30 repetitions/min) inside the bore of the MR device with (BFR condition) and without BFR (control condition). Both exercises were performed in accordance with the rhythm of an electrical metronome at a speed of 60 counts/min; ankle dorsiflexion and plantar flexion were alternately repeated every 1 s. Three of the seven participants first performed the exercise under the BFR condition, whereas the rest started the exercise under the control condition. Cuff pressure was set at 130% of systolic blood pressure at rest (126.3 ± 12.1 mmHg at rest; 164.1 ± 15.9 mmHg during BFR exercise) [7–9] and was automatically maintained during BFR exercise using a specially designed occlusion device (Intercross, Tokyo, Japan). The subjects were required to fold their
arms over the chest to minimize extraneous body motion during each exercise. An assistant stayed in the MR scan room to check whether the weight cage was lifted to the prescribed position during each exercise. All participants completed a total of 120 repetitions of ankle plantar flexion. The occlusion cuff was inflated immediately prior to BFR exercise and was deflated immediately after the completion of the last repetition during BFR exercise.

**31P-MRS measurement**

31P-MRS measurement was performed using the 1.5-T MR device with a 3-in. surface loop coil (outer diameter = 94 mm) (Takashima, Tokyo, Japan), which was fixed firmly on the muscle belly of the MG using non-elastic tapes. Magnetic field homogeneity was optimized by shimming on the proton signal from water, and phosphorus signals were collected with an optical pulse to produce the maximal signal intensity per pulse. For 31P-MRS measurement, we used a transversal two-dimensional spin echo chemical shift imaging sequence. The acquisition parameters were as follows: repetition time = 2,150 ms; flip angle = 60°; number of excitation = 8; spectral width = 2,500 Hz; total number of scans = 24; number of data points = 2,048; acquisition time = 1 min. Spectral measurements were performed at rest and every 1 min during each exercise (1–4 min). Peak areas were automatically calculated by peak fitting and integration after baseline correction using an analysis software (SAGE, GE Healthcare) installed in the MR device. For quantification of energy metabolism, the ratio of Pi to PCr (Pi/PCr) was determined by integrating each peak area. Muscle intracellular pH was calculated from the chemical shift of Pi relative to PCr using the following equation [15]:

\[
\text{Intracellular pH} = 6.75 + \log\left(\frac{\sigma - 3.27}{5.69 - \sigma}\right),
\]

where \(\sigma\) represents the chemical shift of Pi compared with PCr in parts per million.

**NIRS measurement**

The oxygenated and deoxygenated Hb/Mb levels within the localized region of the MG were evaluated as a concentration change (\(\Delta \ \mu\text{mol/L}\)) relative to each baseline value using an NIRS device (NIRO 200, Hamamatsu Photonics, Shizuoka, Japan) with custom-made probes (Hamamatsu Photonics) specially designed for the MR device. The NIRS optodes comprised a light source and a photon detector. In brief, one fiber-optic bundle carried the NIR light produced by laser diodes to the tissue of interest, whereas a second fiber-optic bundle returned the transmitted light from the tissue to a photon detector (photomultiplier tube). The optodes were placed in a black plastic holder and were longitudinally fixed on the muscle belly of the MG with tape (inter-optode spacing = 3 cm). The plastic holder was used for minimizing the intrusion of extraneous light and the loss of signal.
of NIR-transmitted light from the field of interrogation and fixing the relative positions of the optodes to prevent alteration. The position of the plastic holder was marked on the participant’s skin with semipermanent ink to ensure that the same measurement position was selected in the control and BFR conditions.

The oxygenated and deoxygenated Hb/Mb concentration data were successively collected every 1 s for 1 min before and for 4 min during exercise and were converted to 1-min interval data in each measurement period. These variables were expressed as a change in volume with respect to each pre-exercise 1-min value. Tissue oxygenation index (TOI) \((\text{oxygenated Hb/Mb}/(\text{oxygenated Hb/Mb} + \text{deoxygenated Hb/Mb}) \times 100)\) was expressed at 1-min intervals. In this study, the TOI mainly indicates a dynamic balance between muscle \(O_2\) delivery (supply) and \(O_2\) utilization (demand) within the localized region of the MG.

**Ratings of perceived exertion (RPE)**

The participants reported their overall RPE during each exercise in the control and BFR conditions using the Borg 6-20 RPE scale [16].

**Statistical analysis**

Mean and SD were calculated for all variables. For all measurement parameters, interaction effects (condition \(\times\) time) were examined by a two-way repeated-measures analysis of variance (ANOVA). When interactions were present, a one-way ANOVA with a Dunnett’s test was used to detect significant changes from pre-exercise value, and a paired \(t\)-test was used to detect difference between the two exercise conditions at each measurement time. In addition, RPE was compared between both exercise conditions using a paired \(t\)-test. Statistical significance was set at \(P < 0.05\) for all analyses.

**Results**

\(^{31}\text{P}-\text{MRS}\)

*Figure 2* shows the \(^{31}\text{P}-\text{MRS}\) spectra obtained from the MG before and at 4 min during exercise in the control and BFR conditions for a representative subject. The mean \(\text{Pi}/\text{PCr}\) ratios of the MG in both exercise conditions are presented in *Fig. 3*. Two-way repeated-measures ANOVA showed a significant interaction between exercise condition and time in terms of the \(\text{Pi}/\text{PCr}\) ratio \((P < 0.01)\). The \(\text{Pi}/\text{PCr}\) ratio significantly increased at 2–4 min during exercise in both conditions \((P < 0.01)\). There was no significant \(\text{Pi}/\text{PCr}\) difference between the control and BFR conditions in the pre-exercise values, but significant differences between the two conditions were found at 2–4 min during exercise (at 2 min, \(P < 0.05\); at 3 and 4 min, \(P < 0.01\)).

*Figure 4* shows the mean changes in intracellular pH in the MG under both exercise conditions. Two-way repeated-measures ANOVA confirmed a significant interaction between exercise condition and time in terms of the intracellular pH \((P < 0.01)\). The intracellular pH significantly decreased at 2–4 min during BFR exercise (at 2 min, \(P < 0.05\); at 3 and 4 min, \(P < 0.01\)). In the control condition, the intracellular pH significantly increased at 1 min and decreased at 4 min during exercise \((P < 0.05)\). There was no significant difference in the intracellular pH between the control and BFR conditions in the pre-exercise values, but significant differences in intracellular pH between the two conditions were observed at 2–4 min during exercise (at 2 min, \(P < 0.05\); at 3 and 4 min, \(P < 0.01\)).

**NIRS**

*Figure 5* shows the oxygenated and deoxygenated Hb/Mb values of the MG before and during exercise in the control and BFR conditions for a representative subject (the same subject shown in *Fig. 2*). *Figure 6a* shows the mean oxygenated Hb/Mb values of the MG in both exercise conditions. Two-way repeated-measures ANOVA showed a significant interaction between exercise condition and time in terms of the oxygenated Hb/Mb value \((P < 0.01)\). Both exercise conditions showed significantly decreased oxygenated Hb/Mb values at 1–4 min during exercise \((P < 0.01)\). Significant differences in the oxygenated Hb/Mb value were found between the two conditions at all-time points except for Pre \((P < 0.05)\). *Figure 6b* displays the mean deoxygenated Hb/Mb values of the MG in both exercise conditions. Two-way repeated-measures ANOVA showed a significant interaction between exercise condition and time in terms of the deoxygenated Hb/Mb value \((P < 0.01)\). The deoxygenated Hb/Mb values significantly increased at 1–4 min during exercise under both exercise conditions \((P < 0.01)\). There were no significant differences in the deoxygenated Hb/Mb value between the exercise conditions at all-time points except for Pre (at 1 and 2 min, \(P < 0.05\); at 3 and 4 min, \(P < 0.01\)).

The mean TOI values of the MG under both exercise conditions are presented in *Fig. 7*. Two-way repeated-measures ANOVA confirmed a significant interaction between exercise condition and time in terms of the TOI \((P < 0.01)\). The TOI significantly decreased at 1–4 min during exercise under both conditions \((P < 0.01)\). There were no significant differences in TOI between the two conditions at all-time points except for Pre (at 1 and 2 min, \(P < 0.01\); at 3 and 4 min, \(P < 0.05\)).
The BFR condition (17.1 ± 1.3) exhibited a significantly higher RPE value than the control condition (12.6 ± 1.0) \((P < 0.01)\).

**Discussion**

Both exercise conditions showed significantly decreased oxygenated Hb/Mb and increased deoxygenated Hb/Mb concentrations during each exercise. These findings would be caused by increased intramuscular \(O_2\) consumption during each exercise. As a result, the TOI of both exercise conditions significantly decreased during each exercise, indicating decreased intramuscular oxygenation level. In addition, the BFR condition showed significantly lower oxygenated Hb/Mb and higher deoxygenated Hb/Mb values during exercise compared with the control condition. Therefore, as expected, low-load BFR exercise resulted in significantly decreased muscle oxygenation level during exercise than low-load non-restricted exercise since BFR application *per se* causes disruption of arterial inflow into muscle and venous pooling within muscle [10]. Continuous exercise under hypoxic environment may cause an increase in neuromuscular activation (increased electromyography value) [17, 18] and/or additional recruitment of fast-twitch fibers during exercise [8], which can be related to increased muscle size and strength after low-load resistance training with BFR. Moreover, ischemic resistance training can develop muscle capillary network and improve the capacities of microvascular filtration and oxygen delivery within the trained muscles [13, 19, 20]. Therefore, the repetition of low-load BFR exercise may not only enhance muscle size and/or strength but also muscle endurance capacity [21, 22].

Both exercise conditions showed significant increases in \(Pi/PCr\) ratios during exercise. In addition, the BFR condition showed significantly greater \(Pi/PCr\) ratios during exercise than the control condition, which is in line with previous findings [7–9]. The BFR exercise possibly
depended more on anaerobic metabolism than exercise without BFR because of insufficient O₂ supply by arterial occlusion during exercise, even though the exercise load was low (30% of 1RM). Moreover, the two exercise conditions showed temporarily increased intracellular pH at 1 min during exercise (no significant change in the BFR condition). Given that PCr breakdown was the dominant mechanism to ATP production in the initial stage of exercise, the initial pH rise would be related to H⁺ consumption by PCr breakdown for ATP synthesis [23, 24]. Thereafter, the intracellular pH progressively decreased at 2–4 min during exercise in both exercise conditions, which possibly resulted from gradually increased contribution of glycolytic rate to ATP synthesis [5, 11, 23, 24]. Anaerobic glycolysis produces protons via lactate production and occasionally causes cellular acidification [5, 11, 23, 24], which would partly explain the significantly decreased intracellular pH during exercise in both exercise conditions. Jubrias et al. [25] showed that intracellular acidosis inhibits mitochondrial function and limits oxidative ATP supply in exercising muscles. Thus, acidic exercising muscle may depend more on anaerobic metabolism. In this study, the BFR condition showed significantly lower intracellular pH than the control condition, which should be partly attributed to greater lactate production via glycolytic ATP synthesis during low-load BFR exercise compared with during low-load non-restricted exercise [4–6, 11, 18]. It is possible that marked intramuscular acidosis during BFR exercise elicits additional recruitment of fast-twitch fibers [7–9], greater neuromuscular activation [17, 18], and/or greater growth hormone release [4, 5, 26], which may be associated with the anabolic benefits of BFR exercise.

Low-load BFR exercise has been recommended as an effective tool for individuals unable to withstand high-load exercise to increase muscle size and strength. However, depending on the exercise conditions, BFR exercise may be severe, even with low exercise load. In line with previous findings [12, 18], this study also revealed a high Borg’s score (17.1) in the BFR condition. In addition, Manini et al. [26] reported that low-load resistance training with BFR was effective for inducing greater growth hormone response than traditional high-load resistance training, but there was a more potent response in young men than in old men. Therefore, low-load BFR exercise should be recommended after considering age, exercise level, and physical condition.

This study has some limitations. First, because only 31P-MRS and NIRS data during exercise were collected, the effects of BFR exercise on muscle metabolism after exercise remain unknown. Considering that post-exercise hyperemia is greater with low-load BFR exercise than with low-load non-restricted exercise [11], post-exercise comparison of muscle metabolism between BFR and non-restricted exercise may be helpful to further our understanding of the mechanism by which low-load BFR exercise leads to increases in muscle size and strength. Second, we were unable to collect electromyography data due to the strong static magnetic field generated.
around the MR device. Thus, although neuromuscular activation has been shown to increase during low-load BFR exercise [17, 18], the effect of increased neuromuscular activation on high-energy phosphate metabolism, intracellular pH, and oxygenation level within an exercising muscle remains unclear in this study. Third, the levels of metabolites, such as lactate, were also not assessed in this study.

Fig. 5. Oxygenated and deoxygenated Hb/Mb values of the MG in the control and BFR conditions for a representative subject. The oxygenated and deoxygenated Hb/Mb concentration data are displayed every 1 s for 1 min before and for 4 min during exercise.

Fig. 6. Changes in oxygenated (a) and deoxygenated (b) Hb/Mb concentrations of the MG before and during dynamic ankle plantar flexion exercise under both exercise conditions. The asterisks indicate significantly decreased oxygenated Hb/Mb and increased deoxygenated Hb/Mb values from each pre-exercise value (**P < 0.01). Number signs indicate significant differences between the two exercise conditions in the oxygenated and deoxygenated Hb/Mb concentrations (#P < 0.05, ##P < 0.01). Values are mean ± SD.
In conclusion, low-load BFR exercise placed greater stress on intramuscular high-energy phosphate metabolism, and created more pronounced hypoxic and acidic environments within the exercising muscle in comparison with low-load non-restricted exercise. The greater stress on intramuscular energy metabolism during exercise can partly contribute to muscle hypertrophy and strength gain in low-load resistance training with BFR.

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**Authors’ contribution:** OY and MS played their roles in designing the study, searching for previous articles related to this study, and editing the manuscript. In addition, the authors had full access to all data in this study and take responsibility for the integrity of the data and accuracy of the data analysis.

**Conflict of interest:** The authors declare no conflict of interest.

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